Temporal contrast enhancement emerges from distinct pain and sound filtering mechanisms

Short Title: Temporal contrast in pain and audition

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Abstract

The human brain continuously processes sensory inputs whose perceptual impact depends on stimulus intensity, salience, and context. Temporal filtering shapes this processing by dynamically modulating neural responses according to stimulus repetition, temporal structure, and predictive contingencies. Higher-order percepts such as pain are likewise a subject to temporal filtering, as exemplified by temporal contrast enhancement (TCE), a stimulation paradigm eliciting pain inhibition. However, given the prevalence of filtering mechanisms across sensory domains, it remains unclear whether TCE is specific to pain or represents a supramodal filtering mechanism. Here, we contrasted behavioral and neurophysiological responses, including electroencephalography and pupillometry, in a TCE paradigm for painful heat versus uncomfortable auditory stimulation. We sought to establish whether TCE generalizes across modalities and bases on similar or distinct underlying neurophysiological processes. Human participants took part in either a purely behavioral investigation (n = 33) or in a neurophysiological and behavioral investigation (n = 29). Both painful heat and loud sounds induced TCE effects, suggesting a supramodal temporal filtering mechanism with modality-specific temporal dynamics. Increasing pupil size and decreasing power of neural alpha oscillations (~10 Hz) with higher painful heat indicate bottom-up modulation of the autonomic nervous system and a release of neural inhibition, respectively. Critically, expectation of pain – but not loud sound – induced an alpha power increase, demonstrating to-down contributions to temporal filtering of pain. However, no direct neurophysiological correlates of subjectively experienced TCE effects were found. Findings suggests that a supramodal temporal filtering mechanism with modality-specific neurophysiological dynamics shapes the processing of aversive stimulation.

Keywords: Temporal Filtering, Temporal Contrast Enhancement, Offset Analgesia, Auditory System, Pain, Sensory Processing

Abbreviations

ANS	Autonomic nervous system
CT	Constant trial
EEG	Electroencephalography
eVAS	Electronic visual analogue scale
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
OT	Offset trial
TCE	Temporal contrast enhancement

Introduction

Human environments contain a plethora of sensory inputs. Sensory integration is a complex process dependent on stimulus intensity, salience and context (1). Therefore, diverse filtering mechanisms are required to selectively enhance specific aspects of stimuli, evaluate their relevance, and modulate their perceptual processing (2,3). Commonly, these filtering mechanisms are divided into spatial and temporal domains of perceived input, which can be observed in all sensory systems (visual (4,5), auditory (6–8) tactile (9,10)). Well-adapted filtering mechanisms help us make accurate and reliable judgements in constantly changing sensory environments (11). Here, we test the hypothesis that temporal filtering in different modalities shares a common perceptual and neurophysiological basis.

Convergences in temporal filtering have been documented across sensory domains. In the context of auditory perception, temporal summation - alternatively referred to as temporal integration (12) or temporal sound summation (13) - describes the phenomena of a perceived loudness increase when a tone of constant volume is presented for a longer duration. Temporal filtering of auditory percepts is of utmost importance, due to its relevance in vocalization and speech recognition (14), as well as in avoiding uncomfortably loud sound. Temporal summation likewise characterizes nociceptive perception (15), where adaptive temporal filtering is vital for averting tissue injury and protecting the organism. Additional similarities can be observed in filtering processes resulting in adaptation to perceived stimulus inputs. Such phenomena can be observed in (acute) pain or auditory adaptation. When an individual is exposed to a constant stimulus within the appropriate context and depending on the stimulus parameters, a reduction in the perceived intensity of the stimulus can be observed (11,16,17). By contrast, when context signals threat, through salience, magnitude, or affective associations, temporal filtering can amplify perception indicated by pain intensification (17,18) or temporal sound summation (13),

77 highlighting the importance of these factors. Additional current evidence indicates temporal
78 filtering processes share similar mechanisms across modalities and sensory systems (19–22).
79 However, despite their high relevance, the extent to which temporal filtering in auditory and pain
80 processing is based on common perceptual and physiological mechanisms is not yet fully
81 understood.

82 Temporal contrast enhancement (TCE), a putative component of the endogenous pain
83 modulatory system, is conceptualized as a temporal filtering process whose mechanisms remain
84 unclear (23–25). Commonly referred to as offset analgesia, is characterized by a disproportionally
85 large reduction in perceived pain in response to a slight decrease in noxious stimulus intensity(25–
86 27). A variety of mechanisms distributed along the neuroaxis have been postulated as potential
87 mediators of TCE. Several brain imaging studies using functional magnetic resonance imaging
88 (fMRI) showed increased activity of cortical structures such as the primary (24,25,28) and
89 secondary (28) somatosensory cortex, ventromedial (25) and dorsolateral (23,24) prefrontal cortex
90 and subcortical structures such as the putamen and nucleus accumbens (23), insula (24,25) and the
91 spinal cord (29) as evidenced by greater blood oxygenation levels during the TCE interval
92 compared to a control condition. Additionally, structures of the brainstem previously linked to
93 descending pain modulation such as the periaqueductal grey and rostro-ventromedial medulla
94 showed increased activity during TCE (25,28,30).

95 Interestingly, studies investigating the temporal dynamics of TCE using
96 electroencephalography (EEG) seem to be lacking in the field. General investigations of both tonic
97 and phasic pain observed in EEG have been conducted, with the main focus being oscillations in
98 the alpha range (~10Hz), showing a prominent pattern of reduced alpha power during tonic and
99 phasic painful stimuli (31–33). This might relate to the proposed functional inhibition of situational
100 irrelevant information (34–38), which is well-established by alpha power modulation in auditory

attention research (39–41). Additional temporally sensitive and objective measures, such as pupillometry, have been used to characterize neurophysiological correlates of pain and auditory processing. Changes in pupil diameter are closely related to autonomic nervous system activity and have been linked to perceived stimulus intensity and arousal, particularly in response to painful stimuli (42,43). In auditory research, pupil dilation has similarly been associated with loudness of the stimuli, salience, and aversiveness (44–46), highlighting its relevance for tracking perceptual and attentional processes.

Here, we hypothesize that the effects of TCE on noxious stimuli may not reflect pain-specific processes but rather could be indicative of a general temporal filtering mechanism in response to salient stimuli. To determine whether observed effects in pain-research are modality specific or merely reflect general arousal, prior studies have employed salience-matched control stimuli; nevertheless the evidence still remains equivocal and the issue remains unresolved (31,47–50). We therefore conducted a multimodal experiment to determine whether TCE is specific to pain. This was achieved by applying painful heat or uncomfortable auditory stimulation using a typical TCE paradigm. The investigation encompassed behavioral and neurophysiological responses (EEG, pupillometry), with the objective of improving our understanding of temporal filtering mechanisms.

Results

A total of 62 healthy volunteers were recruited in this study (behavioral investigation: n = 33, behavioral + neurophysiological investigation: n = 29). All participants tolerated the selected stimulus intensities without difficulty and exhibited no signs of adverse events (see S1 and S2 Tables for details). Figure 1 illustrates the study design. Both investigations used a similar experimental approach to investigate behavioral responses to the TCE paradigm. Thus, the following analysis consists of the combined behavioral data of both experiments. An overview of

stimulation parameters, as well as additional analyses for each individual experiment can be accessed in the Materials and Methods Section and the Supporting Information (S3 – S5 Tables).

