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Registered Report

The effect of stimulus saliency on the modulation of ongoing neural oscillations related to thermonociception: A registered report

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ABSTRACT

Ongoing oscillations have been shown to be modulated in different frequency bands following phasic, tonic as well as periodic thermonociceptive stimulation. Yet, it remains unclear whether these modulations are related to pain perception, saliency (i.e., the ability of a stimulus to stand out from its environment) or solely the intensity of these stimuli. Thirty-five participants were recruited to investigate the relationship between pain perception and ongoing oscillations as well as the factors likely to modulate them, combining a sustained periodic thermonociceptive stimulation paradigm including periodic oddball events with a frequency-tagging analysis approach. Oddballs were delivered either at a higher or lower intensity ("high oddball" versus "low oddball" condition) than baseline stimuli. Continuous ratings of pain perception were collected during the stimulation to track participants' perception. Despite the stimuli being barely perceived as painful (hence relating predominantly to thermonociception), the continuous ratings of perception clearly reflected the variations of stimulus intensity, but only in the "high oddball" condition. Consistently, the oddball stimulus modulated ongoing oscillations in the "high oddball", but not in the "low oddball" condition. Because of the lack of differentiation between baseline and oddball cycles in the "low oddball" condition – both in perception and at the neural level – these findings do not allow disentangling the differential effects of stimulus intensity and saliency on the perception of thermonociceptive stimuli, or on the modulation of oscillatory activities related to thermonociception. However, they indicate the modulation of ongoing oscillations reflects subjects' perception of thermonociceptive stimuli that are both salient and intense.

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1. Introduction

Saliency can be defined as the feature of a stimulus that makes it stand out from its environment (Egeth & Yantis, 1997). Painful stimuli emerge from the activity of the nociceptive system which is made to respond to high-intensity and potentially damaging somatosensory stimuli. These stimuli are therefore inherently salient and facilitate the involuntarily capture of attention (Eccleston & Crombez, 1999). The effects of saliency on event-related brain potentials (ERPs) evoked by nociceptive stimuli have been broadly studied (Iannetti et al., 2008; Legrain et al., 2003a, 2009; Roa Romero et al., 2013), and evidence emerged that, in the experimental procedures in which they are usually elicited, the modulation of the magnitude of those ERPs can be mostly driven by the saliency of the eliciting nociceptive stimulus rather than its intensity and its painfulness. This dissociation between the saliency of the nociceptive stimuli and their painfulness was demonstrated, among others, by studies showing that the relationship between pain and ERP magnitude can be disrupted when nociceptive stimuli are repeated: repeating the stimulation reduces ERP magnitude while pain perception remains constant (Iannetti et al., 2008). Moreover, novel nociceptive stimuli elicit ERPs of larger magnitude and distract more participants from their primary task than stimuli of the same intensity but presented more frequently (Legrain et al., 2009).

Lately, it has also been shown that painful stimuli not only elicit ERPs, but also modulate the synchrony of ongoing neural oscillations in different frequency bands (Gross et al., 2007; Mouraux et al., 2003; Ploner et al., 2006; Schulz et al., 2011). Yet, it remains unclear whether these pain-related modulations of neural oscillations reflect changes in pain perception, stimulus saliency or merely objective stimulus intensity. Recent investigations were able to show the effects of bottom-up modulation on ongoing oscillatory activity by applying thermonociceptive stimuli of different intensities (Hauck et al., 2015; Tiemann et al., 2015; Wang et al., 2022; Zhang et al., 2012) or longer durations (Nickel et al., 2017; Schulz et al., 2015). While these studies provided evidence that the intensity of a stimulus modulates oscillations in the theta, alpha, beta and gamma frequency band, it remains ambiguous whether the observed effects are related to the saliency of the applied stimuli or solely their intensity.

Using a frequency-tagging approach (Regan, 1989), investigations from our lab demonstrated modulations of ongoing oscillations at the frequency of stimulation within different frequency bands following slow sustained periodic thermonociceptive stimulation in a range of investigations (Colon et al., 2017; Leu et al., 2023, 2024; Liberati et al., 2019; Mulders et al., 2020). While the manipulation of attention (Leu et al., 2023) and stimulus intensity expectation (Leu et al., 2024) did not seem to have an effect on the modulation of ongoing oscillations, differences in oscillatory activity were found either between modalities (thermonociceptive versus vibrotactile stimulation) or between different stimulation intensities (i.e., temperature of stimulation). Yet, whether these differences in modulation are related to variations in the painfulness, intensity or purely the saliency of the applied stimuli remains unclear. Further clarifying this relationship would be an important step to deepen our understanding of the potential association between the modulation of ongoing oscillations and pain perception. More specifically, this could tell us whether the observed neural modulations could indeed be a sign of a preferential modulation of painful stimuli rather than a response related to contextual and unspecific features such as stimulus intensity and saliency. Thus, the clarification whether the modulation of ongoing oscillations is more closely related to stimulus saliency or intensity would help to understand whether the modulation of ongoing oscillations could potentially be used as a physiological marker of pain in humans.

To shed light on the potential role of ongoing oscillations in the perception of salient stimuli, we adopted an oddball paradigm during periodic nociceptive stimulation. Continuously oscillating thermonociceptive stimuli were applied at the same location at a certain frequency, but every fourth stimulus was presented at a higher stimulus intensity (creating the oddball effect, since these stimuli "stood out" from the other stimuli). This effect allowed us to deliberately make some stimuli more salient than others and thus observe the corresponding brain responses, which we hypothesized are not merely related to changes in stimulus intensity. Previous studies using periodic visual stimuli have shown that oddball sensory events embedded in a regular series of stimuli (e.g., human faces among neutral objects, words among nonwords, etc.) elicited in the EEG spectrum, in addition to the baseline response, a response peak specifically at the frequency of occurrence of those oddball stimuli e.g., (De Keyser et al., 2018; Lochy et al., 2016; Rossion et al., 2015), analyzed using a frequency-tagging approach. To this date, no study has extended this oddball approach to the perception of painful nociceptive stimuli.

The aim of this study was to investigate whether changes in stimulus saliency induced a corresponding modulation of ongoing oscillations, and whether these modulations relate more closely to the saliency or the intensity of the stimulus. As saliency and stimulus intensity are inherently tied to each other, this investigation did not aim to quantify the exact contribution of each factor. More so, the goal was to achieve a better understanding of how both these factors (and their interaction) can modulate ongoing oscillations. To this aim, intensity was varied using an oddball paradigm during which the stimulation intensity changed periodically between baseline and oddball cycles which were delivered at a higher stimulation intensity (i.e., "high" oddball). Based on Rossion et al. (2015), we expected to be able to "tag" both the baseline and the oddball response at their respective frequency of stimulation. To disentangle the effect of saliency and intensity, we employed a control condition, during which the oddball cycles were delivered at the same frequency as in the high oddball condition, but with a *lower* stimulation intensity (i.e., "low" oddball). Thus, the main characteristic of this oddball was its saliency, since its low intensity made it different (i.e., "standing out") in comparison to the baseline stimuli. We hypothesized that the oddball cycles in both conditions would be perceived at a different intensity compared to the stimulation cycles at baseline frequency. Further, we expected that the oddball cycles would lead to a

peak at its stimulation frequency for the high oddball condition. While we also expected a modulation for the low oddball cycles if saliency affected the EEG response, no periodic modulation of this oddball would indicate a predominant role of intensity in the modulation of ongoing oscillations. If the amplitude of the neural response in the low oddball condition was similar to the amplitude at the oddball frequency in the high oddball condition, it would suggest that the modulation of ongoing oscillations is mostly affected by change detection rather than intensity. Conversely, if a periodic modulation was found in both conditions, but smaller for the low compared to the high oddball, the results would suggest that the modulation of ongoing oscillations was more closely related to the intensity of the stimulation, but still had an underlying contribution of the saliency of the stimuli.

2. Methods

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2.1. Participants

We recruited a group of 35 healthy adults [15 males, 25.4 ± 4.25 (mean ± std deviation)] who were between 18 and 35 years old (Creac'H et al., 2015). Due to non-compliance or artifacted signals, data of some participants were discarded from the analyses based on the pre-registered exclusion criteria. Ultimately, the EEG data of 31 participants and behavioral data of 33 participants was used for the analysis. Participants were recruited via an established website and social media and were compensated with 25 € for the duration of the experiment (2 visits, lasting around 1.5 h for the EEG assessment and 1 h for the perception assessment). Previous EEG investigations of bottom-up modulations of ongoing oscillations have recruited between 7 (Zhang et al., 2012) and 20 participants (Hauck et al., 2015; Tiemann et al., 2015), while investigations using a visual oddball paradigm with a frequency-tagging approach recruited 12 participants (De Keyser et al., 2018; Rossion et al., 2015). Other pain-related frequency-tagging investigations recruited between 8 and 15 participants (Colon et al., 2017; Mulders et al., 2020). The number of participants was based on a power and effect size estimation using the software G*Power (Faul et al., 2007). For each statistical test, the effect size was estimated and the sample size necessary to reach the desired statistical power was calculated separately.

Based on previous results from our lab (Leu et al., 2023) and results from oddball investigation in the visual field (Rossion, 2014; Rossion et al., 2015), we expect a large effect in our sample for the detection of a peak at the frequency of the baseline stimulation. Given a normally distributed sample, an alpha level of .0125 (corrected for multiple comparisons) and a one-sided Wilcoxon signed-rank test against a constant and an effect size of Cohen's $d = 1.4$, we would need to recruit 10 participants to reach the targeted statistical power. Based on other oddball paradigm investigations (Rossion et al., 2015), we expect a medium-to-large effect size for the detection of peaks related to the oddball stimuli in the two conditions (amplitudes about half the size of the baseline responses). Given a normally distributed sample, a one-sided Wilcoxon signed-rank test against a constant, an alpha level of .0125, power of .9 and an effect size of $d = .7$, we would need to recruit 30 participants to reach our target.

Data on the perceived level of stimulus intensity following sustained periodic heat stimuli is scarce. As an approximation, we used the effect size of the ANOVA main effect of *temperature* reported in Mulders et al. (2020), since a similar sustained periodic stimulation paradigm was used in that investigation with varying surface temperatures (warm, cold). The main effect of *temperature* had an effect size $n_2^p = .658$. As we do not use cold stimuli in a separate trial, but heat stimuli of different intensities, we expect that the effect size in our sample will be smaller. Nevertheless, as the effect found in Mulders et al. (2020) was very large, we can still assume to find effects that are on the larger side. Specifically, for the high oddball condition, we expect a slightly larger effect than for the low oddball condition, based on the observations in our pilot experiment. We estimated an effect size of $n_2^p = .2$ for the high oddball condition and an effect size of $n_2^p = .15$ for the low oddball condition. As sample size calculations for LMMs are not feasible in G*Power, we approximated the model using the calculation for a repeated measures ANOVA, with within factors only. 1 group was compared along 2 measurements, with a correlation among repeated measures of .5 and a non-sphericity correction of 1. A separate calculation was done for each oddball condition. Given these estimated effect sizes, and a target power of .09 with an alpha level of .02, we should test 16 participants for the high oddball condition and 22 participants for the low oddball condition. To satisfy the minimum requirements for each test, we will aim for a minimum sample size of 30 participants and enroll 35 participants in the experiment. More details on the sample size rationale can be found in the Supplementary Materials.

