

## RESEARCH ARTICLE



# Auditory stimulation in-phase with slow oscillations to enhance overnight memory consolidation in patients with schizophrenia?

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## Summary

Sleep-dependent memory consolidation is disturbed in patients with schizophrenia, who furthermore show reductions in sleep spindles and probably also in delta power during sleep. The memory dysfunction in these patients is one of the strongest markers for worse long-term functional outcome. However, therapeutic interventions to normalise memory functions, e.g., with medication, still do not exist. Against this backdrop, we investigated to what extent a non-invasive approach enhancing sleep with real-time auditory stimulation in-phase with slow oscillations might affect overnight memory consolidation in patients with schizophrenia. To this end, we examined 18 patients with stably medicated schizophrenia in a double-blinded sham-controlled design. Memory performance was assessed by a verbal (word list) and a non-verbal (complex figure) declarative memory task. In comparison to a sham condition without auditory stimuli, we found that in patients with schizophrenia, auditory stimulation evokes an electrophysiological response similar to that in healthy participants leading to an increase in slow wave and temporally coupled sleep spindle activity during stimulation. Despite this finding, patients did not show any beneficial effect on the overnight change in memory performance by stimulation. Although the stimulation in our study did not improve the patient's memory, the electrophysiological response gives hope that auditory stimulation could enable us to provide better treatment for sleep-related detriments in these patients in the future.

## KEYWORDS

acoustic stimulation, delta power, non-verbal memory, polysomnography, sleep spindles, verbal memory

## INTRODUCTION

Schizophrenia is a chronic mental disorder that often has a severe impact on patients (McCutcheon et al., 2020). In addition to the

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positive symptoms (e.g., delusion and hallucinations) and negative symptoms (e.g., avolition), specifically cognitive impairment has drawn more attention recently. While positive symptoms are mostly well treatable, negative symptoms and cognitive dysfunction cause long-term disruptions in daily routines of these patients. Memory-related dysfunctions are of particular importance as this deficit reflects one of the strongest markers of long-term functional outcome in schizophrenia (Green et al., 2000; Lepage et al., 2014). Interestingly, sleep-dependent memory consolidation is also significantly disturbed in these patients, with studies indicating impairments within both non-declarative (Genzel et al., 2015; Manoach et al., 2010) and declarative memory domains (Göder et al., 2004, 2015; Weinhold et al., 2021).

The cortical <1 Hz slow oscillations (SO) and thalamo-cortical 12–15 Hz sleep spindles hallmarking non-rapid eye movement (NREM) sleep seem to play an important role in sleep-related memory processes shown by many studies in healthy participants (for review: Rasch & Born, 2013). Also, SO spindle coupling (indicating the precise co-ordination of SO and spindles) has recently received more attention for their role in memory processes (Möller & Born, 2011; Muehlroth et al., 2019; Girardeau and Lopes-dos-Santos, 2021).

Given that aberrant sleep patterns are often reported in schizophrenia (Baglioni et al., 2016; Chan et al., 2017), a connection with sleep-dependent memory impairment is probable. One of the most consistently reported sleep alteration is a reduced number of sleep spindles (Castelnovo et al., 2018; Ferrarelli et al., 2007; Göder et al., 2015; Manoach & Stickgold, 2019), but also reduced slow-wave sleep (SWS) with less (1–4 Hz) delta power (Göder et al., 2006; Keshavan et al., 1998) seems to be evident in these patients. While in medicated patients with schizophrenia the amount of SWS mostly is comparable to healthy controls, patients still showed lower sleep spindle count, reduced delta power during SWS and exhibited reduced spindle power during SO up-states (Ferrarelli et al., 2010; Göder et al., 2006, 2015; Keshavan et al., 1998).

Therefore, one starting point for developing a better treatment for patients with schizophrenia is an attempt to improve memory function by normalising sleep oscillations. However, there is still no effective medication to treat memory deficits in patients with schizophrenia. Thus, attempts utilising non-invasive brain stimulation techniques previously applied in healthy subjects, e.g., transcranial electrical and magnetic stimulation (Göder et al., 2013). In this context, auditory stimulation in particular proved to be practicable and of low risk (Bellesi et al., 2014). With this method endogenous SO during sleep were detected in real-time and brief auditory stimuli applied during their positive peaks (Ngo et al., 2013b). Taking advantage of the overlap in thalamo-cortical networks underlying both auditory processing and memory consolidation, this method evokes activity identical to SO (including the phase-locked spindle activity) triggering memory-related processes (Bellesi et al., 2014). By this activation, an improvement in memory consolidation could be achieved in several studies (Leminen et al., 2017; Ngo et al., 2013b; Ngo et al., 2015; Ong et al., 2018). Despite other studies not finding these effects (Henin et al., 2019; Schneider et al., 2020), real-time auditory stimulation appears to be a promising technique.

Therefore, the aim of our study was to use auditory stimulation in-phase with SO to enhance SO and sleep spindle activity in patients with schizophrenia, in order to improve over-night memory consolidation in these patients.

## METHODS

### Participants

The Ethics Committee of the Medical Department of the Christian-Albrechts-University Kiel (Germany, reference number A 115/14) approved the study and participants' written informed consent was obtained according to the Declaration of Helsinki. We included patients with a diagnosis of schizophrenia or schizoaffective disorder according to the International Classification of Diseases 10th Revision. For validation of stimulation, we also included a smaller sample of healthy participants (for details see Supporting Information). Patients were recruited in the Department of Psychiatry and Psychotherapy (Kiel, Germany). Inclusion criteria were German native language and stable antipsychotic medication. Exclusion criteria were sleep-affecting disorders (e.g., sleep apnea), substance addiction or gamma-aminobutyric acid (GABA)-ergic medication. Participants underwent a semi-structured interview regarding exclusion criteria conducted by one of the investigators (SLW). All participants gave a written informed consent prior to their participation.

### Study design and procedure

The study was conducted at the Centre of Sleep Medicine, Department of Psychiatry and Psychotherapy, University Hospital Schleswig-Holstein, Kiel, Germany. We used a double-blinded sham-controlled crossover design to investigate the effect of auditory stimulation in-phase with SO on sleep parameters and memory consolidation in patients with schizophrenia. All participants were not allowed to take a nap or to drink alcohol or caffeine during experimental days.

Based on a within-subject design, all participants were tested in two sessions: a stimulation and a sham condition with an interval of 2–3 weeks in between. The order of conditions, as well as the order of test versions were balanced across participants.