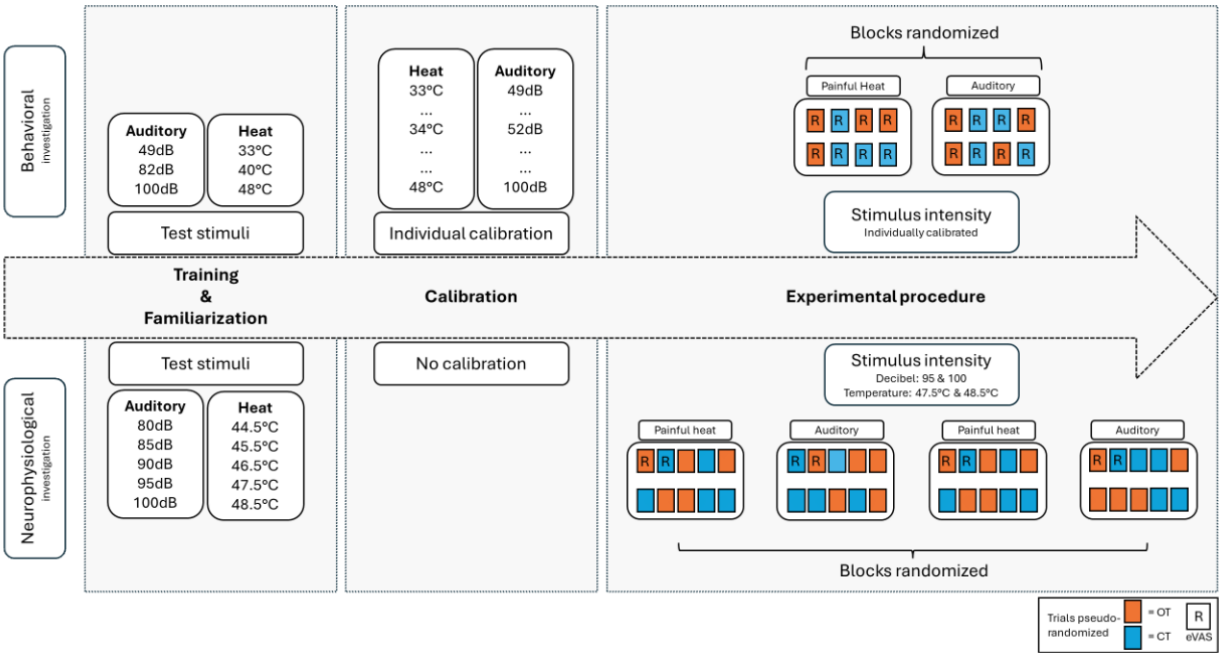


Figure 1. Study design. *Schematic representation of the study design of both experiments. After preparation, participants underwent a training & familiarization phase to accustom to stimuli and the operation of the electronic visual analogue scale (eVAS). In Experiment 1 (top of the figure), stimulus intensities were individually calibrated. The experimental procedure was split into two blocks (1 per modality) consisting of 8 trials with offset (OT) or constant (CT) trials in pseudorandomized sequence. In each trial, participants rated their sensory experience using the eVAS. A two-minute pause was conducted after each trial and a five-minute break was conducted after switching to the other modality. In Experiment 2 (bottom of the figure) fixed stimulus intensities were used. The experimental procedure was split into four blocks (2 per modality) consisting of 10 trials with offset (OT) or constant (CT) trials in pseudorandomized sequence. Each trial was followed by a two-minute break, and after each modality block participants had a five-minute break. The first two trials of each block were fixed to include an OT and CT (being randomized in order) and were used to collect the behavioral response. The remaining 8 trials did not include any eVAS ratings, only collecting neurophysiological responses.*

Temporal contrast enhancement is robust in heat-induced pain and aversive auditory stimulation

Participants were either presented with a sine-tone via headphones (1000 Hz) or with a thermal heat stimulus on the left forearm using a thermal contact stimulator. Stimulation intensity was either constant across a duration of 35 s (constant trial) or increased in the time interval

between 10 and 20 s (offset trial; Figure 2). First, we tested whether participants' ratings of experienced pain (heat) or discomfort (sound) would vary as a function of time interval (T1: 5-10 s, T2: 15-20 s, T3: 25-30 s), trial type (OT: offset trial, CT: constant trial) and modality (heat, auditory). Given a significant main effect of modality and significant interactions involving modality (see S3 Table for details), separate ANOVAs were conducted for each modality.

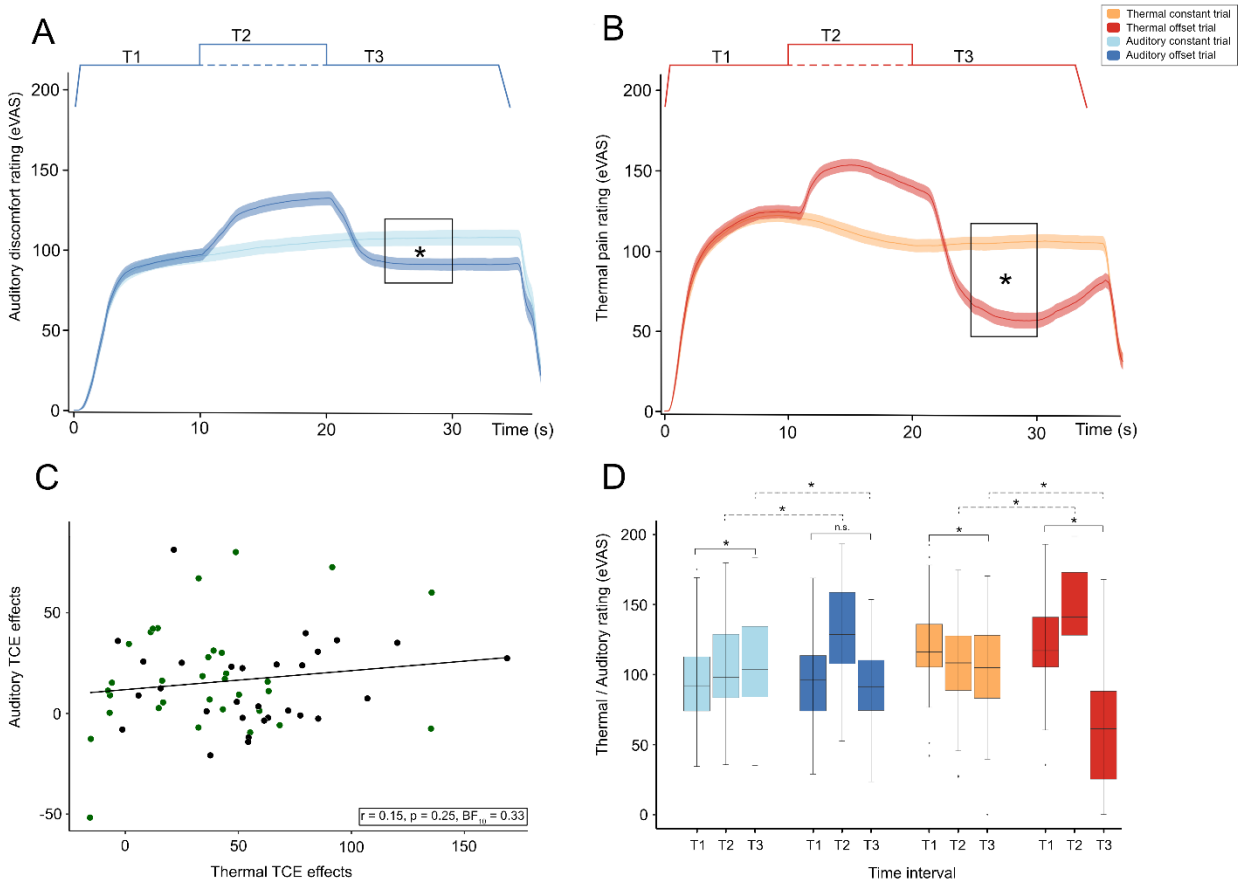


Figure 2: Behavioral Temporal Contrast Enhancement (TCE) response in two modalities*. Means and standard errors of the mean (SEM) for behavioral responses are displayed as obtained by an electronic visual analogue scale (eVAS). Thermal stimulation (A) and auditory stimulation (B) both induced significant (*, p < .05) TCE effects in T3 when comparing offset (OT) (darker colors) and constant (CT) (lighter colors) trials. The correlation of TCE effects (C) (CT-OT at T3) (green = behavioral experiment, black = neurophysiological experiment) between both modalities was not significant. Boxplots of eVAS ratings (D) for each of the four conditions split into three relevant time intervals (T1: 5-10s, T2: 15-20s, T3: 25-30s). Significant (p < .05) within-modality comparisons indicated by solid lines, between-modality comparisons indicated by dashed lines.*

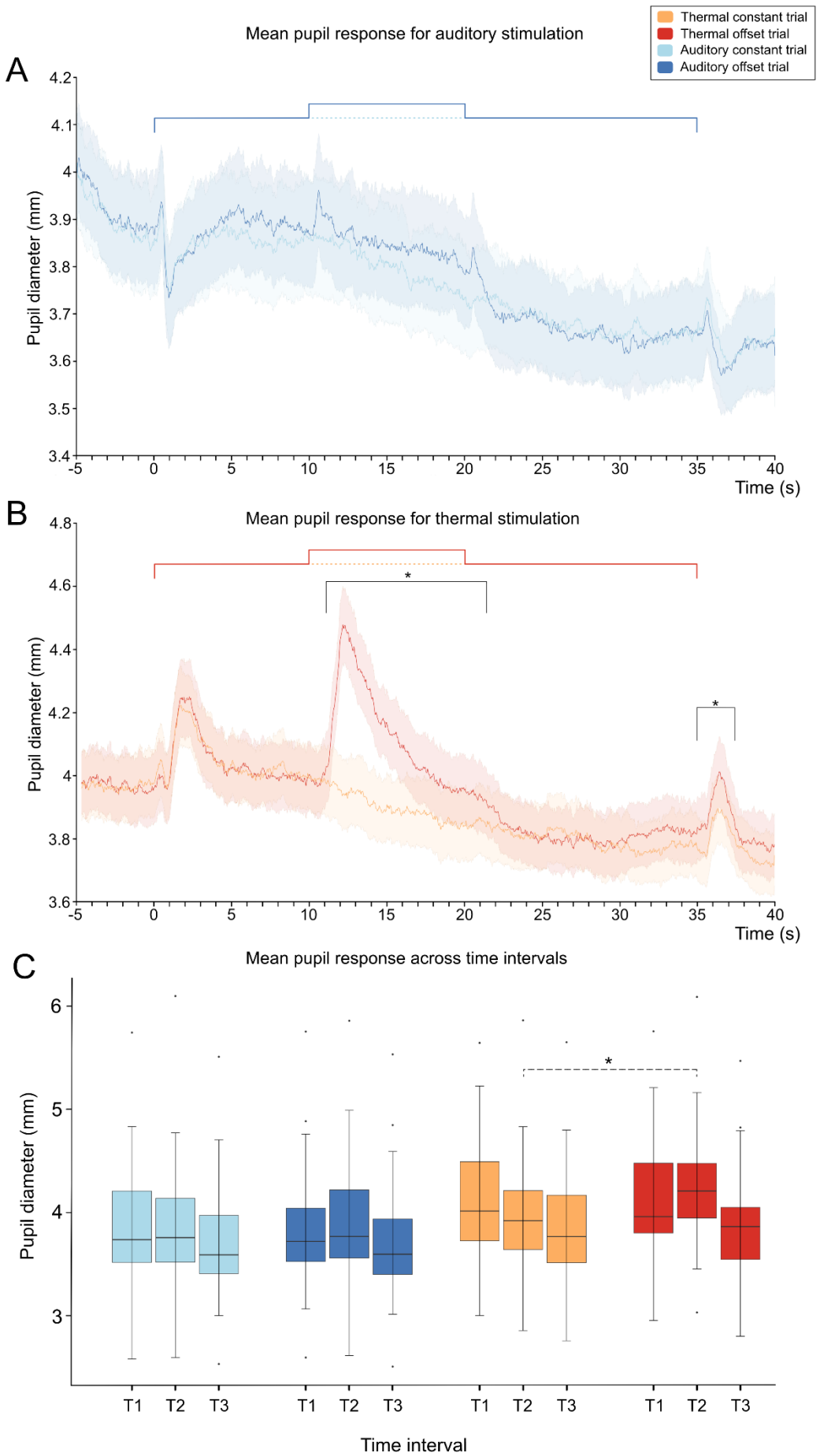
ANOVAs revealed interactions of time interval x trial type for auditory ($F(2, 122) = 102.39$, $p < 0.001$, $\eta_p^2 = 0.63$) and thermal ($F(2, 122) = 186.55$, $p < 0.001$, $\eta_p^2 = 0.75$) stimulation.