The experiment was split into two separate visits to the lab: one to record EEG data and one to record continuous ratings during the same thermonociceptive stimulation paradigm. The order of the visits was counterbalanced across participants.

Exclusion criteria included regular use of psychotropic medication, intake of pain killers such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) within 12 h before the experiment, as well as any severe neurological diseases, psychiatric disorders, or recent upper limb trauma. The local Research Ethics Committee approved all experimental procedures (Commission d'Ethique hospitalo-facultaire, Saint-Luc Hospital & UCLouvain, B403201316436). Participants were informed about all procedures and signed an informed consent form prior to data acquisition. All procedures were carried out according to relevant guidelines and regulations.

2.2. Thermonociceptive stimulation

Thermonociceptive stimuli were applied using a contact heat thermode (TCS II, QST.Lab, Strasbourg, France) using a

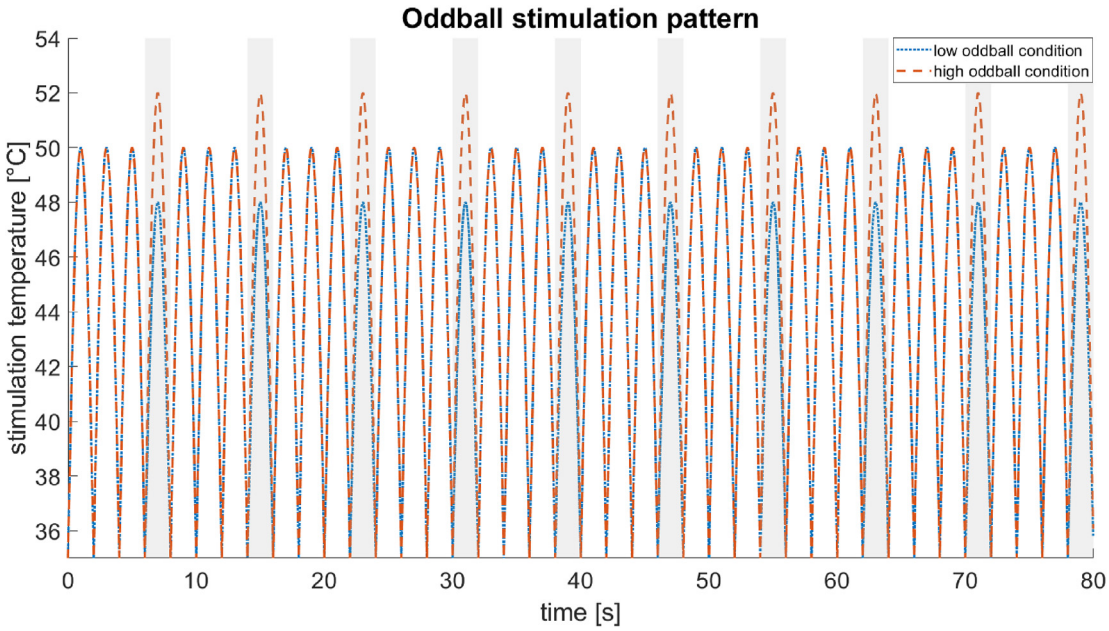


Fig. 1 – Illustration of the sustained periodic stimulation pattern during the "low oddball" (blue) and "high oddball" (red) condition with the example of 50 °C as baseline target temperature. Every fourth stimulation (i.e., $F_{oddball}$ = .125 Hz) will be delivered at 52 °C, which is 2 °C higher than the baseline stimulation or 48 °C, respectively. One trial consists out of 80s of stimulation (i.e., 10 oddball cycles).

cylindrical probe (°T03)[1] applied on the dominant volar forearm of the participant (2 left-handed). The probe consisted of 15 micro-Peltier elements in groups of 3, resulting in a circular stimulation surface of 115,5 mm^2. The maximal heating ramp of this thermode is 300 °C/sec. The stimuli were applied in a sustained periodic manner at a frequency of .5 Hz and oscillated between baseline temperature (35 °C, approximately skin temperature) to a target temperature determined by the staircase procedure in the beginning of the visit (see section 2.3). The stimulation was delivered over a period of 80s and the full stimulation surface was used for each stimulation. The inter-stimulus-interval was self-paced by the experimenter (min. 10 sec) and the thermode was displaced after each trial to avoid habituation or sensitization.

2.2.1. *Oddball paradigm*

To introduce an oddball paradigm, every 4th stimulus (oddball frequency: .125 Hz) was delivered using a higher stimulus intensity (i.e., individual target temperature + 2 °C[2]) to make the oddball stimulus stand out from its environment. An illustration of the stimulation pattern can be found in Fig. 1. A similar oddball paradigm using visual stimuli has been shown to elicit responses which can be easily identified using a frequency-tagging approach (Rossion et al., 2015). We also conducted a pilot study to ensure that the oddball would indeed be perceived as different from the baseline stimulation, and an additional pilot following changes post in-principal-acceptance (IPA) (see Supplementary Materials S.III).

2.2.2. *Control condition*

To disentangle whether possible effects (behavioral and in the EEG) were at least partially related to the saliency of the stimulus or rather to the change in stimulus intensity, a control condition (i.e., "low oddball") was added to the experiment. To ensure that the oddball was still perceived as different but not more intense, the stimulation was delivered at the same frequency as previously described (.125 Hz), but at a *lower* intensity (individual target temperature - 2 °C[3]) than the baseline stimulation (Fig. 1). For some participants, the oddball elicited a qualitatively different perception (i.e., not painful) compared to the other stimuli. While this could be considered a confounding factor, it is this attribute which allowed the stimulus to be salient, i.e., stand out from its environment (the painful baseline stimuli). We then compared behavioral and neural responses between the oddballs (high oddball versus low oddball), which are both salient (i.e., a change from the previous stimuli) but different in their intensity.

2.3. *Staircase procedure*

A staircase procedure (Claus et al., 1990) was implemented to identify the individual pain threshold to which the stimulation temperature of the baseline temperature would be adapted to. The aim was to find a temperature which was tolerable for the full experiment (including high oddball trials),

[1] Changed from IPA on 02.02.2024, originally the use of a larger square probe (T11) was intended (see Supplementary Materials S. III).

[2] Changed from IPA on 02.02.2024, originally +3 °C (see Supplementary Materials S.III).

[3] Changed from IPA on 02.02.2024, originally −3 °C (see Supplementary Materials S.III).

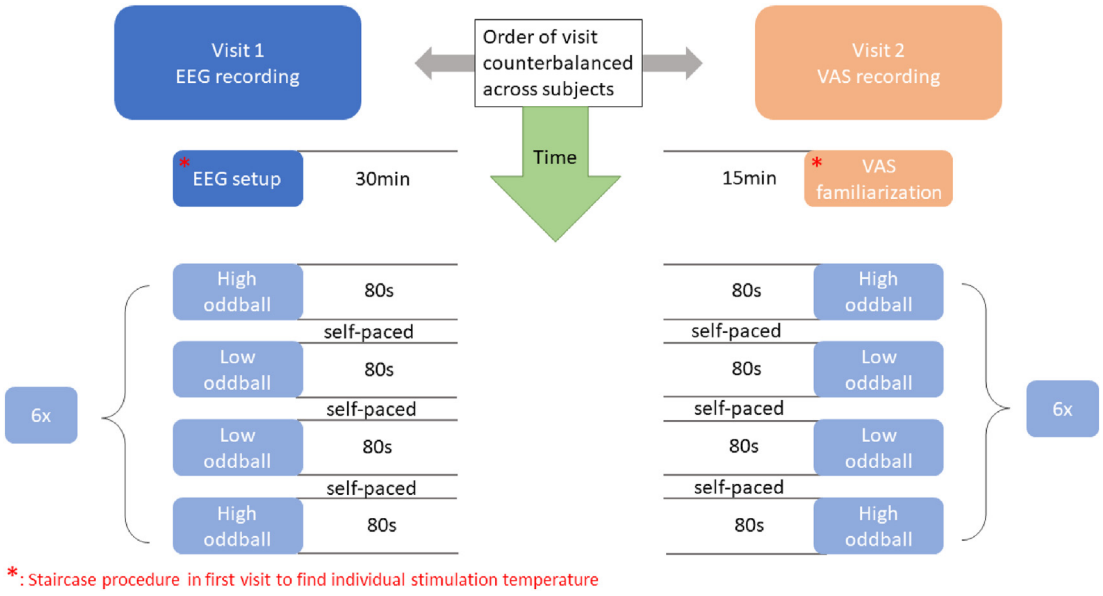


Fig. 2 – Illustration of the organization of the experiment. The visits were one week apart and conducted around the same time of day, and the same stimuli were delivered in both visits. A staircase procedure was implemented at the beginning of the first visit to find the ideal stimulation temperature for each participant, at which the experiment is tolerable but still painful throughout the entire stimulation.

but still painful throughout the entirety of each trial (at the peaks of the stimulation). The stimuli applied in the staircase procedure were 40s long and were delivered in the same periodic sustained fashion as the stimuli in the rest of the experiment, but without the addition of an oddball stimulus. The first stimulus always reached a temperature of 49 °C[4] at every peak. Participants were asked whether they perceived the stimulation as painful (at the peaks) throughout the 40s trial (if so, −.5 °C for the following stimulus), only painful in the first half of the trial (+.5 °C for the following stimulus) or as not painful (+1 °C for the next stimulus). Participants were instructed that painfulness related to either a burning or pricking sensation [since we are predominantly stimulating C-fibers (Colon et al., 2017)]. The threshold for sufficient painfulness of the stimulation was identified when a single step in temperature led to a change in perception of the painfulness in two consecutive trials. For example, in the temperature was increased and the following trial was perceived as "generally painful", the following trial would have a .5 °C lower stimulation temperature. If this lower temperature trial was then perceived as "painful only in first half", we selected the stimulation temperature of the preceding trial for the experiment. This temperature was then used as the "baseline peak temperature", on which the stimulation temperatures for the high and low oddball depend on. The goal of this staircase was to reach a baseline stimulation temperature that was perceived as VAS 5 or higher at its peaks during the entire 80s of the stimulation. The maximal temperature that could be chosen for the baseline stimulation temperature was 51 °C.[5]

On average, the selected baseline stimulation temperature was 50.197 ± .984 °C.

2.4. *Behavioral measures*

Ratings of perceived stimulus intensity were collected using a Visual Analog Scale (VAS) in the form of a slider implemented in a potentiometer. The continuous ratings were digitized at 100 Hz with an analog/digital converter (USB-6343, National Instruments, Texas). No ratings were collected during EEG data acquisition, as the arm movement would have likely artifacted the recordings. Thus, ratings were collected in a separate visit during which no EEG data was acquired. Before the start of the VAS part of the experiment, participants underwent a familiarization phase during which warm innocuous stimuli were delivered at the baseline stimulation frequency of .5 Hz onto the dominant volar forearm of the participant, while they had to rate their perception on the VAS scale. This phase was not considered for the analysis. The minimum of the VAS represented "no perception" and the maximum represented the "maximal pain imaginable", while the middle of the scale (i.e., VAS 5) represented the threshold to pain perception. Participants were asked to trace their perception using the VAS during each thermonociceptive stimulus following the familiarization phase. A pilot study examining whether participants would be able to trace the sustained periodic stimulation and detect the oddball stimuli in both conditions was conducted, a detailed description thereof can be found in the Supplementary Materials.