Both experimental sessions followed the same protocol. Prior to the test night, polysomnographic recordings (PSG) were obtained during an adaptation night. After this, inpatients took part in ward routine while outpatients and healthy controls of validation study went home. The next evening, after preparation for PSG, participants completed questionnaires followed by cognitive performance testing. Starting times were adjusted such that participants would then go to bed between 9:00 p.m. and 11:00 p.m. according to their individual sleep length and were woken up at 6:30 a.m. the following morning. After ~1 h, to account for sleep inertia, participants repeated cognitive performance testing.

## Polysomnography

Electroencephalography (EEG) was recorded using a V-Amp (Brain Products Inc., Gilching, Germany) and goldcup scalp electrodes (Fp1, Fp2, F3, Fz, F4, AFz, C3, Cz, C4, P3, Pz, P4, O1, Oz, O2) referenced to the mastoids according to the international 10–20 System of Electrode Placement. Further electro-oculogram (EOG) and submental electromyogram (EMG) were recorded.

All EEG signals were sampled at a rate of 500 Hz, with a high-pass filter applied at 0.03 Hz and a low-pass filter at 150 Hz. Data were stored together with the stimulation triggers on a personal computer by using Brain Recorder software (version 2.1.2, Brain Products GmbH, Gilching, Germany).

## Auditory stimulation

To perform real-time auditory stimulation in phase with SO, we used an identical setup as described in Ngo et al. (2013). By an additional EEG recording system consisting of a D360 amplifier (Digitimer LTD, UK) and a Power1401 mk3 (Cambridge Electronic Design, UK), SO were detected online at Fpz referenced to linked mastoids. The signal was sampled at 200 Hz and band-pass filtered between 0.25 and 4 Hz. Real-time processing of the incoming prefrontal EEG signal was performing with the Spike2 software (Cambridge Electronic Design, UK) and a custom-made script. Auditory stimulation was triggered automatically whenever the EEG signal crossed an adaptive threshold downwards reflecting the presence of a negative SO half-wave. The threshold's default value was set to  $-80 \mu\text{V}$  and updated every 0.5 s to the minimal instantaneous EEG amplitude within the preceding 5-s interval. Moreover, the threshold did not exceed  $-80 \mu\text{V}$ . The stimuli comprised two brief clicks of pink 1/f noise each of 50-ms duration (5 ms rising and falling time). The first click was presented after an individual delay time, the second followed after a fixed interval of 1,075 ms. Thereafter, stimulation was discontinued for 2.5 s. The individual delay reflecting the time between the detected negative half-wave peak and the succeeding depolarising up-state was determined from the first SWS cycle of the adaptation night. To this end, the stimulation algorithm was executed without presenting any auditory stimuli but marking the time points a SO down-state was detected. Averaging the detection signal time-locked to these so-called Sham-click events allowed the extraction of the endogenous delay between a SO down-state and its subsequent up-state for each participant individually. The resulting signal was then averaged time-locked to the first click and the delay determined. In the test nights, the stimulation was commenced by one of the experimenters 10 min after a minimum of five consecutive SO were observed and stopped after 210 min. Whenever participants showed signs of arousal or transitioned out of NREM sleep, stimulation was halted by the experimenter and continued 5 min after the occurrence of three consecutive SO. During sham conditions, SO detection was performed in the same manner and respective time points were marked, but no auditory stimuli were

presented. The volume of the auditory stimulation during sleep was individually adapted for each participant to a comfortable level while they were awake and then increased by 15 dB (mean [SEM] 57.39 [7.10] dB).

## Electroencephalography analyses

Analyses were performed with Brain Vision Analyser (Brain Products, Germany), Domino 2.7 (Somnomedics, Randersacker, Germany) and Matlab R2018b together with the Fieldtrip toolbox (Oostenveld et al., 2011). Because of many artefacts and low information values, occipital channels were excluded from further analyses.

**Sleep stage scoring:** sleep was scored according to the American Academy of Sleep Medicine (AASM) Manual for Scoring of Sleep and Associated Events (Berry et al., 2015). For sleep scoring, European Data Format (.edf) were created by Brain Vision Analyser and EOG, EMG and relevant EEG signals (F4, C4, O2, F3, C3, O1, M1 and M2) were imported to Domino 2.7 software. EEG signals were imported with a sampling rate of 256 Hz, with a high-pass filter applied at 0.2 Hz and a low-pass filter at 50 Hz. Sleep scoring was performed visually by an experienced rater blinded to the experimental conditions. Stage changes were defined as the number of switches between any stages including wake.

**Spectral analysis:** we performed a spectral analysis for the whole night and for the 210-min stimulation period. To this end, artefact-free NREM sleep was selected and segmented into 5-s intervals (no overlap, 10% Hanning window, 0.125 Hz frequency resolution) and subjected to a fast Fourier transformation. Resulting power spectra were then averaged across all intervals and the band power extracted for SO (0.5–1 Hz), delta (1–4 Hz) and spindle range (12–15 Hz). To account for non-normal distribution of residuals, all power values were log-transformed (to the base 10).

**Event-related potentials (ERPs):** to assess evoked responses upon auditory stimulation, the EEG signal was averaged time-locked to the first click presentation (or corresponding marker in the sham condition) in 5-s windows with a 2-s pre-stimulus interval. In case of an unbalanced number of stimuli between the stimulation and sham condition, a randomised subset from the condition with the higher number was used. The number of stimuli averages in patients with schizophrenia was  $250.1 \pm 57.7$  and respectively  $277.6 \pm 29.3$  in the healthy participants.

**Time-frequency representation (TFR):** based on a window identical to the ERP analysis, we calculated time-locked TFRs using Morlet wavelets for frequencies from 1 to 20 Hz with a 0.5 Hz resolution and a step size of 50 ms. For frequencies  $>5$  Hz, the number of cycles was set adaptively to half of the corresponding frequency (or rounded up to the next integer value) but at least five cycles, resulting in comparable time windows (along the frequency dimension) of  $\sim 500$  ms. For frequencies  $<5$  Hz, that is 1–4.5 Hz, cycle numbers were reduced to values ranging from two to four. All TFRs were subsequently expressed as the relative change in power to a baseline from  $-2.5$  to  $-2$  s pre-stimulus.

## Questionnaires

The following questionnaires were collected prior to the first experimental night: anamnesis questionnaire (age, diseases, native language, etc.), a screening test for alcohol abuse (Rumpf et al., 2001), and the German version of the Eppendorf Schizophrenia Inventory (ESI; self-rating of schizophrenia-typical psychopathological symptoms with the subscales attention and speech impairment, ideas of reference, auditory uncertainty deviant perception and frankness; the first four scales were added up to a total score; Maß, 2009). Further we used Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) at each experimental session.