Comparing trials using false discovery rate (FDR) -corrected post-hoc testing for auditory stimulation revealed no difference between OT and CT during T1 ($p = 0.71$). However, we found significantly higher discomfort ratings for OT vs. CT in T2 ($p < 0.001$) and a reversal of this difference in T3 ($p < 0.001$), indicating that a return to the stimulus intensity of T1 induced a significant TCE effect in the interval of interest (T3). Similarly, post hoc testing for thermal stimulation showed no difference between OT and CT during T1($p = 0.30$), but significantly higher pain ratings for OT vs. CT in T2 ($p < 0.001$) and a reversal of this difference in T3 ($p < 0.001$). These findings demonstrate that TCE – a significant and disproportionate reduction in perceived intensity following a brief decrease in stimulus intensity – occurs for both, painful heat and aversive auditory stimulation.

Having established behavioral TCE effects for thermal and auditory stimulation, we next tested the association between the two. Across participants, TCE effects (i.e. the OT - CT difference in T3) were not significantly correlated between auditory and thermal stimulation ($r = 0.15$, $p = 0.25$; $BF_{10} = 0.33$), indicating a modest tendency of the results to be in favor of the null hypothesis. Additionally, to test temporal filtering within each modality, we calculated dependent-samples t-tests comparing T1 and T3 within each trial type. For auditory stimulation, we found significantly lower discomfort ratings in T1 compared to T3 despite constant stimulation (CT; $t(61) = -5.69$, $p < 0.001$, $d_z = 0.40$, $M_{DIFF} = -14.32$), indicating temporal loudness summation. However, no difference between T1 and T3 was found for offset trials (OT; $t(61) = 0.93$, $p = 0.36$, $d_z = 0.08$, $M_{DIFF} = 2.46$). To the contrary, for thermal stimulation, pain ratings decreased from T1 to T3 despite constant stimulation (CT, $t(61) = 5.05$, $p < 0.001$, $d_z = 0.45$, $M_{DIFF} = 14.53$), indicating temporal adaptation. Furthermore, a pronounced decrease in pain ratings from T1 to T3 was observed for offset trials (OT, $t(61) = 12.17$, $p < 0.001$, $d_z = 1.74$, $M_{DIFF} = 62.57$), resulting in a strong TCE effect. A visual representation of changes over time using boxplots can be seen in **Fehler! Verweisquelle konnte nicht gefunden werden.**.

Pupil size reflects perception of pain but not auditory discomfort

We next examined the event-related pupil dilation (Figure 3) to determine whether TCE is accompanied by modality-dependent autonomic modulation, contrasting auditory versus thermal stimulation. Similarly to the behavioral data, the main effect modality and all interaction effects including modality reached significance ($p < 0.001$; S6 Table). For auditory stimulation, we found a significant main effect of 'time' ($F(2, 56) = 32.67$, $p < 0.001$, $\eta_p^2 = 0.54$). FDR corrected post hoc testing revealed significant reduction in the pupil size for T3 vs. T2 ($p < 0.001$), T3 vs. T1 ($p < 0.001$) but not for T2 vs. T1 ($p = 0.74$). This indicates a gradual decrease in pupil size during the trial.


A
Mean pupil response for auditory stimulation
Thermal constant trial
Thermal offset trial
Auditory constant trial
Auditory offset trial
Pupil diameter (mm)
Time (s)
B
Mean pupil response for thermal stimulation
Pupil diameter (mm)
Time (s)
C
Mean pupil response across time intervals
Pupil diameter (mm)
T1 T2 T3 T1 T2 T3 T1 T2 T3 T1 T2 T3
Time interval

193

Figure 3 Mean pupil response over time. *Mean pupil diameter (mm) over time was measured for auditory (A) and thermal (B) stimulation. Thermal stimulation induced significant changes (*, p < .05; cluster-based permutation test) in the pupil diameter when comparing offset trials (OT, darker colors) with constant trials (CT, lighter colors). No significant clusters could be identified for auditory stimulation, despite visually observable changes to stimulus onset and offset. The timing of the stimulation intensity is displayed as a solid (OT) and dashed (CT) line at the top of the figure and was similar for both modalities. Mean pupil diameter (mm) for each condition (C) split into three time intervals (T1: 0-5s, T2: 15-20s, T3: 20-25s). Significant (p < .05) between-modality comparisons indicated by dashed lines.*

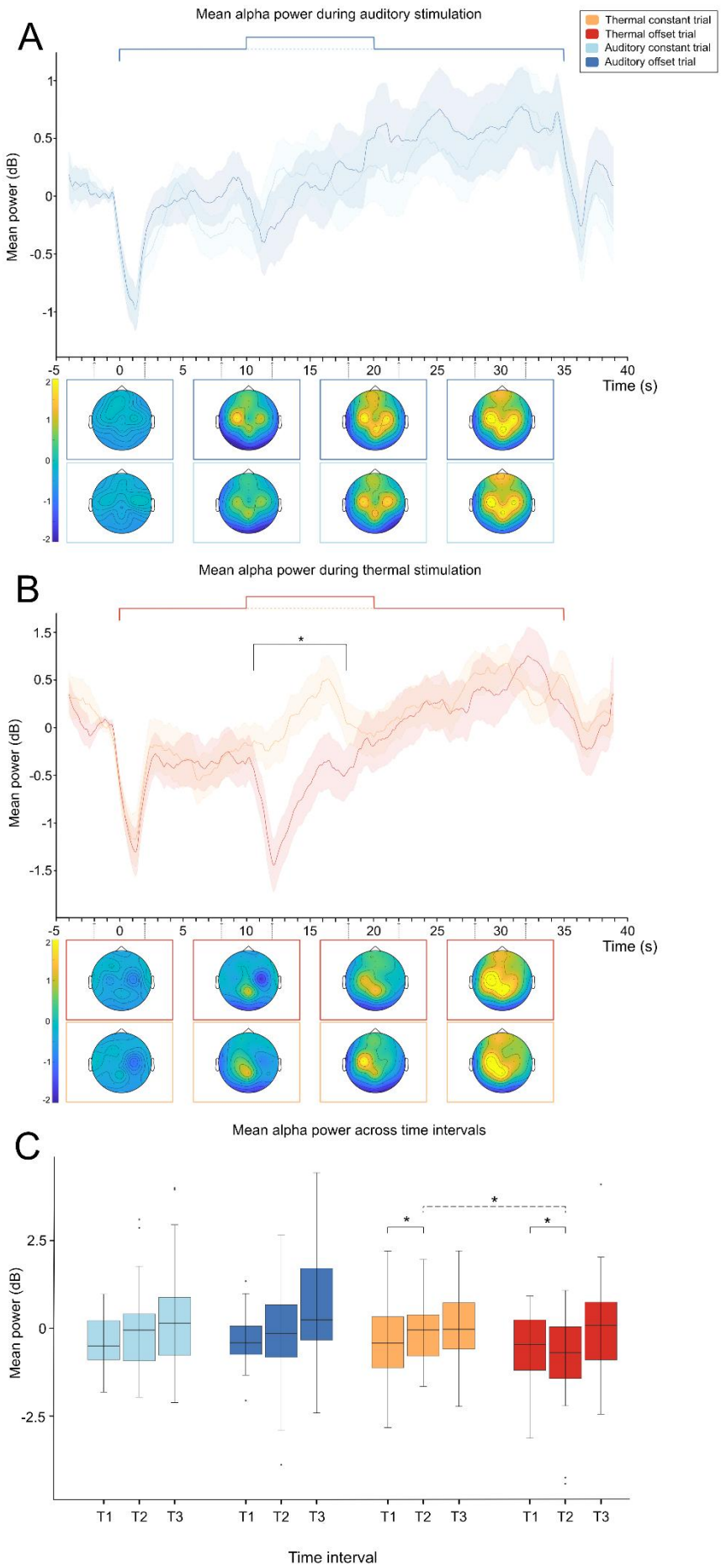
For thermal stimulation, there was a significant interaction effect of 'trial type' and 'time' ($F (2, 56) = 64.35$, $p < 0.001$, $\eta_p^2 = 0.70$). Comparing trial types at different time intervals, we found significantly enhanced pupil size for OT vs. CT in T2 ($p < 0.001$) but not in T1 ($p = 0.88$) and T3 ($p = 0.08$). In addition to these planned statistical analyses, we performed exploratory cluster based permutation test (51), comparing OT and CT during the entire trial time course (see Figure 3).

