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Pupil responses objectively index pharmacologically altered tactile sensitivity

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ABSTRACT

Tactile perception is a subjective experience, yet it can be physiologically quantified. This offers new avenues for studying sensory processing in contexts where verbal feedback is limited or unreliable. A growing body of research uses changes in pupil size, showing that stronger tactile stimuli lead to greater pupil dilation. Building on this, we investigated whether pupil responses could serve as an objective measure of tactile sensitivity. To explore this, we pharmacologically manipulated tactile sensitivity in healthy participants (n = 32). In separate sessions, an anaesthetic cream or a placebo cream was applied to one forearm. At the beginning and/or end of each session, Von Frey assessments and a vibrotactile detection task were conducted to confirm the efficacy of the anaesthetic cream in reducing tactile sensitivity. During each session, pupil responses to vibrotactile stimuli applied to both the cream and non-cream arms were recorded. Our results confirmed that the anaesthetic cream significantly reduced the perceived intensity of tactile stimulation, an effect that persisted throughout the session. Crucially, we observed weaker pupil dilation responses to vibrotactile stimuli applied to the anaesthetised arm compared to the placebo or non-cream arm. Exploratory analyses showed that participants for whom the anaesthetic cream was most effective in reducing tactile sensitivity also showed the weakest pupil responses when the anaesthetised arm was stimulated. Overall, these findings demonstrate that the pupil response is a reliable and objective index of tactile sensitivity, highlighting its potential for studying sensory processing in populations where verbal feedback is limited or unreliable.

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1. Introduction

The skin is our largest sensory organ and the perception of touch on our skin is important for many aspects of our daily lives, including bodily awareness, affective experiences, and interactions with our environment (de Haan & Dijkerman, 2020). While tactile input is important for many higher order perceptual experiences, the most basic aspect of tactile perception is the ability to detect a stimulus on the skin. Sensitivity to tactile input varies considerably between body parts and can be quantified using different psychophysical paradigms such as detection thresholds for light touch assessed using von Frey hairs (von Frey, 1899) and two-point discrimination (for measuring tactile acuity) (Johnson & Phillips, 1981). While these paradigms provide a measure of the perceptual experience of tactile stimuli, they depend on verbal reports and the ability to remain focused on the task for a longer period. Physiological quantification of tactile sensitivity may offer new avenues for studying sensory processing in contexts where verbal feedback is limited or unreliable. Moreover, such measures may provide novel insights into underlying mechanisms of tactile processing and how the nervous system processes touch, for example by examining the time course of activation changes. Recent work on stroke-related tactile deficits has raised calls for a shift from predominantly behavioural assessments toward incorporating physiological measures to achieve greater assessment accuracy and resolution (Paul et al., 2024).

Physiological markers of tactile perception are measurable biological responses that reflect how the nervous system processes touch. These can be assessed at different levels of the sensory pathway. At the neural level, tactile stimulation evokes brain activity in somatosensory areas, measurable with EEG (somatosensory evoked potentials; SEPs) (Allison et al., 1991), magnetoencephalography (MEG) (Hari & Forss, 1999), or via blood oxygen level-dependent (BOLD) signals with fMRI (Hammeke et al., 1994). Peripheral markers include afferent nerve activity recorded with microneurography and involuntary muscle responses to tactile stimuli measured with electromyography (EMG) (McNulty et al., 1999; Vallbo & Johansson, 1984). Skin conductance responses provide another means to pick up on autonomic activity to touch (Sjouwerman & Lonsdorf, 2019). Pupil dilation in response to tactile stimulation may be an additional, easy-to-measure marker of tactile processing (Gusso et al., 2022).

Pupil size responds to changes in luminance or low-level visual features such as contrast or orientation and as part of the near triad, a set of ocular adjustments that occur when shifting gaze between near and far objects (convergence of the eyes, accommodation of the lens, and pupillary constriction) (see Strauch, et al., 2022; Loewenfeld, 1999; Mathôt, 2018 for reviews). More importantly from a psychological perspective, pupil dilations ensue increases in effort, be they mental or physical (Bumke, 1911; Kahneman, 1973; Kahneman & Beatty, 1966; Koevoet et al., 2024; Mathôt, 2018; Strauch et al., 2022) to a degree that it is argued that *any* increase in effort, no matter the origin, is accompanied by pupil dilation (e.g., Bumke, 1911, see; Strauch, 2024). Effort-induced pupil dilations are thought to be due to a reduction in parasympathetic nervous system activity (Braunstein, 1894; Bumke, 1911; Hartgraves & Kronfeld, 1931; Steinhauer et al., 2004). Changes in pupil size are closely associated with activity in the noradrenergic locus coeruleus (LC), a brainstem nucleus with widespread projections to the cortex, especially to frontal areas (Alnaes et al., 2014; Aston-Jones & Cohen, 2005; Joshi et al., 2016; Lloyd et al., 2023; Murphy et al., 2014; Strauch et al., 2022). The LC is thought to coordinate neural activity across the brain, in part through its projections to the thalamus, and plays a key role in flexibly switching between networks and synchronizing activity (Dahl et al., 2022; Poe et al., 2020; Wainstein et al., 2022). Given that brainstem structures like the LC respond earlier to sensory stimulation than cortical areas, such as the somatosensory cortex (Harricharan et al., 2021), we assume that tactile input triggers phasic LC activity early in the processing stream. This activity is needed for subsequent processing in somatosensory cortex and also triggers the evoked pupil dilation observed after the typical delay associated with the pupillary musculature (see Strauch et al., 2022 for the likely circuits connecting LC activity to pupil dilation). Thus, if tactile sensitivity was reduced, we expect a corresponding decrease in pupil dilation as the stimulation is perceived as less intense. While this provides a plausible framework, we avoid stronger mechanistic claims as they go beyond the scope of our study.

In fact, it is today usually overlooked that tactile-induced pupil responses, reflecting the intensity of processing stimulation, stand at the beginning of pupillometry in modern scientific history (Bumke, 1911; Strauch, 2024). Specifically, Schiff and Foa (1875) studied several physiological markers of tactile stimulation in cats and dogs, finding such consistent and strong pupil dilations in response to stimulation that they referred to pupil size change as 'finest physiological aesthesiometer' (see Strauch, 2024). In modern pupillometric literature, pupil dilation has been described primarily in response to painful stimulation (Chapman et al., 1999; Ellermeier & Westphal, 1995; Höfle et al., 2008; Tassorelli et al., 1995; Vassend & Knardahl, 2005; Walter et al., 2005). The first studies into non-painful touch with modern video-based eye trackers are surprisingly recent (Ellingsen et al., 2014, Van Hooijdonk et al., 2019, Gusso et al., 2021, Ten Brink et al., 2024; see Gusso et al., 2022 for a review). What is common to the conclusions of all these works is that the pupil dilates upon stimulation relative to a non-stimulation baseline level, both for stimulations delivered by humans (as in Ellingsen et al., 2014; Van Hooijdonk et al., 2019) and machine-induced tactile stimulation via tactors or vibrators (as in Ellingsen et al., 2014; Gusso et al., 2022; Ten Brink et al., 2024). These effects are stronger for pupil dilations than for blink rates, microsaccade rates, and scalp EEG ERPs (Gusso et al., 2022, in line with Schiff & Foa, 1875). Stronger tactile stimulation is accompanied with stronger pupil dilation, and so is stimulation to more sensitive body parts (Ten Brink et al., 2024). Pupillary responses to tactile stimulation (and any other sensory domains if not visual) are characterized by a rapid increase in pupil size immediately after the stimulus, followed by a return to baseline. Such task-evoked pupil responses carry similar information in the magnitude of baseline-corrected pupil size and the pupil change rate (Strauch et al., 2021). Previous

studies have primarily focused on variations in stimulus intensity, whereas the tactile sensitivity of the individual has not yet been directly manipulated. Here, stimulus intensity refers to the physical strength of a stimulus, and tactile sensitivity to an individual's perceptual responsiveness to that stimulus. Together, and in combination with its unobtrusive video-based assessment, this makes pupil size change an ideal physiological marker of tactile processing.