## Cognitive performance testing

Participants performed a digit span forward test from the Wechsler Adult Intelligence Scale to assess working memory. Next, to test verbal declarative memory performance, we used the word list task (parallel version A and D both with the interference list B) from the German version of the Rey Auditory-Verbal Learning Test (Helmstaedter et al., 2001). During encoding, 15 words were read out to the participants, which they were then asked to repeat in any order. This learning phase was repeated five times. Afterwards, participants were presented a list of 15 new words (interference list) followed by a repetition by the participant. Finally, they were asked to repeat the words from the first list in the evening before going to bed (immediate recall) and again the following morning (delayed recall).

Non-verbal declarative memory was assessed by a complex figure test. For this, we used the Rey-Osterrieth Complex Figure Test (Osterrieth, 1944), and as parallel version the Taylor Complex Figure Test (Hubley & Jassal, 2006). In these tests, the subjects are first required to copy a complex figure in the evening followed by a recall in the morning. Overnight change in memory for both declarative tasks was assessed by the difference in task performance in the morning and evening.

## Statistics

Statistical analyses were performed with the IBM Statistical Package for the Social Sciences (SPSS®) for Mac, version 21. Interval scaled data were described by means and SEMs. For memory tasks we used the variable “overnight forgetting” defined by performance in the evening minus performance in the morning. For statistical hypothesis testing in the patient group, we used paired *t* tests. Spectral power for the SO, delta and spindle band were examined using a repeated-measures analysis of variance (ANOVA) with the within-subject factors CONDITION (stimulation versus sham) and LOBE (prefrontal [mean of Fp1, Fz and Fp2] versus frontal [mean of F3, Fz and F4] versus central [mean of C3, Cz and C4] and parietal [mean of P3, Pz and P4]). The Huynh-Feldt correction of degrees of freedom was applied where appropriate. The significance threshold was set to  $\alpha = 0.05$ . Further post hoc *t* tests with Bonferroni correction for multiple

comparisons and the effect size by Cohen's *d* (Cohen, 1988) were calculated. We used boxplots to exclude extreme outliers ( $\pm 2$  SD from the mean) from statistical analysis. Normality assumption in the distribution of residuals was checked and by the Shapiro-Wilk test. Except for SO power at FP during the stimulation interval, all variables used for parametric analysis had normal distributed residuals. Statistical analyses for ERPs and TFRs relied on non-parametric Monte-Carlo based cluster-permutation statistics to control inflation of type I errors due to multiple comparisons (Maris & Oostenveld, 2007). To this end, samples were selected that showed significant differences between stimulation and sham condition (two-tailed paired-samples *t* tests, sample-level  $\alpha = 0.005$ ). In the resulting statistical map, adjacent samples were grouped into positive and negative clusters for which cluster-level statistics were calculated by summing the *t* values within each cluster. These were tested against a reference distribution (cluster-level  $\alpha = 0.05$ ), generated by shuffling the association of data and conditions (1,000 permutations) and, for each permutation, taking the maximum statistics among all clusters.

## RESULTS

### Sample

We included 18 patients with schizophrenia (nine females, two inpatients). The mean (SEM, range) age was 40.7 (2.2, 23–53) years. In all, 11 patients had paranoid schizophrenia and seven had a schizoaffective psychosis. One patient had comorbid depression, one an anxiety disorder, and two an addiction disorder. Two patients had additional somatic diagnoses (diabetes mellitus type 2 in two and asthma bronchiale in one). All patients received atypical antipsychotics. Most given antipsychotics were amisulpride (nine patients), aripiprazole (five), olanzapine (four), risperidone (four), quetiapine (three), and clozapine (three). Additionally, six patients took antidepressants or mood stabilisers. Detailed information on diagnosis, medication and comorbid diseases are shown in Table S5. Further we included a sample of five healthy participants for proof of setup. For the results of the validation study see the Supporting Information.

### Polysomnography

We first examined the sleep architecture and other sleep parameters in the patients and did not find differences between the stimulation and sham condition (Table 1).

### Spectral analysis

Next we sought to examine the general influence of auditory stimulation on spectral power within sleep-related frequency bands. For the 210-min stimulation interval, auditory stimulation caused a widespread increase in SO ( $F[1,16] = 101.8$  and  $p < 0.001$  for the main

**TABLE 1** Polysomnography data of patients with schizophrenia for the sham and stimulation night

Variable, mean (SEM)	Stimulation	Sham	T	Df	p (two-tailed)
Sleep efficiency, %	83.8 (3.1)	86.3 (1.8)	−0.883	17	0.389
Total sleep time, min	419 (18)	442 (13)	−1.628	17	0.122
Sleep latency, min	36 (6)	32 (5)	0.624	17	0.541
Wake, min	79 (16)	67 (36)	0.889	17	0.386
N1 (total), min	44 (5)	49 (5)	−1.055	17	0.306
N2 (total), min	173 (14)	176 (11)	−0.287	17	0.778
N3 (total), min	144 (14)	149 (11)	−0.726	17	0.478
REM sleep latency, min	146 (20)	130 (15)	1.094	17	0.289
REM sleep (total), min	59 (8)	68 (5)	−1.478	17	0.158
Sleep stage changes, <i>n</i>	172.5 (9.1)	173.7 (10.4)	−0.099	17	0.923
Wake periods, <i>n</i>	21.3 (3.0)	21.3 (3.4)	−0.046	17	0.964
Wake periods >3 min, <i>n</i>	1.7 (0.4)	1.6 (0.5)	0.243	17	0.811
Arousals, <i>n</i>	60.2 (6.4)	78.2 (13.4)	−1.522	17	0.146

Df, degrees of freedom; N1, NREM sleep 1; N2, NREM sleep 2; N3, NREM sleep 3 (also referred to as slow-wave sleep); (N)REM, (non-)rapid eye movement.

