nature portfolio

Peer Review File

Voluntary Attention Regulates Acute Immune Responses in Humans

Corresponding Author: Dr Liron Rozenkrantz

Version 0:

Decision Letter:

20th January 2026

Dear Dr Rozenkrantz,

Thank you once again for your manuscript, entitled "Voluntary Attention Regulates Acute Immune Responses in Humans", and for your patience during the peer review process.

Your Article has now been evaluated by 3 referees. You will see from their comments copied below that, although they find your work of potential interest, they have raised quite substantial concerns. In light of these comments, we cannot accept the manuscript for publication, but would be interested in considering a revised version if you are willing and able to fully address reviewer and editorial concerns.

We hope you will find the referees' comments useful as you decide how to proceed. If you wish to submit a substantially revised manuscript, please bear in mind that we will be reluctant to approach the referees again in the absence of major revisions. We are committed to providing a fair and constructive peer-review process. Do not hesitate to contact us if there are specific requests from the reviewers that you believe are technically impossible or unlikely to yield a meaningful outcome.

I particular, Reviewer #2 remarks the absence of a crucial control condition (comment 3). Because two reviewers express concern regarding the use of lidocaine, we ask that you run the additional control experiment suggested by Reviewer #2 with a substantial sample size to address the issue.

Finally, your revised manuscript must comply fully with our editorial policies and formatting requirements. Failure to do so will result in your manuscript being returned to you, which will delay its consideration. To assist you in this process, I have attached a checklist that lists all of our requirements. If you have any questions about any of our policies or formatting, please don't hesitate to contact me.

If you wish to submit a suitably revised manuscript, we would hope to receive it within 4 months. I would be grateful if you could contact us as soon as possible if you foresee difficulties with meeting this target resubmission date.

With your revision, please:

• Include a “Response to the editors and reviewers” document detailing, point-by-point, how you addressed each editor and referee comment. If no action was taken to address a point, you must provide a compelling argument. When formatting this document, please respond to each reviewer comment individually, including the full text of the reviewer comment verbatim followed by your response to the individual point. This response will be used by the editors to evaluate your revision and sent back to the reviewers along with the revised manuscript.

• Highlight all changes made to your manuscript or provide us with a version that tracks changes.

Please use the link below to submit your revised manuscript and related files:

Link Redacted

Note: This URL links to your confidential home page and associated information about manuscripts you may have submitted, or that you are reviewing for us. If you wish to forward this email to co-authors, please delete the link to your

homepage.

Thank you for the opportunity to review your work. Please do not hesitate to contact me if you have any questions or would like to discuss the required revisions further.

Sincerely,

[redacted]
Nature Human Behaviour

Reviewer expertise:

Reviewer #1: Pain, empathy, mind-body interaction

Reviewer #2: Gut-brain axis, immune responses, neuroscience

Reviewer #3: Neuroimmune modulation, neurobiology, systemic inflammation

REVIEWER COMMENTS:

Reviewer #1 (Remarks to the Author):

This is a truly compelling and highly significant study that makes a groundbreaking contribution to the field of neuroimmunology. The authors rigorously demonstrate, for the first time in humans, that voluntary attention can causally and rapidly modulate acute inflammatory responses. This finding is exciting as it challenges the traditional view of immune responses as purely reflexive and autonomous, instead positing a sophisticated brain-body interaction where cognition plays a direct regulatory role. The strength of the within-subject experimental design, combined with thoughtful mechanistic probes, makes the conclusions highly convincing and impactful. I have some suggestions for further improvements.

1. Heart Rate Variability (HRV) is an indirect measure. Can more direct evidence of vagal efferent activity at the site of inflammation be obtained (e.g., through neurotransmitter assays, local nerve stimulation/blockade techniques)? What specific immune cells or processes are targeted by vagal efferents in the skin, and how does this lead to regulated inflammation?

2. How do these two pathways (sensory-dependent and vagal top-down) interact? Are they additive, synergistic, or context-dependent? Do they involve shared or distinct downstream molecular targets?

3. Histamine-induced inflammation is an acute, localized allergic-type reaction. Would similar attentional modulation be observed in other forms of inflammation, such as those induced by bacterial components, or in models of chronic inflammation, autoimmune conditions, or even infectious diseases? Different inflammatory pathways might be differentially susceptible to cognitive modulation.

4. The study differentiates between "internal attention" and "distraction." However, "internal attention" can take many forms (e.g., catastrophic rumination vs. non-judgmental awareness as in mindfulness). Would different qualities of internal attention (e.g., accepting vs. resisting bodily sensations) lead to different immune outcomes? This could be a critical step for refining clinical interventions.

5. The study focuses on acute, 20-minute responses. What are the long-term effects of sustained attention-based practices (e.g., daily mindfulness meditation) on baseline immune function, inflammatory markers, or susceptibility to illness? Can individuals be trained to enhance their capacity for attentional immune regulation, and does this capacity generalize to real-world stressors or infections?

6. While subjective sensation was enhanced, what are the cellular and molecular mediators? Does amplified interoceptive input directly influence local immune cells (e.g., mast cell degranulation, cytokine release) or primarily modulate the neural processing of these signals, which then leads to downstream immune effects? Is there a specific neural circuit within the spinal cord or brainstem involved in gating this sensory information to immune-regulatory centers?

7. The study was conducted in healthy young adults. How might these findings translate to older individuals, immunocompromised patients, or those suffering from chronic inflammatory conditions, pain, or psychological disorders (e.g., anxiety, depression), where immune dysregulation is prevalent? Are there age- or disease-related differences in the capacity for attentional immune regulation? Given the higher proportion of female participants, exploring potential sex-specific differences in greater depth could also be valuable.

