

RESEARCH ARTICLE

Optimising sounds for the driving of sleep oscillations by closed-loop auditory stimulation

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Summary

Recent studies have shown that slow oscillations (SOs) can be driven by rhythmic auditory stimulation, which deepens slow-wave sleep (SWS) and improves memory and the immune-supportive hormonal milieu related to this sleep stage. While different attempts have been made to optimise the driving of the SOs by changing the number of click stimulations, no study has yet investigated the impact of applying more than five clicks in a row. Likewise, the importance of the type of sounds in eliciting brain responses is presently unclear. In a study of 12 healthy young participants (10 females; aged 18–26 years), we applied an established closed-loop stimulation method, which delivered sequences of 10 pink noises, 10 pure sounds (B note of 247 Hz), 10 pronounced “a” vowels, 10 sham, 10 variable sounds, and 10 “oddball” sounds on the up phase of the endogenous SOs. By analysing area under the curve, amplitude, and event related potentials, we explored whether the nature of the sound had a differential effect on driving SOs. We showed that every stimulus in a 10-click sequence, induces a SO response. Interestingly, all three types of sounds that we tested triggered SOs. However, pink noise elicited a more pronounced response compared to the other sounds, which was explained by a broader topographical recruitment of brain areas. Our data further suggest that varying the sounds may partially counteract habituation.

KEYWORDS

closed-loop auditory stimulation, sleep, slow oscillations, slow-wave sleep

1 | INTRODUCTION

In recent decades, increasing evidence has positioned slow oscillations (SOs), high amplitude oscillations with a period of ~0.8 Hz that are the electroencephalography (EEG) hallmark of slow-wave sleep (SWS), as a major player in neurophysiological phenomena such as glucose metabolism, hormone release, immunity, and memory (Léger et al., 2018).

This proposed role for SWS, coupled with observations of impaired SWS in several pathologies as well as in ageing, has led some researchers to implement methods that could specifically enhance SWS (Léger et al., 2018). Among them, auditory closed-loop stimulation appeared to be an non-invasive, low cost, and promising technique (Bellesi et al., 2014).

The first studies using this method showed that SOs and sleep spindles, which characterise SWS, can be enhanced by the application

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of auditory stimuli (pink noise) near the oscillation peaks (Ngo et al., 2013a, 2015). Such stimulation has been reported in several studies as a way to enhance overnight memory consolidation (Ngo et al., 2013b; Leminen et al., 2017; Papalambros et al., 2017) and change the immune and hormonal milieu (Besedovsky et al., 2017), as well as to change parasympathetic activity (Grimaldi et al., 2019).

Both the phase of the SO at the moment of stimulation (Cox et al., 2014) and the number of clicks within a train of stimulation (Ngo et al., 2015) have been shown to influence the extent to which such closed-loop auditory stimulation impacts on sleep oscillations. One study suggested that there is no real benefit to presenting more than two clicks in a sequence, as the elicited responses lead to a strong refractory period, especially with respect to fast spindles (Ngo et al., 2015), another study showed that a five-click sequence produced a benefit to both SO and fast spindles for every one of the five clicks (Papalambros et al., 2017).

An early and thoughtful review of auditory stimulation (Bellesi et al., 2014) suggested that both the frequency profile of the applied sound and the consistency or variability of sounds within a stimulation train, have a critical impact on the local EEG response. This stands to reason, as repetitive application of the same sound would normally lead to auditory habituation of the non-lemniscal pathway (Bellesi et al., 2014).

Based on these ideas, we set out to investigate whether some sounds elicited stronger response than others. We were particularly interested in comparing broad spectrum pink noise to narrower spectrum “pure” sounds such as the B note of 247 Hz and the pronounced “a” vowel. We also decided to test whether consistency of sounds versus varying the sounds in a sequence (e.g., auditory oddballs) would impact upon responses. We chose a long sequence of 10 clicks as this allowed us to determine whether responses would be observed for all 10 of these clicks, just the first few, or for clicks in which the sound was varied compared to those presented immediately before.

