Voluntary Attention Regulates Acute Immune Responses in Humans

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Attention is a central mechanism for prioritizing and shaping sensory information. For example, directing attention away from injury reduces perceived pain. Whether such cognitive modulation extends to downstream biological processes has remained unknown. Across three preregistered within-subject experiments using acute skin inflammation as a model system, we show that directing attention toward bodily sensations, compared to attentional distraction, produces markedly more regulated immune responses, with distinct temporal dynamics. This effect was highly consistent (~90% of participants across two independent cohorts), and substantial, with ~1.5-fold smaller responses under internal attention. Mechanistically, two complementary pathways emerged: a sensory-dependent route, in which attentional modulation of identical input scaled inflammatory magnitude, and a top-down route engaging parasympathetic vagal activity. These results establish attention as a cognitive mechanism capable of regulating immune function in vivo. Situated within predictive and allostatic models of brain-body control, our results reframe perception as biologically consequential rather than merely experiential.

Main

Attention is a core cognitive mechanism that prioritizes sensory information for neural processing. It not only shapes neural activity but also modulates the perceived intensity of sensory events, including those arising from the body, such as pain and itch[1–3]. These sensory signals provide critical information for the regulation of immune responses. In line with this idea, rodent studies show that disrupting neural pathways conveying inflammatory and nociceptive signals leads to immune dysregulation[4,5]. In humans, attending away from pain or itch reduces perceived unpleasantness[6,7], yet this withdrawal of attention may disrupt the integration of bodily sensations with neural control of immune regulation, a possibility left largely unexplored.

Recent theoretical frameworks propose that cognition contributes to biological regulation through allostasis, the predictive control of internal bodily states[8,9]. In this view, the brain maintains physiological stability by anticipating bodily demands and adjusting autonomic, endocrine, and immune activity accordingly[10–12]. Attention may serve this process by modulating the gain of sensory signals that report on bodily condition, thereby shaping both perception and downstream regulatory responses. In parallel, autonomic circuits, particularly the parasympathetic vagus nerve, provide top-down anti-inflammatory regulation[13,14]. Together, these lines of evidence suggest that attention could influence acute inflammation via two complementary mechanisms: sensory modulation of inflammation-related signals and autonomic engagement of vagal parasympathetic pathway.

Despite these insights, no study has directly tested whether voluntary attention can regulate acute inflammation in humans. Acute inflammation is a fundamental protective response, initiated quickly to contain injury and infection. Traditionally, such responses have been considered reflexive and autonomous, unfolding independently of voluntary influence. Yet immune activity is closely coupled to sensory and autonomic neural circuits, and growing evidence suggests that the brain can shape inflammatory processes[13,15–17]. Understanding whether cognitive states can causally influence acute immune responses in humans would redefine the boundaries of neuroimmune regulation.

To address this gap, we tested whether directing attention toward versus away from bodily sensations regulates the immediate immune response to acute inflammation. An experimenter blinded to experiments' conditions used the standardized histamine skin-prick test[18,19] to induce a brief, well-characterized inflammatory reaction in the skin, an accessible neuroimmune interface densely innervated by sensory fibers and populated by immune cells. This response emerges within minutes, peaks around 15-20 min, and is quantified via wheal (edema) and flare (erythema) (Fig. 1A). Smaller inflammatory responses are commonly interpreted as reflecting more regulated immune activity[6,19–22], consistent with allostatic accounts in which reduced amplitude and faster resolution reflect more efficient biological control.

Across three preregistered within-subjects experiments, from inflammation induction and throughout the 20-min period, participants maintained central fixation while directing attention either internally to sensations at the test site or externally to distractors, in line with prior work contrasting interoceptive and exteroceptive attention[23,24]. In each experiment, conditions were completed within individuals in counterbalanced order, with each participant serving as their

own control, allowing a direct causal test of how attention shapes inflammatory magnitude and temporal dynamics. Experiments varied systematically in their attentional tasks: Experiment 1 contrasted internal attention with video-based distraction, Experiment 2 equated visual input and task structure to isolate attention per se, and Experiment 3 tested mechanistic contributions of sensory signaling. Autonomic pathways were assessed across all three experiments (Methods). Together, these experiments provide convergent tests of whether voluntary attention regulates acute inflammatory responses.

Internal attention versus distraction regulates the acute inflammatory response

We first tested whether voluntarily directing attention toward bodily sensations influences the immediate inflammatory response. In Experiment 1 (Exp 1; N=37), participants underwent histamine-induced skin inflammation while maintaining gaze on a central fixation. Attention was directed either internally toward sensations at the test site, or externally toward distracting video clips (Fig. 1A). Manipulation checks confirmed successful engagement of the instructed attentional state (Section S3).