Neural alpha power reflects pain sensation and expectation

Finally, we tested whether commonalities and differences in behavioral TCE effects for thermal versus auditory stimuli were reflected in neural oscillatory EEG responses (Figure 4). For data analysis, we used baseline-corrected time frequency representations of oscillatory power, averaged across selected channels and frequencies in the alpha range (7–13 Hz) for the defined time bins of interest (for details, see Materials and methods). A visual representation of the event-related potential can be accessed in the Supporting Information (S8 Fig. and S9 Fig.).

We first calculated a combined repeated-measures ANOVA including both modalities (painful heat & aversive sound), which can be accessed in the Supporting Information (S7 Table). Unlike the pupillometry and behavioral results, interactions involving modality did not reach significance (all $p > 0.1$). For interpretability, we nonetheless conducted two modality-specific 2 (trial type) x 3 (time interval) ANOVAs. For auditory stimulation, the analysis revealed a significant main effect of 'time' ($F (2, 56) = 9.92$, $p < 0.001$, $\eta_p^2 = 0.26$), while thermal stimulation displayed a significant interaction effect of 'trial' and 'time' ($F (2, 56) = 5.91$, $p = 0.005$, $\eta_p^2 =$

0.17). Comparing the different time intervals in auditory simulation with FDR corrected post-hoc tests showed a significant difference in alpha power between T1 and T2 ($p = 0.033$), T2 and T3 ($p = 0.004$), and T3 and T1 ($p = 0.004$), indicating an overall alpha power increase over time. The interaction effect in thermal stimulation was driven by a significant difference between OT and CT only for T2 ($p = 0.002$) but not for T1 ($p > 0.05$) and T3 ($p > 0.05$).


A
Mean alpha power during auditory stimulation
Thermal constant trial
Thermal offset trial
Auditory constant trial
Auditory offset trial
Mean power (dB)
Time (s)
B
Mean alpha power during thermal stimulation
Mean power (dB)
Time (s)
C
Mean alpha power across time intervals
Mean power (dB)
T1
T2
T3
Time interval

226

Figure 4: Mean alpha power over time for both modalities. *Auditory (**A**) and thermal (**B**) stimulation-induced mean alpha power (7–13 Hz) averaged across centro-occipital electrodes (P7, P3, O1, C3, POz, Pz, CPz, P8, P4, O2, C4). Topographic maps show spatial distributions of alpha power at time points 0, 10, 20 and 30 seconds (color limits: yellow = +2dB, blue = –2dB). Comparing alpha oscillatory power during Offset (OT) (darker colors) and Constant (CT) (lighter colors) trials using cluster-based permutation tests resulted in significant (*, p < .05) differences only during thermal stimulation. Mean (alpha) power for each condition (C) split into the three time intervals of interest (T1: 0-5s, T2: 10-15s, T3: 20-25s). Significant (p < .05) within-modality comparisons indicated by solid lines, between-modality comparisons indicated by dashed lines.*

Notably, significant alpha modulation in the T2 interval for thermal stimulation was attributable to two distinct underlying mechanisms reflecting the occurrence and expectation of the stimulus (Figure 5). To differentiate these, we performed post-hoc testing to compare a baseline interval during T1 (5–10 s) to the time interval wherein a cluster-based permutation test revealed a significant difference for OT vs. CT (10.6 - 17.8 s; see Figure 4). First, the increase in thermal stimulation intensity induced an alpha power decrease in OT trials, resulting in significantly lower alpha power compared to T1 ($t(28) = -2.61$, $p = 0.015$, $d_z = 0.48$, $M_{DIFF} = -0.40$). Second, an omission of the expected increase in thermal stimulation intensity induced an alpha power increase in CT trials compared to the baseline interval during T1 ($t(28) = 3.34$, $p = 0.002$, $d_z = 0.62$, $M_{DIFF} = 0.49$). These findings demonstrate that temporal filtering of pain sensation (but not auditory discomfort) reflects both stimulus-driven (bottom-up) and expectation-driven (top-down) mechanisms.

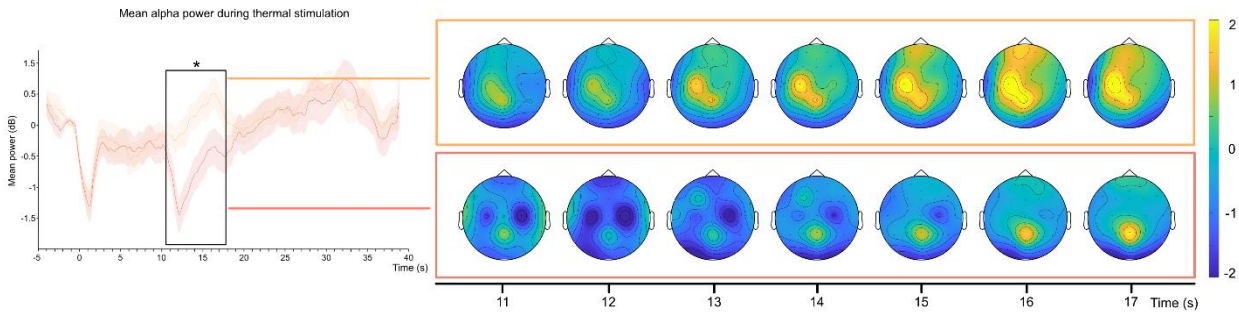


Figure 5: Topographic distribution of alpha power. *Stimulation-induced mean alpha power (7–13 Hz) averaged across centro-occipital electrodes (P7, P3, O1, C3, POz, Pz, CPz, P8, P4, O2, C4). Topographic maps show spatial distributions of alpha power at the significant time point (11 sec – 17 sec, one topography per second) of a cluster-based permutation test (* p < .05) comparing offset (OT) and constant (CT) trials (color limits: yellow = +2dB, blue = –2dB).*

Discussion

Temporal filtering operates across sensory modalities, including vision, audition, and pain perception (20,21). Here, we aimed to delineate behavioral and (neuro-)physiological substrates of temporal filtering and to assess its specificity to pain and unpleasantness. To this end, we employed the phenomenon of temporal contrast enhancement, a temporal filtering mechanism thought to underlie offset analgesia (26). TCE was elicited by pain-inducing heat and aversive sounds, indicating a supramodal temporal filtering process with distinct temporal dynamics across modalities. Pupil dilation, indexing autonomic nervous system activation, and alpha-band oscillations, reflecting cortical inhibition, were both modulated by temporal increases in noxious heat but not by auditory stimulation. These findings suggest pain-specific temporal filtering acting on both the processing of painful input and its temporal expectation.

Modality-specific processes underlie temporal contrast enhancement

Consistent with prior evidence, we were able to successfully induce TCE using thermal stimulation. Noxious heat is known to produce robust TCE effects, indicated by statistically significant decreases in pain sensation following a short heat offset (52). To our knowledge, this is the first experiment investigating TCE using non-painful aversive auditory stimuli, demonstrating that TCE reflects a modality-general (i.e., supramodal) mechanism of afferent contrast filtering rather than a nociception-specific process. In addition to domain-general effects, we observed modality-specific patterns in subjective ratings, suggesting intricate processing differences between modalities during the stimulation paradigm. When comparing different time intervals (T1 vs. T3) during constant stimulation, we found pain ratings decreasing over time while the opposite was observed for subjective auditory discomfort ratings. We argue that these results represent two different temporal filtering mechanisms. First, adaptation to pain, which is well-

known to be induced by tonic heat (16,53). Second, temporal sound summation, reflecting neural integration of auditory energy over time (12,13).

Comparing ratings between time windows of interest for offset trials, we found a typical decrease in perceived pain following heat offset (T3) compared to baseline (T1). In the auditory modality, however, the same contrast was not significant, suggesting a differently constituted TCE effect. Here, TCE was driven by a gradual increase in TSS during constant stimulation, which was absent during offset trials, thereby yielding a comparable overall TCE magnitude. Taken together, these results indicate temporal pain inhibition but an absence of such an effect for auditory stimulation. Importantly, the dissociation of underlying generators of TCE effects for pain and auditory stimulation receives further support from the absence of a correlation between TCE effects, suggesting partly independent generators of what appears like a common filtering mechanism.

Neurophysiological signatures of filtering perception of pain and auditory discomfort

Alongside subjective behavioral responses, we collected objective neuro(physiological) measures (pupillometry and EEG) aiming to better understand the differences between the observed TCE effects for auditory vs. thermal stimulation. Thermal stimulation induced significant differences in pupil size between OT and CT in T2, the interval with the highest stimulus intensity. Reactive increases in pupil diameter to pain-inducing stimuli may reflect autonomic nervous system (ANS) activation, specifically sympathetic arousal associated with heightened awareness and the fight-or-flight response, as observed in previous studies on pupillary responses to pain (43,54–57). Our observed phasic increases in pupil diameter likely reflect bottom-up processes induced by increases in stimulus temperature and are in line with previous research (58). However,

297 auditory stimulation did not display such trial type-specific differences, only eliciting significant
298 decreases of pupil diameter over time. This suggests that auditory discomfort did not elicit sizeable
299 modulation of activity in the ANS. Possible explanations for this difference could be factors such
300 as stimulus intensity or salience, with painful stimulation arguably resulting in a higher perceived
301 threat level compared to auditory stimulation, hence inducing far greater changes in pupil
302 diameter.