8. Future studies incorporating neuroimaging techniques (e.g., fMRI, EEG) could identify the specific brain regions and networks involved in mediating these attention-immune effects. This would provide crucial insights into the neural architecture supporting this novel mind-body interaction. For instance, what are the cortical and subcortical correlates of

"enhanced interoceptive precision" in the context of immune regulation?

Reviewer #2 (Remarks to the Author):

In this work, the authors investigated the role of voluntary attention in regulating acute inflammatory responses in human subjects, specifically through the lens of skin inflammation induced by histamine. Prior to this study, it was understood that attention could modulate sensory perception, such as pain, but its direct influence on immunity remained unexplored. The authors carried out preregistered within-subject experiments to show that directing attention toward the site of insult resulted in significantly smaller inflammatory responses compared to distraction. They further suggested two potential mechanisms that might underlie this regulation: a sensory dependent pathway that amplifies skin inflammatory signaling and a sensory-independent pathway involving parasympathetic vagal activity. Overall, this study provides solid evidence demonstrating that targeted attention, a core component of cognitive processes, plays an important role in the modulation of immune responses. However, the mechanistic details underlying this attention-evoked immunomodulation require additional clarification and investigation.
1) Which aspect of the inflammatory response is modulated by directed attention?
The authors suggest that attention promotes a faster-resolving inflammatory response. However, this interpretation is not fully supported by the experimental data and is unlikely to represent the full scope of attention's effects on inflammation. Across Figs. 1C, 1F, S1C, and S1E, the internal attention group shows a reduced initial inflammatory response, suggesting that attention suppresses the initiation of inflammation. Therefore the apparently faster resolution in the attention group may reflect a reduced inflammatory response overall rather than an active acceleration of resolution. A limitation of the current experimental design is that attention is manipulated from the onset of inflammation, making it difficult to dissociate effects on inflammatory initiation from effects on resolution. To substantiate the claim that attention actively promotes resolution, the authors need to adopt a design in which attention is directed to the prick site only after the inflammatory response has reached a plateau/peak.
2) From Fig. 2E and Table S5.3, the INT and INT + lidocaine groups exhibit very similar inflammatory responses during the rising phase (0 -10 mins). However, whereas the response in the INT group declines after reaching its peak, the response in the INT + lidocaine group remains elevated thereafter. This suggests that under directed attention the sensory mechanism selectively modulates the resolution — but not the initiation of — the inflammatory response. Please discuss this.
3) The persistence of immunomodulation in the lidocaine-treated group does not necessarily support a sensory-independent mechanism, as lidocaine may not fully abolish sensory signaling. A missing control would be to assess perceived inflammation-related sensations in the lidocaine + internal attention group and compare them with those in the distraction group. Without this comparison, residual sensory contributions cannot be ruled out.
4) The parasympathetic nervous system does not innervate the skin of the arm. Therefore the proposed involvement of parasympathetic (vagal) mechanisms in regulating cutaneous inflammation is difficult to reconcile with this established anatomy. Indirect pathways or vagally regulated humoral factors might be involved. Please at least explicitly discuss this point in the manuscript.
5) This study examines only neural mechanisms mediating attention-evoked immune changes and does not explore potential humoral mechanisms. Previous work in both rodents and humans has shown that corticosterone/cortisol plays an important role in modulating immune responses. Did the authors examine whether attention directed to the prick site influences circulating cortisol levels? An potential experiment to test whether systemic humoral factors are involved could be to induce local inflammation in both arms, direct attention to the inflamed site on one arm, and monitor inflammatory responses at the unattended site on the contralateral arm.

Reviewer #3 (Remarks to the Author):

In the present manuscript, the authors investigate whether voluntary attention can modulate acute histamine-induced inflammatory responses in healthy humans. Using three preregistered, well-controlled, and blinded within-subject protocols, they employed the histamine skin-prick test to assess wheal (edema) and flare (erythema) responses over a 20-minute period. The results demonstrate that directing attention toward bodily sensations significantly reduces the magnitude of the inflammatory response and accelerates its resolution compared with external distraction.
The authors further propose two complementary neuroimmune mechanisms: (i) a sensory-dependent pathway that conveys afferent signals necessary for efficient immune regulation, examined through local lidocaine administration, and (ii) a descending efferent pathway mediated by vagal signaling, assessed indirectly via heart rate variability. Importantly, the findings indicate that internally driven neural processes can regulate inflammatory responses independently of conditioning, placebo effects, pharmacological interventions, or other external modulatory approaches.
Overall, the results are robust and internally replicated, supported by well-controlled attentional manipulations across experiments. This study is innovative, well designed, methodologically rigorous, and conceptually ambitious, providing compelling evidence that voluntary attention can regulate acute inflammatory responses in humans. Despite limitations inherent to the experimental model and some degree of interpretative extrapolation, the data strongly support the central conclusion and open important avenues for future research in neuroimmune interactions, cognitive neuroscience, and translational medicine.