2 | SUBJECTS AND METHODS

2.1 | Subjects

A total of 17 volunteers (11 females, aged 18–26 years) were recruited in this study to sleep 1 night under polysomnographic (PSG) monitoring at the sleep laboratory of the University of Manchester. Routine questionnaires ensured that they were non-smokers, had no history of neurological, psychiatric, or endocrine diseases, including any sleep disorder. All participants were free from medication except the women, who were all taking hormonal contraceptives. Participants had followed a regular sleep/wake rhythm for at least 4 weeks previous to the experiment with 7–10 h sleep per night and no daytime naps. Subjects were instructed to abstain from alcohol and caffeine and to get up at 7:00 a.m. on the day of the experiment. The Ethics Committee of the University of Manchester approved the experimental protocol, and all volunteers gave their written consent prior to participation. They received monetary compensation for their time. Subjects were welcomed at 9:00 p.m. to the sleep laboratory where

they were equipped with the PSG. They were aware that sounds might be played during the night without knowing the number and the type of sounds. They were invited to sleep at 11:00 p.m. and were woken up between 7:00 and 8:00 a.m.

In all, 12 volunteers (10 female, aged 18–26 years) were included in the final analyses. One subject had to be removed from the analyses because of an unplugged wire resulting in sham stimulation only. Another four subjects could not be included in the analyses because of a small number of stimulation (<50 trains, either due to small slow waves that did not reach the criteria for stimulation, or to stimulation awakenings)

2.2 | Electroencephalography recordings and auditory stimulation

Sleep monitoring was carried out using a PSG system (Embla model N7000) with RemLogic 1.1 software (both Natus Neurology Inc., Middleton, Canada). Silver-silver chloride (Ag-AgCl) electrodes were held in position using EC2 electrode cream (Grass Technologies, Natus Neurology Inc.) after the scalp was cleaned with NuPrep exfoliating agent (Weaver and Company, Aurora, CO, USA). EEG scalp electrodes were attached according to the international 10–20 system at 14 standardised locations: Fp1, Fp2, Fpz, F3, F4, Fz, C3, C4, Cz, P3, P4, Pz, O1, O2, and each was referenced to the average of two mastoids (A1 and A2). Left and right electro-oculogram (EOG), left, right, and upper chin electromyogram (EMG), and a ground electrode were also attached. All electrodes were verified to have a connection impedance of <5 k Ω . All signals were digitally sampled at a rate of 200 Hz.

Signals were filtered between 0.03–100 Hz and stored with auditory triggers for later offline analysis on a personal computer (PC). Sounds were delivered by intra-auricular headphones (Philips) taped to the subjects’ ears so they would not fall during the night. A MATLAB program was written to send triggers to the Embla system, which placed them in the auditory EEG channel. The sounds were delivered directly from the PC in the control room via an audio extension cable, which the in-ear headphones were plugged into. The RemLogic Software enabled experimenters to record and watch the signal.

Sound stimulation relied on the online detection of negative SO half-wave peaks (i.e., down states) at Fpz (referenced to the average of mastoids) as previously described by Ngo et al., 2013a. The EEG trace at Fpz was filtered between 0.25 and 4 Hz and sampled at 200 Hz. A custom-made MATLAB script enabled response to the incoming EEG signal in real time. Based on the EEG signal obtained from Fpz, an auditory stimulus was triggered whenever the signal crossed an adaptive threshold toward larger negative values. By default, the threshold was set to $-80 \mu\text{V}$, and this was not changed. Upon the detection of a negative SO half-wave peak, the first and all following stimuli were delivered after an individually adapted delay to ensure a temporal coincidence with the upcoming SO up state. These delays were determined during the first 10 min of SWS, based on the analysis of the average delay between the negative and positive SO