To date, however, no works exist that use tactile-induced pupil responses to index different experimentally manipulated tactile sensitivity levels. Demonstrating this principle on a group level is a necessary first step toward developing pupil-based measures of tactile processing. Besides increasing the evidence for a causal link between the intensity of processing in response to tactile stimulation and pupil dilation (Schiff & Foa, 1875; Ten Brink et al., 2024), such effects potentially hold merit for assessment of residual tactile processing in patient samples.

Our primary research question was whether pharmacologically altered tactile sensitivity affects pupil responses to tactile stimuli in healthy participants. An anaesthetic cream was applied to locally numb the skin in order to study how changes in tactile perception influences pupil response. The hypothesis was that reduced tactile sensitivity, induced by the anaesthetic cream, would result in a weaker pupil response – specifically, a smaller pupil dilation – and that this effect would be consistent across different stimulus intensities.

Our secondary aim was to explore whether the pupil response was related to individual differences in tactile sensitivity. We expected that some participants would be unable to detect a low-intensity tactile stimulation on their anaesthetised arm, while others would be able to detect it. We hypothesised that participants who could not reliably detect the tactile stimulation would also show a weaker pupil response as compared to participants who could detect the tactile stimulation. To test the latter hypothesis, participants performed a vibrotactile detection task after the main experiment. Participants received the same tactile stimulation as in the main experiment, but instead of measuring the pupil response we asked participants to indicate whether they felt a stimulus or not. We did not combine the measurement of the pupil response with the vibrotactile detection task to prevent movement-related artifacts on pupil size (Mathôt, 2018; Strauch et al., 2022).

2. Materials and methods

2.1. Participants

Healthy participants (n = 33) took part in the experiment. Health status was based upon self-report, with several specific conditions explicitly ruled out due to exclusion criteria for the use of EMLA cream (e.g., epilepsy, heart conditions, skin diseases).

All participants had either normal or corrected-to-normal vision with contact lenses. Data of one participant had to be excluded due to corrupted pupil data, leaving data of 32 participants between 19 and 25 years of age (M_{age} = 21.61, SD_{age} = 1.39 years; 13 males, 19 females) for analyses. Handedness was assessed using the Edinburgh Handedness Inventory, with the hand scoring highest labelled as the dominant hand (Oldfield, 1971). Of the final sample, 28 were right-handed and 4 left-handed.

The sample size was based on previous studies (e.g., Gusso et al., 2022, n = 26; Ten Brink et al., 2024, n = 32), and constrained by counterbalancing, requiring a multiple of the 8 equally frequent unique combinations (see "Section 2.3" for details).

Participants could choose between a monetary reward or compensation in the form of course credits. All participants provided written informed consent. This study was approved by the Ethics Committee of the Faculty of Social and Behavioural Sciences of Utrecht University filed under number 23-0353.

2.2. Material and tasks

2.2.1. Tactile sensitivity assessment (von Frey monofilaments)

Tactile sensitivity was assessed as the detection threshold for light touch using von Frey monofilaments ranging in force from .008 to 300 g (North Coast Medical Inc., United States of America). Von Frey monofilaments are well validated for assessing tactile sensitivity with high precision, allowing detection of subtle perceptual differences. Participants were blindfolded and had to wear headphones playing white noise to prevent them from anticipating when tactile stimulation would be applied. The area surrounding the stimulation location was shaved to minimise the influence of body hair on tactile perception. Participants were instructed to report whenever they felt any tactile stimulation on their forearm. Von Frey thresholds were determined using a method-of-limits procedure. Per arm, testing began with a mid-range filament and proceeded in ascending or descending order depending on participant responses. A subthreshold was defined as the first filament the participant did not detect after having reached a suprathreshold, and a suprathreshold was defined as the first filament the participant felt after having reached a subthreshold. The number of trials therefore differed between participants. Per forearm, stimuli were provided until 5 subthreshold and 5 suprathreshold estimates were reached (Fruhstorfer et al., 2001; Keizer et al., 2012). The experimenter occasionally waited longer between stimulations, which served as sham trials. The Von Frey assessment was used as a manipulation check for numbing and the persistence of the numbing effect.

2.2.2. Pharmacological manipulation

To locally numb the skin, EMLA plasters (Aspen, Europe & Middle East) were used. EMLA plasters contain the working substances lidocaine (25 mg) and prilocaine (25 mg). These types of plasters were previously found to reduce tactile sensitivity by targeting cutaneous receptors responding to mechanical stimuli (Ehrenström Reiz, G.M.E. & Reiz, 1982; Hallén et al., 1984; Barcohana, Duperon, & Yashar, 2003). As a placebo, odourless body lotion (Neutral 0%) was applied and covered with a transparent medical film.

Each participant took part in two experimental sessions: one with EMLA and one with the placebo cream. In each session,

the EMLA plaster or placebo cream was applied to one forearm (i.e., *cream arm*). The participant was blindfolded during the application to prevent recognition of the type of cream.

The application site was determined by identifying the midpoint between the wrist and the inside of the elbow, and the midpoint of the width of the arm. The forearm was covered with bandage to avoid recognition of the type of cream and to prevent damage to or any movement of the plaster or transparent film.

The EMLA plaster or placebo cream was left on for 2 h. This would be enough time for the EMLA to absorb, according to the EMLA medication's package insert and based upon a pilot study in which we had tested the effectiveness and duration of the numbing effect.

2.2.3. *Main experiment*

Two tactors (Dancer Design, England) were attached to the same location on the ventral side of each forearm as described under 'Section 2.2.2' (see Fig. 1 for the experimental set up).

Each tactor was a miniature electromagnetic solenoid-type stimulator that converted an alternating voltage into a mechanical stimulus. The voltage was applied to a coil which caused a small magnet to move. The motion of the magnet was coupled to the skin via a small plastic rod, diameter 3 mm. The alternating signal was created by a computer sound card and was amplified by a custom-made amplifier to drive the tactor. The duration, intensity, and frequency of the touch stimulus could be modified by adjusting the parameters of the soundcard output signal. The force that was applied to the skin was however not defined in absolute units; we therefore used relative percentages. Vibrotactile stimulation consisted of 0.1s (40 Hz) vibrations with an intensity of 0% (sham), 10% (low), or 100% (high).

The experiment was programmed in Psychopy (version 2021.2.3) (Peirce et al., 2019). An EyeLink 1000+ (SR Research Ltd., Canada) was used to record gaze position and pupil diameter of both eyes at 1000 Hz. The head of the participant was stabilised using a chin and headrest. The visual stimulus, a white cross on a grey background, was presented on an Iiyama G-Master Red Eagle monitor (2560*1440 px, 100 Hz) at 67.5 cm from the participant's eyes.

The experiment started with a 9-point calibration followed by a validation. Participants fixated the central cross during baseline, while tactile stimuli were administered, and during the measurement period after (for the paradigm see Fig. 2). To prevent participants from hearing rather than feeling the tactor on the skin, they had to wear earplugs and noise cancelling headphones playing white noise.