- The authors should consider including a concise paragraph explicitly addressing the main limitations of the study to avoid potential overinterpretation of these preliminary clinical findings. In particular, the absence of direct molecular mechanisms—

such as the quantification of inflammatory mediators, cytokines, or neuroimmune signaling molecules—limits mechanistic resolution. In addition, the experimental stimulus is highly specific, being local, acute, non-infectious, and histamine-mediated, which constrains generalizability. Future studies should examine whether similar attentional mechanisms operate in chronic inflammatory or autoimmune conditions. Importantly, inflammation is an evolutionarily conserved adaptive response, and attenuating it may not universally reflect "better immune regulation." In some contexts, reduced immune responses could compromise host defense against bacterial or viral challenges. Thus, the translational relevance of these findings, while conceptually compelling, remains speculative and should be interpreted with caution.
- The mechanistic discussion would benefit from a stronger emphasis on original experimental studies rather than primarily relying on review articles, including those from the Kevin Tracey group. Foundational work describing the complexity of the cholinergic anti-inflammatory pathway highlights that vagal modulation of immunity involves a multi-level circuit integrating parasympathetic and sympathetic components rather than a simple unidirectional vagal efferent pathway. For example, seminal studies have demonstrated the essential role of the splenic nerve and β_2-adrenergic signaling in immune regulation (Rosas-Ballina M, et al. Splenic nerve is required for the cholinergic anti-inflammatory pathway control of TNF in endotoxemia. Proc Natl Acad Sci U S A. 2008; Vida G, et al. β2-Adrenoreceptors of regulatory lymphocytes are essential for vagal neuromodulation of the innate immune system. FASEB J. 2011). Moreover, given that voluntary attention is mediated by cortical processes, additional clinical and preclinical evidence linking higher-order brain regions to immune modulation could be discussed. Relevant studies include voluntary activation of autonomic pathways in healthy volunteers (Kox et al., 2014) and cortical stimulation studies demonstrating top-down control of inflammation in local and acute arthritis (Kox M, et al. Voluntary activation of the sympathetic nervous system and attenuation of the innate immune response in humans. Proc Natl Acad Sci U S A. 2014; Bassi GS, et al. Cortical stimulation in conscious rats controls joint inflammation. Prog Neuropsychopharmacol Biol Psychiatry. 2018).
- The use of topical lidocaine as a means of attenuating sensory input is methodologically strategic; however, it is important to clarify and discuss its limitations. Lidocaine does not uniformly block all afferent fiber types, and its effects may differ across nociceptive, mechanoreceptive, and autonomic sensory fibers. Partial or fiber-specific blockade could influence the interpretation of the sensory-dependent component of attentional immune regulation and should therefore be explicitly acknowledged.
- Finally, clarification is warranted regarding whether the distraction strategies employed are validated paradigms within cognitive neuroscience or psychophysiology. While the tasks appear well-controlled and thoughtfully designed, referencing prior validation or established use of similar distraction paradigms would further strengthen confidence that the observed effects are attributable specifically to attentional allocation rather than uncharacterized cognitive or affective factors.
-It is necessary to perform some corrections. For example. In Figs. S3.1.D and S4.1. replace "percieved" with "perceived". Page 4S. "visulaization of reposnse" replace with "visualization of response". Other words also must be correct. For example, "singaling" (Page 6 and 7).

Version 1:

Decision Letter:

Our ref: NATHUMBEHAV-25126014A

21st May 2026

Dear Dr Rozenkrantz,

Thank you for submitting your revised manuscript "Voluntary Attention Regulates Acute Immune Responses in Humans" (NATHUMBEHAV-25126014A). It has now been seen by the original referees and their comments are below. As you can see, the reviewers find that the paper has improved in revision. We will therefore be happy in principle to publish it in Nature Human Behaviour, pending minor revisions to satisfy the referees' final requests and to comply with our editorial and formatting guidelines.

We are now performing detailed checks on your paper and will send you a checklist detailing our editorial and formatting requirements within two weeks. Please do not upload the final materials and make any revisions until you receive this additional information from us.

Please do not hesitate to contact me if you have any questions.

Sincerely,

[redacted]
Nature Human Behaviour

Reviewer #1 (Remarks to the Author):

We greatly appreciate the thorough and thoughtful revisions. The additional analyses significantly strengthen the robustness of your findings. While fully recognizing the excellent contributions of this work, we still have a few further questions that aim to deepen our understanding of the complex mechanisms.

1. The authors have shown that internal attention can activate parasympathetic vagal pathways independently of local sensory input. Can you elaborate further on how this "purely" cognitive attention might mechanistically drive vagal efferent activity from cortical levels, in the absence of direct afferent sensory signals? For instance, what specific brain regions or neural circuits might be involved in translating attentional states into vagal output?
2. The authors describe sensory-dependent and top-down pathways as complementary. Could you speculate on how these two pathways might synergistically interact across different temporal phases of the inflammatory response (e.g., initiation, peak, resolution)? For example, might top-down vagal activation play a crucial preparatory role in initiation, while sensory feedback primarily guides resolution?
3. The paper suggests that smaller, faster-resolving inflammatory responses are "more regulated." Considering that inflammation is an adaptive process, under what physiological circumstances might this attention-induced "regulation" (i.e., reduced magnitude and faster resolution) represent an optimal physiological outcome, and when might it pose potential trade-offs or disadvantages? For instance, would the adaptive significance differ between sterile and infectious inflammation?

Reviewer #2 (Remarks to the Author):

The authors have addressed the reviewer's concerns. I support publication.

Reviewer #3 (Remarks to the Author):

no remarks

General Response

We thank the Editor and the Reviewers for their thoughtful, constructive, and encouraging feedback. We greatly appreciate the recognition of the novelty and significance of our findings, as well as the detailed suggestions for strengthening the manuscript.

Before addressing the specific comments, we would like to note that due to the ongoing war in our region, we have been temporarily unable to conduct new human experiments. Following consultation with the Editor, and in light of the overall positive and constructive feedback, we have focused this revision on (i) incorporating additional analyses from existing data, (ii) clarifying the interpretation and scope of the findings, and (iii) expanding the mechanistic and theoretical discussion.
Importantly, we were able to directly address key methodological concerns, particularly regarding residual sensory input in the lidocaine condition and individual differences in responses, using data already collected but not included in the original submission. We believe these changes address the reviewers' concerns while maintaining a clear, more focused and appropriately bounded interpretation of the results. Nevertheless, we remain fully committed to conducting additional experimental work if required, once circumstances allow.