**TABLE 2** Shown are ANOVA results with the within-subject factors CONDITION (stimulation, sham) and LOBE (Fp, F, C, P) for log transformed slow oscillation (SO), delta and spindle power. Cohen's *d* refers to post-hoc comparison of the factor CONDITION

Frequency band	ANOVA					Lobe	Mean (SEM), $\mu V^2$		Cohen's <i>d</i>
	Source	Df	F	<i>p</i>	Df error		Stim	Sham	
SO	Condition	1	101.8	<0.001	16	Fp	2.22 (0.04)	1.94 (0.04)	2.321**
	Lobe	1.744	18.7	<0.001	27.911	F	2.19 (0.04)	1.91 (0.04)	2.550**
	Condition × Lobe	2.230	5.7	0.006	35.673	C	2.03 (0.05)	1.79 (0.04)	1.619**
						P	1.95 (0.05)	1.77 (0.06)	1.679**
Delta	Condition	1	121.6	<0.001	15	Fp	1.58 (0.02)	1.20 (0.03)	3.046**
	Lobe	2.334	105.9	<0.001	35.013	F	1.58 (0.04)	1.22 (0.04)	2.948**
	Condition × Lobe	2.214	27.4	<0.001	33.208	C	1.34 (0.05)	1.06 (0.04)	2.400**
						P	1.12 (0.04)	0.92 (0.04)	1.865**
Spindle	Condition	1	25.1	<0.001	16	Fp	−0.86 (0.05)	−0.97 (0.04)	1.079**
	Lobe	1.416	21.8	<0.001	22.649	F	−0.68 (0.05)	−0.81 (0.05)	1.564**
	Condition × Lobe	1.588	2.9	0.08	25.416	C	−0.70 (0.05)	−0.80 (0.06)	1.034**
						P	−0.78 (0.06)	−0.86 (0.07)	0.730*

ANOVA, analysis of variance; Df, degrees of freedom; SO, slow oscillations. \* for  $p < 0.050$  and by \*\* for  $p < 0.010$  according to Bonferroni correction for multiple comparisons.

effect COND), delta power ( $F[1,15] = 121.6$  and  $p < 0.001$  for the main effect COND) and spindle power ( $F[1,16] = 25.1$  and  $p < 0.001$  for the main effect COND) compared to the sham condition (Table 2). Power increases were limited to the stimulation interval, as an assessment across the whole night revealed comparable spectral power within these frequency bands between the stimulation and sham condition except a typical frontally dominant SO and delta distribution and a centro-parietal spindle topography (Table 3).

## Event-related potentials

To assess the electrophysiological response to the auditory stimulation, we next calculated ERPs time-locked to the first click

presentation. These confirmed an accurate real-time detection of SO and a click presentation in-phase with subsequent SO up-states. Moreover, patients showed a strong SO response, reflected by an evoked negative half-wave, after each click in comparison to the sham condition (Figure 1).

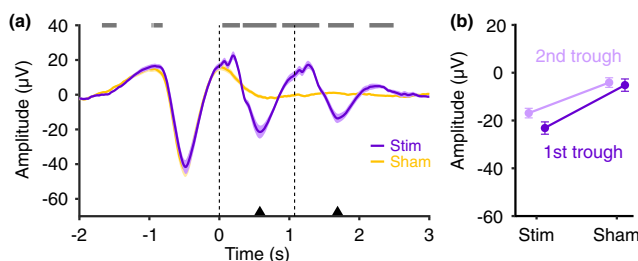
## Time frequency analysis

As a next step and in light of the critical interplay of SO and sleep spindle for memory consolidation, we calculated TFRs to examine stimulation effects on a broader frequency range (Figure 2a). Resulting TFRs revealed a widespread, i.e., found in all EEG channels, increase in power for the stimulation condition compared to the sham

**TABLE 3** Shown are ANOVA results with the within-subject factors CONDITION (stimulation, sham) and LOBE (Fp, F, C, P) for log transformed slow oscillation (SO), delta and spindle power. Cohen's *d* refers to post-hoc comparison of the factor CONDITION

Frequency band	ANOVA					Lobe	Mean (SEM), $\mu V^2$		Cohen's <i>d</i>
	Source	Df	F	<i>p</i>	Df error		Stim	Sham	
SO	Condition	1	0.2	0.631	17	Fp	1.23 (0.04)	1.22 (0.03)	0.202
	Lobe	1.895	16.2	<0.001	32.210	F	1.14 (0.04)	1.13 (0.15)	0.148
	Condition × Lobe	2.312	0.04	0.978	39.303	C	1.04 (0.05)	1.03 (0.04)	0.029
						P	1.06 (0.05)	1.05 (0.04)	0.064
Delta	Condition	1	0.2	0.683	17	Fp	0.42 (0.03)	0.40 (0.03)	0.282
	Lobe	1.945	52.4	<0.001	33.073	F	0.41 (0.04)	0.40 (0.04)	0.176
	Condition × Lobe	1.845	0.6	0.534	31.367	C	0.26 (0.04)	0.26 (0.04)	0.005
						P	0.17 (0.04)	0.18 (0.04)	−0.043
Spindle	Condition	1	1.4	0.256	17	Fp	−1.40 (0.06)	−1.43 (0.05)	0.298
	Lobe	1.214	20.3	<0.001	20.646	F	−1.21 (0.06)	−1.24 (0.06)	0.306
	Condition × Lobe	2.294	0.3	0.808	39.002	C	−1.20 (0.07)	−1.22 (0.07)	0.220
						P	−1.24 (0.08)	−1.26 (0.08)	0.218

ANOVA, analysis of variance; Df, degrees of freedom; SO, slow oscillations. \* for  $p < 0.050$  and by \*\* for  $p < 0.010$  according to Bonferroni correction for multiple comparisons.



**FIGURE 1** Event-related potentials. (a) Mean  $\pm$  SEM of the electroencephalography signal at Cz averaged time-locked to the first auditory click for the stimulation (purple) and sham condition (yellow) in patients with schizophrenia. Vertical dashed lines indicate click presentations. Black triangles highlight evoked troughs further analysed as shown in B, horizontal grey bars indicate significant distances between conditions. Of note, for results in healthy subject or a comparison between stimulation conditions between groups please refer to Figure S1. (b) Mean  $\pm$  SEM amplitude of the troughs following the first (left) and second click (right) as indicated by the black triangles in a for the stimulation and sham conditions in patients with schizophrenia (purple) and our healthy cohort (green)

condition within two clusters: one cluster reflected increases in slow-wave activity predominantly at around 2–3 Hz beginning with the first click and lasting up to 3 s post-stimulus ( $p < 0.001$ ). This pattern corresponds to the previous reported evoked responses after both clicks. A second cluster ( $p = 0.002$ ) encompassed the 12–16 Hz spindle range located between 0.75 and 1.5 s and thus phase-locked to the first induced SO up-state. In light of the strong link between spindle activity and schizophrenia, we quantified the latter in a follow-up analysis. To this end, we averaged TFR power across the 12–16 Hz spindle range and a time interval from 0.75 to 1.5 s (relative to the first click), which revealed an increase in spindle power by the auditory stimulation of several magnitudes (stimulation:  $0.182 \pm 0.064$  and sham:  $-0.008 \pm 0.033$ ;  $t[17] = 2.895$ ,  $p = 0.010$ , Figure 2b).