The task consisted of 6 blocks of 30 trials (6 trials for each of the 5 conditions, randomised sequence), resulting in 36 trials per condition per session. Four stimulation conditions were defined by a 2 (intensity: low, high) × 2 (arm: cream, non-cream) factorial design. A fifth condition, the sham (no stimulation), served as a control and was used as a baseline correction for each of the four conditions per participant.

Each trial started with an interstimulus interval. This interval randomly lasted between 1.5 sec and 2.5 sec to prevent anticipation of tactile stimuli. The final 50 ms of this interval served as baseline for pupillometry analyses. This was followed by tactile stimulation or no stimulation (sham). The pupil response was measured for 1.5 sec. If participants gazed more than 3 visual degrees from the centre or blinked for more than 200 ms, the trial was deemed invalid, fed back by the fixation cross turning red. Invalid trials were repeated at the end of the block in random sequence. There was an inter-trial interval of 2 sec, indicated by the white cross tilting to an 'x'.

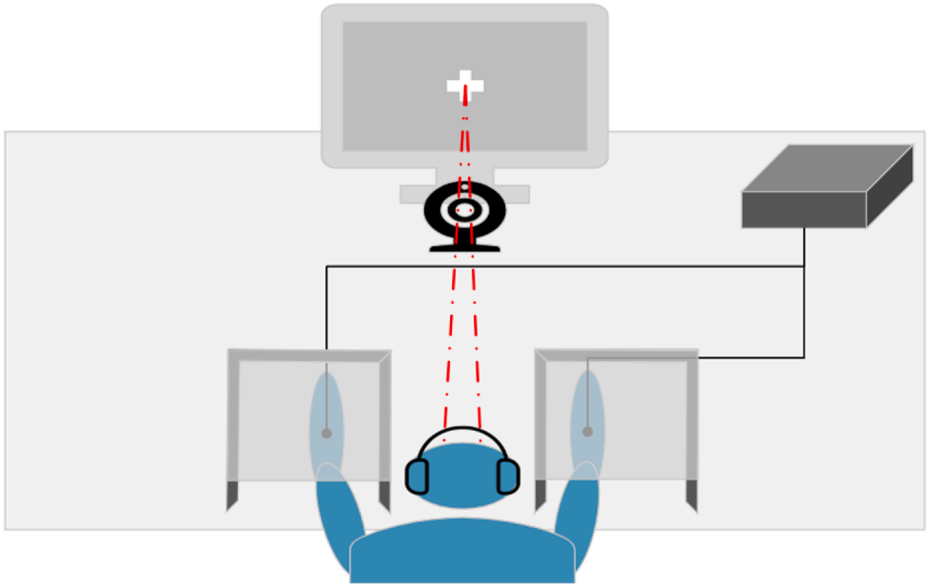

Fig. 1 – Schematic representation of the experimental setup. The participant sat at a desk with their head in a headrest, wearing ear plugs and noise cancelling headphones playing white noise. Both arms were positioned on the table and hidden from view using wooden covers with the ventral side (hand palms) facing up. The two tactors, represented by the black dots, were attached onto the forearms and connected to the amplifier. The distance from the monitor to the eyes was ~67.5 cm. The eye tracker was positioned under the monitor and measured both eyes.

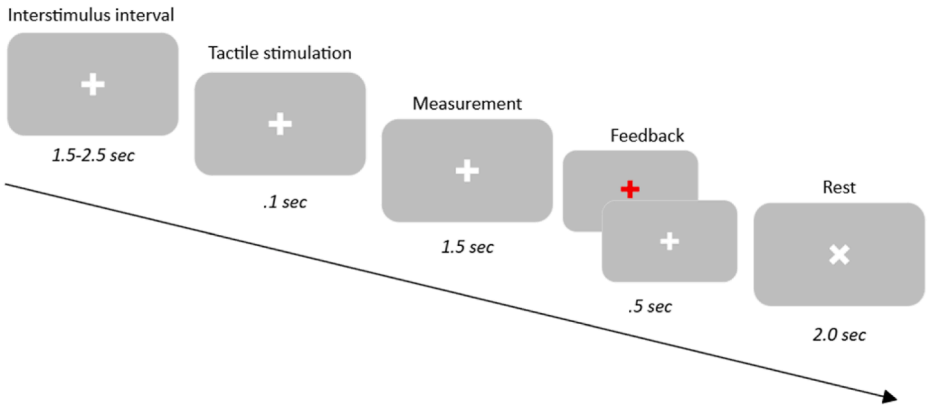

Fig. 2 – Experimental paradigm. Participants fixated a white cross presented on a grey background. After an interstimulus interval of 1.5 sec–2.5 sec, tactile stimulation or no stimulation (sham condition) was applied for .1 sec, followed by 1.5 sec of measurement. Feedback about the trial was provided via a white (valid) or red (invalid) cross for .5 sec. This was followed by a resting period of 2.0 sec. Trials were invalid if gaze was >3 visual degrees from the centre or blinked for >200 ms. Invalid trials were repeated at the end of a block in random sequence.

During this time window, the effect of the tactile stimulus on pupil size from the previous trial could wear off, and participants could blink. Participants could pause the experiment between blocks. If participants moved their head, the eye tracker was recalibrated.

2.2.4. *Vibrotactile detection task*

The detection task required participants to detect and report low- and high-intensity vibrotactile stimulations that were applied on their cream and non-cream arms. A trial used the same white fixation cross on a grey background as the main experiment. After 1 sec, tactile stimulation or sham stimulation was presented. At the end of each trial, the participant was prompted to verbally report whether they felt a stimulation or not. The experimenter logged each response by pressing 'y' (stimulation felt) or 'n' (stimulation not felt) on a keyboard, so that participants did not have to move their arms. No pupil responses were measured during this task. Eighty trials were administered in random sequence, 10 trials for each combination of arm (cream, non-cream) * stimulation intensity (low, high); and 40 sham trials. The vibrotactile detection task was used to explore whether differences in numbing strength were linked to differences in pupil responses.

2.3. *Design*

The experiment consisted of two sessions: an *EMLA session*, in which an EMLA plaster was applied to locally numb the skin, and a *placebo session*, in which odourless body lotion served as placebo. The order of these sessions was counterbalanced across participants.

In each session, either EMLA or a placebo cream was applied to one forearm (*cream arm*), while the opposite forearm served as a control arm (*non-cream arm*). The assignment of cream to the dominant or non-dominant arm was counterbalanced between participants but kept consistent across sessions for each individual. Similarly, the assignment of tactors to the dominant and non-dominant arms was counterbalanced across participants and kept constant between sessions.

As a result, the experimental design included the within-subjects factors *session* (EMLA, placebo), *arm* (cream, non-cream), and *stimulation intensity* (low, high). An additional sham stimulation condition (no vibration) was included to control for non-tactile influences on pupil responses, such as anticipation or auditory cues. Pupil responses to sham trials were subtracted from all other traces to isolate stimulation-related effects.

2.4. *Procedure*

First, baseline tactile sensitivity was assessed on both forearms using von Frey monofilaments, applied by the experimenter. Next, depending on the session, either EMLA or placebo cream was applied to one forearm (the *cream arm*).

After a 2 h absorption period, a second von Frey assessment was conducted only on the cream arm to establish whether the EMLA cream effectively reduced tactile sensitivity or if there were any effects by the placebo cream. The non-cream arm was not assessed further as tactile sensitivity was not expected to change, as there was no manipulation to this arm. This was followed by the main (pupillometry) experiment, not featuring a manual response to prevent artifacts (Mathôt, 2013; Strauch et al., 2022).