Below, we respond to each comment in detail.

Reviewer #1:

This is a truly compelling and highly significant study that makes a groundbreaking contribution to the field of neuroimmunology. The authors rigorously demonstrate, for the first time in humans, that voluntary attention can causally and rapidly modulate acute inflammatory responses. This finding is exciting as it challenges the traditional view of immune responses as purely reflexive and autonomous, instead positing a sophisticated brain-body interaction where cognition plays a direct regulatory role. The strength of the within-subject experimental design, combined with thoughtful mechanistic probes, makes the conclusions highly convincing and impactful. I have some suggestions for further improvements.

We thank the reviewer for their thoughtful and encouraging evaluation of our work.

1. Heart Rate Variability (HRV) is an indirect measure. Can more direct evidence of vagal efferent activity at the site of inflammation be obtained (e.g., through neurotransmitter assays, local nerve stimulation/blockade techniques)? What specific immune cells or processes are targeted by vagal efferents in the skin, and how does this lead to regulated inflammation?

We agree that HRV indeed provides an indirect measure of vagal activity and does not directly identify efferent pathways or cellular targets. In the revised manuscript, we clarify this limitation and expand the mechanistic discussion of potential vagal effects on inflammation.
Specifically, we now discuss that these effects are unlikely to occur via direct innervation of the skin, but rather likely to operate through multi-level pathways involving central autonomic circuits, sympathetic relay systems (e.g., splenic nerve), and downstream modulation of immune cell activity. We also explicitly state that the precise neural and molecular mediators remain to be determined.

Discussion, mechanistic paragraph (pg. 11):
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. ... 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 high-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.

Discussion, limitations paragraph (pg. 12)

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. .... 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. ... 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.

2. How do these two pathways (sensory-dependent and vagal top-down) interact? Are they additive, synergistic, or context-dependent? Do they involve shared or distinct downstream molecular targets?

We thank the reviewer for this insightful question, which, together with related comments from Reviewer 2, encouraged us to further examine the data and refine our interpretation. In the revised manuscript, we now frame the sensory-dependent and top-down processes as complementary, based on several lines of evidence from our results. This clarification is now reflected in the Discussion (cited below).

With respect to downstream molecular targets, as discussed above, the present study does not directly determine whether these pathways converge on shared or distinct immune mechanisms. We now explicitly state this limitation in the manuscript and highlight it as an important direction for future research.

Discussion (pg. 10):

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.

Discussion, limitations paragraph (pg. 12)
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. ... Together, these limitations point to important directions for future work integrating neural, immunological, and physiological measurements…

3. Histamine-induced inflammation is an acute, localized allergic-type reaction. Would similar attentional modulation be observed in other forms of inflammation, such as those induced by bacterial components, or in models of chronic inflammation, autoimmune conditions, or even infectious diseases? Different inflammatory pathways might be differentially susceptible to cognitive modulation.

We agree that the present model reflects a specific form of acute, localized inflammation, and that other forms of inflammation should be examined. We have expanded the limitations section to explicitly address generalizability to other types of immune responses, including infectious, chronic, and autoimmune conditions, and mention it as an important future direction.

Discussion, limitations paragraph (pg. 12)
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. ... 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.

4. The study differentiates between "internal attention" and "distraction." However, "internal attention" can take many forms (e.g., catastrophic rumination vs. non-judgmental awareness as in mindfulness). Would different qualities of internal attention (e.g., accepting vs. resisting bodily sensations) lead to different immune outcomes? This could be a critical step for refining clinical interventions.

We thank the reviewer for raising this point. To address it, we analyzed additional measures collected during the experiment, which capture, separately, both stress-related engagement and acceptance-based engagement (Supplementary Section S9).

These exploratory analyses did not indicate modulation of the primary wheal response. For flare, acceptance-based engagement was associated with modest differences in early-phase responses and overall magnitude, suggesting a potential modulatory role. Importantly, the core attentional effect remained robust across groups.

These findings suggest that variability in attentional quality does not account for the primary effect, although it may modulate specific aspects of the response.

Results (pg. 5):

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).

Supplementary Section S9:

Please note we copied here the text only, supporting tables appear in the Supplementary file.

…

Qualitative differences in internal attention. *We next examined whether variability in how participants engaged with internal attention contributed to immune responses. Internal attention can take multiple forms, ranging from evaluative or stress-related engagement (e.g., worry, tension) to more non-judgmental, acceptance-based engagement. To capture these dimensions, we examined two candidate factors.*

Stress-related engagement was captured by the change in state anxiety (STAI[1]; post - pre) during the attention condition, and acceptance-based engagement was defined as the mean of three items reflecting bodily attention and attunement ("I felt present in my body", "I listened to what my body was telling me", "I was attuned to the sensations elicited"; items adapted from [2]) during the attention condition. Participants were divided into high and low levels of each measure and examined as between-subject factors in analyses of inflammatory responses, both within the attention condition and across conditions.

Stress-related engagement did not modulate wheal or flare responses, either within the attention condition or across conditions (all $p > .213$; Tables S9.3-S9.4).