2.5. *Experimental procedure*

Participants were seated comfortably in a chair during the experiment, while their dominant arm was resting on the table

[4] Changed from IPA on 02.02.2024, originally starting at 50 °C (see Supplementary Materials S.III).
[5] Changed from IPA on 02.02.2024, originally 53 °C (see Supplementary Materials S.III).

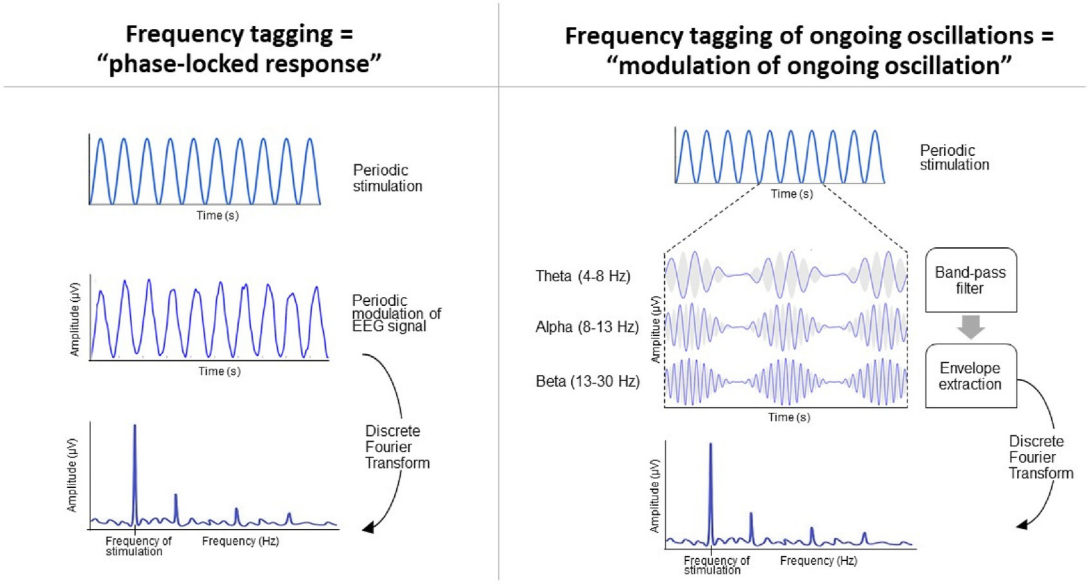


Fig. 3 – Illustration of the frequency-tagging method as well as its extension for the frequency-tagging of ongoing oscillations.

with its volar surface upwards. They were instructed to move as little as possible and kept their gaze constant to avoid interference with the EEG signal acquisition during the thermonociceptive stimulation. They were not informed about the stimulation paradigm or any other details regarding the stimuli or the aim of the investigation. For each condition (i.e., high oddball/low oddball), 12 trials were delivered, distributed over 6 blocks of 4 thermonociceptive stimulation trials (Fig. 2). The breaks between the stimulation blocks were self-paced, with a minimum of 2 min and a maximum of 5 min, while the breaks between trials were self-paced by the examinator (usually between 10s and 30s). The order of the conditions was randomized and counterbalanced across subjects, which was implemented to make the appearance and nature of the oddball less predictable. The same stimuli were delivered on both visits. At the beginning of the first visit, the staircase procedure was implemented to define the stimulation temperatures. The visit including the EEG assessment lasted around 1.5 h in total, while the VAS assessment lasted around 1 h per participant.

2.6. *EEG recordings*

An elastic electrode-cap with 64 active, pre-amplified Ag–AgCl electrodes (BioSemi, Netherlands) arranged in accordance with the international 10-10 system was used to record EEG with a sampling rate of 1024 Hz. To maintain a clear signal, the direct-current offset was limited to 30 mV. All electrodes were re-referenced offline to the average electrode activity. The BioSemi ActiView software stored the recorded signal for subsequent offline analyses. Due to technical difficulties, no external electrodes were added.

2.7. *EEG analysis*

The EEG recordings were analyzed using the Letswave7 (www.letswave.org) toolbox in MATLAB (2022a The MathWorks).

2.7.1. *Analysis of the phase-locked response*

We employed a frequency-tagging analysis approach (Regan, 1989) to analyze the periodic response induced by the slow sustained periodic stimuli, which allowed us to differentiate between oscillatory activity related to our stimuli and other unrelated ongoing activity (Colon, Nozaradan, et al., 2012). The frequency-tagging method is based on the notion that a periodic stimulus elicits a periodic activity which can be identified as periodic responses at the frequency of stimulation in the recorded EEG signals (Colon, Legrain, & Mouraux, 2012; Mouraux, Diukova, et al., 2011) (illustrated in Fig. 3). This approach has been frequently used in our lab, leading to a standardized analysis approach (Colon et al., 2017; Leu et al., 2023, 2024; Mulders et al., 2020). The obtained EEG signal was first filtered using a Butterworth band-pass filter between .05 and 30 Hz. Then, the signal was segmented into epochs of the length of stimulation (80s), relative to the onset of the stimuli. To remove potential muscular artifacts (i.e., from eye movements), an Independent Component Analysis (Fast ICA algorithm) (Hyvarinen & Oja, 2000) was applied, and any trial containing amplitudes larger than ± **500 μV** was removed. On average, ~4 ± 2 independent components supposed to reflect noise signals were removed per participant. 1.3% of trials was removed due to large artifacts (amplitude >500 μV) that could not be removed using the ICA. In 3 participants noisy channels were interpolated using its 3 neighboring electrodes. The electrode locations were flipped for the 2 left-handed participants. Due to their placement on the cap, electrodes Iz, P9 and P10 are often very noisy and were therefore removed from the data set to improve signal quality. The remaining signal was re-referenced to the average of the electrode set, and the waveforms were then averaged across participants. To analyze the signal in the frequency domain, a discrete Fourier transform (FFT) (Frigo & Johnson, 1998) was used. Finally, we subtracted at each electrode and at each frequency bin the average amplitude of the signal measured at the maximum amount of neighboring frequencies (depending on the

location of the electrode, this number varies from 2 to 5) to remove residual noise (Mouraux, Iannetti, et al., 2011). The peak at the frequency of the oddball stimulation (FoS) in each condition was selected for the continuation of the analysis (FoS_{base} = .5 Hz). In a similar (visual) oddball paradigm, it has been shown that responses related to the periodic oddball are the strongest at the first 3 harmonics (i.e., $FoS_{oddball}$ = .125 Hz, FoS_{H2} = .25 Hz and FoS_{H3} = .375 Hz) (Rossion et al., 2015). The signal with the largest response within the first three harmonics was selected and used in the continuation of the analysis. We refrained from summing up any harmonics to avoid the aggregation of overlapping data between the oddball and baseline cycles at the FOS_{base} (.5 Hz), which is also a harmonic of the oddball (Rossion et al., 2015).

2.7.2. *Analysis of the modulation of ongoing oscillations*

The analysis of the modulation of ongoing oscillations only differed from the previously described steps in two points. To isolate the activity related to specific frequency bands (theta: 4–8 Hz, alpha: 8–13 Hz, beta: 13–30 Hz, in accordance with the COBIDAS recommendations Pernet et al., 2020), a 4th order Butterworth bandpass filter was used to filter the EEG signal after the re-referencing step. Additionally, a Hilbert transform was applied to estimate the envelope of the signal. The remaining steps were the same as described in the analysis of the phase-locked response (averaging, FFT, removal of residual noise). The resulting amplitude at the $FoS_{oddball}$ and FoS_{base} in each frequency band, condition, and for all electrodes was considered for the statistical analysis. As for the phase-locked response, the first 3 harmonics of the oddball stimulus were considered in each condition, and the harmonic with the largest modulation (i.e., Wilcoxon signed-rank test statistic) was selected.

2.8. *Statistical analysis*

Statistical analyses were done using R Statistical Software (Version 4.3.1, R Core Team 2023) and MATLAB (2020b The MathWorks). The significance level was set at $p < .05$. A Kenward-Roger approximation generating appropriate type 1 error rates for smaller sample sizes was used to test the significance of the results. A summary of all hypotheses and analyses plans can be found in Table 1.

2.8.1. *Behavioral data*

To analyze the continuous ratings and find peaks related to the oddball in both conditions, each condition was averaged for each participant. A time-window of 1–2.6 sec after each oddball stimulus (i.e., peak of the stimulation) was assessed and the highest rating within this window was selected. The length of this time-window was based on Mulders et al. (2020), who reported that peaks in continuous rating followed on average between 1.35 and 2 sec after the peak of the stimulus delivered at a frequency of .2 Hz, Similar results were found in our own pilot data (see Supplementary Materials S.II). The delay of the peak of the rating in respect to the peak of the TCS stimulation cycle was calculated for each condition, for oddball and baseline, to compare to the preceding investigations. The same procedure was carried out to identify peaks associated with the baseline stimulation. The detected peaks were averaged (summed up and divided by the number of peaks) for each stimulus and condition. To assess whether the ratings related to the oddball differed from the rating of the baseline stimuli, two linear mixed models were used, assessing the effect of the factor *stimulus* (baseline/oddball) on the ratings of perception given during either the high oddball (model 1) or during the low oddball (model 2) condition. *Subject* was added as a random effect to adjust the intercept of the regression model for each participant. Based on the assumption that the high oddball was more salient than the baseline stimuli, we expected that it would be perceived as more painful than the baseline stimuli. In the low oddball condition, we expected the oddball to be perceived as less painful than baseline stimuli, since the oddball was delivered using a lower stimulus intensity. If we failed to get evidence for a difference between baseline and oddball ratings in one of the conditions, we would not expect to find a modulation of ongoing oscillations at the frequency of stimulation of the corresponding oddball ($FoS_{oddball}$).

To be able to compare the ratings related to the oddball in the two conditions relative to the baseline peaks (which are not necessarily of the same amplitude in the two oddball conditions), the difference between baseline and oddball was calculated for each condition (=Δhigh and Δlow). A paired *t*-test was applied to compare the difference between oddballs across the conditions. We expected that the high oddball would be rated as more painful than the low oddball stimuli.

2.8.2. *Phase-locked response*

To control for a non-normal distribution of the data set and to account for potential type I error inflations due to multiple testing, a right-tailed multi-sensor cluster-based permutation test using a one-sample Wilcoxon signed-rank test as test statistic was used to identify amplitudes at the FoS which were significantly different from zero. A Bonferroni corrected alpha level of .0125 (the standard alpha level .05 divided by the number of conditions) was used to account for multiple testing (the median being compared to 0 at each of the 64 channels). The threshold for the cluster-based permutation was also set to .0125, and 2000 permutations were computed. The sensor connection threshold for the multi-sensor analysis was set to .161, thus each channel had 4 neighbors on average. A periodic response was considered when the Wilcoxon signed-rank test (with the conditions specified above) identified an amplitude as significantly different from zero. Electrodes showing a periodic response that are neighboring each other were pooled and analyzed as a cluster (Hauck et al., 2015; Tiemann et al., 2015). Since most of the responses at $FOS_{oddball}$ proved to be not significantly different from zero or not clustered, we created the electrode clusters of interest based solely on the test statistic for FOS_{base} (Fig. 7).