Following the main experiment, participants completed a vibrotactile detection task without measurement of the pupil response as the task of replying would again influence the pupil response. Finally, a third von Frey assessment was performed on the cream arm, to determine whether the effect of the EMLA cream had worn off, or the passing of time in the placebo session changed the tactile sensitivity.

2.5. Data analysis

2.5.1. Tactile sensitivity assessment (von Frey monofilaments)

Tactile sensitivity was determined by calculating the geometric mean of 10 reversal points (5 subthreshold and 5 suprathreshold) using Microsoft Excel. As von Frey monofilament forces increase on a logarithmic scale, the geometric mean was used to calculate sensory thresholds. The outcome represented the tactile detection threshold, defined as the minimal force in grams required to reliably elicit a tactile sensation.

Tactile sensitivity was calculated for the cream arm in each session (EMLA, placebo) for all three measurement points: before application of the cream (T0), immediately before (T1), and after the main experiment (T2). Tactile sensitivity of the non-cream arm was determined only at T0 to compare the sensitivity between arms before application of EMLA or placebo cream within each session. Differences between conditions were evaluated using paired *t*-tests on the geometric averages of von Frey scores, as the number of trials per subject was too small to fit a linear mixed-effects model.

2.5.2. Main experiment

Eye tracking data were down sampled to 100 Hz and subtractively baseline corrected using the average pupil size of the last 50 ms of the baseline interval for each eye, before an average of both eyes was calculated using the python DataMatrix package (1.0.13).

Based on Strauch et al. (2022) and Ten Brink et al. (2024), the first derivative of the pupil response was calculated to minimise the effects of slower frequency trends and drifts on pupil size. This derivative represents the speed of pupil size changes over time. A low-pass Butterworth filter (18 Hz, order of 3) was used to remove high-frequency noise, again following Ten Brink et al. (2024).

To assess differences in pupil responses between *sessions* (EMLA, placebo) and *arms* (cream, non-cream) over time, a linear mixed effect (LME) model was used to analyse the pupil response to the tactile stimulations, with the pupil response derivative as the dependent variable. Per participant, average pupil responses to sham trials were first subtracted from pupil responses of the low- and high-intensity trials. The initial, full set of variables that were considered for the LME included stimulation intensity, session, arm, handedness, tactor assignment, and time elapsed since the first trial. We expected an interaction between session*arm, with smaller pupil response specifically for the EMLA session and cream arm. The time elapsed since the first trial was included to control for possible habituation effects, repeated stimulation at the same location, and the numbing effect of the EMLA cream wearing off over time (see Fig. 3).

The model was selected from the full model including all main effects and interactions, as well as random slopes and intercepts. Following Barr (2013), the model was simplified by removing random slopes and interactions to achieve convergence. As the LME was applied to many time points, we first performed AIC-based backwards model selection on the average pupil derivative within the 500–750 ms interval after stimulation, around the peak response (lme4 and lmerTest R 2024.04.2 packages). As the resulting model had singular fits for 46.6% and did not converge for 11% of time points, we further simplified the model using AIC-based backward selection to obtain a model that provided reliable estimates for >95 % of time points (non-convergence: 4.29 %, singular fit: .6%). This was to ensure a sufficiently complex model while maintaining interpretability of outcomes (Wilkinson notation: "pupil size derivative ~ time elapsed + stimulation intensity * session * arm + (session | participant)").

This model retained the key predictors (time elapsed, stimulation intensity, session, and arm), the interaction of session, arm and stimulation intensity, and accounted for individual variability through random intercepts and slopes for session by participant. Post hoc contrasts were computed with estimated marginal means using the emmeans package (version .14.2) to test for differences within sessions and between conditions (EMLA cream *vs* EMLA non-cream, placebo cream *vs* placebo non-cream, and EMLA cream *vs* placebo cream and EMLA non-cream *vs* placebo non-cream).

For pupil responses, any differences occurring earlier than 250 ms after stimulus onset were discarded, as the response latency of the pupil excludes earlier manipulation-induced effects (Strauch et al., 2022). The contribution of each factor (session, arm, stimulation intensity, and elapsed time) to the

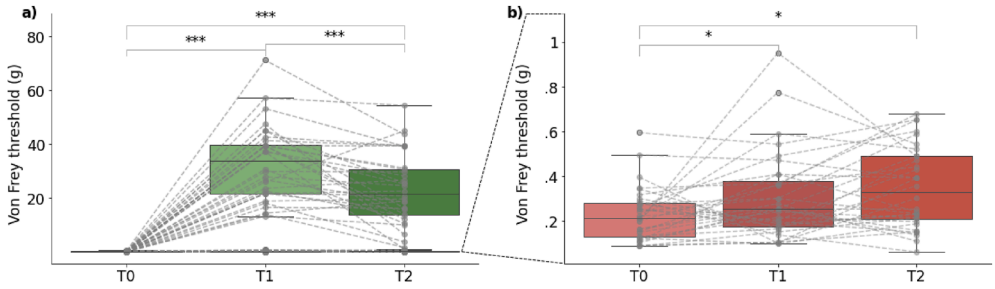

Fig. 3 – Tactile sensitivity as assessed with von Frey monofilaments on the cream arm for the baseline measurement (T0), after 2 h of absorption (T1), and after the main experiment and vibrotactile detection task (T2). Higher thresholds, representing the geometric average of the 10 reversal points in grams, indicate lower tactile sensitivity. Grey dashed lines connect the thresholds of individual participants (dots) per measurement point (*: $p < .001$). a) EMLA (green) and placebo (red) sessions. b) Zoom-in of the y-scale for the placebo (red) session (*: $p < .05$). Note the substantial differences regarding the y-axis scale between a and b.**

main effect was represented by the t-value for each factor. Testing over time comes with a trade-off: while it prevents cherry picking a specific interval for inference testing, it does result in many statistical tests (unlike testing on an average pupil size during an interval), albeit it highly dependent rather than independent ones. We did not apply a correction for multiple comparisons because of this complication. However, we therefore opted for two-sided *p*-value cut-offs and refer the reader to the significance level of principle findings (Fig. 6) that would withstand any reasonable correction.

2.5.3. *Vibrotactile detection task*

Sensitivity (*d'*) was calculated for each combination of session (EMLA, placebo), arm (cream, non-cream), and stimulation intensity (low, high), with the sham condition as the reference, using a custom python script.

For a secondary analysis examining the effects of individual differences in tactile sensitivity on the pupil response, participants were categorized into low and high tactile sensitivity groups based on their d' for the low-intensity stimulus on the EMLA-cream arm. Participants whose mean d' deviated by more than ±3*SD* from the mean in the placebo condition (i.e., low-intensity stimulus on the placebo-cream arm), were classified as having low tactile sensitivity following numbing.

2.6. *Data availability*

Raw data, materials, and analysis scripts are available via the open Science Framework: https://osf.io/q6bs5/

3. Results

3.1. *Manipulation check: Pharmacologically induced numbness reduced tactile sensitivity*

First, we checked whether applying EMLA cream to the skin reduced tactile sensitivity, as assessed using von Frey monofilaments (Fig. 3). We conducted paired t-tests within each session for the cream arm (EMLA, placebo) across three time points (T0: baseline; T1: before main experiment; and T2: after the main experiment and vibrotactile detection task). In the EMLA session, tactile sensitivity on the cream arm was higher before applying the EMLA cream (T0: $M = .30$) compared to immediately after its application [T1: $M = 33.20$, $t(31) = -13.57$, $p < .001$, $d = -2.40$]. Tactile sensitivity remained reduced after the main experiment and vibrotactile detection task (T2: $M = 23.37$) relative to baseline [T0: $t(31) = -10.13$, $p < .001$, $d = -1.79$]. Tactile sensitivity increased from T1 to T2 [$t(31) = 3.89$, $p < .001$, $d = .69$], but it remained substantially lower than baseline sensitivity.