Acceptance-based engagement did not significantly influence the wheal response, either within the attention condition (all p >.386) or across conditions (all p>.162). For flare, a significant Engagement × Time interaction was observed within the attention condition (p=.011; Table S9.5). Post-hoc comparisons indicated smaller, more regulated responses in the first minute of the effect in participants reporting higher acceptance engagement (p=.015), but not in other timepoints (all p >.122; Table S9.6). Across conditions, acceptance-based engagement also modulated flare trajectories, with a significant Engagement × Time interaction (p=.011), with a similar pattern as reported above. In addition, a Condition × Engagement interaction (p=.028) was observed, with post-hoc comparisons indicating that attentional modulation was significant in both high- and low-acceptance groups, but the effect was stronger among participants reporting higher acceptance-based engagement (low group: p=0.017; high group: p<.001; Tables S9.7-S9.8).

5. The study focuses on acute, 20-minute responses. What are the long-term effects of sustained attention-based practices (e.g., daily mindfulness meditation) on baseline immune function, inflammatory markers, or susceptibility to illness? Can individuals be trained to enhance their capacity for attentional immune regulation, and does this capacity generalize to real-world stressors or infections?

Indeed, long term effects and real-world extension are an important next step. Interesting evidence exists to link trained and longer-term attentional practices e.g., mindfulness and symptom-focused monitoring) with changes in inflammatory markers and immune-related outcomes. We have expanded the Discussion to include these practices, and note that they may represent a longer-term extension of the mechanisms identified here. We also highlight longer-term outcomes as an important direction for future work, as reflected in the revised limitations paragraph.

Discussion (pg. 12):

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.*

Discussion (pg. 13):

…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.

6. While subjective sensation was enhanced, what are the cellular and molecular mediators? Does amplified interoceptive input directly influence local immune cells (e.g., mast cell degranulation, cytokine release) or primarily modulate the neural processing of these signals, which then leads to downstream immune effects? Is there a specific neural circuit within the spinal cord or brainstem involved in gating this sensory information to immune-regulatory centers?

We have expanded the mechanistic discussion to consider both local immune processes (e.g., vascular and cellular responses) and central integration of inflammatory signals. We also discuss candidate neural pathways linking afferent input to immune regulation, while clearly stating that these interpretations remain hypothetical.

Discussion (pg. 11):

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 high-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.

Discussion, limitations paragraph (pg. 12)

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. … Together, these limitations point to important directions for future work integrating neural, immunological, and physiological measurements…

7. The study was conducted in healthy young adults. How might these findings translate to older individuals, immunocompromised patients, or those suffering from chronic inflammatory conditions, pain, or psychological disorders (e.g., anxiety, depression), where immune dysregulation is prevalent? Are there age- or disease-related differences in the capacity for attentional immune regulation? Given the higher proportion of female participants, exploring potential sex-specific differences in greater depth could also be valuable.

We agree that generalizability across populations remains an important open question, and have now expanded the limitations section to explicitly note that the present findings were obtained in healthy young adults and may differ across age groups or clinical populations characterized by immune dysregulation, and highlight these as important directions for future research in the limitations section in the Discussion (pg. 12, cited above).
In addition, we examined potential modulation by sex and age within our sample and observed no significant effects. These analyses are detailed in Supplementary Section S9, and referred to from the main text.

Results (pg. 5):
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).

Supplementary Section S9:
Please note we copied here the text only, supporting tables appear in the Supplementary file.
…
Demographic factors (sex, age). *Sex did not significantly influence the wheal response (all p >.128, Table S9.1). For flare, a trend-level Sex x Condition interaction (p=.054) was observed. Post-hoc comparisons indicated that attentional modulation was significant in both men and women, but the effect was stronger in men (women: t=-3.0, p=0.017; men: t=-4.3, p<.001). Age did not significantly modulate attentional effects on wheal (all p > .369) or flare (all p > .176; Table S9.2).*

8. Future studies incorporating neuroimaging techniques (e.g., fMRI, EEG) could identify the specific brain regions and networks involved in mediating these attention-immune effects. This would provide crucial insights into the neural architecture supporting this novel mind-body interaction. For instance, what are the cortical and subcortical correlates of "enhanced interoceptive precision" in the context of immune regulation?

We agree and now explicitly highlight this as an important direction for future research. Specifically, we note that neuroimaging approaches (e.g., fMRI, EEG) could help identify the

cortical and subcortical circuits through which attention influences immune regulation, including regions involved in interoception and autonomic control.
In addition, the revised mechanistic discussion now outlines candidate cortical and subcortical pathways (e.g., insula, anterior cingulate, brainstem-autonomic circuits) through which such effects may be implemented.

Discussion, limitations paragraph (pg. 12)
Several limitations should be considered when interpreting these findings… 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…

Discussion (pg. 11):
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 high-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.

Reviewer #2 (Remarks to the Author):

In this work, the authors investigated the role of voluntary attention in regulating acute inflammatory responses in human subjects, specifically through the lens of skin inflammation induced by histamine. Prior to this study, it was understood that attention could modulate sensory perception, such as pain, but its direct influence on immunity remained unexplored. The authors carried out preregistered within-subject experiments to show that directing attention toward the site of insult resulted in significantly smaller inflammatory responses compared to distraction. They further suggested two potential mechanisms that might underlie this regulation: a sensory dependent pathway that amplifies skin inflammatory signaling and a sensory-independent pathway involving parasympathetic vagal activity. Overall, this study provides solid evidence demonstrating that targeted attention, a core component of cognitive processes, plays an important role in the modulation of immune responses.

We thank the reviewer for their positive feedback and insightful comments.

However, the mechanistic details underlying this attention-evoked immunomodulation require additional clarification and investigation.

1) Which aspect of the inflammatory response is modulated by directed attention?