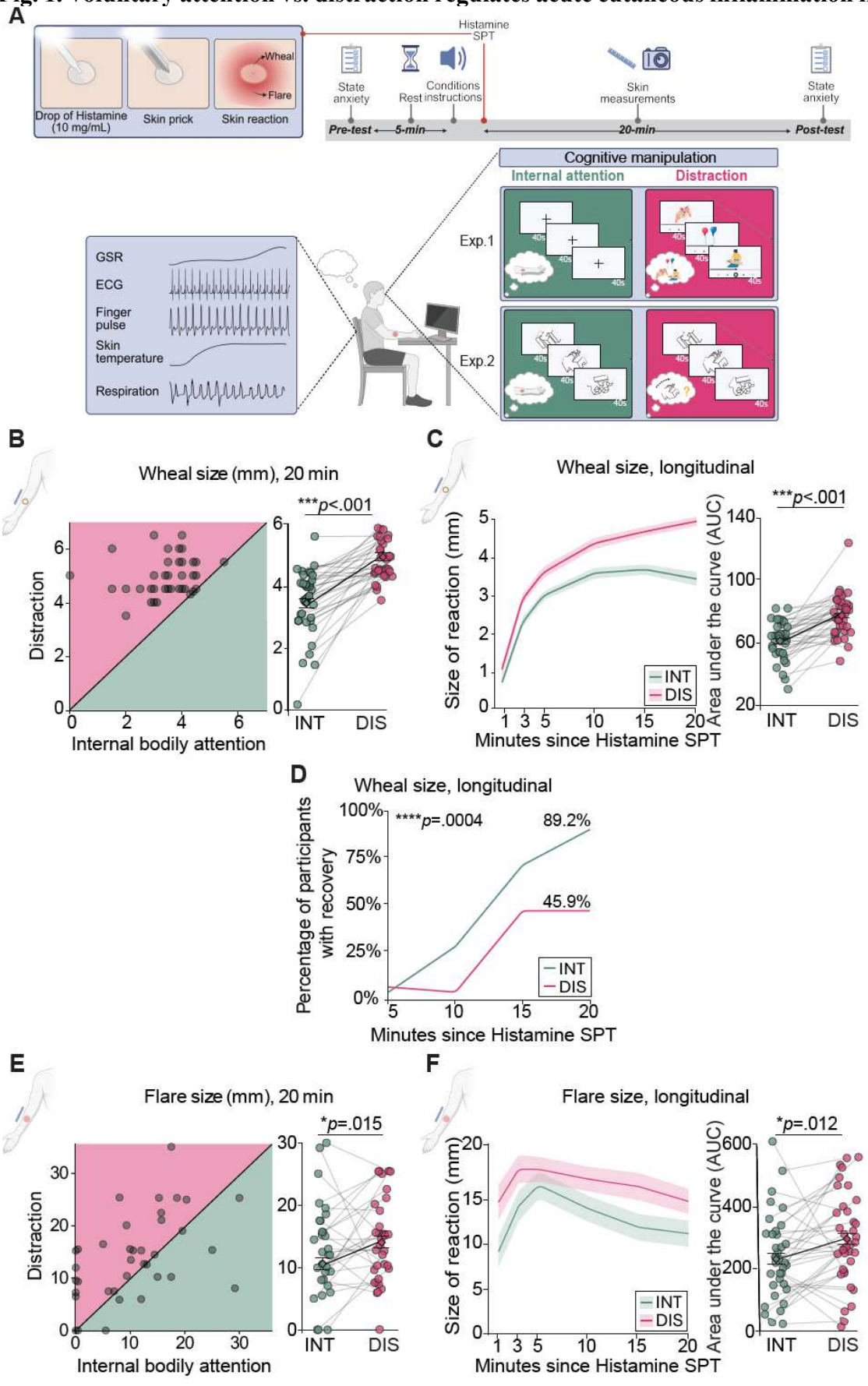
In line with our pre-registered hypotheses, internal attention produced a substantially smaller and more regulated inflammatory response than distraction, with reduced wheal and flare at the 20-min peak (wheal: 3.5±1.1 vs. 5.0±0.7 mm; t_{36}=7.9, p<.001, *Cohen's d*=1.30, 95% CI [0.86,1.73]; flare: 10.6±8.3 vs. 14.0±8.0 mm; t_{36}=2.6, p=.015, d=0.42, 95% CI [0.08,0.75]; Fig. 1B,E). The effect was robust, with up to 90% of participants showing greater inflammation under distraction (Fig. 1B,E, left), and the magnitude was substantial, with wheal and flare increasing by ~1.5-fold on average (Fig. 1B,E, right).

Examining the temporal dynamics of the wheal response (Fig. 1C), internal attention resulted in reduced overall inflammatory activity across the 20-min period (Table S1.2; AUC: t_{36}=6.7, p<.001, d=1.11, 95% CI [0.69,1.51]). It also produced differences in response trajectories (Condition x Time interaction: $F_{2.3,81.6}$=8.7, p<.001, $\eta^2_{partial}$=0.2), with post-hoc tests indicating that significant differences between conditions emerged within 3 minutes and increased over time, peaking at 20 minutes (Table S1.3). To further characterize these dynamics, we conducted a mixed-effects slope analysis focusing on the 10-20-min resolution phase. This analysis revealed a significant difference in the rate of change between conditions (Section S2), consistent with a greater decline toward baseline under internal attention. To isolate recovery dynamics from overall response magnitude, we quantified the proportion of participants showing stabilization or decline of the wheal response by 20 min, irrespective of absolute response size. Nearly 90% of participants in the internal attention condition met this criterion, compared with 46% under distraction (Fig. 1D).

Flare responses also showed a significant reduction in magnitude under internal attention compared to distraction, but did not differ significantly in their trajectories (Fig. 1F; Table S1.2). Consistent with these findings, cumulative analyses indicated that overall inflammatory activity across the 20-min period was ~1.3-fold smaller under internal attention than distraction, for both wheal and flare (Fig. 1C,F; Table S1.4).

Overall, under an identical immune challenge within the same individuals, voluntarily engaging attention with bodily sensations from inflammation site regulated both the magnitude and temporal evolution of the inflammatory response compared with distraction.

Fig. 1. Voluntary attention vs. distraction regulates acute cutaneous inflammation in vivo.



(A) Experimental design. Acute cutaneous inflammation was induced via histamine skin-prick testing (SPT) while participants directed attention either internally to sensations at the test site (itch, burning) or externally to distractors (Exp. 1: video clips, N=37; Exp. 2: shape plausibility task, N=20), in a counter-balanced, within-subject design. Eye gaze was maintained on the screen in both conditions. Wheal (edema) and flare (erythema) were measured at six time points (1-20 min) following SPT, alongside continuous autonomic recordings (heart rate, skin conductance, pulse, skin temperature, respiration). **(B-F)** Internal attention (INT, green) yielded smaller and faster-resolving inflammatory responses than distraction (DIS, pink). **(B)** Scatterplots show individual wheal responses; points above the diagonal depict participants displaying larger wheal sizes under distraction (also see *supplementary note: visualizing within-subject effect magnitude)*. **(C)** Time courses show faster decline of wheal responses under internal attention, confirmed by smaller cumulative activity (AUC) and **(D)** higher recovery rates by 20 min. **(E-F)** Flare responses followed a similar pattern, with reduced magnitude and cumulative activity under internal attention compared with distraction. In all plots, paired lines connect within-subject responses; shaded areas denote ± SEM. Full statistics described in Sections S1-S2.

Attentional regulation of inflammation is independent of task demands

To address the possibility that differences in visual input or task demands contributed to the effects observed in Exp.1, we conducted a second pre-registered experiment on an independent sample (Exp 2; N=20). Here, visual input and task structure were identical across conditions: all participants viewed the same continuous sequence of abstract shapes. In the internal attention condition, participants used each shape change as a cue to return attention to sensations at the inflamed site, whereas in the distraction condition they mentally evaluated whether each shape could plausibly exist in real life (Fig. 1A, Methods). Thus, visual stimulation and task structure were identical, and cognitive demands matched.

Manipulation checks confirmed stronger attentional engagement in internal attention condition than distraction, using both subjective attention ratings and objective task performance measures (Methods, Fig. S3.B-C), with no differences in perceived task difficulty (Fig. S3.D).