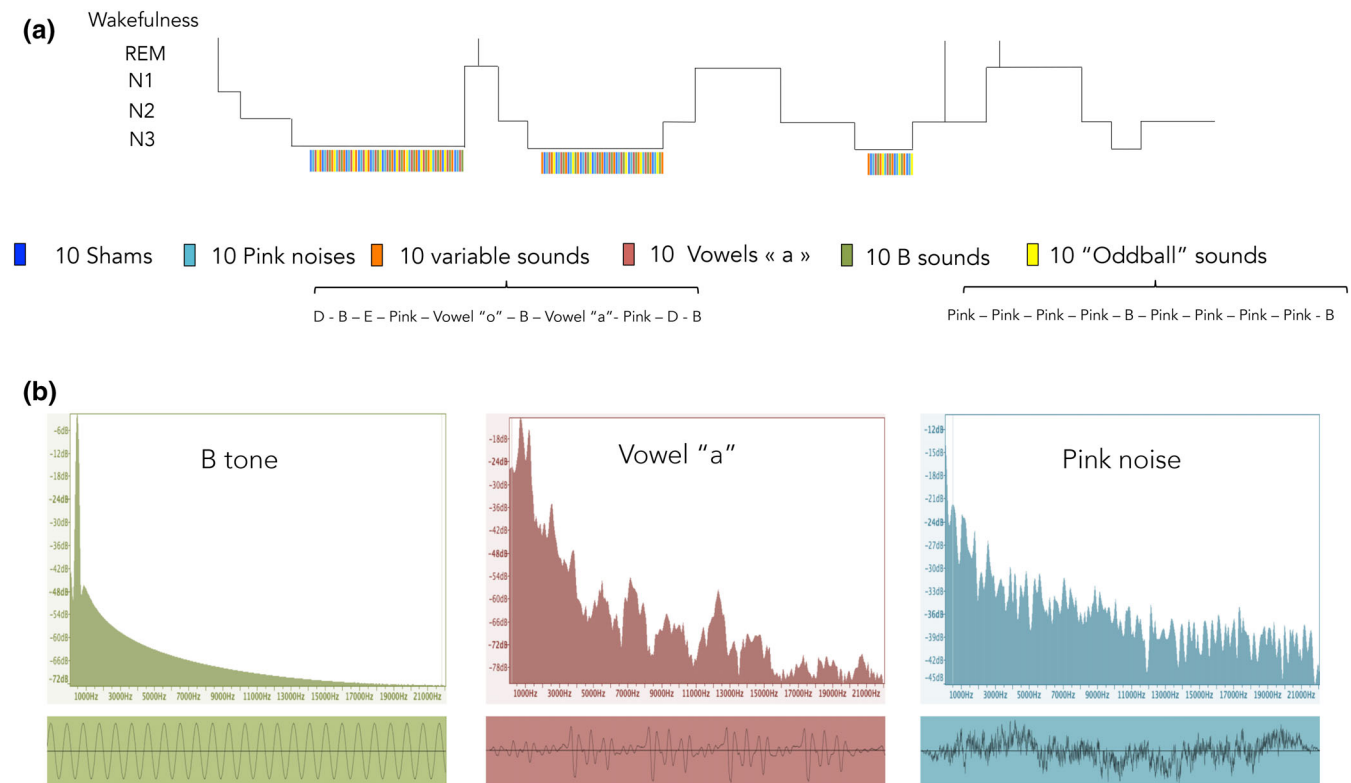


FIGURE 1 (a) Representation of a night of stimulations recorded by the PSG. After 10 min of stable N3, sequences of 10-click trains targeting the up-phase of the SOs were applied by the experimenter until any arousal or sleep stage change was detected. (b) Representation of the amplitude and frequency of each type of sound delivered through the night by earphones taped to the subjects' ears. PSG, polysomnography; REM, rapid eye movement; SO, slow oscillation

peaks for the first stimulus and between two zero crossing for the inter-stimulus interval (ISI).

Auditory stimulations were applied by an experimenter, experienced in sleep scoring, after 10 min of consolidated SWS, and was halted whenever subjects showed arousals or left N3. It was resumed when stable N3 was detected again (Figure 1a).

Sound stimuli, henceforth referred to as "clicks", consisted of a sequence of 10 calibrated sounds of 50 ms at 40 dB with a 5 ms rise and fall time where only the first click was applied in a closed-loop manner, with all subsequent clicks following after a fixed inter-click interval previously determined in line with the subject's average SO frequency. The algorithm paused for 10 s after each train. Six different trains of clicks, referring as six different conditions were played (Figure 1a,b):

- 10 shams: triggers were placed but no sound was delivered.
- 10 pink noises (generated by Matlab).
- 10 vowels "a" (pronounced by a male human voice).
- 10 B tones, (247 Hz, previously generated by the Audacity software).
- 10 variable sounds within a fixed sequence: D, B, E tones, pink, "o" vowel, B tone, vowel "a" pink, D, B tones.
- 10 sounds in an "Oddball" series, (which encompassed deviant sounds in a fixed sequence): Pink, Pink, Pink, Pink, B tone, Pink, Pink, Pink, Pink, B tone.