## Cognitive performance testing

The means and SEMs of the cognitive performance testing are shown in Table 4.

## Word list task

For the verbal declarative task, we found a general decrease in performance in patients with schizophrenia in the morning compared to the evening (sham:  $t[17] = 2.657$ ;  $p = 0.017$ ; stim:  $t[17] = 2.959$ ;  $p = 0.009$ ).

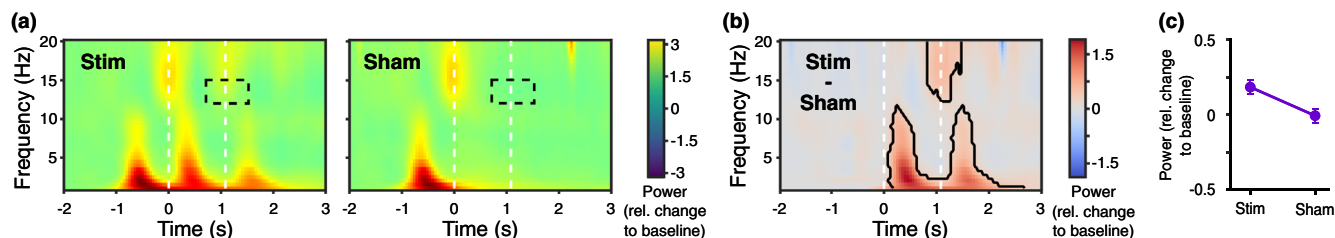
Auditory stimulation did not lead to less overnight forgetting (evening–morning:  $t[17] = -0.570$ ;  $p = 0.576$ ; Figure 3a) in the word list tests. Further, we did not find a significant correlation between the difference in the evoked SO response from the first click between condition, i.e., stimulation minus sham condition, with the corresponding difference for the verbal memory performance on the word list task the next morning ( $r = 0.22$ ,  $p = 0.386$ ; Pearson correlation) or for its overnight change ( $r = -0.30$ ;  $p = 0.234$ ; Pearson correlation).

## Complex figure

For non-verbal declarative memory, we again found a general decrease in performance in the morning (in stimulation and sham condition) compared to the evening in patients with schizophrenia (sham:  $t[17] = 5.226$ ;  $p < 0.001$ ; stim:  $t[17] = 7.762$ ;  $p < 0.001$ ).

However, we found no influence of the stimulation on the degree of overnight forgetting in patients with schizophrenia (evening–morning: Stim =  $11.03 \pm 1.04$ , Sham =  $9.69 \pm 1.86$ ,  $t[17] = 0.996$ ;  $p = 0.167$ ; Figure 3b). Nevertheless, we found a significant correlation between the difference in the evoked SO response from the first click

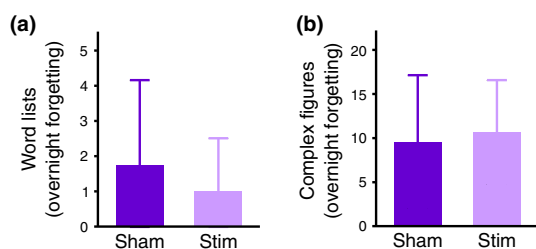




**FIGURE 2** Time frequency representations (TFRs). (a) Grand average of TFRs calculated time-locked to the first click (at Cz) for the stimulation (left) and sham condition (middle) in patients with schizophrenia. Colours reflect relative change in power to a baseline from  $-2.5$  to  $-2$  s pre-stimulus. The far-right plot depicts the difference between the stimulation and sham condition with red colours indicating higher power in the stimulation than sham condition and vice versa for blue colours. Contour lines show significant differences between conditions. Of note, for corresponding results in healthy subjects please refer to Figure S2. (b) Mean  $\pm$  SEM spindle power determined for 12–15 Hz between 0.75 and 1.5 s as indicated in the grey dashed boxes in (a) for the stimulation and sham conditions in patients with schizophrenia

**TABLE 4** Cognitive performance testing results in patients with schizophrenia divided by sham and stimulation condition and testing before (evening) and after the test nights (morning)

			Mean (SEM)
Digit span	Sham	Evening	7.39 (0.57)
		Morning	7.67 (0.54)
	Stimulation	Evening	7.83 (0.48)
		Morning	7.89 (0.50)
Complex figure	Sham	Evening	34.94 (0.34)
		Morning	25.25 (2.02)
		Forgetting	9.69 (1.86)
	Stimulation	Evening	34.42 (0.40)
		Morning	23.39 (1.53)
		Forgetting	11.03 (1.42)
Word list	Sham	Evening	8.78 (0.85)
		Morning	7.33 (0.95)
		Forgetting	1.44 (0.54)
	Stimulation	Evening	10.17 (0.90)
		Morning	9.11 (0.96)
		Forgetting	1.06 (0.36)



**FIGURE 3** Cognitive performance. (a) Mean  $\pm$  SEM performance on the verbal word list task, measured as overnight forgetting, in patients with schizophrenia for the stimulation and sham condition (dark versus light purple). (b) Mean  $\pm$  SEM performance on the non-verbal complex figure task, measured as overnight forgetting, in patients with schizophrenia for the stimulation and sham condition (dark versus light purple)

between condition, i.e., stimulation minus sham condition, with the corresponding difference for the visual memory performance on the complex figure task: the stronger the evoked response the higher patients performed in the complex figure task the next morning ( $r = -0.69$ ,  $p = 0.002$ ; Pearson correlation, Figure 4a) and the lower the overnight forgetting ( $r = 0.64$ ;  $p = 0.004$ ; Pearson correlation; Figure 4b).

### Digit span

For short-term memory assessed by a digit span task, we found no differences between the performance in the evening and morning for patients with schizophrenia (evening:  $t[17] = -1.074$ ;  $p = 0.289$ ; morning:  $t[17] = -0.524$ ;  $p = 0.607$ ).