303 Consistent with the pupillary dynamics, time–frequency EEG analyses revealed a similar
304 modality-specific pattern: thermal stimulation elicited a significant alpha power reduction during
305 offset trials in T2, which was not observed for auditory stimulation. A reduction of alpha power in
306 response to painful stimulation is in line with previous reports of alpha decreases accompanying
307 increased pain perception (31,32,59). Moreover, when comparing T1 and T2 in OTs, we observed
308 a significant alpha desynchronization, reflecting bottom-up processes associated with increased
309 stimulus intensity. In contrast, CTs exhibited significant alpha synchronization (i.e., an alpha
310 power increase) that may reflect top-down processes, possibly induced by expectation of an
311 increase in painful stimulation. This agrees with prior research observing top-down processes
312 influencing alpha oscillations (60). For auditory stimulation, we hypothesized similar spatial and
313 temporal patterns of oscillatory activity; however, no significant changes in alpha power were
314 observed for either stimulation pattern. Given the comparable stimulation paradigm employed in
315 both modalities, one could expect that participants would manifest a comparable increase in alpha
316 power, driven by the anticipation of a change in stimulus intensity. However, no such effects were
317 observed, which lends further support to the view that the neural modulation and representation of
318 auditory discomfort differ from that of painful stimulation.

319 Interestingly, we did not observe any neurophysiological changes mirroring the TCE effect
320 that we observed in behavior. Neither pupillometry, nor EEG displayed any significant

321 modulations by trial type (OT vs. CT) during T3. Based on literature showing a robust link between
322 tonic pain and reduced alpha oscillatory power, we hypothesized that the TCE effect would elicit
323 measurable changes in alpha activity—potentially an alpha increase reflecting the experienced
324 relief - as it has been reported for placebo analgesia (61,62). Contrary, we did not observe any
325 representation of the behavioral TCE effects in neural recordings. One plausible explanation could
326 be that the brain regions responsible for processing or mediating TCE are mainly located
327 subcortically, which would be less accessible to surface EEG. Previous fMRI studies have reported
328 changes to activity in the insula (24,25), structures of the brainstem (25,28), putamen and nucleus
329 accumbens (23) or the spinal cord (29). It might thus be that these structures are more relevant to
330 the construction of TCE compared to the more superficially located ones. Furthermore, one should
331 be cautious expecting identical findings when comparing fMRI to EEG, since both imaging
332 techniques show distinct sensitivities to neural and hemodynamic processes, temporal and spatial
333 resolution, and often can display different correlations depending on measured frequencies
334 (63,64). Additionally, subjective experiences such as changes in pain perception may not always
335 align with objective indices, which could be the case for TCE. Our pupillometry findings provide
336 partial support for this hypothesis, since both modalities displayed temporal filtering as evidenced
337 by decreases in pupil diameter over time. However, these temporal patterns did not correspond
338 with the observed patterns in the subjective domain, where only pain decreased over time, but
339 auditory discomfort increased. However, to our knowledge, studies investigating TCE employing
340 objective measures besides fMRI are scarce (65–67) making it difficult to assess the extent to
341 which subjective and physiological responses to TCE diverge and whether our findings reflect
342 such an incongruence.

343 We replicated robust behavioral TCE responses in both investigations using individually
344 calibrated and fixed-stimulus approaches. For the neurophysiological investigation, we adopted
345 the fixed-stimulus approach, as our first study and previous work indicate that it is better suited

346 for assessing neurophysiological outcomes (68,69). However, this approach may have led to a
347 lower perceived stimulus intensity, which could have potentially reduced our observed effects,
348 especially in pupillary reactions to auditory stimuli. Regardless, we could not have increased the
349 stimulation intensity further since this could have meant potential harm to the participants (70).
350 Nonetheless, we would attribute the smaller changes in pupil diameter to auditory stimulation, to
351 the underlying aversiveness and threat level that painful stimuli impose on the organism. In
352 addition, modality-specific patterns of temporal dynamics were observed, particularly represented
353 in the behavior of participants. An identical stimulation paradigm was employed for all trials,
354 enabling direct comparison between modalities and providing a common framework for
355 interpreting differences in temporal filtering dynamics. As demonstrated in previous research,
356 TCE has been consistently identified as a highly robust filtering mechanism in pain. TCE effects
357 can be induced with a variety of stimulus intervals, temperature changes and even repeated instead
358 of tonic stimuli (52,71,72). However, future research could benefit from the use of variable
359 stimulus sequences to further improve our understanding of these supramodal temporal filtering
360 dynamics, driving TCE across modalities. Additionally, future research should aim to characterize
361 the temporal dynamics of TCE in different sensory modalities without compromising spatial
362 resolution, ideally incorporating approaches that target subcortical regions potentially underlying
363 the effect. Further exploration of pain-specific paradigms, and of potential shared filtering
364 mechanisms across sensory modalities, may provide deeper insight into how such processes shape
365 perceptual experience in our multisensory environment.

366 Conclusion

367 In this study, we probed the specificity of temporal contrast enhancement to pain. We
368 successfully induced TCE using pain-inducing heat but also auditory stimulation, suggesting the
369 existence of a supramodal temporal filtering mechanism. However, divergences in temporal

370 filtering dynamics indicate that adaptation to pain, but temporal summation of sound underlie
371 contrast enhancement. Modality-specific modulations in pupil size and neural oscillations indicate
372 that painful heat – but not auditory – stimulation increases activity of the ANS and neural
373 representation of an occurring, as well as an expected but omitted increase in stimulation intensity.
374 These findings demonstrate the intricate dynamics of temporal filtering mechanisms and their
375 (neuro)physiological basis.

376 Materials and methods

377 Behavioral investigation of the TCE effect in auditory stimulation

378 Participants

379 Participants (n = 33, 22f; age = 23.7, SD = 6.0) were included if they subjectively reported
380 being healthy and pain-free on the day of the procedure. Exclusion criteria were chronic pain (> 3
381 months) within the last two years, diagnosed systemic, neurological, cardiovascular or psychiatric
382 diseases and being with diagnosed hearing loss or tinnitus. All participants were asked not to take
383 any painkillers, consume alcohol or undertake any strenuous physical activity 24 hours before
384 participating in the study. To characterize the study sample age, sex at birth, body mass (kg),
385 stature (cm), handedness and general fear of heat pain and fear of loud noises on a numerical rating
386 scale from 0 (no fear) to 100 (highest possible fear) were recorded for each participant. To measure
387 noise sensitivity the Weinstein Noise Sensitivity Scale (WNSS) was used (73). In addition, the
388 Pain Vigilance and Awareness Questionnaire (PVAQ) was used to measure attention to pain and
389 assesses awareness, consciousness, vigilance, and observation of pain (74) and the Pain
390 Catastrophizing Scale (PCS) was used to assess the catastrophizing behavior (75).

The study was approved by the Ethics Committee of the University of Lübeck (2023-633) and conducted in accordance with the Declaration of Helsinki. The methodology was preregistered on the Open Science Framework (OSF; https://osf.io/643kg).

Equipment

All heat stimuli were applied with a thermal contact stimulator (TCS; André Dufour, University of Strasbourg, France). The probe of the TCS has a total stimulation zone of 9 cm^2 (five equal stimulation zones, each 0.74 x 2.4cm = 8.88cm^2) and was applied to the left forearm. The probe weighs 440g and the TCS has a temperature range of 0°C to 60°C, adjustable at 0.1°C intervals. The maximum temperature rise and fall rate is 100°C/second. For auditory stimulation, a 1000-Hz sine wave tone sampled at 44.100Hz, generated using Adobe Audition (Adobe Systems Software, Dublin, Republic of Ireland), was applied. The sound was presented using over-ear headphones (PXC 550-II, Sennheiser, Wedemark, Germany). Probing pain intensity was conducted with a Python-based eVAS (76,77). The eVAS was displayed using a computer and ranged from 0 "no sensation" to 200 "worst heat pain imaginable", while a value of 100 represented the “pain threshold” for thermal stimulation. For auditory stimulation, the same eVAS was used but it displayed different anchors, 0 representing “no sound audible”, 200 being “maximum discomfort imaginable” and 100 representing the “discomfort threshold”.

Familiarization and calibration procedure

Before attending the main part of the experiment, participants were familiarized to the rating procedure and stimulus intensities. For this, they received three different stimulus intensities, a high (48°C, 100dB), low (33°C, 49dB) and an intermediate (40°C, 82dB) level of intensity for thermal and auditory stimulation, respectively. Afterwards, the stimulation intensities for each modality were calibrated, using a staircase procedure (S10 Fig. in the Supporting

414 Information). Participants were asked to continuously rate their sensory experience using the
415 eVAS scale. The calibration consisted of ascending stimulation intensities, where each stimulation
416 was applied for ten seconds, followed by ten seconds of either no stimulation (0dB) or baseline
417 temperature (32°C) depending on the applied modality. The stimulation started at either 33°C or
418 49dB and increased in 1°C or 3dB steps up until the highest stimulation intensity of 48°C or 100dB
419 was reached. This procedure was repeated for each modality with the modalities being alternated.
420 The stimulation intensities were then derived from the second iteration of each modality by using
421 stimulation intensities that produced perceived pain intensities of 150/200 and 175/200 on the
422 eVAS. These values were used for the initial stimulation intensity (T1) and increase in stimulation
423 intensity (T2) in offset trials (see Experimental paradigm). Mean heat pain that corresponded to
424 150 points on the 0- to 200-point eVAS was 46.4°C (SD 0.8°C) and 47.4°C (SD 0.8°C) for 175/200
425 points respectively. Mean sound stimulation parameters for 150/200 and 175/200 eVAS ratings
426 were 90.8dB (SD 8.0dB) and 95.0dB (SD 7.5dB), respectively.