Despite identical visual stimulation and matched cognitive demands, internal attention again produced markedly smaller inflammatory responses than distraction. Wheal and flare magnitudes were overall ~1.6-fold reduced under internal attention, with 90% of participants again showing larger inflammatory responses under distraction, and wheal trajectories showed differences in temporal dynamics, consistent with a greater decline toward baseline, as observed in Exp. 1 (Fig. S1.1; Sections S1,S2). These results replicate attentional regulation of inflammation and suggest that it is unlikely to be explained by differences in sensory input, distraction source, or perceived difficulty, but instead reflects the direction of attention itself. We further explored whether the effect was influenced by individual differences including age, sex, and qualities of attentional engagement, and observed no evidence of significant modulation of wheal responses, and some variability in flare responses (Section S9).

Sensory signaling contributes to attentional regulation of inflammation

In line with attentional modulation of sensory perception[1–3,6,7], in Exp. 2 participants reported perceiving inflammation-related sensations (itch, burning) as stronger during internal attention than distraction (t_{18}=3.02, p=.017, d=0.61, 95% CI [0.11, 1.09]; Section S4). This confirms that internal attention enhanced perception of inflammation-related sensations, aligning perceptual changes with the observed immune regulation. The observed parallel between increased sensory perception and enhanced inflammatory regulation raised a key question: does attention

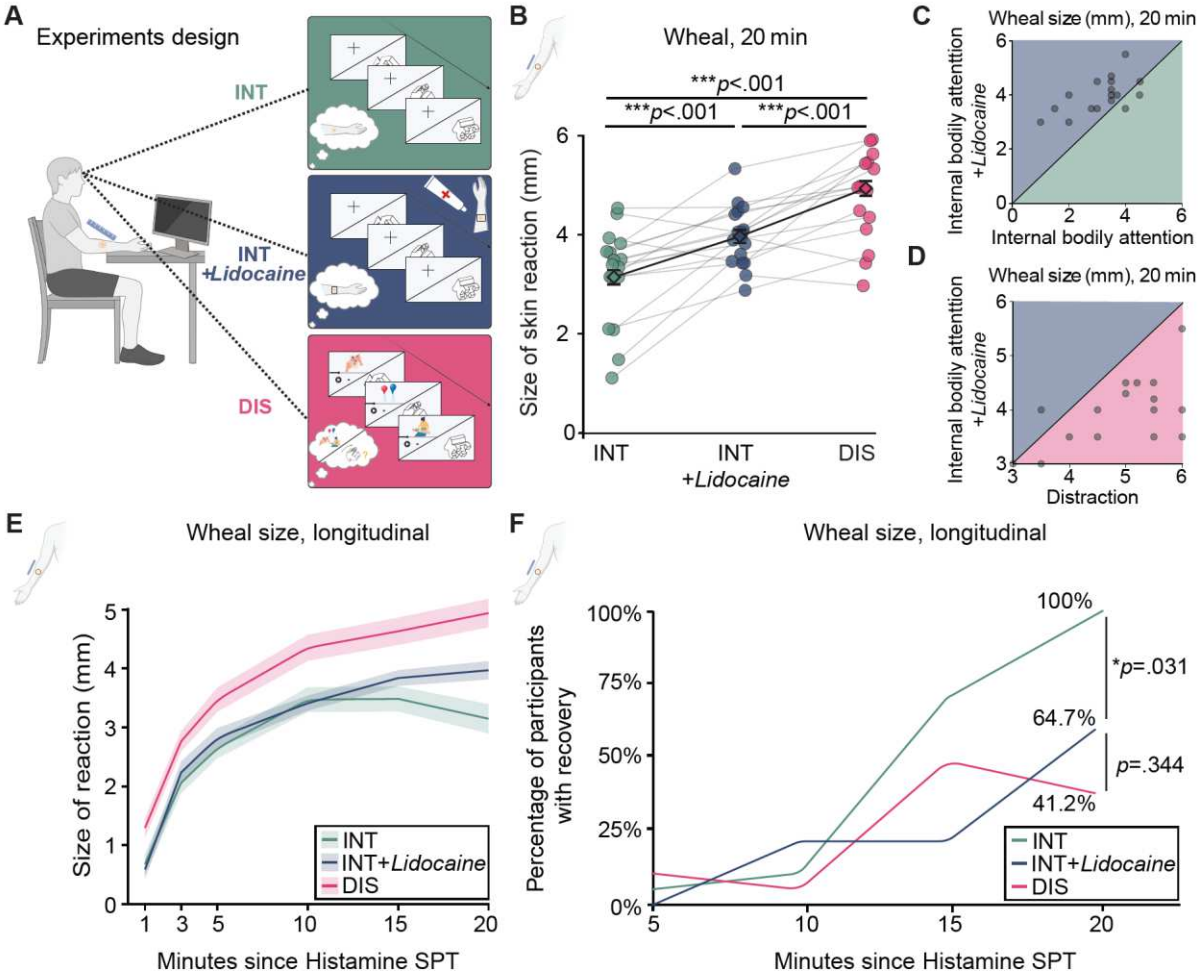
regulate inflammation through sensory feedback, or can it also act independently of it? If sensory amplification contributes to immune regulation, then reducing sensory signaling should diminish the attentional benefit. Animal studies show that ablation of nociceptive neurons disrupts immune regulation[4,5], implying that sensory pathways indeed provide critical input for inflammatory control. To test this, we conducted a preregistered follow-up experiment (Exp. 3, N=17). Participants from earlier experiments again underwent histamine-induced inflammation, this time with sensory signaling pharmacologically attenuated by topical lidocaine, while participants maintained internal attention to the test site (Fig. 2A, Fig. S5.1). Because topical anesthesia (including lidocaine) diminishes the flare response, but not the wheal[25,26], we focused on wheal outcomes to assess whether attenuating sensory signaling would disrupt attentional regulation.