Based on the frequency-tagging premise, we expected to find a periodic response at both FoS_{base}, in both conditions. Previous investigations in our lab using a stimulation frequency of .2 Hz showed that this elicits a very consistent response (Colon et al., 2017; Leu et al., 2023; Mulders et al., 2020). If none of the electrodes showed a significant increase in periodic response at the FoS_{base}, we would have to assume that we failed to induce a periodic modulation of the EEG signal, rendering the data unusable as the fundamental objective of the investigation was not achieved (positive control).

We further expected to find a periodic response at the $FoS_{oddball}$, in both conditions. A peak at the $FoS_{oddball}$ would show that the periodic oddball paradigm adapted from a visual stimulation paradigm also works as intended using much slower, painful stimuli. If a periodic response was found in the high oddball condition but not in the low oddball condition, we could assume that the intensity of the stimulus contributed more to the periodic response than saliency (since both stimuli should be salient, but only one of them is delivered at a high stimulation intensity). A response larger than zero at the $FoS_{oddball}$ in the low oddball condition would show that a stimulus with a lower intensity than baseline could also elicit an oddball response, potentially due to the saliency of the stimulus.

If the oddball response in both conditions was larger than zero, the relative amplitude of the oddball responses was calculated for each condition (=Δhigh and Δlow) and compared using a paired *t*-test. The relative amplitude had been chosen to mitigate potential differences between the responses at the FOS'_{base}. Given the difference in oddball stimulation intensity, the baseline stimuli could also be perceived differently in the different conditions, potentially leading to non-identical responses between the conditions. If the periodic response was driven mainly by the intensity of the stimulus, we expected the amplitude of the high oddball to be larger than the low oddball. If saliency had an additional contribution to the periodic response, the oddballs would show a similar amplitude.

2.8.3. *Modulation of ongoing oscillations*

The analysis of the modulation of ongoing oscillations was identical to the analysis of the phase-locked response but was done separately for each frequency band. Therefore, a right-tailed multi-sensor cluster-based permutation test using a Wilcoxon signed-rank test as test statistic was be used to identify the electrodes with an amplitude significantly larger than zero at both FoS' and in each condition. Corresponding to the analysis of the phase-locked response, for each frequency band, neighboring electrodes exhibiting a large modulation at the frequency of stimulation (i.e., a high test-statistic) were pooled into clusters. We expected to find clusters over contralateral central-parietal areas for the alpha and beta frequency band (Colon et al., 2017; Leu et al., 2023; Mulders et al., 2020) and more fronto-central for the theta frequency band (Colon et al., 2017; Leu et al., 2024; Mulders et al., 2020; Tiemann et al., 2015). As for the phase-locked response, clusters were based on the modulation of ongoing oscillations found at FOS_{base}. As for the phase-locked response, we expected a periodic response at both FoS'_{base} and $FoS'_{oddball}$ in the different frequency bands and conditions. No response at the $FoS_{oddball}$ in the low oddball condition would show that the saliency of the stimulus does not contribute significantly to the modulation of ongoing oscillations and that stimulus intensity was the main contributing factor.

As for the phase-locked response, the difference between baseline and oddball was calculated for each condition and frequency band (if both show a modulation at their FoS). Then, for each frequency band, a paired *t*-test was employed to compare the peaks related to Δhigh and Δlow. If the intensity of the stimulus was the main factor in the modulation of ongoing oscillations, the amplitude for Δhigh would be larger than the amplitude for Δlow (not excluding that saliency might also influence this modulation). If saliency was more relevant than stimulus intensity, the amplitudes of the oddball in the normal and the control condition would be similar to each other.

2.8.4. *Outliers*

Only participants that completed both experimental sessions fully were considered for the analysis. Further, we removed outliers [identified using Cook's distance (Cook, 1977)] as well as data points that violate LMM assumptions of linearity and normality.

Violations of LMM assumptions were identified using a Shapiro–Wilk test to assess the normal distribution of the data. To test the data set for homoscedasticity, Levene's test was used. In case the data did not conform to normality, a log-transform was applied, which was supposed to conform the data to the assumption of normality by correcting right-skewed data into a more normal form (Bland & Altman, 1996). Yet, neither a log nor a square-root transformation normalized the data. Upon further visual inspection using a QQ-plot of the model residuals, the original ratings appeared rather normally distributed. Additionally, as detailed below, no specific data points seem to have influenced the data set overproportionally. Thus, considering that the Shapiro–Wilk test is rather stringent and a positive visual assessment (King & Eckersley, 2019), we considered the data appropriate for LMM use.

Cook's Distance [D] was used to identify data points that over-proportionally influenced the data set. This method calculated how much the fitted values of a given data set change if just one data point was removed. The influence of a data point was expressed in the "distance" D; the larger it was, the more influential the data point (Cook, 1977). Therefore, any data point exceeding a D of 1 was removed from the data set. Cook's distance was calculated for each datapoint within a condition, using a separate calculation for each condition. No data points had to be removed based on Cook's distance. Thus, no outliers were removed from the data set apart from the participants which were rejected pre-statistical analysis.

2.9. *Exploratory analyses*

2.9.1. *Behavioral response*

Given the periodicity of the VAS ratings, an exploratory visual analysis was conducted as a direct comparison to the analysis of the neural responses by transforming the perception ratings into the frequency domain. Mirroring the preprocessing steps of the EEG data, we calculated the group average for each condition, then applied the FFT and corrected the baseline by removing 2–5 neighboring frequency bins from the signal.

2.9.2. *Neural response*

In the primary registered analysis, the amplitude at the frequency of the oddball (or one of the first 2 harmonics) was considered by itself. Yet, in a compelling review by (Retter et al., 2021), it is demonstrated that harmonics are indeed an important part of the neural response in the frequency

domain. This theoretical framework was supported by the EEG spectra found in this investigation in e.g., the alpha frequency band, which showed visually identifiable peaks at the 1st and 2nd harmonic of the oddball of about the same magnitude as the main response at $FOS_{oddball}$ (see Fig. 9). Therefore, to avoid the pitfall of disregarding the harmonics completely and potentially lose information, we added an exploratory analysis to this RR, in which the amplitude at the oddball frequency is aggregated (i.e., summed up) with the amplitudes at the first 2 harmonics. This new amplitude (FOS_{agg}), comprising the amplitudes at .125 Hz, .25 Hz and .375 Hz, and therefore more adequately representing the complete neural response to the oddball stimulation, will then be treated as the $FOS_{oddball}$ for the consecutive analysis (i.e., multi-sensor cluster-based Wilcoxon signed rank test to identify amplitudes significantly larger than 0, and the comparison of the relative amplitudes if both conditions show a modulation of ongoing oscillations at the FOS_{agg}).

3. Results

Data from 1 participant were entirely excluded from the dataset due to non-compliance with the instructions of the experimenter in both sessions and 1 participant did not complete the 2nd testing session. Data from 2 additional participants had to be excluded from the EEG dataset, because the data was too contaminated by artifacts (i.e., amplitudes over 500 μV after ICA).

3.1. *Stimulus perception*

While many participants were able to trace the periodic stimulation using the VAS, the baseline stimulation cycles were often not clearly perceived, rendering the identification of the rating peaks on a single subject level rather difficult (see Supplementary Material S.IV for single subject average examples). Yet, on a group level, rating peaks relating to both oddball and baseline stimulation cycles were clearly identifiable in both conditions (Fig. 4).

The high oddball stimulation was overall perceived as more intense than the low oddball stimulation. Interestingly, only for the high oddball condition, the subjects perceived on average that the oddball cycles were painful (Fig. 4), even though we had aimed to elicit the sensation of pain in both conditions. The oddball cycles in the high oddball condition were visually clearly distinguishable from baseline stimulation cycles, which was not the case in the low oddball condition (relating to hypothesis 1). Nevertheless, the rating peaks related to either oddball were observed with almost the same time delay after the peak of the stimulation (see vertical lines in Fig. 4, avg. delay high oddball: (mean ± std. dev.) 1.834s ± .164s, delay low oddball: 1.717s ± .215s). The rating peaks relating to the oddball stimulation cycles were rated at group average at a VAS of 5.1 ± .2 following high oddball and VAS 4.3 ± .4 for low oddball stimulation (Fig. 4). On group average, participants rated the baseline stimulation cycles at VAS 4.6 ± .3 in the high oddball trials, and at VAS 4.3 ± .4 in the low oddball trials. While these values were based on the group average, for the LMM individual ratings relating to baseline and oddball peaks were extracted based on the maximal rating within a time-window of 1–2.6 sec after the stimulation peak for each trial and participant. This is a rather wide span for such a window and given the high heterogeneity in ratings (see Supplementary Materials S.IV for single subject average examples) it is not surprising that the peaks that were identified with this method deviate slightly in their average from the data reported above. The oddball cycles in the high oddball

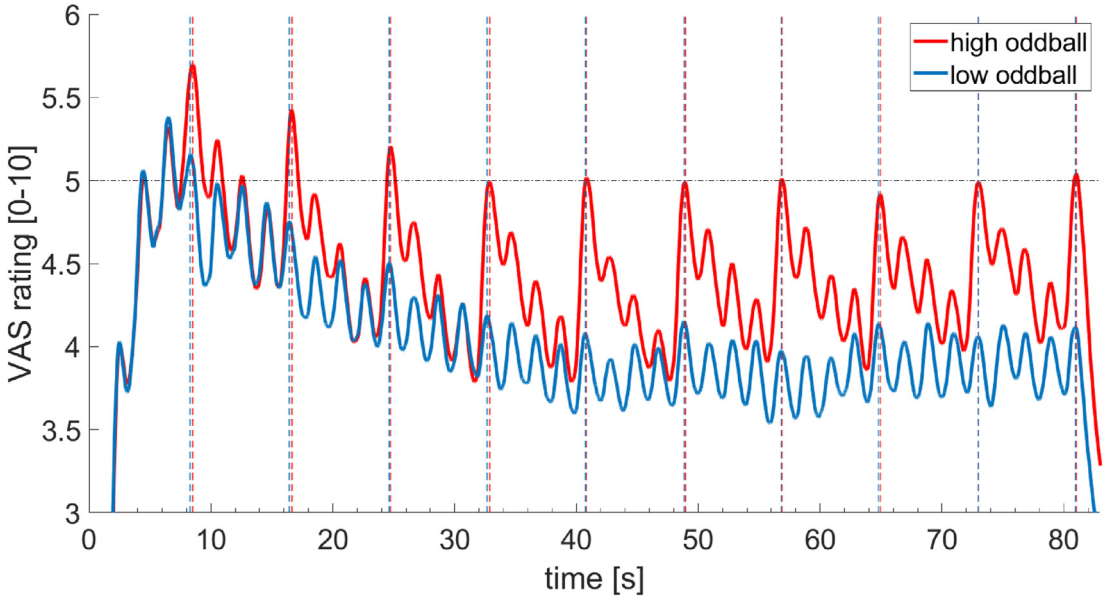


Fig. 4 – Group averages of the continuous ratings of perceived stimulus intensity [0–5] and painfulness [5–10] given on a visual analog scale (VAS) during each stimulation. The high oddball stimulation is colored in red, the low oddball stimulation is colored in blue. Vertical lines indicate the detected peak of the ratings for each condition. The horizontal line indicates the threshold from intensity to painfulness on the VAS.