In the placebo session, tactile sensitivity on the cream arm was also higher before applying the placebo cream (T0: $M = .23$) compared to immediately after application [T1: $M = .31$, $t(31) = -2.22$, $p = .034$, $d = -.39$] and after the main experiment and vibrotactile detection task [T2: $M = .35$, $t(31) = -3.86$, $p = .001$, $d = -.68$]. However, this effect was considerably smaller than the differences observed in the EMLA session.

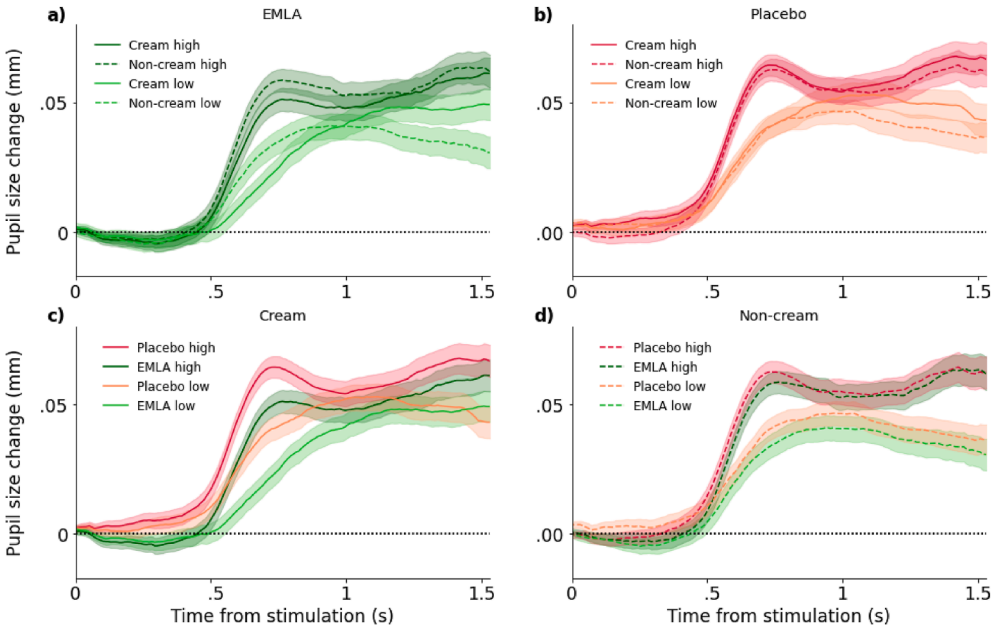

Fig. 4 – Baseline- and sham-corrected pupil response over time after tactile stimulation across conditions. Solid lines represent the cream arm, and dashed lines represent the non-cream arm. Shaded regions surrounding the lines represent the standard error of the mean (SEM). Positive values indicate pupil dilation, negative values pupil constriction. A) EMLA session, with low (light green) and high (dark green) stimulus intensities. B) placebo session, with low (orange) and high (red) stimulus intensities. C) cream arms of the EMLA (green) and placebo (red) sessions, at both low (light) and high (dark) intensities. D) non-cream arm of the EMLA (green) and placebo (red) session, at both low (light) and high (dark) intensities.

In contrast to our expectations, there was a difference in tactile sensitivity before applying any cream (i.e. at baseline) between the EMLA and placebo sessions for both the non-cream arm [t (31) = 2.19, p = .036, d = .39] and the cream arm [t (31) = 2.18, p = .04, d = .39]. The tactile sensitivities between the cream and non-cream arms within each session at baseline did not differ (p > .110, see Supplementary Fig. 1a).

These results show that, as expected, applying EMLA cream reduced tactile sensitivity, as assessed using von Frey monofilaments, throughout the experiment. Although the effects of EMLA began to wear off between the start and end of the experiment, tactile sensitivity remained much lower at the end of the experiment compared to baseline and the placebo condition.

3.2. *Reduced tactile sensitivity weakened pupil responses to tactile stimulation*

We first report baseline-corrected average pupil responses for completeness (with sham responses subtracted for correction; see Supplementary Fig. 1b for average sham and stimulation pupil responses, Supplementary Fig. 2 for only baseline-corrected pupil size). Fig. 4a and b shows the average pupil responses to tactile stimulation. Descriptively, pupils responded stronger to higher stimulation intensity (dark coloured) than low stimulation intensity (light coloured). Furthermore, responses in the EMLA session (green) to the cream arm (solid) were weaker than for non-cream (dashed) or placebo-cream arm (orange; see Fig. 4). However, all statistical analyses and inferences were based on pupil size derivative reported in the following (as in Ten Brink et al., 2024).

Fig. 5 depicts the same data as in Fig. 4, but now for derivative pupil responses (see Supplementary Fig. 3 for non-sham corrected derivative).

We expected stronger pupil responses to the higher stimulation intensity based on Ten Brink et al. (2024). Indeed, the LME, shown in Fig. 6a revealed a clear main effect for stimulus intensity (green), indicating a stronger pupil response for high compared with low stimulation intensity, as can also be seen in Fig. 5. We thus replicated Ten Brink et al. (2024), finding a stronger pupil response to higher intensity stimulation.

We further expected an interaction effect for arm * session. Specifically, we expected the pupil to respond weaker to stimulation on the EMLA cream arm rather than the placebo cream arm and the non-cream arm in the EMLA session. Indeed, we found such a significantly weaker pupil response to the stimulation on the EMLA-cream arm, driving the interaction effect between arm and session around the peak response at 500 ms after stimulation (see Fig. 6a, purple, for a visualization).

The post-hoc analyses showed a clear significant difference around the peak response within the EMLA session (Fig. 6b), but also significant differences between the EMLA cream and placebo cream arms (Fig. 6c).

For a short time window around 1 sec after stimulation onset, there was a difference between the placebo cream and non-cream arm (Fig. 6d). However, as the response was