2.3 | Signal analyses

Recordings with the EEG, EOG, EMG and the auditory outputs were extracted as *.EDF. Each night was scored visually for succeeding 30-s epochs according to American Academy of Sleep Medicine (AASM) criteria (Iber et al., 2007). The experienced sleep scorer was blind to the stimulation triggers. Each recording was then checked to exclude signal portions with poor quality and each stimulation train was visualised to manually remove trains with artefacts or micro-arousals from the analyses. The final analyses included similar numbers of stimulations per condition (Table S1).

Signal analyses were performed in Python. In order to take into account the variable ISI between subjects, EEG signals were normalised time locked to the first stimulation. To do so, the EEG signals between each stimulation (from click one to click 10 + 1 ISI), which is referred here as a "bin" was divided into 150 data points with equal space.

The SO analysis was conducted on the average of all artefact-free central and frontal electrodes referenced to mastoids. The signal was first filtered in the desired frequency band (SWS: 0.5–4 Hz) and subsequently averaged within each subject before being averaged across subjects in each condition. Event related potential (ERP) responses were computed by averaging the SWS band across central frontal channels and across subjects and centred at the first click. However, because the ERP response is an average of many trials, the highest peaks in amplitude are generally smoothed out. Therefore, we evaluated both the summed SO

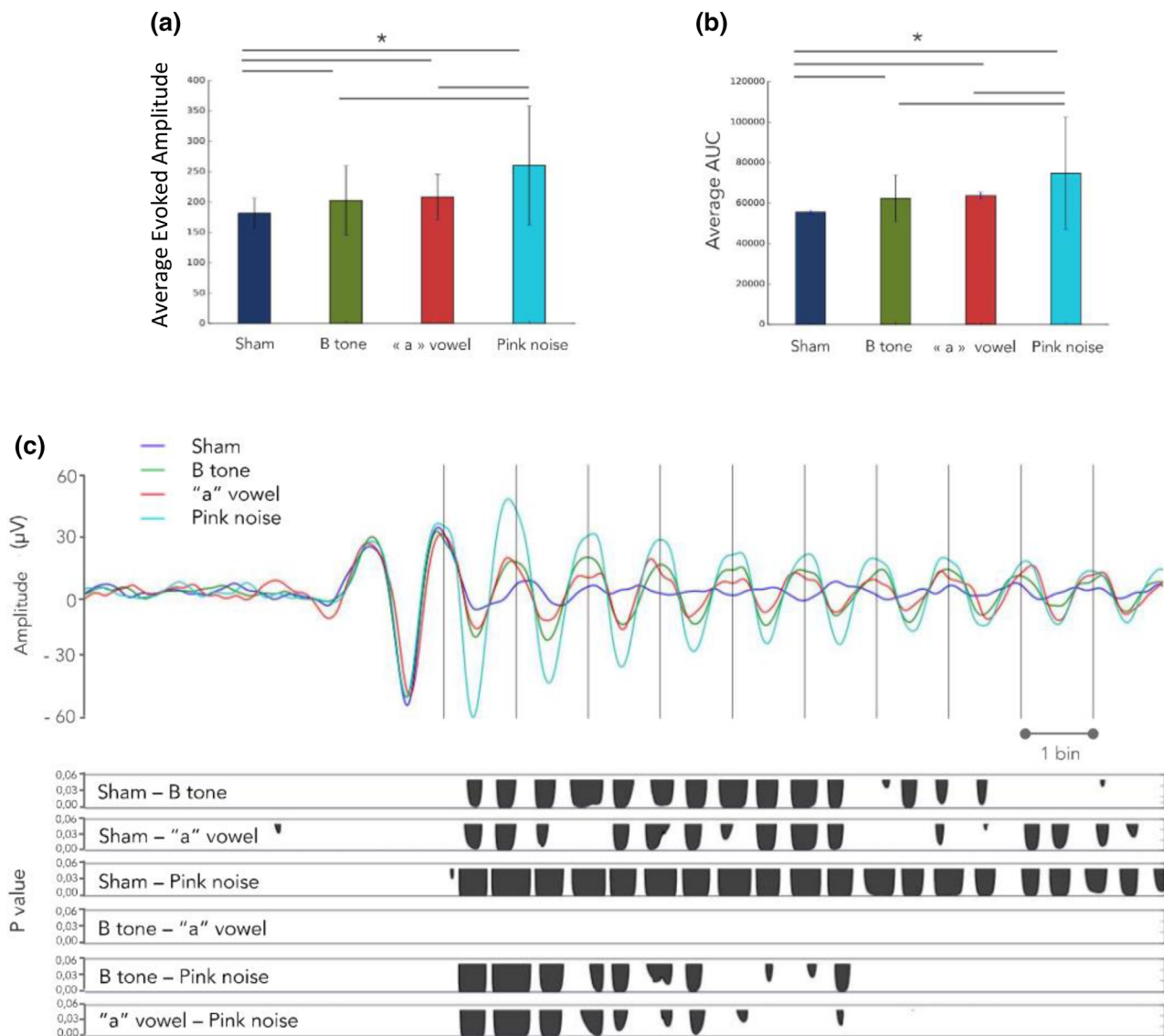


FIGURE 2 (a) Amplitude, (b) area under the curve (AUC), (c) averaged ERPs of each trains type (sham, B tone, “a” vowel and pink noise) time locked to the first stimulation. ERP, event related potential

peak amplitudes across the train of clicks and the area under the ERP curve. SO amplitudes were evaluated as the total along the 10 clicks and then averaged across central and frontal electrodes. Similarly, the total area under the curve (AUC) of the ERP across the 10 clicks was computed and averaged across channels and the compared between sounds. Topographical maps (Figure 2e) represent the log of the p value in each electrode with extrapolation between electrodes.

2.4 | Statistical analysis