Table 1 – Hypotheses and analyses plan as well as potential interpretations given different outcomes for each research question of this investigation.

Question	Hypothesis	Analysis Plan	Interpretation given different outcomes
1) Is the oddball perceived as different than the baseline stimulation in both conditions (i.e., high and low oddball)?	The intensity rating of the oddball stimulation will be different than the rating for the baseline stimulation in both conditions.	LMMs: $Rating_{high}$ ~ stimulus+ (1|subject) $Rating_{low}$ ~ stimulus + (1|subject) $Rating_{high}$ = ratings in the high oddball condition $Rating_{low}$ = ratings in the low oddball condition	A significant simple effect of "stimulus" would indicate that the oddball paradigm is working as intended and elicited a change in perception in this condition. If no difference is perceived in one specific condition, the oddball might not have been salient enough to change perception. In those cases, based on our main hypothesis, we would not expect to find a modulation of ongoing oscillations at the frequency of stimulation of the corresponding oddball ($FoS_{oddball}$). As the sample size is not sufficient to detect the smallest possible effect one would still be interested in (see below), a non-significant result does not necessarily indicate that there is a definitive absence of an effect and no definitive conclusions can be drawn from a non-significant result (Dienes, 2021).
2) Does the relative peak of the rating related to the high oddball differ from the rating of the low oddball?	If the oddball perception is driven by the intensity of the stimulus, the high oddball will be perceived as more intense than the low oddball.	Paired *t*-test of the Δ (baseline-oddball) between high and low condition.	A difference between the ratings would show that the objective intensity of the oddball is driving the subjective perception. If the oddballs had similar peaks, it could indicate that the perception is rather based on the saliency of the stimulus. Yet, no definitive conclusions will be drawn from a non-significant result since the sample size is not sufficient to detect the smallest possible effect one would still be interested in.
Time-locked, phase-locked response			
3a) Does the sustained periodic stimulation lead to a periodic EEG modulation at FoS_{base} in both conditions?	The slow sustained periodic stimulation paradigm will lead to a periodic modulation of the EEG signal at the $FoS_{base.}$	Multi-sensor cluster-based permutation Wilcoxon signed-rank test of amplitudes at the $FoS_{base.}$	*Positive control:* If the expected neural activity is not induced by the baseline stimulation in the stimulation paradigm (results of the one-sided Wilcoxon signed-rank test show that the amplitude at FoS_{base} is not significantly different from zero), the fundamental assumption for using the frequency-tagging approach in this study would not be met.
4a) Does the oddball stimulation lead to a periodic modulation of the EEG signal at the $FoS_{oddball}$ in the high oddball condition?	The oddball paradigm will lead to a periodic modulation of the EEG signal at the frequency at which the oddball was presented in the high oddball condition.	Multi-sensor cluster-based permutation Wilcoxon signed-rank test of amplitudes at the $FoS_{oddball}$ in the high oddball condition.	A modulation (amplitude significantly larger than zero in Wilcoxon signed-rank test) at the frequency of the high oddball would indicate that the paradigm was successful in eliciting a periodic response related to the oddball. If no peak can be detected, the paradigm did not work as intended for the phase-locked response. No definitive conclusions will be drawn from a non-significant result since the sample size is not sufficient to detect the smallest possible effect one would still be interested in.
4b) Does the oddball stimulation lead to a periodic modulation of the EEG signal at the $FoS_{oddball}$ in the low oddball condition?	The oddball paradigm will lead to a periodic modulation of the EEG signal at the frequency at which the oddball was presented in the low oddball condition.	Multi-sensor cluster-based permutation Wilcoxon signed-rank test of amplitudes at the $FoS_{oddball}$ in the low oddball condition.	*Control condition:* A modulation (amplitude significantly larger than zero in Wilcoxon signed-rank test) at the frequency of the low oddball would indicate that an oddball with a lower stimulation intensity than the baseline stimulation is able to elicit a neural response. No peak might indicate that the oddball delivered at a low stimulation intensity was not intense or salient enough to induce a periodic response. No definitive conclusions will be drawn from a non-significant result since the sample size is not sufficient to detect the smallest possible effect one would still be interested in.

(*continued on next page*)

Table 1 – (*continued*)

Question	Hypothesis	Analysis Plan	Interpretation given different outcomes
5) Does the high oddball lead to a larger relative response in the EEG signal at the $FoS_{oddball}$ than the low oddball in the frequency-domain?	The amplitude at the $FoS_{oddball}$ in the high oddball condition will be similar to the amplitude at the $FoS_{oddball}$ in the low oddball condition.	Paired *t*-test of the difference (Δbaseline-oddball) between high and low oddball condition.	A similar amplitude of the oddball in the high and low oddball condition would support the notion that the oddball response is mainly driven by the saliency of the stimulus. If the oddball in the low oddball condition leads to a smaller response compared to the oddball in the high oddball condition, it could suggest that the intensity of the stimulus is more prominently reflected in the periodic response related to the oddball than saliency. No definitive conclusions will be drawn from a non-significant result since the sample size is not sufficient to detect the smallest possible effect one would still be interested in.
Time-locked, non-phase-locked response			
3b) Does the sustained periodic stimulation lead to a periodic EEG modulation at FoS_{base} in both conditions?	A periodic modulation of the EEG signal will be elicited in all frequency bands for the FoS_{base} in both conditions.	Multi-sensor cluster-based permutation Wilcoxon signed-rank test of amplitudes at the FoS_{base}[a].	A modulation (amplitude significantly larger than zero in Wilcoxon signed-rank test) at the frequency at FoS_{base} indicates that sustained periodic stimulation leads to a periodic response in the different frequency bands (Colon et al., 2017) in both conditions. No periodic response would indicate that the sustained periodic stimulation paradigm was not successful in inducing a periodic modulation.
6a) Does the oddball stimulation lead to a modulation of ongoing oscillations at the $FoS_{oddball}$ in the high oddball condition?	The oddball paradigm will lead to a modulation of ongoing oscillations at $FoS_{oddball}$ in the high oddball condition.	Multi-sensor cluster-based permutation Wilcoxon signed-rank test of amplitudes at the $FoS_{oddball}$ in the high oddball condition.	A modulation (amplitude significantly larger than zero in Wilcoxon signed-rank test) at the frequency of the oddball would indicate that the paradigm was successful in eliciting a neural response related to the oddball. No peak at $FoS_{oddball}$ would indicate that the chosen oddball parameters were not intense or salient enough to elicit a modulation of ongoing oscillations. No definitive conclusions will be drawn from a non-significant result since the sample size is not sufficient to detect the smallest possible effect one would still be interested in.
6b) Does the oddball stimulation lead to a periodic modulation of the EEG signal at the $FoS_{oddball}$ in the low oddball condition?	The oddball paradigm will lead to a modulation of ongoing oscillations at $FoS_{oddball}$ in the low oddball condition.	Multi-sensor cluster-based permutation Wilcoxon signed-rank test of amplitudes at the $FoS_{oddball}$ in the low oddball condition.	Control condition: A modulation (amplitude significantly larger than zero in Wilcoxon signed-rank test) at the frequency of the oddball would indicate that an oddball with a lower stimulation intensity than the baseline stimulation is able to elicit a neural response. No peak at $FoS_{oddball}$ might indicate that the oddball in the low oddball condition was not intense or salient enough to lead to the expected response. No definitive conclusions will be drawn from a non-significant result since the sample size is not sufficient to detect the smallest possible effect one would still be interested in.
7) Does the high oddball lead to a larger relative response in the EEG signal at the $FoS_{oddball}$ than the low oddball in the different frequency bands?	The amplitude at the $FoS_{oddball}$ in the high oddball condition will be similar to the amplitude at the $FoS_{oddball}$ in the low oddball condition.	Paired *t*-test of the Δ (baseline-oddball) between high and low oddball condition.[a]	A similar amplitude of the oddball in the high and low oddball condition would suggest that the oddball response is mainly driven by the saliency of the stimulus. If the oddball in the low oddball condition would lead to a smaller response compared to the oddball in the high oddball condition it would suggest that the intensity of the oddball stimulus is reflected more prominently in the corresponding modulation of ongoing oscillations than saliency.

Abbreviations. LMM: Linear mixed model; $amplitude_{FoS}$: amplitude at the frequency of stimulation FoS_{base}: amplitude at frequency of baseline stimulation; $FoS_{oddball}$: amplitude at frequency of oddball stimulation.

[a] One test for each frequency band (theta, alpha, beta).

condition were identified to be rated at VAS 5.5 ± 2.4, while the oddball cycles in the low oddball condition were identified at VAS 4.7 ± 2.3. Rating peaks related to the baseline stimulation cycles were identified at VAS 5.0 ± 2.1 for the high oddball condition and VAS 4.7 ± 2.0 for the low oddball condition. The LMM for each condition showed that oddball cycles were perceived as more intense than baseline cycles in the high oddball condition [$F(750) = 30.066$, $p < .001$], while no significant difference was found between oddball and baseline cycles in the low oddball condition stimulation [$F(750) = .0404$, $p = .841$] (Fig. 5). This confirmed hypothesis 1 for the high oddball, but not the low oddball condition. The relative difference between the VAS ratings relating to the oddball and baseline rating peaks was calculated for each condition (hypothesis 2). This showed that the relative oddball ratings were significantly different from each other [$t(391) = 7.437$, $p < .001$]; high oddball peaks were perceived as more intense than low oddball peaks (Fig. 8).

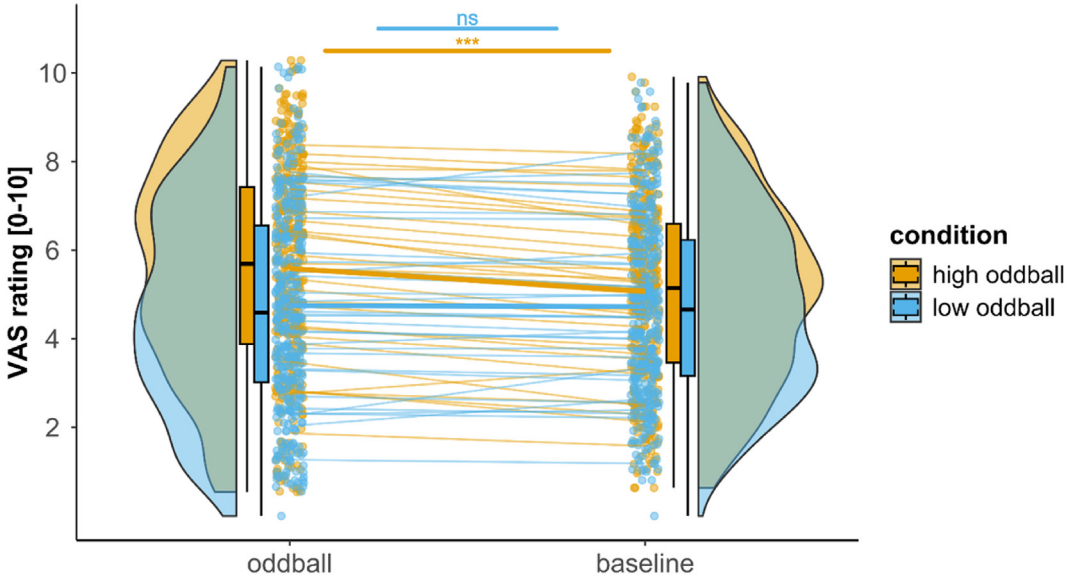


Fig. 5 – Continuous VAS ratings extracted at the maximal rating 1–2.6 sec after the stimulation peaks of both oddball and baseline stimulation. A separate model was run for each condition. The results of both LMM's are indicated using asterisks: ***$p < .001$, $^{ns}p < .05$.