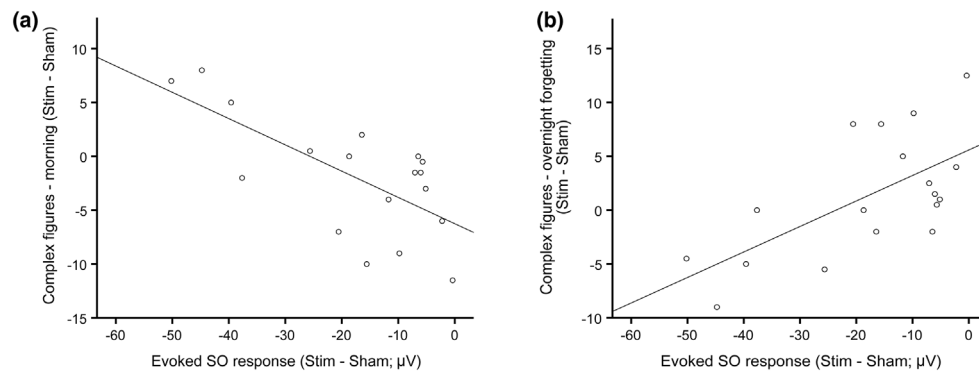
## DISCUSSION

In summary, our results show that even in patients with schizophrenia, real-time auditory stimulation in-phase with SO can trigger a neurophysiological response similar to that in healthy participants. However, the stimulation in patients with schizophrenia did not provoke the expected positive effects on memory performance in our study.

Patients with schizophrenia showed no sleep architecture differences between the stimulation and the sham condition. It is promising that there was no increase of sleep fragmentation by auditory stimulation as there was no effect on the number of awakenings, duration of wakefulness or the number of arousals in both samples. This indicates that sleep was not disturbed by the stimulation.

The ERPs time-locked to the first click presentation showed accurate real-time SO detection with correct click presentation in the SO up-state in schizophrenia, as well as in healthy participants (Figures 1a and S1).

In regard to the morphology of the evoked potentials, the findings in the patients with schizophrenia are in accordance with the results of our proof-of-setup study and the results from other studies (Ngo



**FIGURE 4** Correlation between evoked response and memory performance. (a) Scatter plot of the evoked slow oscillations (SO) response from the first click (stimulation – sham condition; horizontal axis), and the corresponding difference of complex figure task performance the next morning (vertical axis). The significant correlation ( $r = -0.69$ ,  $p = 0.002$ , Pearson correlation) demonstrate the stronger the (negative) SO response the better the performance in the morning. (b) Scatter plot of the evoked SO response from the first click (stimulation – sham condition; horizontal axis), and the corresponding difference in overnight forgetting for the complex figure task (vertical axis), yielding a significant correlation ( $r = 0.64$ ,  $p = 0.004$ , Pearson correlation). The correlation demonstrates the stronger the (negative) SO response the less forgetting. Please note, the change in polarity stems from an assessment of forgetting, i.e., smaller values correspond to less forgetting and therefore better memory consolidation

et al., 2013b; Ngo et al., 2015). Patients showed comparable results, i.e., both the spontaneous pre-stimulus SO triggering the click presentations and the evoked responses were similar. This is a first indication that acoustic stimulation is also effective in patients with schizophrenia, at least at the neurophysiological level.

Along this line, as demonstrated by earlier studies in healthy subjects (Ngo et al., 2013a, 2013b; Papalambros et al., 2017; Weigenand et al., 2016), auditory stimulation translated into a strong enhancement of slow-wave activity. The enhancement was not only evident in acute intervals time-locked to the stimulation but also manifested itself into an overall increase in spectral power across the 210-min stimulation interval and thus confirms a resonant response in this cardinal frequency range. Intriguingly, our findings suggest an altered spindle dynamic in patients with schizophrenia. While acute surges in spindle activity in-phase with induced SO are in line with findings in healthy participants across different age ranges (Ngo et al., 2013a, 2013b, 2015; Papalambros et al., 2017; Schneider et al., 2020), elevated spindle activity was likewise found across the whole 210-min intervention interval. Conversely, previous studies utilising an identical stimulation protocol with two clicks in healthy subjects did not show such cumulative spindle enhancement. They instead revealed that spindle generation is governed by a refractoriness balancing or rather limiting an external facilitation of spindle activity that is even more pronounced with older age (Ngo et al., 2015; Schneider et al., 2020). Altogether, patients with schizophrenia may rely primarily on a diminished sleep spindle expression but in addition, and rather counter-intuitively, alterations in the underlying thalamo-cortical networks appear to point towards a stronger sensitivity to sensory/auditory induced spindle generation.

Regarding memory tasks, we did not find an increase in memory performance in patients with schizophrenia after stimulation, neither in verbal nor in figural memory task in contrast to other studies (Ngo et al., 2015, 2013b; Ong et al., 2016) and to our proof-of-setup

sample. As there were no differences in the attention test, it is unlikely that the memory performance was influenced by attention deficits. The central question that arises from missing memory effects is why the neurophysiological changes in the patients did not lead to an improvement in memory performance (as in the healthy subjects in this and in other studies). It seems most likely that although there is a significant increase in SO and delta power, this is not sufficient to achieve visible effects. It is also possible that when using tests that are more sleep sensitive, such as associative learning tasks (compare Ngo et al. 2015), a correspondingly smaller effect would be seen in patients with schizophrenia as well. Another reason for missing effects of stimulation on memory performance could be that the disturbed nocturnal memory consolidation in patients depends on other mechanisms, such as a correct co-ordination of SO and spindles, rather than on the number or density of slow waves and spindles. As shown in our data, there appeared to be no effect of the acoustic stimulation on the SO-spindle timing in patients with schizophrenia.

Another possibility, given the link between first evoked response and visual memory performance, is that the stimulation effect was not strong enough in all patients. This could indicate that the initiation of processes underlying memory consolidation depend highly on the efficacy to evoked SO with an auditory stimulus and may warrants further attempts to specifically optimise stimulation parameters in such patient cohorts (Navarrete et al., 2020).

One of the major limitations of the study is the small group size of the healthy sample and the resulted unequal size of the two samples. Therefore, no reliable comparisons between healthy individuals and patients can be made. This would be desirable because stimulation, despite its influence on the neurophysiological level, has no effect on memory tasks. Another limitation is the fact that the patients were all medicated. However, as the medication was stable during the study period and the results based on repeated measurements, it is of little importance within the patient sample. A further



minor limitation is a possible caffeine withdrawal, as participants were asked to abstain from caffeine for all 4 test days. However, as for the medication, a potential effect should influence both the sham and stimulation condition equally.

This is the first study with brain state-dependent auditory stimulation in patients with schizophrenia. Despite the limitations, the stimulation seems to have a neurophysiological effect on sleep in patients with schizophrenia. Thus, we have an alternative approach to affect SO phase-locked spindle power and delta power in patients with schizophrenia. As mentioned in the introduction, there are many indications that altered sleep could play a role in disturbed over-night memory consolidation in patients with schizophrenia. There is still hope that auditory stimulation could indirectly improve memory performance by altering the microstructure of sleep. However, this requires further studies in patients with schizophrenia, e.g., using different cognitive tasks (e.g., associated word pair tasks) and comparable healthy control groups. In the future, maybe acoustic stimulation could provide better treatment for these patients.