Statistical analysis was performed using the SciPy library of Python. SOs were analysed using a two-way analysis of variance (ANOVA) test with the type of sounds as a factor. These ANOVA tests were computed from the summary statistics taken from the figures, as the original data were lost (Larson, 1992; Cohen, 2002). If significant, we performed post hoc

Tukey honesty tests. Data are presented as mean (\pm standard deviation [SD]). A $p < 0.05$ was considered as statistically significant.

3 | RESULTS

3.1 | Effects of the type of sound on evoked responses

Both the amplitude (Figure 2a) and AUC (Figure 2b) were significantly enhanced when the pink sounds were presented as compared to the sham condition. Within the different types of sounds, the pink noise had a significantly greater impact than the “a” vowel and the B tone with regard to these two parameters (see Tables S2 and S3 for statistics, noting that these have been calculated based on measurements taken from the figures as the original data were lost).

Examination of the averaged ERP in each condition as a function of time (Figure 2c) showed that pink noise was able to induce a significantly higher amplitude than sham in every click, from the first to the 10th click. Sounds with reduced frequency content such as the “a” vowel and the B tone also induced a higher amplitude than the sham, but the effect tapered off after approximately the eighth click. Effects of the pink noise were significantly greater than the other sounds until the sixth click. No difference between the “a” vowel and the B tone was observed.

3.2 | Effects of irregularities

To assess the effect of irregularities in the sequence of sounds, we tested the effect of both a sequence with sounds changing at each

click, the “variable sounds” train, and a sequence with deviant sounds at a specific point: the “oddball” train.

3.2.1 | Effect of a variable sequence of sounds on the boosting of SOs

Taking the sequence as a whole, both the pink noise train and the “variable sounds” train significantly increased the amplitude and the SO AUC as compared to the sham train (Figure 3a,b; see Tables S4 and S5 for statistics, noting that these have been calculated based on measurements taken from the figures since the original data were lost). In the “variable sounds” train, the significant increase in amplitude as compared to the sham tapered off after the second click (Figure 3c). Interestingly, we observed another increase after the

