

Sensory encoding and memory retrieval are coordinated with propagating waves in the human brain

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

This manuscript from Yang et al. reports analyses of several publicly available large-scale datasets—including Neuropixels recordings in mice and 7T fMRI in humans—in support of the claim made in the title: “Propagating cortical waves coordinate sensory encoding and memory retrieval in the human brain”. The primary observation is that particular phases of a previously described traveling wave process are preferentially associated with improved memory encoding or recall, as operationalized according to encoding/decoding neural network models. The work builds on the group’s prior studies describing these waves in humans and relevant behavioral results in mice.

Overall, I found this to be a thoughtful piece of work, with a reasonable set of analyses that were carefully executed. It is a valuable, novel contribution to the literature and will be of broad interest. I have no major technical concerns—just a few comments on the framing that I hope will help clarify the authors’ message.

1. There is a certain conceptual ambiguity at the heart of this study—namely, what specifically is the role of propagating waves in promoting memory encoding and recall? Personally, I don’t see this ambiguity as a major flaw of the study, nor is it obvious how to get to the bottom of it; however, I do think it is a limitation that should be more explicitly discussed.

As the authors acknowledge, prior studies have separately demonstrated the existence of these waves, their correspondence with indices of fluctuating arousal, and—in mice—modulation of sensory encoding according to arousal/pupil size. The current paper is an important demonstration that these arousal-associated waves persist during task performance, and that decodability from human brain images covaries with pupil size fluctuations. These are two valuable findings—but I’m not sure that much more can be said beyond these points. In this sense, claims that “these waves in human fMRI promote sensory information encoding and memory retrieval alternatively” (from the abstract) seem to sneak in causal inferences that go beyond what the data can tell us.

2. Related to this ambiguity, in certain places (e.g. the abstract and lines 145-148), the language slips into framing “cascades” as the key regulator of memory in mice, and waves as the key regulator in humans. Are we sure this isn’t simply because invasive electrophysiology was used in mice and brain-wide imaging was used in humans? In other words, very many processes covary with arousal fluctuations; it’s not clear what can be specifically attributed to waves (or cascades) versus any other correlate of these fluctuations (e.g., changes in pupil size, delta power, sharp-wave ripples etc.).

3. Given this broader context, wouldn’t it be just as reasonable to contextualize the present observations within a broader literature on arousal modulation of sensory encoding/recall rather than modulation by these waves per se (e.g., (Harris and Thiele, 2011; Vinck et al., 2015; Lee et al., 2020); or in humans, e.g., (Goldinger and Papesch, 2012; Kucewicz et al., 2018))?

a. To this point, it could be nice to present Fig. 3C-D (perhaps in the supplement) in a manner that aligns everything to pupil size, rather than using the global fMRI signal as a reference in humans and firing patterns in mice. It would also be nice to show such a representation without an estimated hemodynamic delay, as such a delay seems ill-defined in the presence of these biphasic patterns.

4. Related to this point, at present, the review of the rodent literature is very limited. The second paragraph of the Introduction summarizes this literature through a total of three self-citations (each of these studies being performed on previously

published datasets). It would be nice to acknowledge a broader body of work in this space on which the present group's current and past works build. This includes some of the original studies reporting widespread coupling of neuronal firing rates to pupil fluctuations (including their diverse delays and organization into two main clusters) (Okun et al., 2019; Stringer et al., 2019), as well as prior arguments for the sort of exteroceptive-interoceptive (including memory encoding-retrieval) switching that the present study is highlighting (e.g., (Buzsáki, 1989; Hasselmo, 1995)); see (Honey, Newman and Schapiro, 2017) for an extensive review of this theme).

5. The question of whether spiking cascades and waves represent the same neurophysiological process is framed as a key question addressed in this study. But to the extent that this question is (or even could be) answered by the current study—namely, by interrelating phenomena observed asynchronously across not only different datasets, but different species—it is already supported by prior literature. Specifically, although the connection between these waves and pupil fluctuations is described here as the missing link, such a connection is apparent from prior works (Yellin, Berkovich-Ohana and Malach, 2015; Raut et al., 2021; Bolt et al., 2023; Podvalny, Sanchez-Romero and Cole, 2024).

All this said, I believe it is an intriguing hypothesis that the propagating waves are directly involved in memory-related processes, or that they may be a key, largely overlooked component of the arousal-related modulation of encoding/recall in general. I hope that consideration of the above points will help the authors clarify their particular interpretations in relation to a broader literature on arousal modulation of memory systems—and also clarify where those interpretations go beyond what the data currently permit one to conclude.

References

Bolt, T.S. et al. (2023) 'A Unified Physiological Process Links Global Patterns of Functional MRI, Respiratory Activity, and Autonomic Signaling'. *bioRxiv*, p. 2023.01.19.524818. Available at: <https://doi.org/10.1101/2023.01.19.524818>.

Buzsáki, G. (1989) 'Two-stage model of memory trace formation: A role for "noisy" brain states', *Neuroscience*, 31(3), pp. 551–570. Available at: [https://doi.org/10.1016/0306-4522\(89\)90423-5](https://doi.org/10.1016/0306-4522(89)90423-5).

Goldinger, S.D. and Papesch, M.H. (2012) 'Pupil Dilation Reflects the Creation and Retrieval of Memories', *Current Directions in Psychological Science*, 21(2), pp. 90–95. Available at: <https://doi.org/10.1177/0963721412436811>.

Harris, K.D. and Thiele, A. (2011) 'Cortical state and attention', *Nature Reviews Neuroscience*, 12(9), pp. 509–523. Available at: <https://doi.org/10.1038/nrn3084>.

Hasselmo, M.E. (1995) 'Neuromodulation and cortical function: modeling the physiological basis of behavior', *Behavioural Brain Research*, 67(1), pp. 1–27. Available at: [https://doi.org/10.1016/0166-4328\(94\)00113-T](https://doi.org/10.1016/0166-4328(94)00113-T).

Honey, C.J., Newman, E.L. and Schapiro, A.C. (2017) 'Switching between internal and external modes: A multiscale learning principle', *Network Neuroscience*, 1(4), pp. 339–356. Available at: https://doi.org/10.1162/NETN_a_00024.