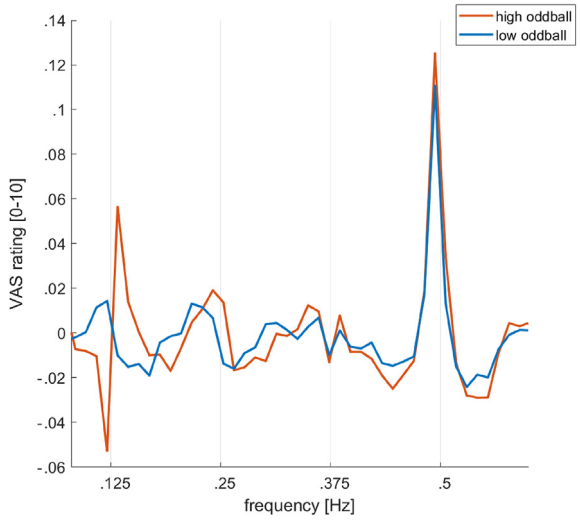


Fig. 6 – Exploratory behavioral analysis. Frequency-tagged continuous VAS ratings. Vertical lines indicate the $FOS_{oddball}$ and its harmonics (i.e., .125 Hz, .25 Hz, …) as well as FOS_{base} (i.e., .5 Hz).

3.2. *EEG recordings*

3.2.1. *Phase-locked response*

In the phase-locked response, amplitudes significantly larger than zero (i.e., significant periodic response) were found at the FOS_{base} in both the high and low oddball condition (hypothesis 3a, positive control). Similarly, the right-tailed multi-sensor cluster-based permutation Wilcoxon signed-rank test identified a significant peak at the $FOS_{oddball}$ in both conditions (hypotheses 4a and 4 b). A full table with the test-statistics can be found in the Supplementary Materials. Based on the electrodes with the largest test statistics at the FOS_{base} that were adjacent to each other, clusters of interest were built. Given the different topographies, these clusters vary between the conditions: for the high oddball condition, a fronto-central cluster was identified (CPz, Cz, C2, FC2, FCz). In the low oddball condition, the cluster was shifted towards contralateral parietal regions (C3, C5, CP5). A secondary cluster was identified which resembled more the cluster in the high oddball condition (CPz, Cz, C2, FCz, FC2, Fz).

The relative change in amplitude between oddball and baseline response was calculated for each condition and the relative change was compared between the conditions. While the peak related to the oddball stimulus was clearly

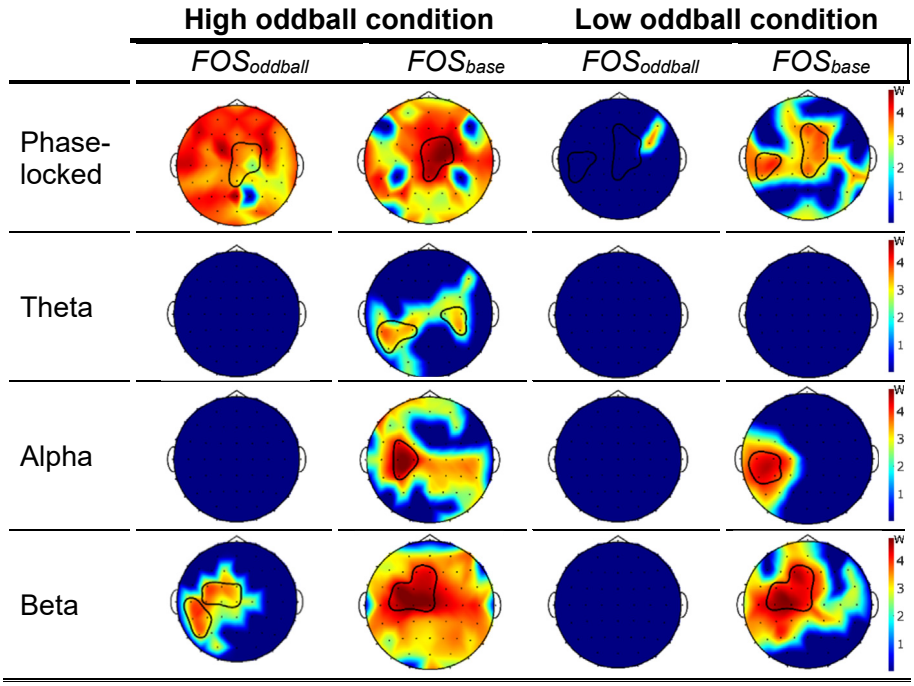


Fig. 7 – Topographies illustrating the magnitude of the right-tailed multi-sensor cluster-based permutation Wilcoxon signed-rank test statistic (W) for each condition and stimulation type. No significant modulation of ongoing oscillations was found at the FOSoddball in the low oddball condition. All topographies were plotted using the same scale.

distinguishable in the high oddball condition [W(31) = 414, $p < .001$], this was not the case in the clusters in the low oddball condition [W(31) = 299, $p = .327$; W(31) = 219, $p = .581$] (Fig. 7). The comparison of the relative change between the conditions using a non-parametric paired t-test (hypothesis 5) revealed that the relative peak at the FOSoddball in the high oddball condition was significantly larger than the peaks at $FOS_{oddball}$ of the central [W(31) = 430, $p < .001$] and parietal cluster [W(31) = 365, $p = .021$] in the low oddball condition (Fig. 8).

3.2.2. *Modulation of ongoing oscillations*

In the theta frequency band, the right-tailed multi-sensor cluster-based permutation Wilcoxon signed-rank test identified amplitudes significantly different from zero only at the FOS_{base} (hypothesis 3 b) in the high oddball condition, but not at either of the $FOS_{oddball}$ (hypotheses 6a and 6 b) (Fig. 7). Two clusters were identified, a centro-parietal one contralateral (CP1, CP3, CP5, P5) as well as a smaller cluster ipsilateral to the stimulation side (CP4, C4, C2).

In the alpha frequency band, the responses at the FOS_{base} were significantly different from zero (i.e., showing a modulation of ongoing oscillations) in both conditions (hypothesis 3 b). In the high oddball condition, a cluster at central electrodes contralateral to the stimulation side was identified (C1, C3, CP3, FC3). A very similar cluster was detected in the low oddball condition, shifted slightly to more parietal regions (C3, C5, CP3, CP5). Fig. 9 illustrates the alpha band responses in those clusters in the frequency spectrum. No significant periodic response was detected at either $FOS_{oddball}$ (hypotheses 6a and 6 b).

Only in the beta frequency band, a modulation of ongoing oscillations was found at both the FOS_{base} (hypothesis 3 b) as well as the $FOS_{oddball}$ in the high oddball condition (hypothesis 6a). The response at FOS_{base} was relatively widespread in both conditions, leading to the identification of the same large cluster including central electrodes and electrodes contralateral to the stimulation side (Fz, F1, FCz, FC1,FC3, Cz, C1, C3). While no significant modulation was found at the $FOS_{oddball}$ in the low oddball condition (hypothesis 6 b), some electrodes in the baseline cluster were also modulated in the response at $FOS_{oddball}$. Thus, 2 clusters of activity were identified at the $FOS_{oddball}$. One cluster composed of central electrodes (FCz, FC1, FC3, Cz, C1,C3) and one cluster of parietal electrodes (C5, CP3, CP5, P5).

As no modulation of ongoing oscillations was found at the frequency of the oddball in the low oddball condition in any of the frequency bands, no comparison of the relative oddball amplitudes between high and low oddball condition were carried out (as pre-registered, hypothesis 7).

3.3. *Exploratory analyses*

3.3.1. *Ratings*

In addition to the registered analysis, we also employed the frequency-tagging analysis method to the continuous VAS rating. Given its high periodicity at the group-level, this exploratory analysis seemed to be an informative addition to the study as it allows a direct comparison with the obtained EEG responses. The continuous ratings in the frequency domain are illustrated in Fig. 6. The visualization of the frequency spectrum of the continuous ratings highlights the

tendency which has already been visible in the time domain: while a (visually) clear response was found at the $FOS_{oddball}$ in the high oddball condition, this was not the case for the low oddball condition. At the FOS_{base}, the magnitude of the responses seems to be similar. Generally, the rating peaks that relate to the FOS's are very close to the actual stimulation frequencies, showing that overall, the participants were quite accurate at following the periodicity of the stimulation with only small but consistent delays.

3.3.2. *EEG*

Based on the clear peaks that could be visually identified in the spectra of the neural response in the frequency bands (see Fig. 9 for an example), an exploratory analysis was added which took all harmonics up to the FOS_{base} into account for the analysis of the oddball response. Interestingly, the aggregation of the $FOS_{oddball}$ and its first two harmonics up to FOS_{base} (i.e., FOS_{agg}) did not change any results for the low oddball condition; as for the main analysis, no modulation of ongoing oscillations was found at the FOS_{agg}. Contrarily, including the first two harmonics in the high oddball condition (additional to the frequency of stimulation) showed that the oddball stimulation did lead to a significant modulation of ongoing oscillations at the aggregated amplitude in all three frequency bands (Fig. 10). To be consistent with the previous analysis, no new electrode clusters of interests were formed, but rather the clusters identified by the Wilcoxon signed-rank test at FOS_{base} were fitted onto the topographies of the FOS_{agg} test statistic. For the alpha and beta frequency bands, this approach led to a rather good match of electrodes with a high Wilcoxon test statistic between FOS_{base} and FOS_{agg}. Since none of the frequency bands showed a response at FOS_{agg} in the low oddball condition that was significantly different from zero, the relative oddball amplitudes were not compared (as pre-registered).

4. Discussion

In this investigation, we aimed to disentangle the relationship between stimulus intensity, saliency and the thereby elicited modulation of ongoing oscillations. To achieve this, a sustained periodic oddball paradigm was designed, eliciting two main responses in the frequency domain at the $FOS_{oddball}$ (i.e., .125 Hz) and FOS_{base} (i.e., .5 Hz), which were measured both using scalp EEG as well as continuous ratings on a VAS scale. To differentiate between effects of intensity and saliency which are inherently tied to each other in a high intensity stimulation, a lower intensity control oddball stimulation was added.

At the group level, participants were able to trace the cycles of the sustained periodic stimulation throughout the entire trial in both conditions. The ratings associated to the oddball cycles in the high oddball condition were clearly distinguishable from the ratings relating to the baseline stimulation cycles, which was not the case for the low oddball condition. Further, the ratings of the high and low oddball cycles relative to their baseline differed significantly from each other. Taken together, these results suggest that – in this experimental design and in absence of a valid control condition - it was mainly the intensity of the stimulation that drove the ratings of perception.