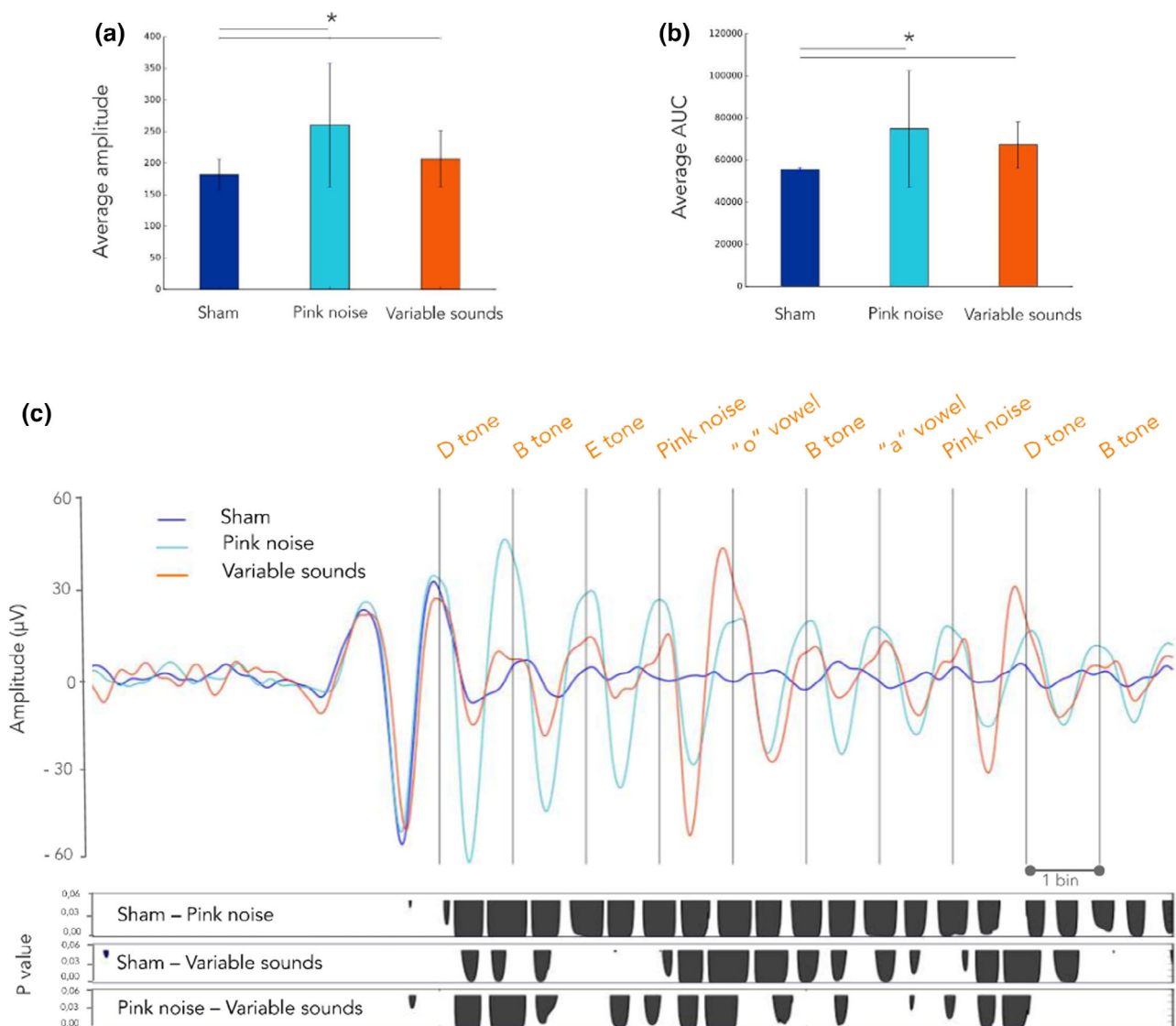


FIGURE 3 (a) Amplitude, (b) area under the curve (AUC), (c) averaged ERPs for each type of trains (sham, pink noise, and variable sounds) time locked to the first stimulation. Vertical grey bars indicate each click. Horizontal black bars indicate time points when differences between two conditions were significant ($p < 0.05$). ERP, event related potential