Kucewicz, M.T. et al. (2018) 'Pupil size reflects successful encoding and recall of memory in humans', *Scientific Reports*, 8(1), p. 4949. Available at: <https://doi.org/10.1038/s41598-018-23197-6>.

Lee, C.C.Y. et al. (2020) 'State-Dependent Changes in Perception and Coding in the Mouse Somatosensory Cortex', *Cell Reports*, 32(13), p. 108197. Available at: <https://doi.org/10.1016/j.celrep.2020.108197>.

Okun, M. et al. (2019) 'Distinct Structure of Cortical Population Activity on Fast and Infralow Timescales', *Cerebral Cortex*, 29(5), pp. 2196–2210. Available at: <https://doi.org/10.1093/cercor/bhz023>.

Podvalny, E., Sanchez-Romero, R. and Cole, M.W. (2024) 'Functionality of arousal-regulating brain circuitry at rest predicts human cognitive abilities', *Cerebral Cortex*, 34(5), p. bhae192. Available at: <https://doi.org/10.1093/cercor/bhae192>.

Raut, R.V. et al. (2021) 'Global waves synchronize the brain's functional systems with fluctuating arousal', *Science Advances*, 7(30), p. eabf2709. Available at: <https://doi.org/10.1126/sciadv.abf2709>.

Stringer, C. et al. (2019) 'Spontaneous behaviors drive multidimensional, brainwide activity', *Science*, 364(6437), p. eaav7893. Available at: <https://doi.org/10.1126/science.aav7893>.

Vinck, M. et al. (2015) 'Arousal and Locomotion Make Distinct Contributions to Cortical Activity Patterns and Visual Encoding', *Neuron*, 86(3), pp. 740–754. Available at: <https://doi.org/10.1016/j.neuron.2015.03.028>.

Yellin, D., Berkovich-Ohana, A. and Malach, R. (2015) 'Coupling between pupil fluctuations and resting-state fMRI uncovers a slow build-up of antagonistic responses in the human cortex', *NeuroImage*, 106, pp. 414–427. Available at: <https://doi.org/10.1016/j.neuroimage.2014.11.034>.

(Remarks on code availability)

(Remarks to the Author)

The authors present novel analyses of several publicly available datasets, extracting evidence that relates neural activity fluctuations across the brain in mice and humans to 1) fluctuations in pupil diameter, and BOLD-signal fluctuations in humans across the brain to memory encoding strength and memory recall performance, which they assess using a deep-learning decoder they developed. Overall, I found the results original and interesting. My main critique of the manuscript is that the interpretations were quite unclear at various points. There was also a tendency to make quite big claims that were not necessarily supported by the analyses presented, or formal testing could be included (for instance when comparing the humans and rodent data, rather than saying 'they look similar').

- Line 66 and elsewhere: Saying that the brain may 'switch between exteroceptive and interoceptive modes' is highly suggestive language in my opinion, and could be phrased much in a more factual manner. In general, it would improve the quality of the paper if the authors stayed closer to the actual findings.

- Terminology: I do not think the term 'fMRI waves' which is used throughout the manuscript, is appropriate. They are fMRI BOLD-signal fluctuations, not 'waves'.

- Line 128: Was there any pattern in neuronal firing from different regions recorded, corresponding to negative or positive delays?

- Can the authors give any details on how much the length of the BOLD signal fluctuation varies within participants?

- Line 269 'The hippocampus is activated at the late wave phase, corresponding to enhanced memory recall': this is unsurprising given the hippocampus is part of the DMN. Could the authors make this claim stronger, that hippocampal activity is causally involved here in supporting memory recall? E.g. did the magnitude of hippocampal activity or the peak of hippocampal activity in the fMRI signal fluctuation predict memory encoding/recall performance?

Minor:

- Line 80: persist during stimulation: what do the authors mean by this?

- 'The representation similarity analysis confirmed the alignment between fMRI and caption embeddings' there are ways to formally test this, see the original RSA papers by Kriegeskorte et al.

- Line 265 'short-term and long-term memory': short-term memory is defined in the supplementary materials, but I could not find a clear definition of 'long-term memory' (which no. presentation, how long was between the sessions?)

- for Figure 1G, did the authors regress the pupillometry data onto the fMRI signal?

- The methods mention an EEG-fMRI dataset; it's not clear to me for what result this dataset was actually used?

- Line 141: please clarify what is meant by 'similar changes'

(Remarks on code availability)

I can't comment on the quality of the code, but a read-me file or annotation on how to use the code were not included.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

Many thanks to the authors for edits/clarifications that largely address my original points and have improved an already strong manuscript. There is one remaining point of clarification that I believe to be important, although relatively straightforward to address.

As raised in my initial point 3a., the interpretation of hemodynamic delay is complicated here. The authors provide reasonable justification for their approach—namely, shifting all BOLD signals by 6 seconds to account for a presumed global hemodynamic delay—although this does make certain conclusions dependent on this choice. For instance, the 6 second shift is necessary to support claims regarding the temporal alignment of brain processes across datasets (e.g., in lines 359-363). The cycle in question is ~11 seconds, meaning that not implementing a hemodynamic delay would lead to the opposite conclusions regarding how things are aligned in time (i.e., in-phase relationships would become anti-phase).

The reason this matters is because the concept of hemodynamic delay, and how exactly that is modeled, remains an actively debated topic. The authors' choice is reasonable to me, but I do feel it would be valuable to include an additional Discussion/supplementary paragraph (referenced where relevant in the Results section—e.g. Figs 3 and 4, and around line 254 and onward) that (1) clearly notes which temporal relationships and interpretations depend upon the chosen hemodynamic delay (e.g., coincidence of ripples and DMN activity, or relation between encoding performance and BOLD activity in particular regions) and (2) discusses rationale for the global 6-s shift, and how conclusions might differ with alternative choices (e.g., different global delay, regionally-optimized delays, or no hemodynamic delay). (Note: I saw that Line 255 references a Methods section that supposedly discusses implementation of the hemodynamic delay, but I couldn't find said Methods section—so perhaps the authors accidentally omitted text speaking to the various points raised here.)