The authors suggest that attention promotes a faster-resolving inflammatory response. However, this interpretation is not fully supported by the experimental data and is unlikely to represent the full scope of attention's effects on inflammation. Across Figs. 1C, 1F, S1C, and S1E, the internal attention group shows a reduced initial inflammatory response, suggesting that attention suppresses the initiation of inflammation. Therefore the apparently faster resolution in the attention group may reflect a reduced inflammatory response overall rather than an active acceleration of resolution. A limitation of the current experimental design is that attention is manipulated from the onset of inflammation, making it difficult to dissociate effects on inflammatory initiation from effects on resolution. To substantiate the claim that attention actively promotes resolution, the authors need to adopt a design in which attention is directed to the prick site only after the inflammatory response has reached a plateau/peak.

We agree that the current design does not allow a full dissociation between effects on initiation and resolution, as attention was manipulated from the onset of inflammation. We have therefore revised the manuscript to avoid interpreting the findings as accelerated resolution per se, and instead describe them as reflecting differences in temporal dynamics consistent with greater return toward baseline.

At the same time, analyses of the late-phase response (10-20 min) indicate that attention influences response dynamics beyond overall magnitude, as shown by both slope-based models and recovery classification designed to dissociate these components. We now clarify this distinction in both the Results and Discussion.

Notably, the lidocaine findings are also consistent with this interpretation: while early-phase responses were similar, differences emerged in the later phase, suggesting sensitivity to response dynamics beyond initial magnitude (pg. 6). However, we emphasize that the current design does not fully dissociate initiation from resolution.

Results (pg. 3):

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).

Discussion (pg. 12):

Several limitations should be considered when interpreting these findings… Third, the current design does not fully dissociate effects on inflammation initiation versus resolution, as attention was manipulated from the onset of inflammation.

2) From Fig. 2E and Table S5.3, the INT and INT + lidocaine groups exhibit very similar inflammatory responses during the rising phase (0 -10 mins). However, whereas the response in the INT group declines after reaching its peak, the response in the INT + lidocaine group remains elevated thereafter. This suggests that under directed attention the sensory mechanism selectively modulates the resolution — but not the initiation of — the inflammatory response. Please discuss this.

We thank the reviewer for this insightful observation. We have incorporated this point directly into both the Results and Discussion. We now explicitly state that sensory signaling selectively contributes to response dynamics, consistent with the reviewer's observation.

Results (pg. 6):

..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.

Discussion (pg. 10):

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.

3) The persistence of immunomodulation in the lidocaine-treated group does not necessarily support a sensory-independent mechanism, as lidocaine may not fully abolish sensory signaling. A missing control would be to assess perceived inflammation-related sensations in the lidocaine + internal attention group and compare them with those in the distraction group. Without this comparison, residual sensory contributions cannot be ruled out.

This concern is well taken, and we agree that lidocaine does not uniformly block all afferent input, which we now explicitly acknowledge as a limitation in the manuscript.

Importantly, we also report analyses of subjective sensation ratings (collected but not previously reported), showing no significant difference between the distraction and internal attention + lidocaine conditions (t(34)=1.1, *p*=.290, *d*=0.36, 95% CI [-0.31, 1.02]), suggesting that residual sensory input is unlikely to account for the observed immunoregulatory effects. This is now added to the Results section and the Discussion.

Results (pg. 6):

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.

Discussion:

Several limitations should be considered when interpreting these findings. ... 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.

4) The parasympathetic nervous system does not innervate the skin of the arm. Therefore the proposed involvement of parasympathetic (vagal) mechanisms in regulating cutaneous inflammation is difficult to reconcile with this established anatomy. Indirect pathways or vagally regulated humoral factors might be involved. Please at least explicitly discuss this point in the manuscript.

We agree, and have revised the manuscript to make this explicit. We now clarify that parasympathetic effects on cutaneous inflammation are unlikely to occur via direct innervation, and discuss the indirect pathways through which vagal activity may nonetheless influence immune responses, including brainstem nuclei, sympathetic relay pathways such as the splenic nerve, and humoral mechanisms.

Discussion, mechanistic paragraph (pg. 11):

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. ... 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 high-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.

Discussion, limitations paragraph (pg. 12)

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. …. 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… 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.

5) This study examines only neural mechanisms mediating attention-evoked immune changes and does not explore potential humoral mechanisms. Previous work in both rodents and humans has shown that corticosterone/cortisol plays an important role in modulating immune responses. Did the authors examine whether attention directed to the prick site influences circulating cortisol levels? An potential experiment to test whether systemic humoral factors are involved could be to induce local inflammation in both arms, direct attention to the inflamed site on one arm, and monitor inflammatory responses at the unattended site on the contralateral arm.

We agree that humoral pathways, including cortisol-mediated mechanisms, represent an important candidate mechanism that was not assessed in the present study. We now explicitly acknowledge this as a limitation in the manuscript (cited below). The bilateral arm design proposed by the reviewer is an elegant approach to isolating systemic humoral contributions, and represents a promising direction for follow-up work.