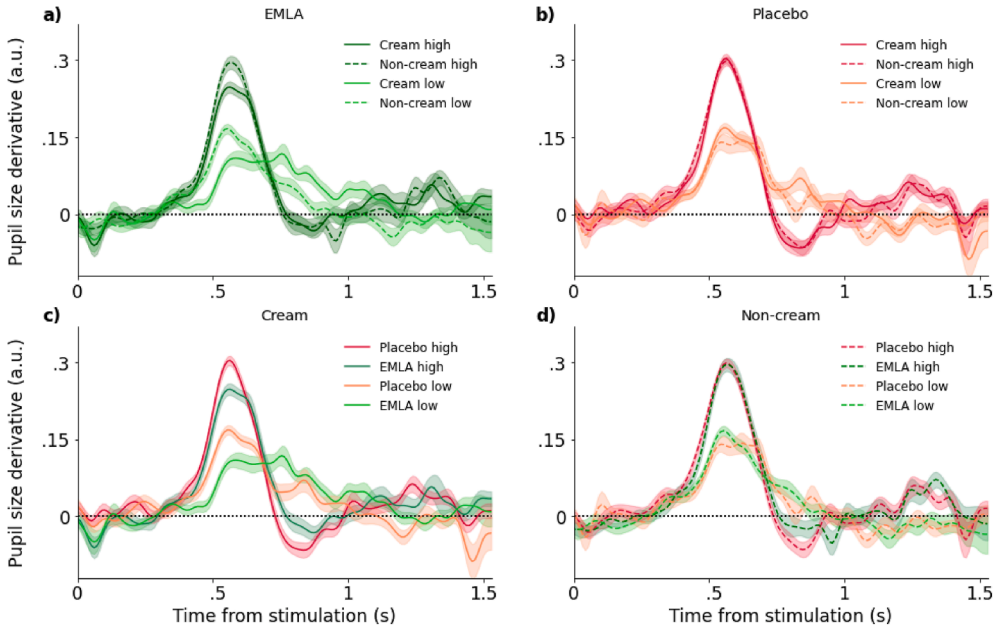

Fig. 5 – Baseline- and sham-corrected pupil response (first derivative of pupil size change) across conditions. Solid lines represent the cream arm, and dashed lines represent the non-cream arm. Shaded regions surrounding the lines represent the standard error of the mean (SEM). A) EMLA session, with low (light green) and high (dark green) stimulus intensities. B) placebo sessions, with low (orange red) and high (red) stimulus intensities. C) cream arms of the EMLA (green) and placebo (red) sessions, at both low (light) and high (dark) intensities. D) non-cream arm of the EMLA (green) and placebo (red) sessions, at both low (light) and high (dark) intensities.

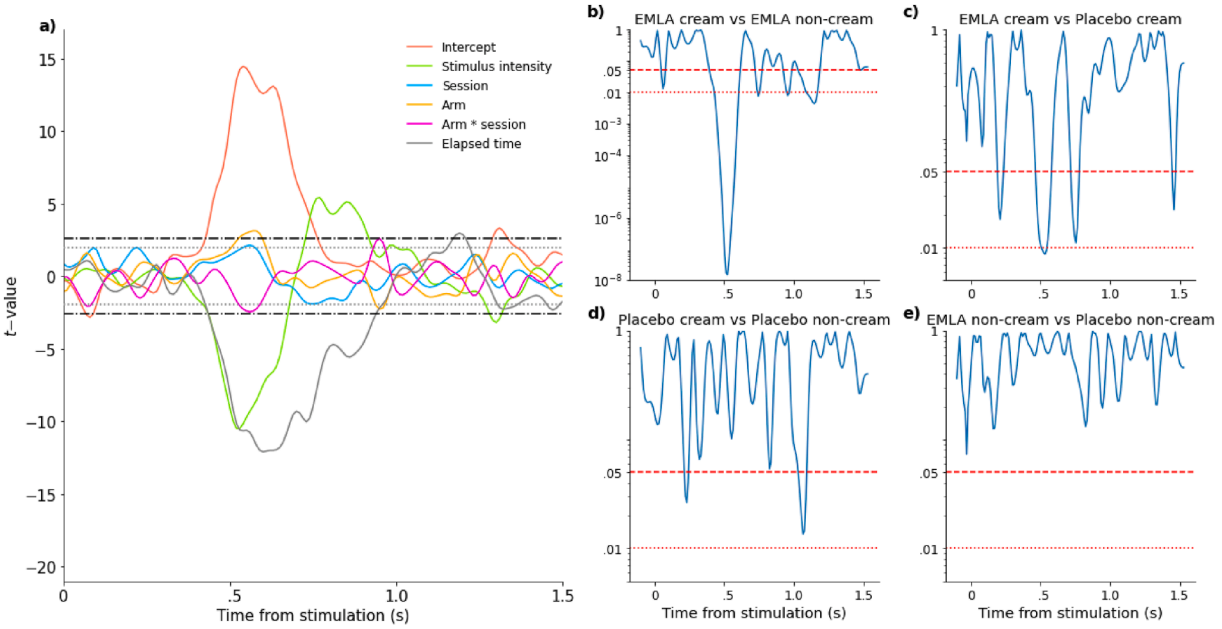

Fig. 6 – Linear mixed effects model results and post-hoc analysis using estimated marginal means per condition. a) The t-value for each factor and intercept are plotted over time. The grey, dotted line represents $t = \pm 1.96$, corresponding to $p = .05$. The black, dashed line represents $t = \pm 2.85$, corresponding to $p = .01$. When a colored line representing a factor crosses one of these horizontal lines it indicates that the contribution of the factor was significant at the respective time point. b-e) For each of the four main comparisons (EMLA cream *vs* non-cream, EMLA cream *vs* placebo cream, placebo cream *vs* non-cream, and EMLA non-cream *vs* placebo non-cream) the *p*-value corresponding to the difference between the traces are shown (blue line). Red lines indicate significance thresholds (dashed red: $p < .05$, dotted orange: $p < .01$), the pupil responses differed significantly.

relatively late and appears inconsistent compared to the main task evoked pupil response, we caution against over-interpreting this difference. As expected, the pupil responses to stimulation on the non-cream arms showed no differences (Fig. 6e). Lastly, with more time elapsed, pupillary responses to stimulation weakened. The decisive main effect of pharmacological numbing of the skin is depicted in Fig. 7 with horizontal bars indicating statistical significance (based on the functionally applied LME, Fig. 6). The data did not allow for a more complex model including random slopes for stimulus intensity and arm*session. We therefore ran a repeated measures ANOVA as simplified analysis (see Supplementary Tables 1 and 2). These results align with the outcomes of the LME, providing converging evidence.

3.3. *Stronger numbing more strongly reduces the pupil response to tactile stimulation*

To further investigate the effect of tactile sensitivity on the pupil response, a vibrotactile detection task was administered after the main experiment.

Supplementary Fig. 5 shows the tactile sensitivity (d') to the low-intensity vibrotactile stimulations on the cream arm for both the EMLA and placebo sessions. Tactile sensitivity for the EMLA-cream arm showed greater variability compared to the placebo-cream arm, as confirmed by Levene's test for equality of variances ($F(1, 62) = 11.31$, $p = .0013$). See full set of d' scores per session, arm and stimulation intensity in Supplementary Table 3.

Participants were categorised into two groups based on the sensitivity to the low-intensity tactile stimulation on the EMLA-cream arm: a low sensitivity group (d' < 3.43, $n = 11$) and a high sensitivity group (d' > 3.43, $n = 21$). Given the small sample size of the low sensitivity group ($n = 11$), the following analyses should be considered as exploratory, intended to generate hypotheses for future research rather than to support definitive statistical conclusions.

Fig. 8 shows the pupil responses to low- and high-intensity stimulations for the EMLA-cream arm, split for the low and high sensitivity groups. For low-intensity stimulations, the low sensitivity group (blue) showed a weaker pupil response with a longer latency compared to the high sensitivity group (orange). However, for high-intensity stimulations, pupil responses were similar between the low and high sensitivity groups. This indicates that specifically for tactile stimulation around or below the detection threshold (i.e., the low-intensity stimulation in the low sensitivity group), the pupil response was reduced.