All in all, I look forward to seeing this important contribution published.

(Remarks on code availability)

Reviewer #2

(Remarks to the Author)

Thank you for the revisions to the manuscript and the response to the reviewers' comments, including the clarifying analyses. The changes have resulted in a stronger and more nuanced manuscript.

(Remarks on code availability)

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Response to Reviewer #1

This manuscript from Yang et al. reports analyses of several publicly available large-scale datasets—including Neuropixels recordings in mice and 7T fMRI in humans—in support of the claim made in the title: “Propagating cortical waves coordinate sensory encoding and memory retrieval in the human brain”. The primary observation is that particular phases of a previously described traveling wave process are preferentially associated with improved memory encoding or recall, as operationalized according to encoding/decoding neural network models. The work builds on the group’s prior studies describing these waves in humans and relevant behavioral results in mice.

Overall, I found this to be a thoughtful piece of work, with a reasonable set of analyses that were carefully executed. It is a valuable, novel contribution to the literature and will be of broad interest. I have no major technical concerns—just a few comments on the framing that I hope will help clarify the authors’ message.

We sincerely thank the reviewer's supportive and valuable feedback, and for recognizing the value and novelty of our work.

In response to the suggestions below, we have revised the phrasing and tone throughout the manuscript to improve clarity and precision. We have also incorporated the reviewer’s suggestions regarding additional literature context to better situate our findings within the broader field. We believe these changes have significantly strengthened the manuscript.

Below, we provide detailed, point-by-point responses to address each of the comments raised.

[R1C1] 1. There is a certain conceptual ambiguity at the heart of this study—namely, what specifically is the role of propagating waves in promoting memory encoding and recall? Personally, I don’t see this ambiguity as a major flaw of the study, nor is it obvious how to get to the bottom of it; however, I do think it is a limitation that should be more explicitly discussed.

As the authors acknowledge, prior studies have separately demonstrated the existence of these waves, their correspondence with indices of fluctuating arousal, and—in mice—modulation of sensory encoding according to arousal/pupil size. The current paper is an important demonstration that these arousal-associated waves persist during task performance, and that decodability from human brain images covaries with pupil size fluctuations. These are two valuable findings—but I’m not sure that much more can be said beyond these points. In this sense, claims that “these waves in human fMRI promote sensory information encoding and memory retrieval alternatively” (from the abstract) seem to sneak in causal inferences that go beyond what the data can tell us.

We thank the reviewer for this thoughtful and constructive comment.

We agree that the original phrasing—“these waves in human fMRI promote sensory information encoding and memory retrieval alternatively”—implies a causal role that goes beyond what the data directly support. Attributing a regulatory or causal function to these waves could be an overstatement.

To address this, we have revised the language throughout the manuscript to emphasize that the waves are accompanied by / associated with / linked to / related to alternating changes in sensory encoding

and memory recall, rather than implying that they waves directly cause these changes. We also changed the title to address this concern.

Please see the title, line 41, line 87, lines 92-94, line 155, line 351 for changes we made with respect to this comment.

[R1C2] 2. Related to this ambiguity, in certain places (e.g. the abstract and lines 145-148), the language slips into framing “cascades” as the key regulator of memory in mice, and waves as the key regulator in humans. Are we sure this isn’t simply because invasive electrophysiology was used in mice and brain-wide imaging was used in humans? In other words, very many processes covary with arousal fluctuations; it’s not clear what can be specifically attributed to waves (or cascades) versus any other correlate of these fluctuations (e.g., changes in pupil size, delta power, sharp-wave ripples etc.).

We agree, and this is similar to the point above. It is true that many neural and physiological processes covary with arousal fluctuations, and that both the spiking cascades observed in mice and the fMRI waves observed in humans may reflect broader brain-wide manifestations of internal arousal dynamics. To acknowledge that attributing a “regulatory” role specifically to cascades or waves is premature and unwarranted, and we have revised the manuscript to reflect a more cautious and precise interpretation.

To address the reviewer’s concern, we have revised the language in the abstract and in lines 155–156 to clarify that the cascade/fMRI wave is “**linked to**”, rather than causally regulating, the alternating enhancement of sensory encoding and memory recall. We believe this revision presents a more accurate and appropriately cautious interpretation of our findings.

[R1C3] 3. Given this broader context, wouldn’t it be just as reasonable to contextualize the present observations within a broader literature on arousal modulation of sensory encoding/recall rather than modulation by these waves per se (e.g., (Harris and Thiele, 2011; Vinck et al., 2015; Lee et al., 2020); or in humans, e.g., (Goldinger and Papesh, 2012; Kucewicz et al., 2018))?

a. To this point, it could be nice to present Fig. 3C-D (perhaps in the supplement) in a manner that aligns everything to pupil size, rather than using the global fMRI signal as a reference in humans and firing patterns in mice. It would also be nice to show such a representation without an estimated hemodynamic delay, as such a delay seems ill-defined in the presence of these biphasic patterns.

We thank the reviewer for this insightful suggestion and for highlighting the broader context of arousal-related modulation of sensory encoding and memory recall. We tried to include the key literature on how sensory coding changes with arousal modulations and have now added more relevant references in the revised manuscript, including those suggested by the reviewer.

We also make it clear in the revised manuscript that some of phenomena we studied should be overlapped with these prior observations around arousal modulations (line 76-77). Nonetheless, the present study is the first to reveal the human network dynamics (fMRI waves) and mouse neural dynamics (cascades) are both highly structured and have similar relationships to sensory processing efficacy, arousal fluctuations, and possibly aspects of hippocampal function. The results suggest that

the changes in these global brain dynamics (i.e., the cascades and waves) could be the more essential basis of the arousal modulations than the pupil size. For example, as we've shown previously (Yang et al., Advanced Science, 2025), these two could be disassociated at certain conditions (i.e., the stationary-locomotion transitions) with the global brain activity change precedes (by seconds) and predicts the pupil size change and other behaviors (locomotion and coding accuracy). In addition, the study of these global fMRI waves allowed us to look into these arousal modulations from a brain network perspective, letting us better understand how these sensory coding and memory retrieval are facilitated in distinct phases of network (SM vs. DMN) activations. Finally, they are practical considerations pupil based analyses. In the NSD dataset, pupillometry data are available for only a small subset of sessions (12 out of 260 scan sessions, and 144 out of 3120 fMRI runs; i.e. <5% data). Aligning all analyses to pupil size would greatly reduce the usable dataset and limit statistical power, making it impractical for the broader analysis.