427 **Experimental paradigm**

428 A TCE paradigm with three successive periods (T1-T2-T3) consisting of an OT and a CT
429 was performed (78). CTs were administered for a duration of 35 seconds, during which continuous
430 heat or sound stimulation was applied at a calibrated intensity corresponding to 150/200 on the
431 eVAS. The OTs consisted of an intensity corresponding to 150/200 (T1), followed by ten seconds
432 of 175/200 (T2) and then decreased back to the stimulation intensity of T1 for 15 seconds (T3).
433 Rise and fall rates were kept constant (100°C/s). Each trial was performed four times (4x OT, 4x
434 CT) with a break of 2 min in between the trials. The order of trials was pseudorandomized in a
435 counterbalanced manner.

436 Participants continuously rated the experienced pain intensity throughout each trial and
437 were instructed to attend carefully and indicate even very subtle sensations or changes. This

procedure was repeated once for each modality, resulting in a total of 16 trials per participant. All trials were completed for one modality before the other modality was tested. This transition was preceded by a 5-min interval of no stimulation to reduce possible carry-over effects.

Statistical analysis

Sample size calculation was based on the previously described OA effect size (78). With an estimated effect size of $d_z = 0.76$ (27), an estimated group size of $n = 25$ participants for paired comparisons (two-sided t-test, $\alpha = 5\%$) was required to reach statistical power of 95% (G*Power, University of Düsseldorf) (79). To preserve planned power, improve precision, and mitigate sex imbalance, we prospectively oversampled to n=33 (80).

Statistical analyses were performed using R Studio (RStudio version 2024.04.11 with R version 4.5.0, R Foundation for Statistical Computing, Vienna, Austria) (81) and MATLAB (The Mathworks Inc., 2024) (82) Parametric data is presented in means ($\bar{x}$) with standard deviations (SD) and nonparametric data in median (M) with ranges (R) or absolute and relative frequencies. The average eVAS ratings were obtained for each time interval (T1, T2 and T3). The first 5s of T1, T2 and T3 and the last 5s of T3 were not considered in our analysis. This is an approach we have chosen before to consider the delay in pain response and extract stable pain ratings (83,84). We calculated a 2x3 repeated measures ANOVA with the factors 'trial' (CT, OT) and 'time' (T1, T2, T3). If there were significant findings, FDR corrected (85,86) t-tests were performed. The level of significance was set at $p < 0.05$. We deviated from our initial analysis plan (dependent t-tests) in the preregistration to achieve more coherence in context of the analysis of the second study. An additional ANOVA analysis including both modalities in a 2 x 2 x 3 ANOVA can be accessed in the Supporting Information (S4 Table).

Neurophysiological expression of TCE in auditory and thermal stimulation

In this experiment, we aimed to investigate neural and autonomic nervous system responses using a similar stimulation paradigm and the same modalities as explained above. For this, we collected EEG data, pupillometry data and behavioral ratings. The study was approved by the Ethics Committee of the University of Lübeck (2023-633) and conducted in accordance with the Declaration of Helsinki. Again, the methodology was preregistered on the Open Science Framework (OSF; https://osf.io/v37mp).

Participants

A total of 29 healthy participants (sex = 19f; age = 24.6, SD = 5.7) were used for analysis. In- and Exclusion criteria were similar for both experiments. None of the volunteers that participated in the behaviorally focused experiment were recruited for the second experiment.

Equipment

The same stimulation equipment as in the previous experiment was used for all procedures. Behavioral data were collected using an eVAS similar in style and anchors, but the visual presentation, data collection and stimulus control was achieved using MATLAB (The Mathworks Inc., 2024). For visual presentation purposes, the psychophysics toolbox (87) was used. The EEG was recorded at 24 passive scalp electrodes (SMARTING, mBrainTrain, Belgrade, Serbia) at a sampling rate of 500 Hz (DC to 250 Hz bandwidth), referenced against electrode FCz. Electrode impedances were kept below 10 kΩ. The amplifier was attached to the EEG cap (Easycap, Herrsching, Germany) and the EEG data were transmitted via Bluetooth to a nearby computer, which recorded the data using the Smarting Streamer (Version 3.4.2). For pupillometry, a Tobii

482 X3-120 Eye Tracker (Tobii Technology Inc., Stockholm, Sweden) was used with sampling rate of
483 120Hz. Pupillometry data were directly recorded via MATLAB.

484 Familiarization and calibration procedure

485 Contrary to the first experiment, we did not individually calibrate the stimuli. This
486 approach was chosen due to the robust effects seen in the first experiment. Furthermore, the
487 application of constant stimulation intensities ensures uniform stimulus input across all
488 participants, a feature that assumes greater significance in the context of neurophysiological
489 investigations (68). We derived stimulus intensities from mean values of the stimulation
490 parameters of the behavioral experiment. The initially derived stimulation parameters from the
491 first experiment that were used for thermal stimulation led to major pain habituation effects
492 resulting in close to zero pain felt by the participants after a few trials. Due to this, we increased
493 the temperature by 1.5°C (initially 46°C and 47°C) to reduce these habituation effects. The
494 participants (n = 11) that received the stimulation protocol prior to this change were excluded from
495 the analysis. In order to account for the missing practice using the eVAS, the participants
496 underwent a brief familiarization procedure. This procedure comprised five stimuli in ascending
497 order, either starting from 44.5°C for thermal stimulation and increasing in 1°C steps or starting
498 from 80dB and increasing in 5dB steps. Each stimulus was presented for 10 seconds and then
499 followed by a 10-second pause (matching the calibration procedure from the first experiment).

500 Experimental paradigm

501 The TCE paradigm was the same as the one used for the behavioral investigation but
502 consisted of fixed stimulation intensities of 47.5°C or 95dB for T1, 48.5°C or 100dB for T2 and
503 47.5°C or 95dB for T3, respectively. Each modality was tested twice, and each stimulation block
504 consisted of ten trials. The first two trials per block were designated as an OT or CT, with the

objective of collecting behavioral data. Participants were tasked with continuously rating their perceived stimulus intensity. For the remaining eight trials, participants were instructed to maintain their gaze on a fixation cross, focusing on their sensory experience without moving. The order of trials was pseudorandomized to a matching number of trials per block. Each "modality block" was followed by a 5-min break and then alternated to the other modality. For an overview of the procedure, consult Figure 1.

Statistical analysis

The determination of sample size was based on the effect sizes derived from the first experiment. For the auditory modality, an effect size of $d_z = 0.64$ (thermal $d_z = 1.09$), with statistical thresholds set at alpha = 0.05 and beta = 0.1 (90% power), indicated an estimated sample size of 28 participants. Due to the mentioned changes in temperature (see Familiarization and calibration procedure) and the exclusion of 11 participants that were previously recorded the final sample size for analysis was n = 29.

Statistical analyses were performed using R Studio (RStudio version 2024.04.11 with R version 4.5.0, R Foundation for Statistical Computing, Vienna, Austria) (81) and MATLAB (82). Parametric data is presented in means ($\bar{x}$) with standard deviations (SD) and nonparametric data in median (M) with ranges (R) or absolute and relative frequencies. We calculated a 2x3 repeated-measures ANOVA with the factors 'trial' (CT, OT) and 'time' (T1, T2, T3). If there were significant effects, FDR corrected (85,86) post-hoc t-tests were performed. The level of significance was set at $p < 0.05$. An additional ANOVA analysis including both modalities in a 2 x 2 x 3 ANOVA can be accessed in the Supporting Information (S5 Table). For behavioral data analysis, the extracted time intervals matched the ones chosen in the first study. For the analysis of EEG and pupillometry data, we shifted the extracted time intervals to right after onset of the

stimulus, since we did not expect any delay in response compared to the behavioral data, resulting in T1 being 0-5s, T2 being 10-15s and T3 being 20-25s.

EEG preprocessing and analysis

The continuous EEG data were high-pass (1 Hz) and low-pass filtered (100 Hz), re-referenced to the average reference across all electrodes, and epoched from –5 to +40s relative to the onset of auditory/thermal stimulation. An independent component analysis (ICA) was used to remove components related to eye-blinks, eye-movements and muscle activity. Remaining artefactual epochs were removed afterwards by visual inspection. All data analyses were carried out in Matlab (R2024b), using custom scripts and the Fieldtrip toolbox (88). Time-frequency oscillatory power representations of single-trial EEG data were obtained using Fast Fourier Transform (FFT) with multi-tapering (DPSS, discrete prolate spheroidal sequences) for a moving time window (length: 2s; moving in steps of 0.1s through the trial) for frequencies 1–80Hz in steps of 1 Hz with 2Hz spectral smoothing.

Pupillometry preprocessing

Similarly to EEG analysis, we used Fieldtrip (88) to conduct the necessary preprocessing steps for the pupillometry data. First, samples reflecting physiologically implausible pupil changes were identified using a velocity-based criterion: data points whose dilation speed exceeded three standard deviations above the mean velocity within each trial were marked as invalid. Next, short gaps of missing data (< 500 ms) were interpolated using a cubic spline method to reconstruct brief blink-related signal loss, following the recommendations of Sebastiaan Mathôt and Kret and Sjak-Shie (89,90). Longer gaps were left unaltered to avoid introducing artificial signal. Finally, pupil size data from the left and right eye were averaged to obtain a single mean for subsequent analyses.