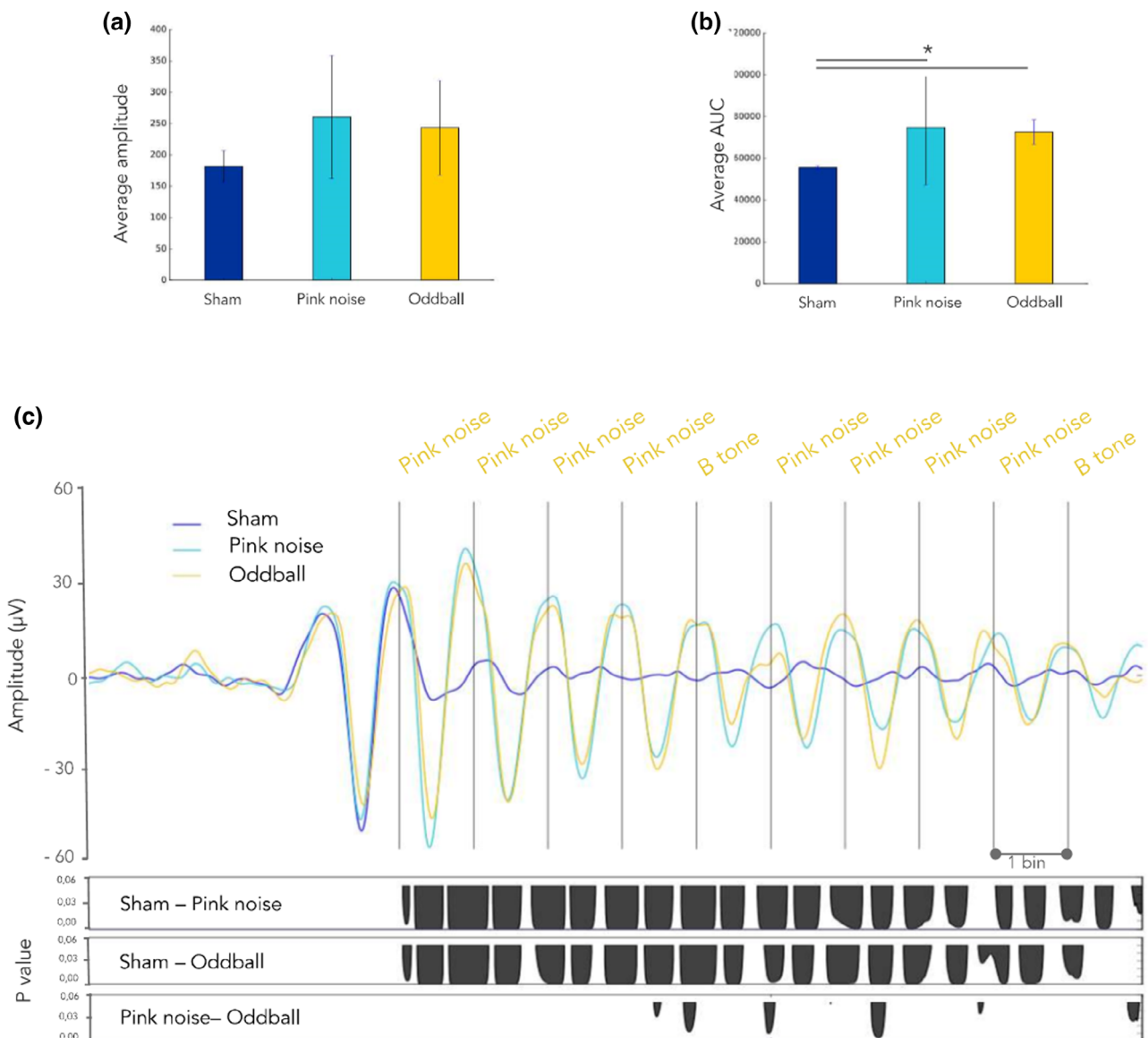


FIGURE 4 (a) Amplitude, (b) area under the curve (AUC), and (c) averaged ERPs for each type of trains (sham, pink noise, oddball) time locked to the first stimulation. Vertical grey bars indicate each click. Horizontal black bars indicate time points when differences between two conditions were significant ($p < 0.05$). ERP, event related potential

fourth click (which was a pink noise) that lasted until the seventh click and was boosted again after the eighth click (which was a pink noise again). The pink noise only train, induced a greater boosting than the “variable sounds” train until the fourth click.

3.2.2 | Effect of a fixed sequence of sounds with deviants (oddball) on the SO boosting

Both the pink noise train and the oddball train induced a significant increase of the AUC of the SO, as compared to the sham train (Figure 4b; Tables S6 and S7), but SWS amplitude was not significantly modified (Figure 4a), although the post hoc tests did show significant differences (Table S6). Both the pink noise and the oddball

trains induced a significant increase of the SO amplitude from the first to the 10th click as compared to the sham (Figure 4c). Significant differences were observed between the pink noise and the oddball trains after the fifth click, when the B tone occurred.