Attenuated sensory input weakened, but did not abolish, the regulatory effect of attention. At the 20-min peak, wheal responses were larger when sensory signaling was attenuated compared to when it was intact, despite attention being directed internally in both conditions (4.0±0.6 vs. 3.1±1.0 mm; t_{16}=4.3, p<.001, d=1.04, 95% CI [0.44,1.63]; Fig. 2B-C). At the same time, regulatory effects persisted even when sensory signaling was attenuated. Wheal responses under lidocaine remained significantly smaller than under distraction at the 20-min peak (4.0±0.6 vs. 5.0±1.0 mm; t_{16}=4.9, p<.001, d=1.19, 95% CI [0.55,1.80]; Fig. 2B,D), and across the entire response period (Fig. 2E; Table S5.2). Importantly, sensation ratings did not differ between the lidocaine and the distraction conditions (t_{34}=1.1, p=.29, d=0.36, 95% CI [-0.31, 1.02]), indicating comparable levels of perceived sensory experience across these conditions, and suggesting that differences in perceived sensory experience are unlikely to fully account for the observed immune effects.

Analyses of temporal dynamics revealed a dissociation between conditions: while both internal attention conditions (with and without sensory attenuation) resulted in a reduced overall inflammatory response relative to distraction, intact sensory signaling produced a greater decline toward baseline (Fig. 2E; Table S5.2), with a higher proportion of participants showing stable or decreasing wheal size by 15-20 minutes (Fig. 2F; Table S5.4). In contrast, recovery dynamics under sensory attenuation did not differ significantly from distraction (Fig. 2F; Table S5.2), suggesting that sensory signaling specifically contributes to differences in the resolution phase of the response, under internal attention.

Together, these findings provide evidence that intact sensory signaling is mechanistically involved in attentional regulation of inflammation in humans. However, it does not fully account for the effect, suggesting an additional contribution of non-sensory, potentially top-down processes to inflammatory control.

Fig. 2. Sensory signaling contributes to attentional regulation of inflammation.



(A) Experimental design. Participants from the earlier experiments completed a third condition in addition to prior ones (internal attention, INT, green; distraction, DIS, pink), wherein sensory signaling was attenuated with topical lidocaine while attention was directed inward (INT+lidocaine, blue, N=17). **(B-F)** Lidocaine weakened, but did not abolish, the regulatory effect of internal attention. Scatter and trajectory plots show larger wheal responses under lidocaine than under intact sensation (B,C,E), and larger still under distraction (D,E). Recovery was slower when sensory signaling was reduced (F). In all plots, paired lines connect within-subject data; shaded areas denote ± SEM. Full statistics described in Tables S5.1-5.4.

Attention-driven inflammatory regulation involves top-down autonomic control

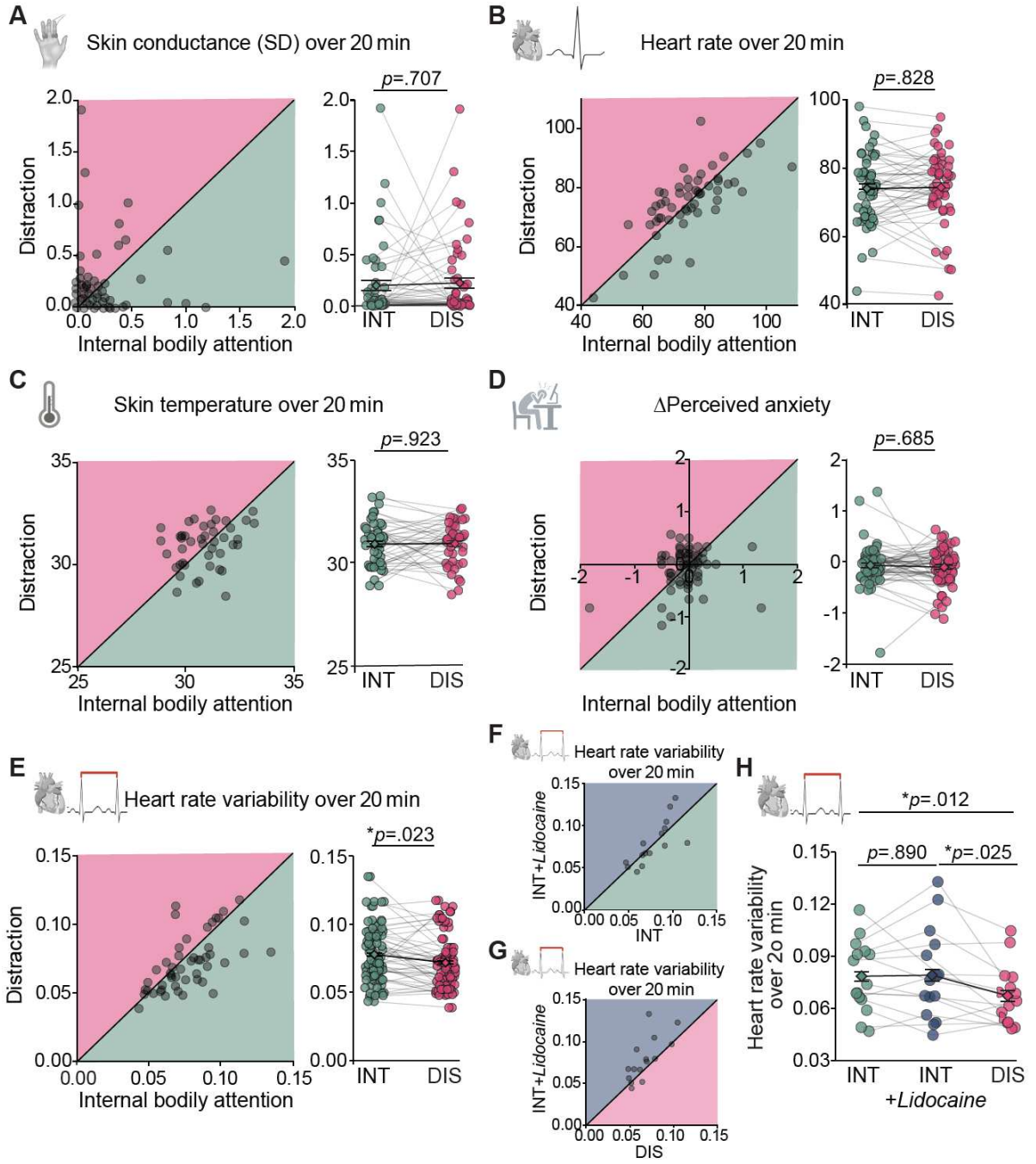
The sensory findings suggest that attentional processes contribute to immune regulation through mechanisms beyond sensory signaling. One possibility is that the sympathetic nervous system plays a part in response regulation, potentially through stress or increased autonomic arousal, which have been shown to influence inflammation[27,28]. Another possible mechanism is parasympathetic vagal activation, a well-established neural route for anti-inflammatory control[16,29,30], including in the skin[31–33]. We therefore tested whether the immune effects observed above were accompanied by one of these autonomic profiles.

