

Peer Review Information

Journal: Nature Human Behaviour

Manuscript Title: The direction of theta and alpha traveling waves modulates human memory processing

Corresponding author name(s): Joshua Jacobs

Reviewer Comments & Decisions:

Decision Letter, initial version:

17th August 2023

Dear Dr Jacobs,

Thank you once again for your revised manuscript, entitled "The direction of theta and alpha traveling waves modulates human memory processing," and for your patience during the re-review process.

Your manuscript has now been evaluated by Reviewers #1 and #4 from the original round of review, as well as a new Reviewer #5 with expertise in traveling waves. All reviewer feedback is included at the end of this letter. Although all reviewers found your manuscript to have substantially improved during revision, Reviewer #5 raises some important outstanding concerns. We remain very interested in the possibility of publishing your study in Nature Human Behaviour, but would like to consider your response to these outstanding concerns in the form of a revised manuscript before we make a decision on publication.

In particular, we ask that you address all remaining concerns by Reviewers #4 and #5, and that you pay particular attention to point 4 raised by Reviewer #5 about the fact that propagation speeds would appear to be inconsistent with the central claims in the paper.

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.

In sum, we invite you to revise your manuscript taking into account all reviewer and editor comments. 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.

We hope to receive your revised manuscript within 4-8 weeks. 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. This response will be used by the editors and reviewers to evaluate your revision.
- 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:

[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.

We look forward to seeing the revised manuscript and 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 these revisions further.

Sincerely,

Giacomo Ariani
Editor
Nature Human Behaviour

Reviewer expertise:

Reviewer #1: ECoG

Reviewer #4: ECoG

Reviewer #5: Traveling waves across recording modalities

REVIEWER COMMENTS:

Reviewer #1:

Remarks to the Author:

I greatly appreciate the work invested by the authors in improving the paper. Overall, the revised manuscript provides a clearer introduction and discussion and a more inclusive interpretation of the results. The authors also provide further population analyses and figures as well as a larger number of subjects. Finally, they included additional analyses beyond the Rayleigh test to examine traveling wave propagation and its relation to memory encoding, and addressed most of my prior concerns regarding the primary analyses and their interpretation. The paper is far improved and would make a solid addition to the literature on the topic. I would support its publication.

Reviewer #4:

Remarks to the Author:

The authors have returned a good revision which addressed my concerns. This is an interesting paper with strong implications for advancing computational neuroscience and the understanding of complex human cognition.

Of note, the first point (novelty) was only marginally addressed by removing the phase analyses, since the modulation of traveling wave direction by cognitive task stimuli has been shown in humans and the authors even allude to this briefly in citations 25 & 39 (Pang et al 2020 using scalp EEG and Kleen et al 2021 using a human hippocampal recording). Both studies found anterior moving waves from a visual stimulus (similar to here), and posterior moving waves when the visual stimulus was not present. That said, the latter (absence of stimulus) is not comparable to free recall which is a more "active" cognitive process in which the patient is engaged and it is even more operationally distinct from encoding the visual cue. Hence the direction reversal here seems more interesting and is novel. The scope of the directional changes according to behavior/cognition measured --from majority of the human cortex intracranially-- is a major advance as well (not to mention the aliasing analyses below, and other novel advances herein). It may be helpful to emphasize these distinctions from prior work more in the text. The new rigorous assessment of spatial aliasing is also a welcome and novel methodological addition; I found this to be reassuring in general for my concerns regarding coarse spatial resolution. The illustrations are helpful, but the potential variability in some of the phase lag illustrations in Supplementary Figure 1 raises the question whether issues of spatial undersampling could be exacerbated by using fewer and fewer electrodes (hence data points for modeling) in an electrode cluster. The authors set a minimum of only five electrodes per cluster (might seem low for reliable two-dimensional phase modeling of traveling waves). While this is unlikely to be a major issue in light of the newly added aliasing approaches, it may be helpful to add a simple check to the paper of whether the number of electrodes in an oscillation cluster is predictive of the cluster having bidirectional traveling waves.

The other analytical justifications and methodology details in the text related to my comments are expanded and improved.

Reviewer #5:

Remarks to the Author:

In this work, the authors analyze intracranial recordings from human clinical patients during a memory encoding and recall task. The authors detect alpha-, theta-, and beta-band oscillations and then analyze traveling waves across the electrode array. They find the direction of the theta and alpha traveling

waves changes when subjects are encoding memories versus recalling them.