We appreciate the reviewer's suggestion in this alternative framing, and we hope this explanation clarifies our rationale for centering our analyses on the propagating wave structure rather than pupil size.

[R1C4] 4. Related to this point, at present, the review of the rodent literature is very limited. The second paragraph of the Introduction summarizes this literature through a total of three self-citations (each of these studies being performed on previously published datasets). It would be nice to acknowledge a broader body of work in this space on which the present group's current and past works build. This includes some of the original studies reporting widespread coupling of neuronal firing rates to pupil fluctuations (including their diverse delays and organization into two main clusters) (Okun et al., 2019; Stringer et al., 2019), as well as prior arguments for the sort of exteroceptive-interoceptive (including memory encoding-retrieval) switching that the present study is highlighting (e.g., (Buzsáki, 1989; Hasselmo, 1995)); see (Honey, Newman and Schapiro, 2017) for an extensive review of this theme).

We thank the reviewer for this helpful suggestion and for providing a set of excellent references, particularly the review paper by Honey et. al..

We fully agree that incorporating this broader foundational literature is essential for properly contextualizing our study. In response, we have revised the second paragraph of the Introduction to include the suggested references.

The revised paragraph now reads:

"

Analogous global brain dynamics have been observed at the single neuron level in the mouse. These widespread fluctuations in neuronal firing are often coupled to spontaneous behaviors such as pupil dilation and locomotion, and show distinct delays between two major clusters of neurons (13, 14). More recently, these dynamics were shown to manifest as massive spiking cascades involving ~70% of recorded neurons across the forebrain and playing out over several seconds during stationary rest (15). During both spontaneous activity and periods of visual stimulation, spiking cascades were coordinated in time with hippocampal sharp-wave ripples (SPW-Rs), a neurophysiological event known to be involved in memory functions (16). In the case of visual stimulation, each cascade cycle involved a transition from a phase of high-efficiency sensory encoding to a phase of lower encoding during heightened SPW-Rs (17). These transitions appear to reflect switches between exteroceptive sensory sampling and internal mnemonic processes over the timescale of seconds. This type of

continuous alternations between external and internal processing modes has been observed across various brain systems, particularly the hippocampus, at multiple temporal scales (18, 19), and is hypothesized to play a critical role in learning (20).

"

[R1C5] 5. The question of whether spiking cascades and waves represent the same neurophysiological process is framed as a key question addressed in this study. But to the extent that this question is (or even could be) answered by the current study—namely, by interrelating phenomena observed asynchronously across not only different datasets, but different species—it is already supported by prior literature. Specifically, although the connection between these waves and pupil fluctuations is described here as the missing link, such a connection is apparent from prior works (Yellin, Berkovich-Ohana and Malach, 2015; Raut et al., 2021; Bolt et al., 2023; Podvalny, Sanchez-Romero and Cole, 2024).

We thank the reviewer for this insightful comment and suggested literature. We acknowledge that prior studies, including ours, have linked the resting-state global fMRI signal to arousal modulations, including those indexed by pupil fluctuations (e.g., Yellin et al., 2015; Liu et al., 2018; Raut et al., 2021; Bolt et al., 2023; Podvalny et al., 2024). However, to our knowledge, no previous work has demonstrated a trial-level correspondence between individual pupil dilation events and the propagating waves (specifically along the SM-to-DMN direction) observed in fMRI data. Even in the study focusing the global fMRI waves, the link between pupil size and resting-state fMRI was reported as their significant coherence at the low-frequency range (Figure 2 in Raut et. al.,2021). These correlations/coherences are not equivalent to the correspondence between spontaneous pupil dilation and SM-to-DMN waves.

Importantly, the alignment to pupil events also allows us to make a direct comparison, and thus link, between the spiking cascades observed in mice with the SM-to-DMN waves observed in humans. For all those reasons, we believe that the result presented in Figure 1 is a critical piece of the current study.

At the same time, we totally agree we should include suggested literature regarding the correlation/coherence seen between resting-state fMRI signals and pupil size. Please see lines 76-77 for the added references and associated discussion in the revised manuscript.

All this said, I believe it is an intriguing hypothesis that the propagating waves are directly involved in memory-related processes, or that they may be a key, largely overlooked component of the arousal-related modulation of encoding/recall in general. I hope that consideration of the above points will help the authors clarify their particular interpretations in relation to a broader literature on arousal modulation of memory systems—and also clarify where those interpretations go beyond what the data currently permit one to conclude.

We sincerely thank the reviewer for her/his comments and suggested references, which helped us improve the manuscript significantly.

Reference

Bolt, Taylor, et al. "A unified physiological process links global patterns of functional MRI, respiratory activity, and autonomic signaling." *bioRxiv* (2023): 2023-01.

Liu, Xiao, et al. "Subcortical evidence for a contribution of arousal to fMRI studies of brain activity." *Nature communications* 9.1 (2018): 395.

Raut, Ryan V., et al. "Global waves synchronize the brain's functional systems with fluctuating arousal." *Science advances* 7.30 (2021): eabf2709.

Podvalny, Ella, Ruben Sanchez-Romero, and Michael W. Cole. "Functionality of arousal-regulating brain circuitry at rest predicts human cognitive abilities." *Cerebral Cortex* 34.5 (2024).

Yang, Yifan, et al. "Sensory Encoding Alternates With Hippocampal Ripples across Cycles of Forebrain Spiking Cascades." *Advanced Science* 12.16 (2025): 2406224.

Yellin, Dov, Aviva Berkovich-Ohana, and Rafael Malach. "Coupling between pupil fluctuations and resting-state fMRI uncovers a slow build-up of antagonistic responses in the human cortex." *NeuroImage* 106 (2015): 414-427.