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References

1. Zhu Y, Nachtrab G, Keyes PC, Allen WE, Luo L, Chen X. Dynamic salience processing in paraventricular thalamus gates associative learning. Science. 2018 Oct 26;362(6413):423–9.

2. Choi I, Lee JY, Lee SH. Bottom-up and top-down modulation of multisensory integration. Curr Opin Neurobiol. 2018 Oct;52:115–22.

3. Noppeney U. Perceptual Inference, Learning, and Attention in a Multisensory World. Annu Rev Neurosci. 2021 July 8;44:449–73.

4. Fredericksen RE, Hess RF. Estimating multiple temporal mechanisms in human vision. Vision Research. 1998 Apr 1;38(7):1023–40.

5. Snowden RJ, Hess RF. Temporal frequency filters in the human peripheral visual field. Vision Research. 1992 Jan 1;32(1):61–72.

6. Mehta AH, Feng L, Oxenham AJ. Neural auditory contrast enhancement in humans. Proc Natl Acad Sci U S A. 2021 July 20;118(29):e2024794118.

7. Allen D. Spatial summation in the evoked cortical response to auditory stimuli. Perception & Psychophysics. 1968 Nov 1;4(6):355–6.

8. Sollini J, Mill R, Sumner CJ. Spatial Processing Is Frequency Specific in Auditory Cortex But Not in the Midbrain. J Neurosci. 2017 July 5;37(27):6588–99.

9. Ordás CM, Alonso-Frech F. The neural basis of somatosensory temporal discrimination threshold as a paradigm for time processing in the sub-second range: An updated review. Neurosci Biobehav Rev. 2024 Jan;156:105486.

10. Lieber JD, Bensmaia SJ. The neural basis of tactile texture perception. Curr Opin Neurobiol. 2022 Oct;76:102621.

11. Willmore BDB, King AJ. Adaptation in auditory processing. Physiol Rev. 2023 Apr 1;103(2):1025–58.

12. Pedersen CB, Salomon G. Temporal integration of acoustic energy. Acta Otolaryngol. 1977;83(5–6):417–23.

13. Buus S, Florentine M, Poulsen T. Temporal integration of loudness, loudness discrimination, and the form of the loudness function. J Acoust Soc Am. 1997 Feb 1;101(2):669–80.

14. Mauk MD, Buonomano DV. The neural basis of temporal processing. Annu Rev Neurosci. 2004;27:307–40.

15. Chen KK, Rolan P, Hutchinson MR, de Zoete RMJ. Reliability of Temporal Summation of Pain in Healthy and Clinical Populations: A Systematic Review and Meta-Analysis. European Journal of Pain. 2025;29(8):e70097.

16. Hashmi JA, Davis KD. Effects of temperature on heat pain adaptation and habituation in men and women. Pain. 2010 Dec;151(3):737.

17. Koyama Y, Koyama T, Kroncke AP, Coghill RC. Effects of stimulus duration on heat induced pain: the relationship between real-time and post-stimulus pain ratings. Pain. 2004 Feb;107(3):256.

18. Weissman-Fogel I, Dror A, Defrin R. Temporal and spatial aspects of experimental tonic pain: Understanding pain adaptation and intensification. European Journal of Pain. 2015;19(3):408–18.

19. Sathian K, Lacey S. Cross-Modal Interactions of the Tactile System. Current Directions in Psychological Science [Internet]. 2022 July 25 [cited 2025 Sept 30]; Available from: https://journals.sagepub.com/doi/10.1177/09637214221101877

20. Grothe B, Klump GM. Temporal processing in sensory systems. Current Opinion in Neurobiology. 2000 Aug 1;10(4):467–73.

21. Di Stefano N, Spence C. Perceiving temporal structure within and between the senses: A multisensory/crossmodal perspective. Atten Percept Psychophys. 2025 July 1;87(5):1811–38.

22. Cariani P, Baker JM. Survey of temporal coding of sensory information. Front Comput Neurosci. 2025;19:1571109.

23. Zhang S, Li T, Kobinata H, Ikeda E, Ota T, Kurata J. Attenuation of offset analgesia is associated with suppression of descending pain modulatory and reward systems in patients with chronic pain. Mol Pain. 2018;14:1744806918767512.

24. Nahman-Averbuch H, Martucci KT, Granovsky Y, Weissman-Fogel I, Yarnitsky D, Coghill RC. Distinct brain mechanisms support spatial vs temporal filtering of nociceptive information. Pain. 2014 Dec;155(12):2491–501.

25. Yelle MD, Oshiro Y, Kraft RA, Coghill RC. Temporal filtering of nociceptive information by dynamic activation of endogenous pain modulatory systems. J Neurosci. 2009 Aug 19;29(33):10264–71.

26. Yelle MD, Rogers JM, Coghill RC. Offset analgesia: A temporal contrast mechanism for nociceptive information. Pain. 2008 Jan;134(1):174–86.

27. Grill JD, Coghill RC. Transient analgesia evoked by noxious stimulus offset. Journal of Neurophysiology. 2002;87(4):2205–8.

28. Derbyshire SWG, Osborn J. Offset analgesia is mediated by activation in the region of the periaqueductal grey and rostral ventromedial medulla. Neuroimage. 2009 Sept;47(3):1002–6.

29. Sprenger C, Stenmans P, Tinnermann A, Büchel C. Evidence for a spinal involvement in temporal pain contrast enhancement. NeuroImage. 2018 Dec 1;183:788–99.

30. Brooks J, Tracey I. REVIEW: From nociception to pain perception: imaging the spinal and supraspinal pathways. Journal of Anatomy. 2005;207(1):19–33.

31. Peng W, Hu L, Zhang Z, Hu Y. Changes of Spontaneous Oscillatory Activity to Tonic Heat Pain. PLOS ONE. 2014 Mar 6;9(3):e91052.

32. Nickel MM, Ta Dinh S, May ES, Tiemann L, Hohn VD, Gross J, et al. Neural oscillations and connectivity characterizing the state of tonic experimental pain in humans. Hum Brain Mapp. 2020 Jan;41(1):17–29.

33. Nir RR, Sinai A, Moont R, Harari E, Yarnitsky D. Tonic pain and continuous EEG: prediction of subjective pain perception by alpha-1 power during stimulation and at rest. Clin Neurophysiol. 2012 Mar;123(3):605–12.

34. Jensen O, Bonnefond M, VanRullen R. An oscillatory mechanism for prioritizing salient unattended stimuli. Trends in Cognitive Sciences. 2012 Apr 1;16(4):200–6.

35. Jensen O, Mazaheri A. Shaping Functional Architecture by Oscillatory Alpha Activity: Gating by Inhibition. Front Hum Neurosci [Internet]. 2010 Nov 4 [cited 2025 Sept 30];4. Available from: https://www.frontiersin.org/journals/human-neuroscience/articles/10.3389/fnhum.2010.00186/full

36. Clements GM, Gyurkovics M, Low KA, Kramer AF, Beck DM, Fabiani M, et al. Dynamics of alpha suppression index both modality specific and general attention processes. NeuroImage. 2023 Apr 15;270:119956.

37. Strauß A, Wöstmann M, Obleser J. Cortical alpha oscillations as a tool for auditory selective inhibition. Front Hum Neurosci [Internet]. 2014 May 28 [cited 2025 Apr 8];8. Available from: https://www.frontiersin.org/journals/human-neuroscience/articles/10.3389/fnhum.2014.00350/full

38. Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: The inhibition–timing hypothesis. Brain Research Reviews. 2007 Jan 1;53(1):63–88.

39. Wöstmann M, Herrmann B, Maess B, Obleser J. Spatiotemporal dynamics of auditory attention synchronize with speech. Proceedings of the National Academy of Sciences. 2016 Apr 5;113(14):3873–8.

40. Wöstmann M, Alavash M, Obleser J. Alpha Oscillations in the Human Brain Implement Distractor Suppression Independent of Target Selection. J Neurosci. 2019 Dec 4;39(49):9797–805.

41. Schneider D, Herbst SK, Klatt LI, Wöstmann M. Target enhancement or distractor suppression? Functionally distinct alpha oscillations form the basis of attention. European Journal of Neuroscience. 2022;55(11–12):3256–65.

42. Kyle BN, McNeil DW. Autonomic Arousal And Experimentally Induced Pain: A Critical Review of the Literature. Pain Research and Management. 2014;19(3):536859.

43. Chapman CR, Oka S, Bradshaw DH, Jacobson RC, Donaldson GW. Phasic pupil dilation response to noxious stimulation in normal volunteers: relationship to brain evoked potentials and pain report. Psychophysiology. 1999 Jan;36(1):44–52.

44. Liao HI, Kidani S, Yoneya M, Kashino M, Furukawa S. Correspondences among pupillary dilation response, subjective salience of sounds, and loudness. Psychon Bull Rev. 2016 Apr 1;23(2):412–25.

45. Zekveld AA, Koelewijn T, Kramer SE. The Pupil Dilation Response to Auditory Stimuli: Current State of Knowledge. Trends Hear. 2018;22:2331216518777174.