Discussion, limitations paragraph (pg. 12)

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. …. In addition, humoral mechanisms, such as cortisol-mediated pathways, were not assessed and may contribute to attentional modulation of immune responses… Together, these limitations point to important directions for future work integrating neural, immunological, and physiological measurements…

Reviewer #3 (Remarks to the Author):

In the present manuscript, the authors investigate whether voluntary attention can modulate acute histamine-induced inflammatory responses in healthy humans. Using three preregistered, well-controlled, and blinded within-subject protocols, they employed the histamine skin-prick test to assess wheal (edema) and flare (erythema) responses over a 20-minute period. The results demonstrate that directing attention toward bodily sensations significantly reduces the magnitude of the inflammatory response and accelerates its resolution compared with external distraction. The authors further propose two complementary neuroimmune mechanisms: (i) a sensory-dependent pathway that conveys afferent signals necessary for efficient immune regulation, examined through local lidocaine administration, and (ii) a descending efferent pathway mediated by vagal signaling, assessed indirectly via heart rate variability. Importantly, the findings indicate that internally driven neural processes can regulate inflammatory responses independently of conditioning, placebo effects, pharmacological interventions, or other external modulatory approaches.
Overall, the results are robust and internally replicated, supported by well-controlled attentional manipulations across experiments. This study is innovative, well designed, methodologically rigorous, and conceptually ambitious, providing compelling evidence that voluntary attention can regulate acute inflammatory responses in humans. Despite limitations inherent to the experimental model and some degree of interpretative extrapolation, the data strongly support the central conclusion and open important avenues for future research in neuroimmune interactions, cognitive neuroscience, and translational medicine.

We thank the reviewer for their positive evaluation and constructive suggestions.

- The authors should consider including a concise paragraph explicitly addressing the main limitations of the study to avoid potential overinterpretation of these preliminary clinical findings. In particular, the absence of direct molecular mechanisms—such as the quantification of inflammatory mediators, cytokines, or neuroimmune signaling molecules—limits mechanistic resolution. In addition, the experimental stimulus is highly specific, being local, acute, non-infectious, and histamine-mediated, which constrains generalizability. Future studies should examine whether similar attentional mechanisms operate in chronic inflammatory or autoimmune conditions. Importantly, inflammation is an evolutionarily conserved adaptive response, and attenuating it may not universally reflect "better immune regulation." In some contexts, reduced immune responses could compromise host defense against bacterial or viral challenges. Thus, the translational relevance of these findings, while conceptually compelling, remains speculative and should be interpreted with caution.

We thank the reviewer for this important suggestion. In the revised manuscript, we have added a dedicated limitations paragraph that explicitly addresses the main constraints of the present study and clarifies the scope of our conclusions. This paragraph covers the absence of direct molecular measurements, the specificity of the experimental model, limited generalizability to other inflammatory conditions, and the adaptive nature of inflammation, noting that attenuated responses may not universally reflect beneficial regulation and could in some contexts compromise host defense.

Regarding the interpretation of smaller responses as reflecting more regulated immune activity, we follow prior literature in histamine skin-prick studies. In line with the reviewer's comment, we explicitly mention this in the main text of the manuscript and have revised the text to temper this interpretation (now phrased as "commonly interpreted"), and to explicitly qualify its scope in the limitations section.

Main (pg. 2):

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.

Discussion, limitations paragraph (pg. 12)

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.

- The mechanistic discussion would benefit from a stronger emphasis on original experimental studies rather than primarily relying on review articles, including those from the Kevin Tracey group. Foundational work describing the complexity of the cholinergic anti-inflammatory pathway highlights that vagal modulation of immunity involves a multi-level circuit integrating parasympathetic and sympathetic components rather than a simple unidirectional vagal efferent pathway. For example, seminal studies have demonstrated the essential role of the splenic nerve and β_2-adrenergic signaling in immune regulation (Rosas-Ballina M, et al. Splenic nerve is required for the cholinergic anti-inflammatory pathway control of TNF in endotoxemia. Proc

Natl Acad Sci U S A. 2008; Vida G, et al. β2-Adrenoreceptors of regulatory lymphocytes are essential for vagal neuromodulation of the innate immune system. FASEB J. 2011). Moreover, given that voluntary attention is mediated by cortical processes, additional clinical and preclinical evidence linking higher-order brain regions to immune modulation could be discussed. Relevant studies include voluntary activation of autonomic pathways in healthy volunteers (Kox et al., 2014) and cortical stimulation studies demonstrating top-down control of inflammation in local and acute arthritis (Kox M, et al. Voluntary activation of the sympathetic nervous system and attenuation of the innate immune response in humans. Proc Natl Acad Sci U S A. 2014; Bassi GS, et al. Cortical stimulation in conscious rats controls joint inflammation. Prog Neuropsychopharmacol Biol Psychiatry. 2018).

We thank the reviewer for this important suggestion. In the revised manuscript, we have expanded the mechanistic discussion to better reflect the multi-level nature of neuroimmune regulation and to incorporate primary experimental literature. Specifically, we now discuss evidence for indirect vagal pathways involving sympathetic relay circuits (e.g., splenic nerve) and immune cell modulation, and include relevant foundational studies (e.g., Rosas-Ballina et al., 2008; Vida et al., 2011), as well as work linking higher-order brain processes to immune regulation (Kox et al, 2014, Bassi et al 2018).

Discussion (pg. 11):

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 high-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.

- The use of topical lidocaine as a means of attenuating sensory input is methodologically strategic; however, it is important to clarify and discuss its limitations. Lidocaine does not uniformly block all afferent fiber types, and its effects may differ across nociceptive, mechanoreceptive, and autonomic sensory fibers. Partial or fiber-specific blockade could influence the interpretation of the sensory-dependent component of attentional immune regulation and should therefore be explicitly acknowledged.

We now explicitly discuss that lidocaine does not uniformly block all afferent fiber types and may leave residual signaling intact. In addition, we now complement this limitation with empirical evidence from our dataset showing comparable subjective sensation across conditions, which constrains the extent to which residual sensory input can explain the observed effects.

Results (pg. 6):

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.

Discussion:

Several limitations should be considered when interpreting these findings. … 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.

- Finally, clarification is warranted regarding whether the distraction strategies employed are validated paradigms within cognitive neuroscience or psychophysiology. While the tasks appear well-controlled and thoughtfully designed, referencing prior validation or established use of similar distraction paradigms would further strengthen confidence that the observed effects are

attributable specifically to attentional allocation rather than uncharacterized cognitive or affective factors.