4 | DISCUSSION

We here demonstrate that the brain continues to respond to auditory stimulations even when 10 clicks are delivered in a row, where the first click was timed to co-occur with the SO peak in a closed-loop fashion. The SO response reduces gradually on each click but is still significantly enhanced compared to sham even at the 10th click. Notably, this response is stronger for pink noise than for narrow

spectrum noises, particularly for the first four clicks (Figure 2c). Pink noise elicits a response across a larger area of the cortex during these first four clicks, particularly on left hemispheric temporal electrodes. Interestingly, we also observed responses to changing the sounds throughout the sequence, particularly when the deviant sounds used pink noise, suggesting that habituation may be a problem when the same noise is presented repeatedly.

4.1 | Narrow versus broad spectrum sounds

Our analysis shows that broad spectrum sounds, such as pink noise, trigger a stronger SO response, that habituates less with repeated stimulation compared to other sound types. Interestingly, our topographical plots show that these sounds trigger responses in a broader area of the cortex. Presumably, recruitment of a broad selection of areas facilitates a strong SO response, as the latter stems from highly synchronised firing in cortical networks. Similarly, recruitment of these broad networks is likely to provide some protection against habituation, as it is possible that different subsets of neurones will be recruited each time a click is delivered.

4.2 | Habituation and the use of oddball stimuli

The second part of our study aimed to test the habituation effect, as discussed by Bellesi et al. (2014) who hypothesised that when auditory clicks elicit SO they do so via the non-lemniscal pathway. This pathway is mainly responsible for detecting environmental change and is characterised by rapid habituation to repeating stimuli. The non-lemniscal pathway projects to associative cortex and is able to strongly activate these areas when changes are detected in a previously monotonous sequence. Due to these characteristics, Bellesi et al. (2014) suggested that auditory clicks would be more likely to elicit SOs through the non-lemniscal pathway if the frequency of the click sounds was varied in an unpredictable manner. Our original intention was to test this hypothesis by comparing responses to a sequence of fixed sounds (pink noise), to both a sequence of 10 clicks in which the sound frequencies used to create the click varied across the sequence (“variable sounds” condition) and a single deviant sound within a sequence of fixed clicks (“oddball” condition). Notably, however, the fact that the broad and narrow spectrum sounds we used had different impacts when applied in a fixed sequence, made it difficult for us to fully address this question, as responses to pink noise were always stronger than responses to the B tone or “a” vowel. In future studies, it would be interesting to place different broad-spectrum sounds (pink versus white versus brown noise) in an oddball sequence to cope with habituation or to address the effect of varying the delay between stimulation to disturb the regularity of a sound sequence. Nevertheless, we speculate that the mismatch auditory response that we observed might occur because pink noise includes a broad range of frequencies while the other sounds include only a single frequency.

Indeed, with respect to the mismatched negativity effect, we can think of the simple tones as a standard frequency while the pink noise is the “different” stimulus that might activate more neurones because of its broad frequency range.

AUTHOR CONTRIBUTIONS

Study concept and design: Eden Debellemanière, Pierrick J. Arnal, Mounir Chennaoui, Mathieu Galtier, Penelope A. Lewis.

Technical setup: Eden Debellemanière, Jules Schneider, Alexander J. Casson, Mathieu Galtier, Penelope A. Lewis.

Data acquisition: Eden Debellemanière, Jules Schneider.

Data analysis: Eden Debellemanière, Clémence Pinaud, Pierrick J. Arnal, Mathieu Galtier, Miguel Navarrete.

Writing and reviewing the manuscript: all authors

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CONFLICT OF INTEREST

Eden Debellemanière, Clémence Pinaud, Pierrick J. Arnal, Mathieu Galtier are employees of Dreem. The other authors declare no commercial or financial conflicts of interest in conducting this research.

DATA AVAILABILITY STATEMENT

We confirm that no third-party code was used in collecting or analysing the data. Instead, this was done using purpose-written Python and Matlab scripts. These scripts are available upon request.

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SUPPORTING INFORMATION

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

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