Response to Reviewer #2

The authors present novel analyses of several publicly available datasets, extracting evidence that relates neural activity fluctuations across the brain in mice and humans to 1) fluctuations in pupil diameter, and BOLD-signal fluctuations in humans across the brain to memory encoding strength and memory recall performance, which they assess using a deep-learning decoder they developed. Overall, I found the results original and interesting. My main critique of the manuscript is that the interpretations were quite unclear at various points. There was also a tendency to make quite big claims that were not necessarily supported by the analyses presented, or formal testing could be included (for instance when comparing the humans and rodent data, rather than saying ‘they look similar’).

We sincerely thank the reviewer for the encouraging and constructive feedback. We are especially grateful for your recognition of the originality of our work, as well as your thoughtful critique regarding the clarity of interpretations and the need for more rigorous support for some of the claims.

In response to your suggestions below, we have improved the readability and interpretability of the results. Additionally, we have performed several further analyses to assist in the interpretation of the results. We’ve also changed the language to avoid any suggestions on the casual role of these global dynamics on behavioral changes (also see our responses to R1C1 and R1C2). We believe these changes have enhanced the manuscript greatly.

Below, we provide detailed responses to address each of the points raised.

[R2C1] Line 66 and elsewhere: Saying that the brain may ‘switch between exteroceptive and interoceptive modes’ is highly suggestive language in my opinion, and could be phrased much in a more factual manner. In general, it would improve the quality of the paper if the authors stayed closer to the actual findings.

We thank the reviewer for this suggestion.

We acknowledge that the phrase “exteroceptive and interoceptive modes” may be suggestive. To stay grounded in our empirical findings, we have revised the wording in the manuscript to use the more descriptive and specific terms “exteroceptive sensory sampling” and “internal mnemonic processes.”

These revised terms are directly supported by our observations:

- Exteroceptive sensory sampling refers to the sensory encoding measured for both human and mouse.
- Internal mnemonic processes refer to hippocampal ripple activity in mice and memory recall performance in humans.

We believe these changes improve clarity while ensuring the terminology remains closely aligned with the observed phenomena.

[R2C2] Terminology: I do not think the term ‘fMRI waves’ which is used throughout the manuscript, is appropriate. They are fMRI BOLD-signal fluctuations, not ‘waves’.

We sincerely thank the reviewer for raising this important point regarding terminology. We understand the distinction, but believe that the terminology must somehow capture the previously demonstrated spatiotemporal propagation of the spontaneous fMRI fluctuations. These directional waves over the cortex have been demonstrated independently by at least three studies, including Gu et al. Cerebral Cortex, 2021, Raut et al. Science Advances, 2021, and Bolt et al. Nature Neuroscience, 2022. Basically, the use of “wave” term is to follow the convention established in these prior studies. The prior papers included more details regarding why such global dynamics were described as “waves”, their detailed propagating trajectories within sensory systems, and similar findings from large-scale monkey electrophysiological recordings to exclude the possibility that they arise from hemodynamic delay differences. In our paper, Figure 1 shows how the regional activations at these events showed gradually increased delays in the direction of principal gradient (PG), conforming to the definition of “wave” dynamics defined in physics.

To aid visualization and clarify the dynamic nature of these events, we included a supplementary video showing the brain activation transition during these waves, which better demonstrates the propagation between different networks over time (see **Movie S1**).

We hope this explanation clarifies our use of the term and supports its usage within the manuscript.

[R2C3] Line 128: Was there any pattern in neuronal firing from different regions recorded, corresponding to negative or positive delays?

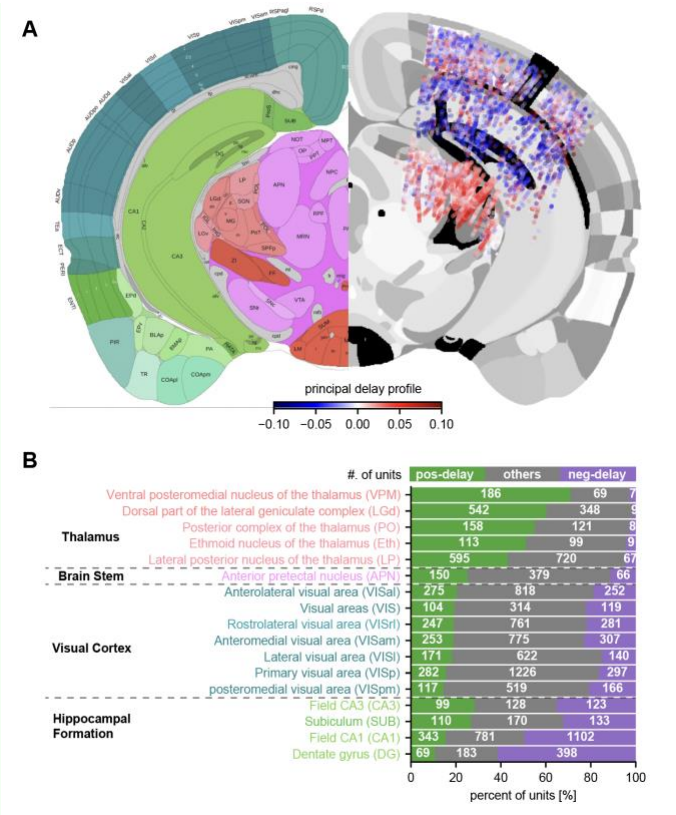


Figure R1. Spatial organization of neurons with negative and positive delays from 32 mice with Allen Brain Observatory stimulus set. (A) Spatial map of the principal delay profile values, where each dot represents a channel of the Neuropixels probe. The principal delay profile value is averaged for neurons detected by each channel. (B)

Boxplot showing the region-specific distribution of the percentage of three neuron groups: positive-delay neurons (green), negative-delay neurons (purple), and other neurons (gray).

We thank the reviewer for the insightful question.