Sympathetic indices (skin conductance, heart rate, skin temperature), as well as perceived anxiety, showed no differences between internal attention and distraction across experiments 1 and 2 (all p>.685; Fig. 3A-D; Section S6). This indicates that attentional effects on inflammatory responses are unlikely to be explained by physiological arousal, stress or

perceived anxiety. In contrast, heart rate variability (HRV), a widely used indirect index of vagal activity[34], was significantly higher during internal attention than distraction (t_{48}=2.4, p=.023, d=0.34, 95% CI [0.05,0.62]; Fig. 3E), reflecting greater parasympathetic engagement when directing attention internally.

Finally, we tested whether such parasympathetic activation depends on intact sensory signaling or can be sustained by top-down attention alone. In Exp. 3, where sensory signaling was attenuated with lidocaine while attention was directed internally, HRV remained significantly higher than in distraction (t_{14}=2.5, p=.025, d=0.65, 95% CI [0.08,1.20]), yet was indistinguishable from internal attention with intact sensory signaling (t_{14}=0.1, p=.89, d=0.04, 95% CI [-0.47,0.54]; Fig. 3F-H). This suggests that attention can sustain vagal activation even when sensory signaling is reduced. Together with the persistence of inflammatory regulation under sensory attenuation (Fig. 2), these findings are consistent with the possibility that top-down processes can engage anti-inflammatory pathways, and that this engagement does not depend on sensory input.

Fig. 3. Attentional regulation of inflammation is accompanied by vagal activation, independent of sensory signaling.



(A-D) Sympathetic indices and state anxiety. Internal attention (INT, green) and distraction (DIS, pink) did not differ in skin conductance (A, N=53), heart rate (B, N=54), skin temperature (C, N=44), or perceived anxiety (D, N=56) (all p>.685, Table S6.1). **(E-H)** Parasympathetic (vagal) activity, indexed by heart-rate variability (HRV), was higher during internal attention than distraction (E) and remained elevated under lidocaine (F-H; INT vs. INT + lido: t_{14}=0.1, p=.890; INT + lido vs. DIS: t_{14}=2.5, p=.025, d=0.7; INT vs. DIS: t_{14}=2.9 p=.012, d=0.75, 95% CI [0.16,1.32]), indicating preserved vagal engagement despite attenuated sensory input. In all plots, paired lines connect within-subject data; shaded areas denote ± SEM.

Discussion

Attention has long been understood as a mechanism for shaping perception and neural representations of both external and internal sensory signals. Here, we asked whether such modulation extends to the regulation of downstream physiological processes. By contrasting two ecological attentional states under an identical immune challenge within the same individual, we demonstrate that directing attention toward inflammation-related sensations produces smaller inflammatory responses, with temporal dynamics indicating faster return toward baseline compared to external distractions. This effect was highly consistent across participants, and replicated across two independent cohorts. Our findings therefore establish a causal link between attention and immune regulation in vivo, suggesting that processes often considered autonomously regulated, such as inflammatory responses, are influenced by the voluntary allocation of attentional resources.

Beyond the overall effect, our data indicate that attentional regulation of inflammation involves both sensory-dependent and top-down processes. Directing attention toward inflammation-related sensations shifted immune responses while also enhancing their subjective perception, linking perceptual experience to inflammatory magnitude. To probe the role of sensory input more directly, we attenuated peripheral signaling using lidocaine while participants maintained internal attention. This manipulation selectively disrupted the later phase of the response: compared to internal attention with intact sensory signaling, the subsequent decline toward baseline was diminished, and fewer participants showed recovery, pointing to a role for sensory signaling in the resolution phase. Critically, however, this contribution depended on attentional state: although the distraction condition retained intact sensory signaling, it showed no comparable decline toward baseline, indicating that peripheral input supports these late-phase dynamics specifically when attention is directed internally. At the same time, immune responses under lidocaine remained overall more regulated than under distraction, despite comparable perceived sensation ratings between these conditions. Together, these findings indicate that intact sensory signaling supports the return toward baseline of the inflammatory response when attention is directed inward. Yet internal attention alone appears sufficient to sustain a degree of inflammatory regulation.

We therefore examined whether attentional regulation of inflammation involves a complementary top-down pathway. The effects of internal attention were accompanied by increased heart-rate variability (HRV) compared to distraction, consistent with parasympathetic vagal engagement and its known anti-inflammatory influence[13,35,36]. Since sympathetic measures of stress (including skin conductance, heart rate, and skin temperature) and perceived anxiety were comparable between conditions, it is unlikely that this effect reflects generalized stress or arousal. Importantly, the parasympathetic effects remained evident when sensory input was attenuated, with comparable HRV increases across internal attention conditions regardless of sensory attenuation, supporting the idea that this pathway operates independently of sensory input. Together, these findings suggest that sensory-dependent and top-down processes contribute through complementary mechanisms, although their precise interaction remains to be determined.

At a mechanistic level, the skin provides a useful model for such interactions, as a densely innervated neuroimmune interface in which sensory, vascular, and immune processes are closely coupled. Afferent sensory fibers convey inflammation-related signals to spinal and brainstem circuits, which project to higher-order regions involved in interoception and regulation (e.g., insula, anterior cingulate cortex)[37–39]. In this context, attentional amplification of inflammation-related signals may enhance central representation of inflammatory state, potentially enabling more precise regulation of the response. This interpretation converges with work in rodents showing that sensory afferents are necessary for immune regulation[4,5], and extends it by suggesting that not only the presence of sensory input, but also its attentional weighting, shapes downstream immune responses. In parallel, higher-order brain processes such as internal attention may engage neuroimmune circuits that regulate inflammation through autonomic and humoral routes. This framework is in line with increased HRV observed during internal attention. Although the parasympathetic nervous system does not directly innervate the skin, vagally mediated immunoregulation is thought to operate through the anti-inflammatory reflex, a multi-level circuit involving afferent inflammatory signaling, brainstem nuclei, sympathetic relay pathways such as the splenic nerve, and downstream modulation of immune cell activity, including cytokine release by macrophages and other innate immune cells[40–42]. These pathways may also influence vascular processes such as vasodilation and vascular permeability, which directly shape wheal and flare responses[19,43]. The link between higher-order brain regions, autonomic activation and inflammation is further supported by evidence from animal models demonstrating that cortical stimulation can exert top-down control over peripheral inflammation[44], and with evidence in humans that voluntary engagement of autonomic pathways by trained participants can modulate inflammatory responses during experimental endotoxemia[45]. Together, these observations provide a biological framework through which parallel sensory-dependent and top-down processes may influence inflammation regulation. However, the precise neural and molecular mediators remain to be determined, and it is unclear whether these pathways converge on shared or distinct downstream immune mechanisms.