46. Wang CA, Munoz DP. A circuit for pupil orienting responses: implications for cognitive modulation of pupil size. Current Opinion in Neurobiology. 2015 Aug 1;33:134–40.

47. Horing B, Sprenger C, Büchel C. The parietal operculum preferentially encodes heat pain and not salience. PLOS Biology. 2019 Aug 12;17(8):e3000205.

48. Valentini E, Halder S, McInnerney D, Cooke J, Gyimes IL, Romei V. Assessing the specificity of the relationship between brain alpha oscillations and tonic pain. NeuroImage. 2022 July 15;255:119143.

49. Lee IS, Necka EA, Atlas LY. Distinguishing pain from nociception, salience, and arousal: How autonomic nervous system activity can improve neuroimaging tests of specificity. Neuroimage. 2020 Jan 1;204:116254.

50. Mouraux A, Iannetti GD. Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. J Neurophysiol. 2009 June;101(6):3258–69.

51. Gerber EM. permutest [Internet]. 2025 [cited 2025 Oct 5]. Available from: https://de.mathworks.com/matlabcentral/fileexchange/71737-permutest

52. Hermans L, Calders P, Van Oosterwijck J, Verschelde E, Bertel E, Meeus M. An Overview of Offset Analgesia and the Comparison with Conditioned Pain Modulation: A Systematic Literature Review. Pain Physician. 2016 July;19(6):307–26.

53. Greene LC, Hardy JD. Adaptation of thermal pain in the skin. Journal of Applied Physiology. 1962 July;17(4):693–6.

54. Chouchou F, Fauchon C, Perchet C, Garcia-Larrea L. An approach to the detection of pain from autonomic and cortical correlates. Clinical Neurophysiology. 2024 Oct 1;166:152–65.

55. Eisenach JC, Curry R, Aschenbrenner CA, Coghill RC, Houle TT. Pupil responses and pain ratings to heat stimuli: Reliability and effects of expectations and a conditioning pain stimulus. Journal of Neuroscience Methods. 2017 Mar 1;279:52–9.

56. Chapman CR, Bradshaw DH, Donaldson GW, Jacobson RC, Nakamura Y. Central noradrenergic mechanisms and the acute stress response during painful stimulation. J Psychopharmacol. 2014 Dec;28(12):1135–42.

57. Szabadi E. Modulation of physiological reflexes by pain: role of the locus coeruleus. Front Integr Neurosci [Internet]. 2012 [cited 2025 Dec 10];6. Available from: http://journal.frontiersin.org/article/10.3389/fnint.2012.00094/abstract

58. Chapman CR, Oka S, Bradshaw DH, Jacobson RC, Donaldson GW. Phasic pupil dilation response to noxious stimulation in normal volunteers: relationship to brain evoked potentials and pain report. Psychophysiology. 1999 Jan;36(1):44–52.

59. Hauck M, Domnick C, Lorenz J, Gerloff C, Engel AK. Top-down and bottom-up modulation of pain-induced oscillations. Front Hum Neurosci. 2015 July 2;9:375.

60. Peng W, Babiloni C, Mao Y, Hu Y. Subjective pain perception mediated by alpha rhythms. Biological Psychology. 2015 July 1;109:141–50.

61. Huneke NTM, Brown CA, Burford E, Watson A, Trujillo-Barreto NJ, El-Deredy W, et al. Experimental Placebo Analgesia Changes Resting-State Alpha Oscillations. PLoS One. 2013 Oct 11;8(10):e78278.

62. Li L, Wang H, Ke X, Liu X, Yuan Y, Zhang D, et al. Placebo Analgesia Changes Alpha Oscillations Induced by Tonic Muscle Pain: EEG Frequency Analysis Including Data during Pain Evaluation. Front Comput Neurosci. 2016 May 10;10:45.

63. Laufs H, Kleinschmidt A, Beyerle A, Eger E, Salek-Haddadi A, Preibisch C, et al. EEG-correlated fMRI of human alpha activity. NeuroImage. 2003 Aug 1;19(4):1463–76.

64. Murta T, Leite M, Carmichael DW, Figueiredo P, Lemieux L. Electrophysiological correlates of the BOLD signal for EEG-informed fMRI. Hum Brain Mapp. 2015 Jan;36(1):391–414.

65. Szikszay TM, Adamczyk WM, Panskus J, Heimes L, David C, Gouverneur P, et al. Psychological mechanisms of offset analgesia: The effect of expectancy manipulation. PLoS One. 2023;18(1):e0280579.

66. Nahman-Averbuch H, Dayan L, Sprecher E, Hochberg U, Brill S, Yarnitsky D, et al. Sex differences in the relationships between parasympathetic activity and pain modulation. Physiol Behav. 2016 Feb 1;154:40–8.

67. Van Den Houte M, Van Oudenhove L, Bogaerts K, Van Diest I, Van den Bergh O. Endogenous Pain Modulation: Association with Resting Heart Rate Variability and Negative Affectivity. Pain Med. 2018 Aug 1;19(8):1587–96.

68. Adamczyk WM, Szikszay TM, Nahman-Averbuch H, Skalski J, Nastaj J, Gouverneur P, et al. To Calibrate or not to Calibrate? A Methodological Dilemma in Experimental Pain Research. The Journal of Pain. 2022 Nov 1;23(11):1823–32.

69. Nahman-Averbuch H, Coghill RC. Pain-autonomic relationships: implications for experimental design and the search for an “objective marker” for pain. Pain. 2017 Nov;158(11):2064–5.

70. Chan HS. Occupational noise exposure; criteria for a recommended standard [Internet]. National Institute for Occupational Safety and Health. Division of Biomedical and Behavioral Science.;National Institute for Occupational Safety and Health. Education and Information Division.; 1998 [cited 2023 July 22]. (DHHS publication). Available from: https://stacks.cdc.gov/view/cdc/6376

71. Szikszay TM, Adamczyk WM, Luedtke K. The Magnitude of Offset Analgesia as a Measure of Endogenous Pain Modulation in Healthy Participants and Patients With Chronic Pain: A Systematic Review and Meta-Analysis. The Clinical Journal of Pain. 2019 Feb;35(2):189.

72. Szikszay TM, Adamczyk WM, Lévénez JLM, Gouverneur P, Luedtke K. Temporal properties of pain contrast enhancement using repetitive stimulation. European Journal of Pain. 2022;26(7):1437–47.

73. Zimmer K, Ellermeier W. Eine deutsche Version der Lärmempfindlichkeitsskala von Weinstein. Zeitschrift für Lärmbekämpfung. 1997;44:107–10.

74. McCracken LM. Pain Vigilance and Awareness Questionnaire (PVAQ). APA PsycTests. 1997;

75. Meyer K, Sprott H, Mannion AF. Cross-cultural adaptation, reliability, and validity of the German version of the Pain Catastrophizing Scale. J Psychosom Res. 2008 May;64(5):469–78.

76. Morin C, Bushnell MC. Temporal and qualitative properties of cold pain and heat pain: a psychophysical study. Pain. 1998 Jan 1;74(1):67–73.

77. Gouverneur P, Li F, Luebke L, Szikszay TM, Roelen SD, Krajewski J, et al. eVAS: A user-friendly electronic Visual Analogue Scale. JOSS. 2025 Mar 20;10(107):6876.

78. Szikszay TM, Adamczyk WM, Luedtke K. The magnitude of offset analgesia as a measure of endogenous pain modulation in healthy participants and patients with chronic pain. Clinical Journal of Pain. 2019;35(2):189–204.

79. Faul F, Erdfelder E, Buchner A, Lang AG. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods. 2007;39(2):175–91.

80. Anderson CJ. Central Limit Theorem. In: Weiner IB, Craighead WE, editors. The Corsini Encyclopedia of Psychology [Internet]. 1st ed. Wiley; 2010 [cited 2025 Dec 10]. p. 1–2. Available from: https://onlinelibrary.wiley.com/doi/10.1002/9780470479216.corpsy0160

81. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2024. Available from: https://www.R-project.org/

82. The Mathworks Inc. MATLAB version: 24.1.0.2578822 (R2024a) [Internet]. Natick, Massachusetts, United States: The MathWorks Inc.; 2024. Available from: https://www.mathworks.com

83. Luebke L, von Selle J, Adamczyk WM, Knorr MJ, Carvalho GF, Gouverneur P, et al. Differential Effects of Thermal Stimuli in Eliciting Temporal Contrast Enhancement: A Psychophysical Study. The Journal of Pain. 2024 Jan 1;25(1):228–37.

84. Szikszay TM, Melz N, Von Glasenapp B, Adamczyk WM, Luedtke K. Effects of stimulation area and temperature rates on offset analgesia. PAIN Reports. 2022 Nov;7(6):e1043.

85. Benjamini Y, Yekutieli D. The Control of the False Discovery Rate in Multiple Testing under Dependency. The Annals of Statistics. 2001;29(4):1165–88.

86. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society: Series B (Methodological). 1995;57(1):289–300.

87. Brainard DH, Vision S. The psychophysics toolbox. Spatial vision. 1997;10(4):433–6.

88. Oostenveld R, Fries P, Maris E, Schoffelen JM. FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Computational Intelligence and Neuroscience. 2011;2011(1):156869.

89. Mathôt S, Vilotijević A. Methods in cognitive pupillometry: Design, preprocessing, and statistical analysis. Behav Res. 2023 Sept 1;55(6):3055–77.

90. Kret ME, Sjak-Shie EE. Preprocessing pupil size data: Guidelines and code. Behav Res. 2019 June 1;51(3):1336–42.