We thank the reviewer for this point. We have revised the manuscript to clarify that the attentional manipulation aligns with established interoceptive versus exteroceptive attention paradigms, and have added relevant references (both in the main text and the methods section).
Several features of the design support the interpretation that the observed effects reflect attentional allocation specifically rather than task-related confounds: attentional engagement was verified using both subjective and objective measures; Experiment 2 matched visual input, task structure, and cognitive load across conditions, isolating attentional direction; and sympathetic arousal and perceived anxiety did not differ between conditions across experiments, ruling out generalized stress as an alternative explanation.

Main (pg. 2):
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].

Experimental cognitive manipulation description, pg. 16
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].

Results (pg. 5), Exp. 2:
Despite identical visual stimulation and matched cognitive demands, internal attention again produced markedly smaller inflammatory responses than distraction [...] suggesting that the effect is unlikely to be explained by differences in sensory input, distraction source, or perceived difficulty, but instead reflects the direction of attention itself.

-It is necessary to perform some corrections. For example. In Figs. S3.1.D and S4.1. replace "percieved" with "perceived". Page 4S. "visulaization of reposnse" replace with "visualization of response". Other words also must be correct. For example, "singaling" (Page 6 and 7).

All typographical and formatting issues have been corrected as suggested by the Reviewer.

Response letter

We thank the Editor and the Reviewers for their thoughtful, constructive, and encouraging feedback. We greatly appreciate the recognition of the novelty and significance of our findings, as well as the detailed suggestions for strengthening the manuscript.

Below, we respond to each comment in detail.

Reviewer #1:

We greatly appreciate the thorough and thoughtful revisions. The additional analyses significantly strengthen the robustness of your findings. While fully recognizing the excellent contributions of this work, we still have a few further questions that aim to deepen our understanding of the complex mechanisms.

We thank the reviewer for their positive evaluation of the manuscript and for these insightful questions regarding the broader interpretation and mechanistic implications of our findings. We have expanded the Discussion accordingly. Our responses are provided below.

1. The authors have shown that internal attention can activate parasympathetic vagal pathways independently of local sensory input. Can you elaborate further on how this "purely" cognitive attention might mechanistically drive vagal efferent activity from cortical levels, in the absence of direct afferent sensory signals? For instance, what specific brain regions or neural circuits might be involved in translating attentional states into vagal output?

We thank the reviewer for this important question. We have expanded the Discussion (pg. 12) to discuss possible neural mechanisms. Specifically, we note that internally directed attention may engage cortical regions implicated in interoception and autonomic regulation, including the insula and anterior cingulate cortex, which are connected to brainstem autonomic nuclei through descending pathways. We emphasize that these mechanisms require direct investigation in future work.

Discussion, mechanistic paragraph (pg. 12):
In parallel, higher-order brain processes such as internal attention may engage neuroimmune circuits that regulate inflammation through autonomic and humoral routes. One possibility is that internally directed attention may engage cortical systems involved in bidirectional interoceptive-autonomic signaling, including insular and cingulate cortices, which are linked to brainstem autonomic nuclei through descending regulatory pathways and have been implicated in parasympathetic control[40–42]. Within this framework, attentional states may bias descending autonomic control signals even in the absence of changes in peripheral sensory input. This interpretation is consistent with the increased HRV observed during internal attention versus distraction, despite identical inflammation induction, yet the specific neural pathways and efferent mechanisms remain to be established.

2. The authors describe sensory-dependent and top-down pathways as complementary. Could you speculate on how these two pathways might synergistically interact across different temporal phases of the inflammatory response (e.g., initiation, peak, resolution)? For example, might top-down vagal activation play a crucial preparatory role in initiation, while sensory feedback primarily guides resolution?

We thank the reviewer for this suggestion. We have expanded the Discussion to discuss a potential temporal interaction between the two pathways. Specifically, our findings raise the possibility that top-down attentional engagement contributes to early preparatory regulation, whereas ongoing sensory feedback may become particularly important for updating and resolving inflammatory activity over time. We now explicitly note that this interpretation remains speculative because our design was not optimized to dissociate initiation and resolution phases.

Discussion, mechanistic paragraph (pg. 12):
Although their precise interaction remains to be determined, the temporal profile observed here raises the possibility that top-down attentional engagement supports preparatory or anticipatory regulation early in the response, whereas ongoing sensory feedback becomes particularly important for updating and resolving inflammatory activity over time.

3. The paper suggests that smaller, faster-resolving inflammatory responses are "more regulated." Considering that inflammation is an adaptive process, under what physiological circumstances might this attention-induced "regulation" (i.e., reduced magnitude and faster resolution) represent an optimal physiological outcome, and when might it pose potential trade-offs or disadvantages? For instance, would the adaptive significance differ between sterile and infectious inflammation?

We agree with the reviewer and have clarified this point in the Discussion and Limitations sections. We now emphasize that reduced inflammatory magnitude is not universally beneficial. While faster resolution may be advantageous in sterile or excessive inflammatory states, excessive attenuation during infection could compromise host defense. Accordingly, the adaptive significance of attention-related immune regulation is likely to depend on physiological context.

Discussion, limitations paragraph (pg. 14):
… 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, whose optimal magnitude and duration depend on context[61]. In sterile or excessive inflammatory states, faster resolution may support efficient tissue recovery and reduce unnecessary physiological cost, whereas in infectious contexts excessive attenuation could compromise host defense.

Reviewer #2:

The authors have addressed the reviewer's concerns. I support publication.

Reviewer #3:

no remarks