Moreover, we checked whether the reduced pupil response for the participants with the low tactile sensitivity could be attributed to an overall lower sensitivity for both arms regardless of the EMLA application, as compared to other participants. We therefore compared the pupil response for the low-intensity stimulations between the EMLA-cream and

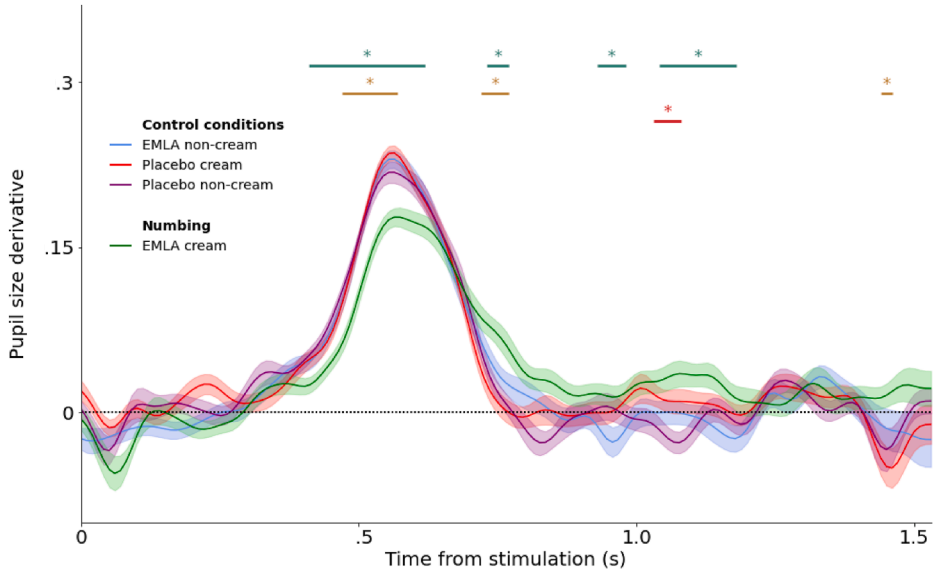

Fig. 7 – Comparison of pupil responses over time for the EMLA-cream arm versus the control conditions. Shaded regions represent the standard error of the mean. Bold horizontal lines indicate statistical significance between conditions (*: $p < .05$), based on results visualized in Fig. 6b–e (gold: EMLA cream *vs* placebo cream, dark green: EMLA cream *vs* EMLA non-cream, red: placebo cream *vs*. placebo non-cream). Note that differences between the EMLA session cream arm and the placebo session non-cream arm are not tested as these conditions do not overlap in factors.

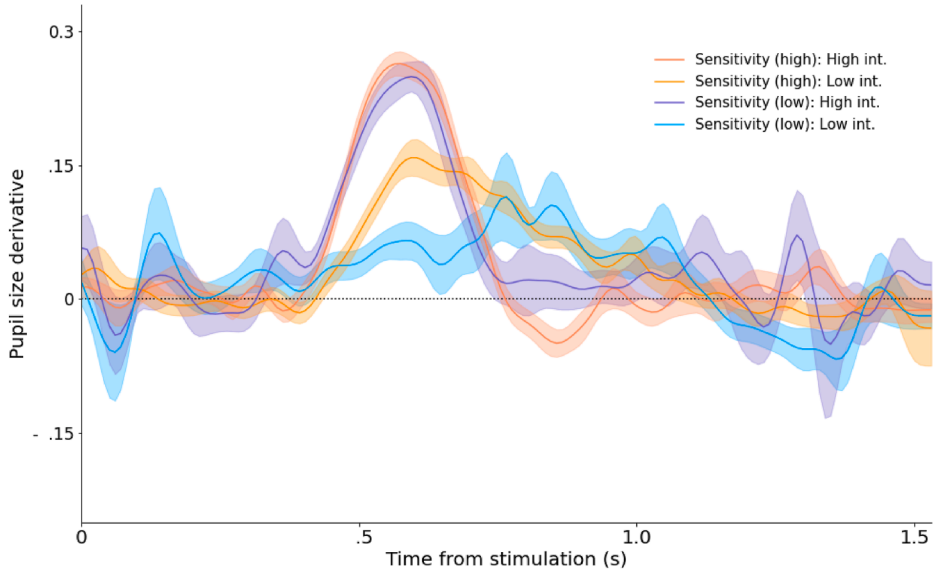

Fig. 8 – Pupil responses to low- and high-intensity tactile stimulations for low and high sensitivity groups. Shaded regions represent the standard error of the mean. Dark blue/blue: low sensitivity group (d' < 3.43, $n = 11$), Orange/red: high sensitivity group (d' >3.43, $n = 21$).

non-cream arms for both groups of participants. Supplementary Fig. 6 shows the pupil response to low-intensity stimulations applied to the cream and non-cream arms during the EMLA session, for the low sensitivity (blue) and high sensitivity (orange) groups.

In the low sensitivity group, the pupil response was much weaker, and showed a longer latency, for the EMLA-cream arm compared to the non-cream arm. In the high sensitivity group, there seemed to be only a small difference in pupil response regarding latency and peak amplitude for the EMLA-

cream arm compared to the non-cream arm. This pattern is consistent with the expected effect of applying the numbing cream.

Additionally, the pupil response to stimulation on either the cream or non-cream arm, for the low sensitivity group, was lower compared to the high sensitivity group. This indicates that the reduced pupil response and longer latency in the low sensitivity group can be partially attributed to an overall lower pupil response to the tactile stimulation for participants with a lower sensitivity. However, this effect may interact with the numbing of the EMLA cream as the difference between the cream *vs* non-cream arm of the low sensitivity group is bigger than the difference in the high sensitivity group.

Combining these findings, participants who experienced the strongest effect of the EMLA cream, and consequently had the lowest tactile sensitivity, showed the weakest pupil response and the longest latency for the peak amplitude. However, due to the small sample size of the low sensitivity group, no statistical analyses were performed, and we again stress the exploratory nature of these analyses.

4. Discussion

Our primary aim was to investigate whether reduced tactile sensitivity of the skin would also reduce the pupil response to tactile stimulation. We temporarily anaesthetised a part of the skin on the arm using EMLA cream. First, we confirmed that EMLA cream effectively reduced tactile sensitivity, assessed using von Frey monofilaments, and this reduced tactile sensitivity persisted throughout the experiment. Next, we demonstrated that the pupil dilated in response to tactile stimulation, with a stronger response for high-intensity versus low-intensity tactile stimuli, replicating the findings of Ten Brink et al. (2024).

Most importantly, as hypothesised, the pupil response was weaker following tactile stimulation on the anaesthetised arm compared to the non-anaesthetised arm. This reduction in pupil response for the anaesthetised arm was seen for both low- and high-intensity tactile stimuli. To rule out the alternative explanation that the application of *any* cream might affect pupil responses, we included a placebo condition in which a neutral cream was applied. There were no differences in pupil responses between the placebo-cream and non-cream arms, showing that the placebo cream had no effect on the pupil response. Additionally, the reduced pupil dilation seen during the EMLA session was also present when comparing the EMLA-cream to the placebo-cream arm, further confirming that the effect was solely due to EMLA.

Our findings build on previous research showing that pupil size increases with tactile stimulus intensity (Gusso et al., 2021; Ten Brink et al., 2024; Van Hooijdonk et al., 2019), and that stimulation of more sensitive body parts elicits larger pupil responses (Ten Brink et al., 2024). We extend this work by demonstrating that pharmacologically reducing tactile sensitivity leads to weaker pupil responses, even when the physical stimulus remains unchanged. Task-evoked pupil dilations as observed here have previously been connected to LC activity, as introduced earlier. We therefore interpret reduced pupil dilations to weaker tactile stimulation or numbed skin as evidence for reduced activity in the LC-norepinephrine system. Pupil responses reflect the intensity of felt stimulation, not only for the tactile domain, as demonstrated here, but also for other domains, such as auditory stimulation where louder sounds are followed by larger responses (Liao et al., 2016).