Our findings also extend prior evidence for the neural regulation of immunity in humans. Previous work has demonstrated that immune responses can be shaped by top-down cognitive processes, including conditioning, stress, and expectancy effects[21,46–52], which typically rely on contextual or learned conditions. In contrast, the present findings show that immune modulation can arise from a purely endogenous shift in attention, without external cues, deception, training, or peripheral manipulation. These findings further suggest a competitive relationship between interoceptive and exteroceptive processing. While such competition is well established in perception[23,24], the present results indicate that it extends to physiological regulation, such that allocating attention to bodily signals influences how those signals are used to shape downstream inflammatory responses. This positions subjective sensory experience as a functional component of immune regulation, rather than a mere byproduct, and raises the possibility that such perceptual processes may similarly influence regulation in other physiological systems.

Why might processes typically considered autonomous, such as inflammation, be sensitive to attentional state? Within predictive and allostatic frameworks of brain-body control[9,12,15,53], the

brain is thought to continuously anticipate and regulate bodily demands. In this context, attention can be understood as a contextual and preparatory signal, informing the brain about potential bodily demands and enabling efficient allocation of metabolic and immune resources. In the present findings, directing attention externally may disrupt this preparatory regulation, whereas deliberate engagement with bodily sensations supports efficient allostatic control by enhancing the precision of interoceptive signals. This account provides a mechanistic bridge between perception and physiology, whereby attentional gain on interoceptive signals directly shapes the updating of internal models that govern immune responses.

Although the present work was conducted in healthy participants, the results have broader implications. Turning attention away from unpleasant sensations is a common habit, and even a clinical practice[54,55], used to reduce discomfort. Our results suggest that such strategies, in certain contexts, may come at a physiological cost, impairing the body's ability to regulate inflammation. Furthermore, they raise the possibility that habitual avoidance of symptoms, whether through distraction or reliance on painkillers, could potentially contribute to the persistence of conditions such as chronic pain or inflammation, though this remains to be tested. Conversely, directing attention toward bodily sensations may support immune regulation. Attention-based interventions such as mindfulness and pain reprocessing therapy, which involve sustained engagement with bodily sensations and symptom-focused monitoring, have been shown to improve both symptoms and physiological outcomes, including inflammatory markers[56,57]. Importantly, these interventions are typically multi-component and unfold over time, making it difficult to isolate the specific cognitive mechanism driving physiological change. The present findings complement this literature by isolating a controlled attentional manipulation with real-time physiological consequences.

Several limitations should be considered when interpreting these findings. First, the present study does not directly measure the molecular or cellular mediators, limiting mechanistic resolution. Although our findings implicate sensory and autonomic pathways, the specific immune targets and signaling cascades remain to be established. Second, the experimental model reflects a localized, acute, histamine-induced inflammatory response in healthy participants, and it is unclear to what extent these findings generalize to other forms of immune responses, including infectious, chronic inflammatory, or autoimmune conditions. In addition, reduced inflammatory magnitude may not universally reflect beneficial regulation, as inflammation is an adaptive process, and attenuation could compromise host defense in some contexts. Third, the current design does not fully dissociate effects on inflammation initiation versus resolution, as attention was manipulated from the onset of inflammation. Fourth, topical lidocaine does not uniformly block all afferent fiber types and may leave residual sensory input intact. Although perceived inflammation-related sensations did not differ between the lidocaine and distraction conditions, residual sensory contributions cannot be fully excluded. Fifth, heart-rate variability provides an indirect index of vagal activity, and more direct assessments of autonomic pathways will be required to fully characterize the underlying mechanisms. In addition, humoral mechanisms, such as cortisol-mediated pathways, were not assessed and may contribute to attentional modulation of immune responses. Finally, neuroimaging approaches (e.g., fMRI, EEG) may help identify the central brain systems through which attention influences immune regulation, including regions involved in interoception and autonomic

control. Together, these limitations point to important directions for future work integrating neural, immunological, and physiological measurements, and extending these paradigms to clinically relevant populations, including those with immune dysregulation, as well as to other inflammatory conditions and longer-term outcomes.

To conclude, these findings establish that voluntary attention can directly regulate acute inflammation in humans. More broadly, they extend the role of attention from shaping perception to influencing physiological control. In this context, the results point to an attention-perception-regulation loop, in which attentional allocation shapes the processing of bodily signals, and the resulting subjective perception informs physiological responses. Crucially, this effect arose from a purely endogenous cognitive shift, without conditioning, external cues, or pharmacological intervention, demonstrating that voluntary attentional engagement alone is sufficient to regulate acute immune responses. Together, these findings implicate subjective sensory experience as an active contributor of immune regulation and extend predictive and allostatic models of brain-body interaction to include attention as an active regulatory component.

Methods

Pre-registrations

All experiments were pre-registered in advance and deposited in an online repository (open science foundation, OSF), including sample size estimations, inclusion and exclusion criteria and analyses plan. Pre-registration helps prevent selective reporting and analytic flexibility, thereby increasing the transparency and credibility of the findings. To maintain double-blind review, the non-anonymized URLs have been temporarily removed, yet their anonymized content can be found in Supplementary S2-S4.

Participants

Participants were recruited from February 2024 to July 2025. A total of N=59 participants were enrolled following an initial online screening for inclusion and exclusion criteria (see below). Exp.1 (distraction as video clips) and Exp.2 (matched distraction as shape plausibility task) included independent sets of participants, whereas Exp.3 included returning participants from both these experiments. Three participants overall did not meet criteria and were therefore excluded from analyses, two in Exp.2, and one in Exp. 3. Therefore, a total of N=57 participants were included in the final analyses (Exp.1: N=37, 75% women, aged 21-42, M_{age}=26.8±4, Exp.2: N=20, 60% women, aged 22-33, M_{age}=26.2±2.9, Exp.3: N=17, 88.2% women, aged 21-31, M_{age}=24.2±2.9). All participants provided written informed consent prior to participation. The study was approved by the Helsinki Committee (specific details will be added post-review), approval no. 0045-23, and was conducted in accordance with the ethical principles of Declaration of Helsinki.