We analyzed the spatial organization of negative- and positive-delay neurons across brain regions (**Fig. R1**). Consistent with our previous findings (Liu et al., 2021), there is a clear regional preference: the thalamus is dominated by positive-delay neurons, while the hippocampus is predominantly composed of negative-delay neurons. Interestingly, no significant bias was observed in visual regions. This organization provide another support to the results in **Fig. 3D**: the phase of low arousal, with activation of negative-delay neurons (dominating hippocampus), shows high occurrence of memory-related hippocampal ripples. On the other hand, the phase of high arousal, with activation of positive-delay neurons (dominating arousal-related thalamus), shows elevated visual coding efficiency.

[R2C4] Can the authors give any details on how much the length of the BOLD signal fluctuation varies within participants?

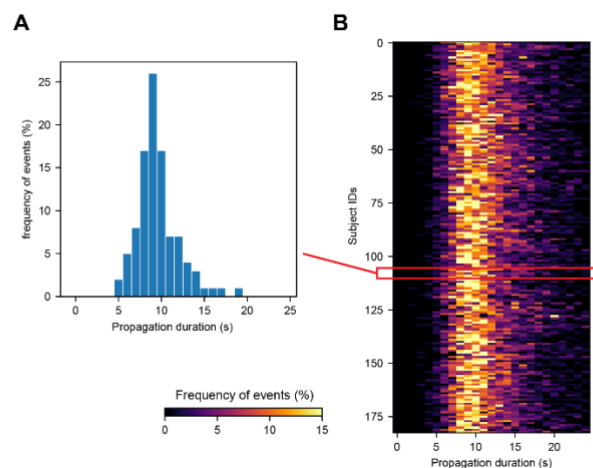


Figure R2. Distribution of SM-to-DMN wave durations. (A) Histogram showing the distribution of SM-to-DMN wave durations for a representative subject. (B) Heatmap showing the distribution of wave durations across all subjects in the HCP-7T dataset. Each row corresponds to one subject, with color intensity representing the frequency of events, similar to (A).

As requested, we analyzed the duration of each propagating wave defined as the duration between the onset of SM activation and the ending of DMN activation (not the intervals between waves) and reported their variability in individual participants. These results are summarized in **Figure R2B**, where each row shows the distribution of detected event over duration for a single subject (**Figure R2A**). On average, the within-subject standard deviation of event duration is 4.23 seconds.

The majority of detected events across subjects exhibited a consistent duration of approximately 10 seconds. This observation aligns with our earlier analysis regarding the influence of brain size on propagation duration (**Figure S5**), where subjects were categorized into three groups (small, medium, large brain size). No significant differences in event duration were found across these

groups (one-way ANOVA, $p = 0.7$), suggesting that these propagations may reflect an intrinsic mechanism across individuals and largely independent of brain size.

[R2C5] Line 269 ‘The hippocampus is activated at the late wave phase, corresponding to enhanced memory recall’: this is unsurprising given the hippocampus is part of the DMN. Could the authors make this claim stronger, that hippocampal activity is causally involved here in supporting memory recall? E.g. did the magnitude of hippocampal activity or the peak of hippocampal activity in the fMRI signal fluctuation predict memory encoding/recall performance?

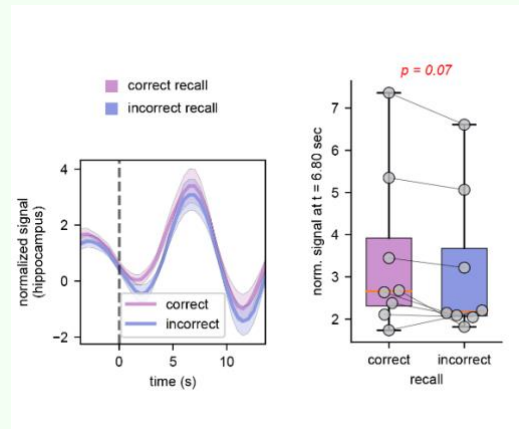


Figure R3. Association between hippocampal activity and memory recall performance. *Correct recall is associated with higher hippocampal activity. Left: Time courses of hippocampal activity for correct (purple) and incorrect (blue) recall conditions. Shaded regions denote the standard error of the mean (SEM). Right: Boxplot comparing peak hippocampal activity between correct and incorrect recall conditions, with a trend toward significance ($p = 0.07$).*

We sincerely thank the reviewer for this comment.

The quoted sentence was to emphasize the phase of hippocampal activation is NOT against its known association with memory functions, but we have no intention to claim that the hippocampal activations are causally responsible for the observed changes in memory recalling. In fact, our paper focuses on the global brain activity much beyond the hippocampus, which might be more related to memory function than hippocampal activation alone.

Following the reviewer’s suggestion, we performed an additional analysis of hippocampal responses across the wave cycle. We extracted trial-wise hippocampal responses (considered HRF) and analyzed the changes of hippocampal response across the wave cycle. We examined whether hippocampal activation differed between correct and incorrect recall trials (**Figure R3**). While the hippocampal response was higher for correct trials, a paired t-test on peak activity (at $t = 6.8$ seconds) yielded a p-value of 0.07 ($N = 8$), which does not reach conventional statistical significance. Thus, the hippocampal activation amplitude doesn’t seem to play a major role in determining memory recall.

We have added this new analysis (**Figure R3**) in the supplementary materials as **Figure S11D** and now discuss it briefly in lines 277-278 .

Minor

|| [R2C6] Line 80: persist during stimulation: what do the authors mean by this?

We thank the reviewer for raising this important question—this observation represents one of the key findings of our study.

Cross-hierarchical fMRI propagating waves have been previously reported only during rest (e.g., Gu et al., *Cerebral Cortex*, 2021; Raut et al., *Science Advances*, 2021; Bolt et al., *Nature Neuroscience*, 2022), and have not been observed under stimulation or task conditions. In contrast, our study demonstrates that these propagating events also persist during stimulation, meaning that they continue to occur even under stimulation and task performance.

This persistence is significant because it suggests that the occurrence of these waves is not driven by external stimulation, but rather reflects an internally generated, spontaneous process—consistent with what has been observed at rest. We further confirmed this by showing that the timing of the events is not locked to stimulus presentation (Figure S9B), indicating that they are not stimulus-evoked.

Importantly, the presence of these spontaneous waves during stimulation enabled us to investigate their functional relevance—we found that their occurrence correlates with systematic changes in sensory encoding and memory recall, as inferred from the stimulation condition.