A significant modulation of ongoing oscillations was found at the FOS_{base} in the theta, alpha and beta frequency bands in electrode clusters mostly contralateral to the stimulation side at frontal, central and parietal electrodes. Only in the beta

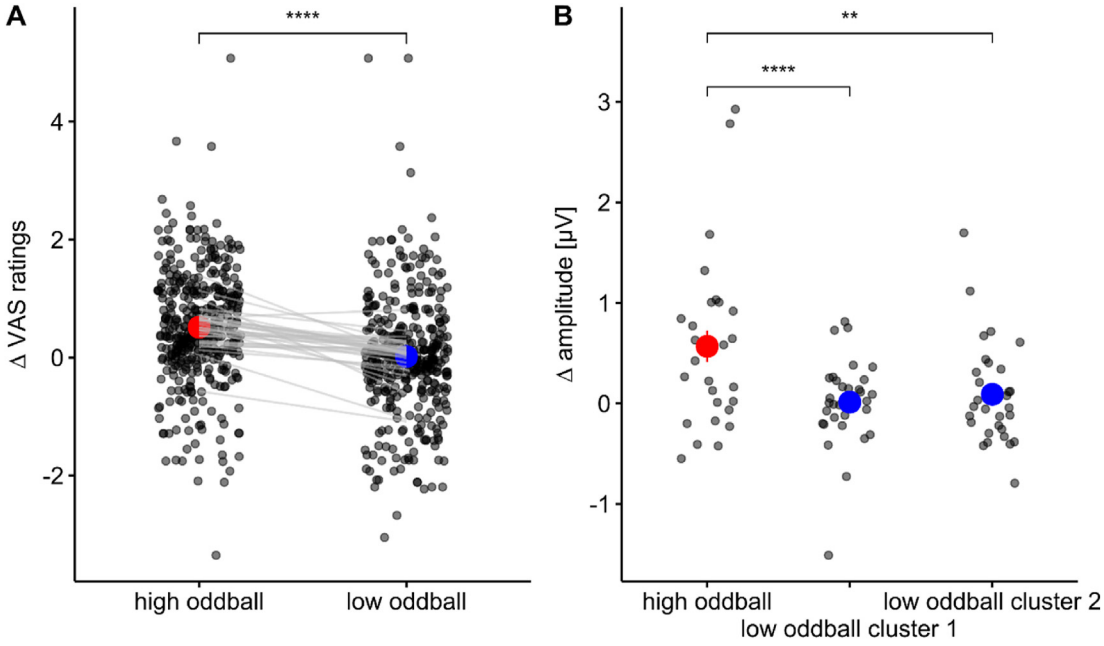


Fig. 8 – Oddball ratings (A) and phase-locked amplitudes (B) relative to each condition's baseline. Grey horizontal lines indicate the mean for each subject, colored dots indicate the mean for each condition. The following electrode clusters were formed: high oddball condition CPz, Cz, C2, FC2, FCz, low oddball condition cluster 1: CPz, Cz, C2, FCz, FC2, Fz and cluster 2: C3, C5, CP5 for the phase-locked response. Wilcoxon paired *t*-test: **$p < .01$, ****$p < .0001$.

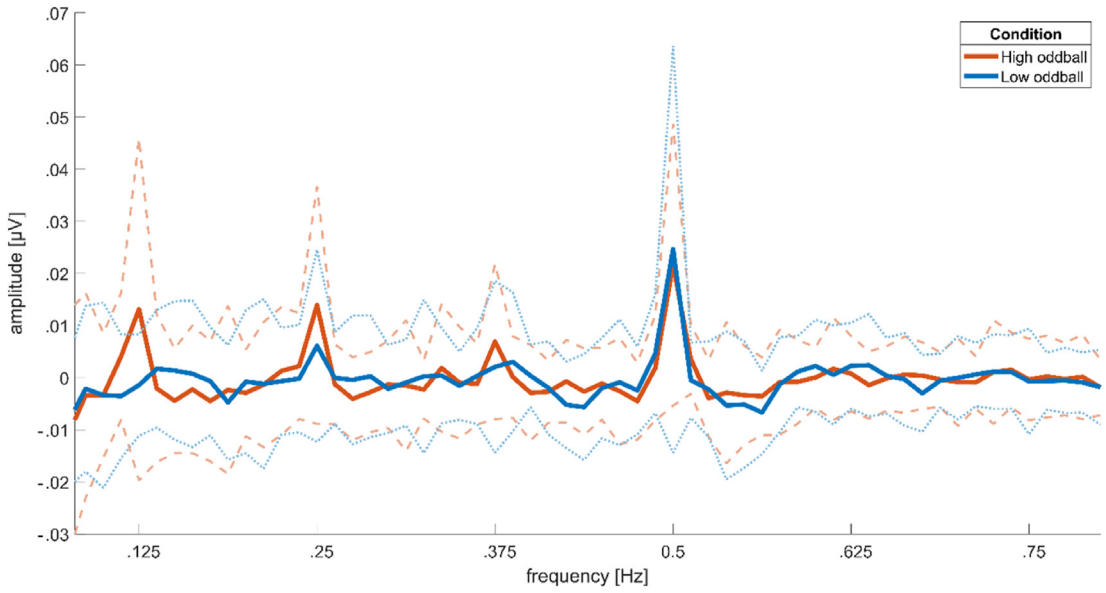


Fig. 9 – Spectrum of the estimated envelope of the EEG response in the alpha frequency band, illustrating the modulation of ongoing oscillations at the first few harmonics. X-axis indicators match the frequency of the oddball stimulation ($FOS_{oddball}$ = .125 Hz). The group mean for each condition is indicated in bold, dashed lines indicate the standard deviation from the mean. The electrode cluster in the high oddball condition comprises electrodes C1, C3, CP3, FC3; the low oddball cluster is made of electrodes C3, C5, CP3, CP5.

frequency band during the high oddball condition, a modulation of ongoing oscillations was evidenced at $FOS_{oddball}$. Exploratory analyses demonstrated the importance of taking the harmonics of the $FOS_{oddball}$ into account and revealed that a modulation of ongoing oscillations could be found at the $FOS_{oddball}$ in all frequency bands, but only in the high oddball condition.

These results could indicate that both stimulus perception as well as the modulation of ongoing oscillations are mainly influenced by stimulus intensity. Yet, the fact that the oddball was not perceived as significantly different from the baseline stimulation in the low oddball condition indicates that the chosen parameters might have not been sufficient to create an oddball that is salient (or intense) enough to elicit a clear response and is therefore not a valid control condition for our hypotheses. These results can therefore not disentangle the involvement of stimulus saliency or intensity in stimulus perception or modulation of ongoing oscillations.

4.1. *Behavioral response*

Extracting ratings for oddball and baseline stimulation cycles using the pre-registered method proved difficult at the single-subject level. Particularly in the low oddball condition, many participants had difficulty in perceiving the individual stimulation cycles. Given these ambiguous ratings, the wide 1–2.6 sec time window after the peak of each stimulus cycle resulted in potentially arbitrary data points, as it was unclear whether they truly corresponded to the perception at the peak of the stimulus cycle. Comparing single-subject data (Fig. 5) to group averages (Fig. 4) revealed a consistent shift of VAS .3., and given the consistency of this difference, the data points extracted on single subject level seemed appropriate for further analysis.

The LMM's confirmed that the oddball cycles led to significantly higher ratings of perception compared to baseline cycles of the stimulation in the high oddball condition. Additionally, this was the only stimulation that was on average perceived as painful (i.e., VAS rating $\geq$5). On the contrary, in the low oddball condition, the oddball cycles were not perceived significantly different from the baseline cycles of the stimulation. Thus, hypothesis 1 could only be confirmed for the high oddball condition.

A similar difference between a high and low intensity (unattended) deviants has been observed in an ERP study using auditory stimuli (Rinne et al., 2006) brief laser stimuli (Legrain, Guérit, et al., 2003), in which only the strong intensity deviants led to the emergence of the P3a - an ERP component linked to novelty detection/involuntary orienting of attention - suggesting that the stimulus was not salient enough to capture involuntary attention. The underlying neuronal mechanism might be "transient detection", a mechanism through which brief changes in the environment reset the neuronal adaptation to a stimulus, contributing to its saliency (Escera et al., 2000). This mechanism is highly relevant, especially in the context of painful stimuli, as they imply potential physical harm and an early detection of such an event is thus an innate protection mechanism.

There are other likely reasons as to why the low oddball cycles were not perceived as salient, such as the speed of the stimulation; it might be that the dip in intensity of the oddball stimulation cycle was too fast to be differentiated from the quickly following baseline stimulation cycle, creating a more diffuse sensation rather than a clearly perceivable negative peak. This is supported by the fact that for many participants,

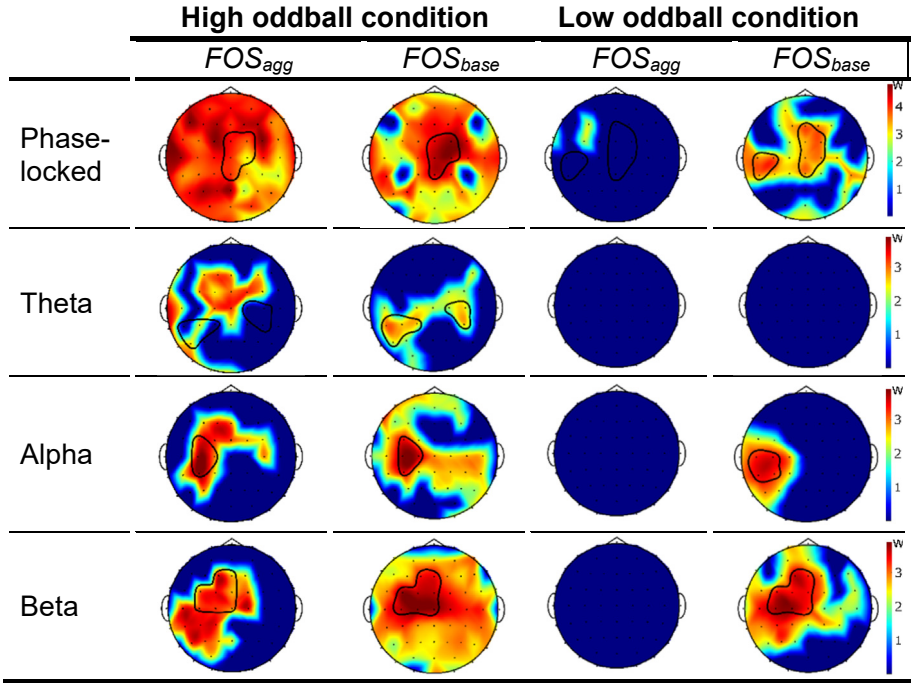


Fig. 10 – Exploratory analysis. The EEG signal at $FOS_{oddball}$ and its first 2 harmonics (i.e., .125 Hz, .25 Hz, .375 Hz) were aggregated into the FOS_{agg}. Topographies illustrate the magnitude of the right-tailed multi-sensor cluster-based permutation Wilcoxon signed-rank test statistic (W) for each condition and extracted amplitudes. No significant modulation of ongoing oscillations was found at the FOSoddball in the low oddball condition.