## AUTHOR CONTRIBUTIONS

Conception and design: Sara Lena Weinhold, Hong-Viet V. Ngo, Robert Göder; acquisition: Sara Lena Weinhold, Nele Timm, Anja Hansen, Robert Göder; analysis and interpretation of data: Sara Lena Weinhold, Julia Lechinger, Hong-Viet V. Ngo, Robert Göder, drafting the work: Sara Lena Weinhold, revising: Julia Lechinger, Nele Timm, Anja Hansen, Hong-Viet V. Ngo, Robert Göder; final approval: Sara Lena Weinhold, Julia Lechinger, Nele Timm, Anja Hansen, Hong-Viet V. Ngo, Robert Göder.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

## DATA AVAILABILITY STATEMENT

Datasets are available from the corresponding author on request.

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## REFERENCES

- Baglioni, C., Nanovska, S., Regen, W., Spiegelhalder, K., Feige, B., Nissen, C., Reynolds, C. F., & Riemann, D. (2016). Sleep and mental disorders: A meta-analysis of polysomnographic research. *Psychological Bulletin*, 142(9), 969–990. <https://doi.org/10.1037/bul0000053>
- Bellesi, M., Riedner, B. A., Garcia-Molina, G. N., Cirelli, C., & Tononi, G. (2014). Enhancement of sleep slow waves: Underlying mechanisms and practical consequences. *Frontiers in Systems Neuroscience*, 8, 1–17. <https://doi.org/10.3389/fnsys.2014.00208>
- Berry, R. B., Brooks, R., Gamaldo, C. E., Harding, S. M., Lloyd, R. M., Marcus, C. L., Vaughn, B. V., & for the American Academy of sleep medicine. (2015). *The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications, version 2.2*. [www.aasmnet.org](http://www.aasmnet.org). American Academy of Sleep Medicine.
- Buyse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research*, 28(2), 193–213. [https://doi.org/10.1016/0165-1781\(89\)90047-4](https://doi.org/10.1016/0165-1781(89)90047-4)
- Castelnovo, A., Graziano, B., Ferrarelli, F., & D'Agostino, A. (2018). Sleep spindles and slow waves in schizophrenia and related disorders: Main findings, challenges and future perspectives. *European Journal of Neuroscience*, 48(8), 2738–2758. <https://doi.org/10.1111/ejn.13815>
- Chan, M.-S., Chung, K.-F., Yung, K.-P., & Yeung, W.-F. (2017). Sleep in schizophrenia: A systematic review and meta-analysis of polysomnographic findings in case-control studies. *Sleep Medicine Reviews*, 32, 69–84. <https://doi.org/10.1016/j.smrv.2016.03.001>
- Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Routledge. <https://doi.org/10.4324/9780203771587>
- Ferrarelli, F., Huber, R., Peterson, M. J., Massimini, M., Murphy, M., Riedner, B. A., Watson, A., Bria, P., & Tononi, G. (2007). Reduced sleep spindle activity in schizophrenia patients. *American Journal of Psychiatry*, 164(3), 483–492. <https://doi.org/10.1176/ajp.2007.164.3.483>
- Ferrarelli, F., Peterson, M. J., Sarasso, S., Riedner, B. A., Murphy, M. J., Benca, R. M., Bria, P., Kalin, N. H., & Tononi, G. (2010). Thalamic dysfunction in schizophrenia suggested by whole-night deficits in slow and fast spindles. *American Journal of Psychiatry*, 167(11), 1339–1348. <https://doi.org/10.1176/appi.ajp.2010.09121731>
- Genzel, L., Dresler, M., Cornu, M., Jäger, E., Konrad, B., Adamczyk, M., Friess, E., Steiger, A., Cizisch, M., & Goya-Maldonado, R. (2015). Medial prefrontal-hippocampal connectivity and motor memory consolidation in depression and schizophrenia. *Biological Psychiatry*, 77(2), 177–186. <https://doi.org/10.1016/j.biopsych.2014.06.004>
- Girardeau, G., & Lopes-dos-Santos, V. (2021). Brain neural patterns and the memory function of sleep. *Science*, 374(6567), 560–564. <https://doi.org/10.1126/science.abi8370>
- Göder, R., Aldenhoff, J. B., Boigs, M., Braun, S., Koch, J., & Fritzer, G. (2006). Delta power in sleep in relation to neuropsychological performance in healthy subjects and schizophrenia patients. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 18(4), 529–535. <https://doi.org/10.1176/jnp.2006.18.4.529>
- Göder, R., Baier, P. C., Beith, B., Baecker, C., Seeck-Hirschner, M., Junghanns, K., & Marshall, L. (2013). Effects of transcranial direct current stimulation during sleep on memory performance in patients with schizophrenia. *Schizophrenia Research*, 144(1–3), 153–154. <https://doi.org/10.1016/j.schres.2012.12.014>
- Göder, R., Boigs, M., Braun, S., Friege, L., Fritzer, G., Aldenhoff, J. B., & Hinze-Selch, D. (2004). Impairment of visuospatial memory is associated with decreased slow wave sleep in schizophrenia. *Journal of Psychiatric Research*, 38(6), 591–599. <https://doi.org/10.1016/j.jpsychires.2004.04.005>
- Göder, R., Graf, A., Ballhausen, F., Weinhold, S., Baier, P. C., Junghanns, K., & Prehn-Kristensen, A. (2015). Impairment of sleep-related memory consolidation in schizophrenia: Relevance of sleep spindles? *Sleep Medicine*, 16(5), 564–569. <https://doi.org/10.1016/j.sleep.2014.12.022>
- Green, M. F., Kern, R. S., Braff, D. L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the right stuff? *Schizophrenia Bulletin*, 26(1), 119–136. <https://doi.org/10.1093/oxfordjournals.schbul.a033430>
- Helmstaedter, C., Lendt, M., & Lux, S. (2001). *Verbaler Lern- und Merkfähigkeitstest (VLMT)*. Beltz Verlag.
- Henin, S., Borges, H., Shankar, A., Sarac, C., Melloni, L., Friedman, D., Flinker, A., Parra, L. C., Buzsaki, G., Devinsky, O., & Liu, A. (2019). Closed-loop acoustic stimulation enhances sleep oscillations but not memory performance. *Eneuro*, 6(6), 1–15. [ENEURO.0306-19.2019](https://doi.org/10.1523/ENEURO.0306-19.2019)
- Hubley, A. M., & Jassal, S. (2006). Comparability of the Rey-Osterrieth and modified Taylor complex figures using Total scores, completion times, and construct validation. *Journal of Clinical and Experimental Neuropsychology*, 28(8), 1482–1497.
- Keshavan, M. S., Reynolds, C. F., Miewald, J. M., Montrose, D. M., Sweeney, J. A., Vasko, R. C., & Kupfer, D. J. (1998). Delta sleep deficits