Inclusion-exclusion criteria. All participants were above the age of 18. Exclusion criteria included: (1) contra-indications to histamine SPT or lidocaine, including pregnancy or breastfeeding, past anaphylaxis, asthma, and G6PD deficiency in the lidocaine experiment; (2) current acute respiratory virus or using medications that could interfere with test results, particularly antihistamines, tricyclic-antidepressants, beta-blockers, and immunosuppression; (3) current skin infections or inflammation on the left forearms, or any acute or chronic dermatological problems; and (4) not completing the two experimental sessions; and (5) known infectious diseases that could be transmitted through needlestick or blood exposure (e.g., hepatitis B/C, HIV, tuberculosis).

Sample size calculation. All calculations used the G*Power tool[58] and are mentioned in the pre-registrations. In Exp.1, based on the results of a pilot study, we set a priori medium effect size of 0.5 with a power of 80%. This provided us with a required sample size of N=35 participants, and we therefore collected N=37. In Exp. 2, based on the large effect size observed in Exp. 1 (*Cohen's d* = 1.3), a power analysis suggested that only six participants are sufficient for 80% power. To ensure robustness, we performed an additional calculation with more conservative assumptions (d = 0.8, 95% power), which indicated a required sample size of N=19 for a one-sided hypothesis (distraction>internal attention). This corresponds to 90% power for a two-sided test, and we collected N=20. Finally, in Exp.3, the required sample size (taking a conservative approach of d=0.8 and 80% power) was N=15, and we collected N=17.

In-vivo acute cutaneous inflammation induction

Acute cutaneous inflammation was induced using a standardized histamine skin prick test (SPT[18,19]), which develops immediately, peaking within 15-20 minutes, and is indexed by the size of the wheal (edema) and flare (erythema). Smaller responses are interpreted as more regulated inflammatory activity[6,20–22]. The histamine SPT was applied to the middle third of the left forearm, with location controlled individually across sessions. A trained experimenter, blinded to experiment's conditions, placed one drop of histamine (10mg/mL), and pricked the skin with a sterile allergy lancet (Heinz Herenz Medizinalbedarf GmbH, Hamburg, Germany). After 30 seconds, the experimenter wiped off the remaining substance with a soft tissue. The histamine vial was removed from refrigeration 15 minutes before use and allowed to acclimate to room temperature.

Experimental setup and paradigm

We employed a within-subject, counterbalanced design, participants attended two laboratory sessions at the same hour, 3-5 days apart. Sessions were conducted in a laboratory room under controlled light and temperature conditions. Participants were informed that the experiment involved an allergy skin test, but the pharmacological agents (histamine and lidocaine) were not disclosed. Before each session, participants were instructed to avoid consuming alcohol, shaving their forearm, and applying new topical or systemic treatments within the 12 hours prior to testing. At the beginning of each session, participants provided informed consent and reported their current health status, medication use, smoking, caffeine and alcohol consumption, physical activity, and eating habits over the preceding 72 hours. Before and after each session, participants rated their state anxiety (STAI[59]), with no significant differences between conditions (3.4±0.5 vs. 3.5±0.8, p=.685, Fig 3.D, Table S6.1), ensuring that attentional effects were not confounded. Female participants also reported the phase of their menstrual cycle. All participants were blinded to the study's aim and conditions. Behavioral data were collected using Qualtrics survey software platform (Qualtrics, Provo, UT, USA).

Each experimental session began with a 5-min baseline rest, followed by pre-recorded presentation of the attentional instructions in a counterbalanced manner, and administration of the histamine skin prick test (SPT) to induce acute local inflammation. Participants followed the instructions from the moment of the prick and throughout the subsequent 20 min. Inflammatory responses were measured 6 times following the SPT (1, 3, 5, 10, 15, and 20 minutes), by measuring the wheal and flare diameter with a standard ruler. Autonomic activation was recorded and detailed below (see *Physiological recordings and pre-processing*). In Exp.2, participants additionally rated cutaneous sensations (e.g., itch, burning) on a visual analog scale (VAS) ranging from 1-100. In Exp.3, the procedure was identical to Exp.2, except that before the rest period a fixed area 3*3 cm around the prick area was marked, and a total of 0.3 gram of lidocaine 5% cream (Esracain, Rafa) was applied over it.

At the end of the final session, participants were asked to guess the purpose of the study. Responses were coded into thematic categories[60] (Section S7). Fourteen percent (N=8) correctly identified the link between attentional state and allergy test outcomes, while the majority gave broader or unrelated answers. Importantly, those who guessed correctly did not differ in their response patterns from the rest of the sample. All participants received compensation of 60 NIS (~$16) per hour for their participation in each session.

Experimental cognitive manipulation

Participants listened to pre-recorded instructions accompanied by on-screen text, counterbalanced for condition's order, and were informed that they would later be asked questions about these instructions. The instructions were identical across experiments in both wording and delivery; the only difference concerned the direction of bodily attention, which was guided either toward or away from sensations arising at the test site, in line with prior work contrasting interoceptive and exteroceptive attention[23,24].

Exp.1. Participants maintain gaze on the screen throughout the experiment. They either viewed a fixation cross and were instructed to direct their attention toward their bodily sensations (internal attention) or viewed neutral, engaging video clips and were instructed to direct their attention toward them, (distraction). Participants received the following instructions (presented verbatim): (1) Internal attention: "*During the test and until the end of the experiment, a fixation cross will appear on the screen. You are asked to look at the screen but pay attention only to your hand, where the test is being performed. Please pay attention to the sensations arising from your hand. If your attention wanders naturally, try to bring it back to your hand*."; (2). Distraction: "*During the test and until the end of the experiment, video clips will appear on the screen. You are asked to look at the screen but pay attention only to these video clips. Pay attention to the ideas presented in each of them. If your attention wanders naturally, try to bring it back to the videos*".

Exp.2. Participants viewed a sequence of 37 shapes presented on a screen, each displayed for 40s. Of these, 18 were structurally plausible and 19 implausible[61], violating basic spatial principles. The sequence order was mixed but held constant across sessions and participants. While the visual input remained identical between conditions, the instructions regarding allocation of attention to the immune response directed participants either toward or away from sensations at the test site as follows (presented verbatim): (1) Internal attention: "*During the test and until the end of the experiment, a sequence of different shapes will appear on the screen. You are asked to look at the screen but pay attention only to your hand, where the test is being performed. Please pay attention to the sensations arising from your hand. The shapes are intended to remind you to stay focused on your hand. If your attention wanders naturally, try to bring it back to your hand*"; (2) Distraction: "*During the test and until the end of the experiment, a sequence of different shapes will appear on the screen. You are asked to look at the screen and pay attention only to the shapes that will be displayed. Please concentrate on the shapes. Pay attention to their lines and structure. Try to imagine whether they could exist in reality. There are no right or wrong answers. If your attention wanders naturally, try to bring it back to the shapes*".