it was not possible to trace the stimulation cycle by cycle even for the baseline stimulation, making it even more difficult to perceive a brief change in the stimulation pattern at a lower intensity. Additionally, the temperature of the low oddball stimulation cycles in combination with the relatively low temporal precision of the underlying nociceptors should be considered. On one hand, C-fiber nociceptors [which are known to be primarily activated in this slow sustained periodic paradigm (Colon et al., 2017)] have rather low firing rate of around 15–20 Hz and it has been demonstrated that this firing rate correlates/rises with the steepness of the heating ramp of the applied thermonociceptive stimulation (Yarnitsky et al., 1992). On the other hand, the temperature and heating profile with which the stimulation is applied at the skin surface does not necessarily correspond to the properties reaching the nociceptors (Magerl & Treede, 1996). This so called "heat sink-effect" from skin surface to the nociceptor level gets progressively larger, the faster the heating rate of the applied thermonociceptive (Tillman et al., 1995). Additionally, pain perception related to C-fiber nociceptor activation has been shown to be strongly influenced by spatial and temporal summations (Treede et al., 1990). Using stimuli of different durations (.5s, 1s, 2s), a recent investigation demonstrated that only the longest stimulus duration led to pain ratings which could be differentiated (Wang et al., 2022). While direct comparison with their study is not possible due to individualized target temperatures this investigation highlights that - especially considering lower stimulation temperatures – temporal precision of perception is limited. This effect is potentially amplified in the present experiment, as only a fraction of the 2s cycle was spent at the target temperature. Conversely, slower periodic stimulation paradigms have been shown to be easily trackable using continuous ratings, despite relatively small differences in stimulation intensity (Guo et al., 2020; Mulders et al., 2020), supporting the notion that temporal summation is an important aspect in the pain response to C-fiber activation using heat stimulation.

Furthermore, the offset analgesia phenomenon – characterizing a disproportionally large reduction in pain perception to a relatively small decrease in applied temperature of stimulation (Grill & Coghill, 2002) - should be considered as a contributing factor for the relatively low ratings of stimulus perception. Even though the underlying mechanisms are not yet fully elucidated and are likely a combination of peripheral and central mechanisms, the effect seems to be generally driven by a temporal filtering of the sensory experience (Mørch et al., 2015). Thus, an offset analgesic-like effect in the downward slope of the thermonociceptive stimulation could have overall attenuated the pain perception of the participants, despite the stimulation temperature being over generally accepted C-fiber related pain threshold (Treede et al., 1990).

Unsurprisingly given the above-mentioned results, the relative oddball ratings in the high oddball condition were significantly larger than in the low oddball condition (confirming hypothesis 2). While this could be interpreted as stimulation intensity being the main driving factor behind the perception of sustained periodic thermonociceptive stimulation, it should not be disregarded that the oddball in the low oddball condition failed to be perceived as significantly different from the baseline stimulation in the first place and is therefore not a valid control condition for this experiment.

Hence, no direct conclusions can be made regarding the involvement of saliency in the perception of these stimulations.

4.2. Neural response

The stimulation led to a significant periodic response at FOS_{base}, thus confirming the predefined positive control for the EEG response to the sustained periodic thermonociceptive stimulation (hypothesis 3a). In the phase-locked response, a widespread periodic response was found at the $FOS_{oddball}$ in the high oddball condition (confirming hypothesis 4a). In contrast, while a periodic modulation was found in very few electrodes also at $FOS_{oddball}$ in the low oddball condition (hypothesis 4 b), the localization of those electrodes suggests that the recorded activity might be related to muscular artifacts. Additionally, many electrodes showed a periodic response between .1 Hz and .125 Hz, further supporting the notion that the low oddball stimulation was potentially "washed out" among the other ongoing activities. The comparison of the amplitude relative to baseline at the $FOS_{oddball}$' showed a significantly larger periodic response in the high oddball condition (hypothesis 5). Yet, before these results are interpreted as evidence that intensity is the main contributing factor for the periodic response, it should be considered that the clusters of activity did not match between responses to oddball and baseline stimulation, making it difficult to build meaningful comparisons. Furthermore, given the minimal and diffuse effect the oddball had in the low oddball condition, this comparison should be interpreted cautiously.

A modulation of ongoing oscillations was found at the FOS_{base} of each frequency band in both conditions (hypothesis 3 b), except for the low oddball condition in the theta frequency band. This illustrates that generally, the sustained periodic stimulation pattern was successful, even though slightly adapted parameters were used compared to previous experiments using this approach (Colon et al., 2017; Leu et al., 2023, 2024; Mulders et al., 2020). The electrode clusters found in the alpha frequency band that showed a modulation of ongoing oscillation were located over the contralateral central-parietal (/sensorimotor) areas, matching previous results using sustained periodic sinusoidal stimulations (Colon et al., 2017; Leu et al., 2023, 2024; Mulders et al., 2020). The electrodes exhibiting a modulation of ongoing oscillations in the beta band were more widespread to frontal electrodes than expected; the previously mentioned investigations found activity within this frequency band to be primarily located at the same central-parietal electrodes as in the alpha band. Nevertheless, the clusters in both frequency bands were fairly consistent in the high and low oddball condition. This was not the case for the theta frequency band; instead of exhibiting a modulation in fronto-central electrodes as expected, activity was observed in an ipsilateral and contralateral parietal cluster (Colon et al., 2017). Electrodes showing a modulation of ongoing oscillations have been inconsistent in previous experiments using similar stimulation parameters (Colon et al., 2017; Leu et al., 2023, 2024); some did not even find a significant modulation at all (Mulders et al., 2020).

Given the behavioral result, we did not expect to see a significant neural response at the $FOS_{oddball}$ (i.e., .125 Hz) in the low oddball condition. Indeed, the main analysis revealed a significant modulation only in the beta frequency band at central and parietal electrodes at the $FOS_{oddball}$ in the high oddball condition (hypothesis 6a). This could indicate that the oddball stimulation cycles were not able to elicit a consistent modulation of ongoing oscillations (hypothesis 6 b), regardless of the stimulation intensity and thus that ratings and neural response would be dissociated from each other in this experiment. Yet, at the time of writing the Stage 1 of this RR, the author team had underestimated the relevance of the harmonics that are inherently present in the frequency representation of a signal. Retter et al. (2021) published a compelling discussion of the importance of these harmonics and provided evidence that, if harmonics are neglected in the analysis, a relevant portion of the neural response is lost. Additionally, they demonstrated that both low stimulation frequencies and non-sinusoidal stimulation patterns led to a larger number of relevant harmonics (Retter et al., 2021). Given our experimental setup, it was thus worth examining the obtained frequency spectra (see Fig. 9) and relevant activity was found at least at the first 2 harmonics of the $FOS_{oddball}$ before the frequency relating to the baseline stimulation (FOS_{base}). We therefore added an exploratory analysis to this RR, which included these two harmonics for the assessment of the response at the $FOS_{oddball}$ (Heinrich et al., 2009; Milton et al., 2020). The results of this exploratory analysis showed a significant modulation of ongoing oscillations at the aggregated oddball frequency (FOS_{ass}) in the high oddball condition for all frequency bands (confirming hypothesis 6a). The lack of such a significant modulation in the low oddball condition (hypothesis 6 b) might indicate that (at least given the present experimental setup and obtained statistical power) stimulus intensity could be the main driving factor behind the magnitude of synchronized neural activity leading to a measurable modulation of ongoing oscillations. We cannot exclude that an adapted experimental design with a larger statistical power would lead to a divergent result.

4.3. Relationship between neural and behavioral responses

While not a primary outcome of this Registered Report, the obtained results invite for a comparison between the obtained neural and behavioral responses. Specifically, this potential relationship is illustrated in the comparison of modulation of ongoing oscillations and variations in the perception of the stimulation in the frequency domain. Both spectra show significant peaks at the $FOS_{oddball}$ in the high oddball condition only, suggesting that perception and modulation of ongoing oscillations are to some extent related to each other. This falls in line with other investigations that found that ongoing oscillations are modulated relative to the (perceived) intensity of the applied stimulation (Hauck et al., 2015; Nickel et al., 2017; Schulz et al., 2015; Tiemann et al., 2015; Wang et al., 2022; Zhang et al., 2012). Yet, just as these other investigations, we were not able to determine to which extent the observed relationship is based on the (perceived) stimulus intensity or saliency.

In closing, we would like to highlight the difficulty of designing an experimental paradigm that is able to

differentiate between stimulus intensity and saliency, two factors that are inherently tied to each other. The "triplet ERP paradigm" is a very elegant solution to this problem, applying triplets of brief laser stimulations at the same intensity and with a predictable inter-stimulus-interval, thereby reducing the saliency of the stimulation with each repetition while keeping the objective intensity constant (Iannetti et al., 2008). Adapting this approach to fit the necessary periodic stimulation parameters to be able to frequency-tag the modulation of ongoing oscillations proved to be a challenge. While in the final paradigm, a rather simple variation of intensity was used to elicit the oddball sensation, we piloted a multitude of alternatives involving changing stimulation surfaces, temperatures and frequencies of stimulation, of which all had serious caveats for the interpretation of the results. Thus, it seems that frequency-tagging is perhaps not the ideal technique to disentangle effects of saliency and intensity in behavioral and neural responses elicited by the thermonociceptive stimulation.

4.4. *Conclusion*

In conclusion, our results suggest that stimulus intensity has a potentially large effect on both the modulation of ongoing oscillations and the stimulus perception elicited by sustained periodic thermonociceptive stimulation. Yet, given the fact that our control condition did not have the desired effects on the behavioral and neural level, we are not able to disentangle to which extent stimulation saliency affected the observed responses. These findings highlight the challenges of unraveling the contributions of saliency and intensity to the modulation of ongoing oscillations by integrating an oddball paradigm into the frequency-tagging approach.

CRediT authorship contribution statement

Chiara Leu: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sébastien Forest:** Writing – review & editing, Software, Methodology, Investigation. **Valéry Legrain:** Writing – review & editing, Methodology. **Giulia Liberati:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

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Scientific transparency statement

DATA: All raw and processed data supporting this research are publicly available: https://doi.org/10.7910/DVN/542CLY.

CODE: All analysis code supporting this research is publicly available: https://doi.org/10.7910/DVN/542CLY.

MATERIALS: All study materials supporting this research are publicly available: https://doi.org/10.7910/DVN/542CLY.

DESIGN: This article reports, for all studies, how the author(s) determined all sample sizes, all data exclusions, all data inclusion and exclusion criteria, and whether inclusion and exclusion criteria were established prior to data analysis.

PRE-REGISTRATION: At least part of the study procedures was pre-registered in a time-stamped, institutional registry prior to the research being conducted: https://osf.io/qbrf2 At least part of the analysis plans was pre-registered in a time-stamped, institutional registry prior to the research being conducted: https://osf.io/qbrf2 The analyses that were undertaken deviated from the preregistered analysis plans. All such deviations are fully disclosed in the manuscript.

For full details, see the *Scientific Transparency Report* in the supplementary data to the online version of this article.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2025.02.009.

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