- in schizophrenia: Evidence from automated analyses of sleep data. *Archives of General Psychiatry*, 55(5), 443. <https://doi.org/10.1001/archpsyc.55.5.443>
- Leminen, M. M., Virkkala, J., Saure, E., Paajanen, T., Zee, P. C., Santostasi, G., Hublin, C., Müller, K., Porkka-Heiskanen, T., Huottilainen, M., & Paunio, T. (2017). Enhanced memory consolidation via automatic sound stimulation during non-REM sleep. *Sleep*, 40(3), 1–10. <https://doi.org/10.1093/sleep/zsx003>
- Lepage, M., Bodnar, M., & Bowie, C. R. (2014). Neurocognition: Clinical and functional outcomes in schizophrenia. *The Canadian Journal of Psychiatry*, 59(1), 5–12. <https://doi.org/10.1177/070674371405900103>
- Manoach, D. S., & Stickgold, R. (2019). Abnormal sleep spindles, memory consolidation, and schizophrenia. *Annual Review of Clinical Psychology*, 15(1), 451–479. <https://doi.org/10.1146/annurev-clinpsy-050718-095754>
- Manoach, D. S., Thakkar, K. N., Strojnowski, E., Ely, A., McKinley, S. K., Wamsley, E., Djonlagic, I., Vangel, M. G., Goff, D. C., & Stickgold, R. (2010). Reduced overnight consolidation of procedural learning in chronic medicated schizophrenia is related to specific sleep stages. *Journal of Psychiatric Research*, 44(2), 112–120. <https://doi.org/10.1016/j.jpsychires.2009.06.011>
- Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods*, 164, 177–190.
- Maß, R. (2009). Das Eppendorfer Schizophrenie-Inventar (ESI) als methodischer Ansatz in der High-Risk- und Schizotypieforschung. *Diagnostica*, 55(3), 153–159. <https://doi.org/10.1026/0012-1924.55.3.153>
- McCutcheon, R. A., Reis Marques, T., & Howes, O. D. (2020). Schizophrenia—An overview. *JAMA Psychiatry*, 77(2), 201–210. <https://doi.org/10.1001/jamapsychiatry.2019.3360>
- Mölle, M., & Born, J. (2011). Slow oscillations orchestrating fast oscillations and memory consolidation. *Progress in Brain Research*, 193, 93–110. <https://doi.org/10.1016/B978-0-444-53839-0.00007-7>
- Muehlroth, B. E., Sander, M. C., Fandakova, Y., Grandy, T. H., Rasch, B., Shing, Y. L., & Werkle-Bergner, M. (2019). Precise slow oscillation-spindle coupling promotes memory consolidation in younger and older adults. *Scientific Reports*, 9(1), 1940. <https://doi.org/10.1038/s41598-018-36557-z>
- Navarrete, M., Schneider, J., Ngo, H. V., Valderrama, M., Casson, A. J., & Lewis, P. A. (2020). Examining the optimal timing for closed-loop auditory stimulation of slow-wave sleep in young and older adults. *Sleep*, 43(6), 1–14. <https://doi.org/10.1093/sleep/zsz315>
- Ngo, H.-V. V., Claussen, J. C., Born, J., & Mölle, M. (2013a). Induction of slow oscillations by rhythmic acoustic stimulation: *Acoustic stimulation during sleep*. *Journal of Sleep Research*, 22(1), 22–31. <https://doi.org/10.1111/j.1365-2869.2012.01039.x>
- Ngo, H.-V. V., Martinetz, T., Born, J., & Mölle, M. (2013b). 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>
- Ngo, H.-V. V., Miedema, A., Faude, I., Martinetz, T., Mölle, M., & Born, J. (2015). Driving sleep slow oscillations by auditory closed-loop stimulation—A self-limiting process. *Journal of Neuroscience*, 35(17), 6630–6638. <https://doi.org/10.1523/JNEUROSCI.3133-14.2015>
- Ong, J. L., Lo, J. C., Chee, N. I. Y. N., Santostasi, G., Paller, K. A., Zee, P. C., & Chee, M. W. L. (2016). Effects of phase-locked acoustic stimulation during a nap on EEG spectra and declarative memory consolidation. *Sleep Medicine*, 20, 88–97. <https://doi.org/10.1016/j.sleep.2015.10.016>
- 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), 1–11. <https://doi.org/10.1093/sleep/zsy031>
- Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience*, 2011, 1–9. <https://doi.org/10.1155/2011/156869>
- Osterrieth, P. (1944). Le test de copie d'une figure complexe. *Archives de Psychologie*, 30, 206–356.
- Papalambros, N. A., Santostasi, G., Malkani, R. G., Braun, R., Weintraub, S., Paller, K. A., & Zee, P. C. (2017). Acoustic enhancement of sleep slow oscillations and concomitant memory improvement in older adults. *Frontiers in Human Neuroscience*, 11, 1–14. <https://doi.org/10.3389/fnhum.2017.00109>
- Rasch, B., & Born, J. (2013). About sleep's role in memory. *Physiological Reviews*, 93(2), 681–766. <https://doi.org/10.1152/physrev.00032.2012>
- Rumpf, H., Hapke, U., & John, U. (2001). LAST - Lübecker Alkoholabhängigkeits- und -missbrauchs-Screening-Test. Hogrefe.
- Schneider, J., Lewis, P. A., Koester, D., Born, J., & Ngo, H.-V. V. (2020). Susceptibility to auditory closed-loop stimulation of sleep slow oscillations changes with age. *Sleep*, 43(12), zsa111. <https://doi.org/10.1093/sleep/zsaa111>
- Weigenand, A., Mölle, M., Werner, F., Martinetz, T., & Marshall, L. (2016). Timing matters: Open-loop stimulation does not improve overnight consolidation of word pairs in humans. *European Journal of Neuroscience*, 44(6), 2357–2368. <https://doi.org/10.1111/ejn.13334>
- Weinhold, S. L., Lechinger, J., Ittel, J., Ritzenhoff, R., Drews, H. J., Junghanns, K., & Göder, R. (2021). Dysfunctional overnight memory consolidation in patients with schizophrenia in comparison to healthy controls: Disturbed slow-wave sleep as contributing factor? *Neuropsychobiology*, 1–12, 104–115. <https://doi.org/10.1159/000517858>

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