Exp.3. In Exp.3 the instructions were kept identical to those used in the internal attention condition of the previous experiments (Exp.1 or 2), with participants hearing the exact format they had previously received.

Manipulation success verification

To confirm compliance with experimental instructions, participants in Exp.1-3 completed manipulation checks at the end of each session.

Exp.1-2. Participants rated to what extent they monitored sensations at their arm (i.e., the test site; "*To what extent did you monitor what was occurring on your hand*?"), on a Likert scale from 1 (not at all) to 5 (very much). As expected, participants reported significantly greater attention to their arm under internal attention as compared to distraction (Section S3).

Exp. 2. An objective manipulation check was included to assess task-related attention. In both sessions and across conditions, participants answered three questions designed to probe different aspects of the shape stream: (i) to recall the overall number of shapes presented, (ii) to estimate the proportion of structurally plausible shapes, and (iii) to discriminate plausibility between two exemplars. Each response was scored for accuracy according to its proximity to the correct value, with "*I do not remember*" and "*I did not notice*" responses coded as 0. Summed across items, this yielded a total accuracy score ranging from 0 to 3. As predicted in our pre-registration, scores were significantly higher in the distraction condition than in the internal attention condition (Section S3), confirming that participants devoted more attention to the shapes when instructed to do so. Finally, Experiment 2 also assessed perceived task demands across conditions using VAS (0-100) post-task evaluation (internal attention; "*How much effort did you put into sensing the sensations from your hand*", distraction; "*How much effort did you put into imagining whether the shapes could exist in reality*?"), with no significant differences between conditions (Section S3), providing no evidence that cognitive load accounted for the observed immune effects (Section S3).

Exp. 3. Participants completed manipulation checks at the end of the session. Specifically, we used the same question as in Exp. 1 and 2 ("*To what extent did you monitor what was occurring on your hand*?"), and then compared their responses under this condition to their responses under intact sensory signaling conditions (internal attention, distraction). Participants reported no significant difference in attention to their hand between the two internal attention conditions, regardless of sensory attenuation (4.1±0.7 vs. 4.3±0.7, $t(16)=1.3$, $p=.206$). In contrast, participants reported significantly greater attention to their hand during internal attention with sensory attenuation compared to distraction (4.3±0.7 versus 3.1±1.2, $t(15)=3.4$, $p=.004$, *Cohen's d*=0.9, Section S5). This indicates that participants were able to maintain internal attention even with sensory signaling attenuated.

Physiological recordings and pre-processing

Autonomic nervous system activation was recorded from baseline and throughout the experiment using a PowerLab data acquisition system (ADInstruments, Dunedin, New Zealand). Physiological measurements included electrocardiogram (ECG), pulse finger, Galvanic Skin Response (GSR), and skin temperature. ECG was recorded using pre-gelled adhesive electrodes: two placed on the wrists, and a reference electrode placed on the right leg above the medial malleolus. The GSR was recorded using bipolar electrodes attached with straps to the middle phalanges of the first and third fingers of the left hand. Prior skin preparation involved washing the hands without soap and thoroughly drying them. A finger pulse sensor was placed on the upper phalanx of the second finger, and a skin temperature sensor on the medial aspect of the inner elbow, both on the left hand. In Exp. 2, respiration was recorded using a nasal cannula connected via PVC tubing to a pressure transducer (Sniff Logic Ltd.). The respiratory signal was exported as an analog signal (±5 V) to the PowerLab device.

Sympathetic activation was assessed using LabChart software as follows: (1) heart rate (beats per minute, BPM) was extracted from the ECG signal using a 40 Hz low-pass filter and the Cyclic Measurements function; (2) tonic GSR was obtained by applying a 0.05–35 Hz band-pass filter and calculating the signal's standard deviation[62]; (3) skin temperature was analyzed directly from the sensor signal without additional processing. Parasympathetic activity was assessed using heart rate variability (HRV), quantified as the coefficient of variation of RR intervals (CVRR). CVRR expresses the standard deviation of RR intervals normalized by their mean, capturing beat-to-beat fluctuations in heart rate that primarily reflect vagal (parasympathetic) modulation of cardiac activity. Calculations were performed with LabChart's HRV module, restricted to RR intervals between 600-1200 ms and complexity set to 1-1.5. For all autonomic measures, we computed the average across the 20 minutes experiment period, with data time-aligned to the 1-min wheal and flare assessments.

As preregistered, participants with missing or invalid physiological data were excluded from the respective analyses. In Exp. 1, missing data included N=3 with missing GSR data, N=1 with missing ECG data, and N=13 with missing skin temperature data. Invalid data included N=1 invalid GSR standard deviation values and N=3 invalid HRV data. In Exp. 2, N=2 participants displayed invalid HRV data.

Data analysis

Data were analyzed using JASP version 0.95.1 and R Studio version 2025.05.0. Following our pre-registered analysis plan, comparisons between conditions in Exp.1 and Exp.2 (internal attention versus Distraction) were performed using two-sided paired tests. For Exp.3, comparisons between pharmacological manipulation (with versus without local anesthesia) were performed using two-tailed paired t-test. When the Shapiro-Wilk test indicated a deviation from normality, the corresponding analyses were repeated with non-parametric tests, reported in the Supplementary (Section S8). Importantly, all significant results remained significant. To examine the trajectories of wheal and flare responses over time in all experiments, we performed repeated-measure ANOVA. Sphericity was assessed using Mauchly's test, and when violated, Greenhouse-Geisser correction was applied. Area Under the Curve (AUC) was calculated using the trapezoidal rule to quantify the cumulative skin wheal and flare responses. AUC was computed for each participant across six time points (1-20 minutes following the histamine SPT). Finally, to examine recovery patterns over time, we created a dichotomous variable for each participant at the last time intervals (15-20 minutes): a decrease or no change in wheal or flare was coded as 1, and an increase was coded as 0. We then compared the experimental conditions using McNemar's test. In Experiment 2, because the initial recovery analysis did not yield significant group differences, we conducted a complementary analysis focused specifically on the resolution phase. See section S2 for more details. All significance thresholds were defined as p=0.05.

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