To address this comment, we've changed “persist” to “continue to occur” in the quoted sentence (line 87 and line 330).

|| [R2C7] ‘The representation similarity analysis confirmed the alignment between fMRI and caption embeddings’ there are ways to formally test this, see the original RSA papers by Kriegeskorte et al.

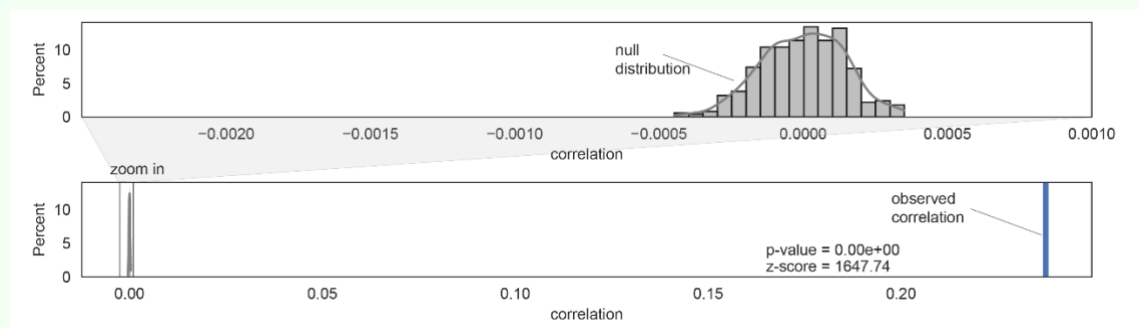


Figure R4. Statistical testing of representational similarity between fMRI and caption embeddings. Top: Null distribution of correlation values between representational dissimilarity matrices (RDMs), generated by randomly permuting stimulus labels across 500 iterations. Bottom: The observed correlation between the fMRI-derived RDM and the caption-derived RDM (blue line) is significantly greater than the null distribution, indicating a significant similarity ($p = 0.00$, $z = 1647.74$).

We sincerely thank the reviewer for this valuable suggestion.

In response, we conducted a formal statistical test following the method proposed by Kriegeskorte et al. (Neuron, 2008), specifically using randomization of stimulus labels to assess the significance of representational similarity between the fMRI and caption embedding RDMs.

We constructed a null distribution by randomly permuting the stimulus labels to shuffle the rows and columns of one of the two RDMs, and then computing the correlation between the permuted and unpermuted RDMs. This procedure was repeated 500 times to simulate the null hypothesis that the two RDMs are unrelated (**Figure R4, top**). The p-value was then computed by comparing the actual observed correlation to this null distribution (**Figure R4, bottom**).

All observed correlations between fMRI and caption embedding RDMs were found to be statistically significant, with $p = 0$ under the permutation test.

We now report the p-values estimated from the above analysis in the captions of **Figure 2B** and **Figure S6B** to indicate the significance of the RDM similarities, and we have updated the Methods section (line 645-652) to include a detailed description of the statistical testing procedure.

[R2C28] Line 265 ‘short-term and long-term memory’: short-term memory is defined in the supplementary materials, but I could not find a clear definition of ‘long-term memory’ (which no. presentation, how long was between the sessions?)

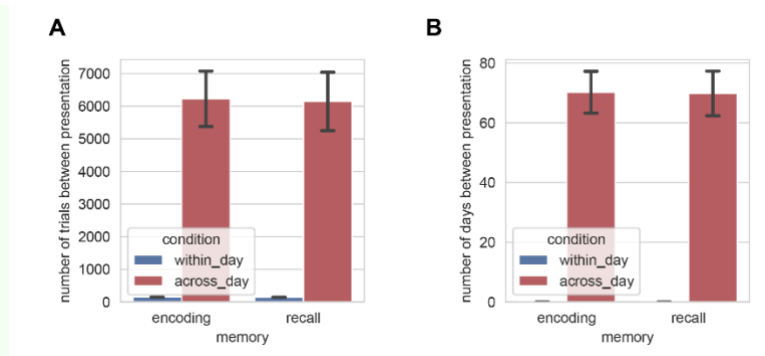


Figure R5. Distinction between short-term and long-term memory conditions.

(A) Bar plot comparing the number of intervening trials between repeated presentations of the same stimulus for within-day (short-term) and across-day (long-term) conditions. (B) Bar plot showing the corresponding number of intervening days between stimulus repetitions. Error bars represent the standard deviation. These results illustrate the temporal distinctions used to define short-term versus long-term memory conditions.

We sincerely thank the reviewer for pointing out this potential confusion.

The short-term and long-term memory conditions referred to the within-day and across-day conditions in **Figure S10** (the original **Figure S9**). Specifically, short-term memory refers to within-day memory performance, where the two consecutive presentations of the same stimulus occur on the same day. In contrast, long-term memory refers to across-day memory performance, where the two presentations of the same stimulus occur on different days.

Each subject completed approximately 30–40 sessions spread across an entire year. On average, the interval between consecutive sessions was 8.3 ± 1.2 days. To provide insight into the data, we

summarize the average interval (in terms of both trials and days) between the two stimulus presentations under short-term and long-term memory conditions in Figure R5. For long-term memory, the average interval between the two presentations was 69.9 ± 7.5 days for recall and 70.2 ± 7.0 days for encoding.

To address the reviewer's comment, we've added the definition in the quoted sentence and incorporated the results of **Figure R5** to **Figure S10** to clarify the temporal distinction between short-term and long-term memory conditions. We have also revised the caption of **Figure S10** for definitions of both conditions to improve clarity.

|| [R2C9] for Figure 1G, did the authors regress the pupillometry data onto the fMRI signal?

We thank the reviewer for the question.

No, we did not regress the pupillometry data onto the fMRI signal. The pupil and fMRI data were preprocessed separately. Figure 1G simply presents the averaged fMRI changes with respect to detected pupil dilations. Further details on the preprocessing pipelines for both modalities are provided in the Methods section.

|| [R2C10] The methods mention an EEG-fMRI dataset; it's not clear to me for what result this dataset was actually used?