Interestingly, however, stronger pupil responses are sometimes observed for *weaker* or noisy auditory stimuli (Koelewijn et al., 2018; Zekveld et al., 2010). For example, understanding degraded auditory speech can lead to larger pupil dilations compared to clear speech, as it demands greater attentional and mental effort to filter the signal (e.g., Kahneman, 1970; Zekveld et al., 2010). This leads to an interesting hypothesis: If, akin to auditory stimulation, tactile stimulation was task relevant, then pupils might dilate *more* instead of less with reduced sensitivity. As a consequence, pupil dilation could serve as an objective relevant marker of tactile processing abilities in meaningful tactile tasks, a clear and important avenue for future work. In contrast, participants here passively received tactile stimulation without being required to detect, discriminate, or respond to. In such passive scenarios, we thus expect pupil dilation to scale with perceived stimulation intensity.

Our secondary aim was to explore whether the pupil response was related to tactile sensitivity. After the main experiment, participants completed a vibrotactile detection task, in which they had to indicate whether they felt the vibrotactile stimulation. A subset of participants ($n = 11$) showed difficulties in detecting the low-intensity tactile stimulation on the anaesthetised arm, while the remaining participants ($n = 21$) could reliably detect it. As expected, this subset of participants for whom the anaesthetic effect was the largest, showed a weak or even absent pupil response to tactile stimulation on the anaesthetised arm. These findings align with those of Gusso et al. (2022), who showed that for tactile stimuli below the conscious detection threshold, the pupil did not dilate compared to stimuli that were consciously perceived. Additionally, the same subset also showed a weaker pupil response on their non-anaesthetised arm. This might indicate that there is a lower sensitivity for both arms, and thus a lower pupil response. The pupil response for the low stimulation intensity on the anaesthetised arm descriptively differed more between the low and high sensitivity groups, compared to the non-anaesthetised arms. It is therefore possible that there is also an interaction effect between the anaesthetic and tactile sensitivity. However, due to the small sample size of the low sensitivity group in the current study, no strong conclusions can be drawn.

Previous studies have shown that tactile sensitivity of the non-anaesthetic arm can *increase* as the tactile sensitivity of the anaesthetic arm is reduced (Björkman et al., 2009; Voller et al., 2006). Based on the current findings and those of Ten Brink et al. (2024), we expected this increased sensitivity to be associated with greater pupil dilation in response to tactile stimulation on the non-cream arm during the EMLA-session. However, we did not observe any differences in the pupil response to stimulation on the non-cream arm between the EMLA and placebo sessions. This lack of effect may be due to the small area of skin anaesthetised in our study, compared to

previous studies where the entire arm was anaesthetised (Björkman et al., 2009; Voller et al., 2006).

4.1. Limitations

There are several limitations in the current study. While we showed that EMLA cream reduced tactile sensitivity, as assessed using von Frey monofilaments, the numbing effect decreased (i.e., sensitivity increased) by the end of the test session. In the placebo session, we observed a small decrease of tactile sensitivity throughout the test session. This habituation effect might result from repeated exposure to stimulation.

The anaesthetic was applied locally to a ~25 cm^2 area, which may have allowed surrounding mechanoreceptors in the skin, those not anaesthetised, to detect the vibrotactile stimuli. This could have reduced the effect of the EMLA cream on the pupil response. Using a larger numbed area (e.g. the entire arm) should thus lead to even stronger effects.

4.2. Future directions

For a practical protocol using the pupil response to non-noxious touch, studies that have used the pupillary pain index to assess the depth of analgesia (Eisenach et al., 2017; Wildemeersch et al., 2018) could serve as valuable inspiration. In these studies, baseline pupil size was measured after the onset of anaesthetics but before any surgical incisions. During procedures, the pupil response to noxious stimuli (e.g., electric pulses) was monitored in real-time, with changes in pupil size used to determine whether the level of anaesthesia needed to be adjusted. A similar approach could be applied in clinical settings for non-noxious touch, i.e. to identify (remaining) tactile processing in stroke patients.

Current methods for examining tactile deficits generally rely on subjective behavioural measures and do not assess underlying neural mechanisms (Paul et al., 2024). Furthermore, the pupil response offers a minimally invasive, remote, and affordable alternative to other physiological methods used to assess perception, such as EEG or fMRI. As pupillometry is an objective measure of processing intensity, it could improve diagnosis and treatment, providing more information on tactile processing under different conditions. Importantly, while this study shows that the pupil is responsive to changes in sensitivity following peripheral modulation of tactile input, it remains to be determined whether it responds in a similar way after changes to central processing of tactile input, such as following a stroke.

The current study was conducted under relatively optimal conditions, in which participants were likely attending to, and were consciously aware of, the tactile stimuli. This may limit generalizability to patient populations or scenarios with reduced attention or awareness. We deliberately used low-intensity stimulation and a mild anaesthetic manipulation for ethical reasons, to provide a proof of concept in near-threshold conditions. Even with this conservative design, we observed reliable differences in pupil dilation. This provides evidence for the potential translational value of this method. However, our results also demonstrate that only stronger stimulation intensities will suffice to produce pupil size changes that might be of diagnostic value for individuals. Future studies should investigate whether the pupil response can be used as a measure of tactile perceptual impairments after central lesions, or perhaps can uncover residual tactile processing even in the absence of conscious detection of the stimulus, similar to blindsight in the visual domain (Sahraie et al., 2013).

Indeed, stimulation below detection threshold might elicit pupil dilation akin to decision making effects that show larger pupil dilation not only for targets relative to distractors (de Gee et al., 2014; Klingner, 2010; Strauch et al., 2020), but even for misses relative to distractors (Cai et al., 2025; de Gee et al., 2014). The latter suggests that even the build-up of information below a consciousness threshold is reflected by pupil size.

In contrast, Gusso et al. (2022) found no modulations of pupil size in response to sub-threshold tactile stimulation. The tentative and apparent absence of a response to low-intensity stimulation in participants with low sensitivity reported here would be in line with this finding. Only when a tactile stimulus exceeded this threshold, the pupil response appears to scale with the perceived intensity. Possibly access to consciousness results in larger pupil dilation. Only when reaching this threshold may stimulation intensity then be reflected in pupil dilation, akin to the stronger dilations to stronger stimulation reported here and in Ten Brink et al. (2024).

Future studies could further investigate these hypotheses by taking consciousness thresholds into account. This could be tested using a staircase approach (e.g., after numbing), allowing to determine the stimulation intensity that falls below an individual's detection threshold and is therefore expected to generate no pupil response. This personalized threshold could then be used to tailor low- and high-intensity stimuli per participant.

5. Conclusion

We showed that pupil responses can serve as an objective index of tactile sensitivity. By pharmacologically reducing tactile sensitivity using an anaesthetic cream, we observed a corresponding reduction in pupil dilation to vibrotactile stimuli. Importantly, this effect was most pronounced in participants for whom the anaesthetic effect was strongest. These findings are consistent with previous research suggesting that pupil dilation reflects sensory perception and can be modulated by the strength of the tactile input.

CRediT authorship contribution statement

Bernd T. Douze: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Antonia F. Ten Brink:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **H. Chris Dijkerman:** Writing – review & editing, Writing – original draft, Supervision. **Christoph Strauch:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Open practices section

The data and materials used in this study are available at: https://osf.io/q6bs5/

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None.

Declaration of competing interest

None.

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Scientific transparency statement

DATA: All raw and processed data supporting this research are publicly available: https://osf.io/q6bs5/
CODE: All analysis code supporting this research is publicly available: https://osf.io/q6bs5/
MATERIALS: All study materials supporting this research are publicly available: https://osf.io/q6bs5/
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: No part of the study procedures was pre-registered in a time-stamped, institutional registry prior to the research being conducted. No part of the analysis plans was pre-registered in a time-stamped, institutional registry prior to the research being conducted.
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.2025.10.001.

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