We thank reviewer for pointing out this potential confusion.

The EEG-fMRI dataset was used to analyze changes in delta-band (1–4 Hz) activity across the fMRI propagating wave cycle. This analysis is described in the original manuscript at line 141, and the corresponding results are presented in Figure S4.

We observed that delta power exhibits consistent modulation across the wave cycle, closely resembling the temporal dynamics of delta-band fluctuations observed during the spiking cascades in mice. This finding provides additional evidence supporting the cross-species correspondence between the human fMRI propagating waves and spiking cascade in mice.

To address the confusion, we make it explicitly in the revised manuscript, lines 148-150:

"

Simultaneous EEG-fMRI recordings also revealed associated changes in delta-band (1-4 Hz) activity across the fMRI wave cycle, similar to those observed across the cascade cycle (Fig. S4).

"

|| [R2C11] Line 141: please clarify what is meant by 'similar changes'

We thank the reviewer for requesting clarification.

We've discussed in the Results section about the correspondence between the fMRI waves and spiking cascades: "Specifically, the SM-activated phase of the fMRI wave matched a period within the cascade cycle (0–0.5 sec) of improved stimulus encoding, whereas the DMN-activated phase aligned with a different period within the cascade cycle (0.5–2 seconds) of increasing hippocampal SWP-R rate, which was also associated with pupil dilation".

The two phases discussed above are similarly associated with the decrease and increase of the simultaneously measured delta-band (1–4 Hz) activity in both the mouse local field potential (LFPs) data and human EEG, respectively (Figure S4).

Remarks on code availability

[R2C12] I can't comment on the quality of the code, but a read-me file or annotation on how to use the code were not included.

We thank the reviewer for this helpful comment.

In response, we have added a README file to the code repository, which provides instructions on how to execute the code. Additionally, we have included Python notebooks that demonstrate the analysis workflow and reproduce the main figures presented in the paper. The updated codebase is now available through the provided code link in the paper (<https://zenodo.org/records/17065604>).

Reference

Bolt, Taylor, et al. "A parsimonious description of global functional brain organization in three spatiotemporal patterns." *Nature Neuroscience* 25.8 (2022): 1093-1103.

Gu, Yameng, et al. "Brain activity fluctuations propagate as waves traversing the cortical hierarchy." *Cerebral cortex* 31.9 (2021): 3986-4005.

Kriegeskorte, Nikolaus, et al. "Matching categorical object representations in inferior temporal cortex of man and monkey." *Neuron* 60.6 (2008): 1126-1141.

Liu, Xiao, David A. Leopold, and Yifan Yang. "Single-neuron firing cascades underlie global spontaneous brain events." *Proceedings of the National Academy of Sciences* 118.47 (2021): e2105395118.

Raut, Ryan V., et al. "Global waves synchronize the brain's functional systems with fluctuating arousal." *Science advances* 7.30 (2021): eabf2709.

Response to Reviewer #1

Many thanks to the authors for edits/clarifications that largely address my original points and have improved an already strong manuscript. There is one remaining point of clarification that I believe to be important, although relatively straightforward to address.

As raised in my initial point 3a., the interpretation of hemodynamic delay is complicated here. The authors provide reasonable justification for their approach—namely, shifting all BOLD signals by 6 seconds to account for a presumed global hemodynamic delay—although this does make certain conclusions dependent on this choice. For instance, the 6 second shift is necessary to support claims regarding the temporal alignment of brain processes across datasets (e.g., in lines 359-363). The cycle in question is ~11 seconds, meaning that not implementing a hemodynamic delay would lead to the opposite conclusions regarding how things are aligned in time (i.e., in-phase relationships would become anti-phase).

The reason this matters is because the concept of hemodynamic delay, and how exactly that is modeled, remains an actively debated topic. The authors' choice is reasonable to me, but I do feel it would be valuable to include an additional Discussion/supplementary paragraph (referenced where relevant in the Results section—e.g. Figs 3 and 4, and around line 254 and onward) that (1) clearly notes which temporal relationships and interpretations depend upon the chosen hemodynamic delay (e.g., coincidence of ripples and DMN activity, or relation between encoding performance and BOLD activity in particular regions) and (2) discusses rationale for the global 6-s shift, and how conclusions might differ with alternative choices (e.g., different global delay, regionally-optimized delays, or no hemodynamic delay). (Note: I saw that Line 255 references a Methods section that supposedly discusses implementation of the hemodynamic delay, but I couldn't find said Methods section—so perhaps the authors accidentally omitted text speaking to the various points raised here.)

All in all, I look forward to seeing this important contribution published.

We appreciate the reviewer's thoughtful and encouraging comments and fully agree that clarifying the treatment and interpretation of hemodynamic delay is important for the accurate interpretation of our results.

We fully agree that we should discuss the potential influence of the assumed hemodynamic delay. Accordingly, we have added the following paragraph to the Discussion section (Lines 287-293):

“Notably, we applied a global 6-sec shift to the fMRI BOLD signals to infer underlying network activity with accounting for hemodynamic delays (**Fig. 3C** and **4C**). A 1-2 second deviation of this modeled delay from the true value would be minimal relative to the duration of fMRI waves and, therefore, is not expected to affect our interpretation of their temporal relationship to modulations in sensory and memory functions. Without this time shift, however, the periods of stronger semantic encoding and poorer memory retrieval would correspond to the baseline preceding the SM-to-DMN waves, rather than to the SM-activated phase.”

We also thank the reviewer for noting the unclear reference at Line 255. To address this, we added the following sentence to the Methods section “Modulation Across Propagating Wave Cycles” (Lines 684-686):

“To present the temporal relationship between these trial-based measurements and the neural dynamics underlying fMRI waves, we shifted the fMRI BOLD wave backward in time by 6 seconds to account for the hemodynamic delay. ”

Response to Reviewers

Response to Reviewer #2

Thank you for the revisions to the manuscript and the response to the reviewers' comments, including the clarifying analyses. The changes have resulted in a stronger and more nuanced manuscript.

We sincerely thank the reviewer for the encouraging feedback and thoughtful evaluation. We appreciate the reviewer's constructive insights throughout the review process.