As a substitute reviewer, I read the submission and the response to previous comments in full. I believe the authors have adequately addressed many of the Reviewers' previous concerns. However, I believe that there are major technical issues of concern with this submission.

First, there is not enough information provided to accurately assess many technical details of the analysis. The authors state that their detection of oscillation clusters finds well-isolated narrowband peaks in the PSD. It would be really important, however, to have evidence documenting this. For example, showing the PSD for specific instances and for the average over all trials included in the analysis would be important in establishing that the oscillations analyzed are in fact well-formed peaks in the power spectrum. In looking for this information, I also noted that there are no units for power given in Table S3.

Second, the method for quantifying propagation direction is much more complicated than what is normally used. Propagation direction is normally calculated by the gradient of phase (Rubino et al., *Nature Neuroscience*, 2006; Alexander et al., *PLoS Comp Biol*, 2019). The fitting procedure used here is much more complicated than what is used in previous work. Because propagation direction is the central focus of the present manuscript, it is unclear why a method that is so much more complicated than the straightforward calculation of phase gradient would be used. Lastly, it's not clear how the preferred propagation directions are aligned to anatomical landmarks when comparing across all subjects. If the alignment is done in Talairach coordinates, could this introduce any confound?

Third, how does Figure 4B show an increase in the rate of successful memory encoding? The manuscript text mentions that the rate of success nearly doubled if waves are propagating in the preferred direction and points to Fig. 4B; however, the y-axis for Fig. 4B reads "normalized % in preferred direction", with around 10% increase. The calculation here appears to be related to the propagation direction, and not to the rate of success. For example, the cluster-based permutation test is related to the propagation direction. No other details, either in the main text or Methods, provide more about the increase in behavioral performance, which is really the critical feature here. Lastly, the baseline normalization for each cluster is unclear - what does it mean to normalize "the observed percent of TWs propagating in the preferred encoding direction relative to the cluster's non-memory baseline"? Does this involve dividing a percentage in one condition by a percentage in another?

Fourth, the observed propagation speeds could be inconsistent with the central hypothesis in the paper. The propagation speeds are reported in Table S3 to be approximately 0.5 m/s for theta and 0.9 m/s for alpha. If we take the example in Figure 2C, where a traveling wave moves across 6-7 electrodes and about 5-6 cm of cortex (considering an inter-electrode distance of 1 cm), then the temporal offset would be 120 ms for theta across these areas. The white-matter fibers connecting these regions, however, have axonal conduction speeds in the range of 2-8 m/s. Spikes conducting along the myelinated fiber network at this speed would travel across the same distance in 30 ms, at least four times faster. If these traveling waves are in fact organizing neural activity, then the activity along the traveling waves would be traveling at the wrong speed to interact with other regions, posing a contradiction to the central hypothesis. There are several possibilities why the true wave speed could be different from what's reported here, including the possibility that temporal smoothing from the filter or spatial smoothing from the estimation of phase gradient could artifactually reduce the estimate of propagation speed. At the

same time, however, this contradiction may pose a strong concern for the central hypothesis of this work.

Author Rebuttal to Initial comments

Point by point response to comments from Reviewer 1:

Reviewer #1:

Remarks to the Author:

I greatly appreciate the work invested by the authors in improving the paper. Overall, the revised manuscript provides a clearer introduction and discussion and a more inclusive interpretation of the results. The authors also provide further population analyses and figures as well as a larger number of subjects. Finally, they included additional analyses beyond the Rayleigh test to examine traveling wave propagation and its relation to memory encoding, and addressed most of my prior concerns regarding the primary analyses and their interpretation. The paper is far improved and would make a solid addition to the literature on the topic. I would support its publication.

We appreciate the reviewer's support of this work for publication and believe that their initial comments motivated us to substantially improve our methodology in this line of work.

Reviewer #4:

Remarks to the Author:

The authors have returned a good revision which addressed my concerns. This is an interesting paper with strong implications for advancing computational neuroscience and the understanding of complex human cognition.

Of note, the first point (novelty) was only marginally addressed by removing the phase analyses, since the modulation of traveling wave direction by cognitive task stimuli has been shown in humans and the authors even allude to this briefly in citations 25 & 39 (Pang et al 2020 using scalp EEG and Kleen et al 2021 using a human hippocampal recording). Both studies found anterior moving waves from a visual stimulus (similar to here), and posterior moving waves when the visual stimulus was not present. That said, the latter (absence of stimulus) is not comparable to free recall which is a more “active” cognitive process in which the patient is engaged and it is even more operationally distinct from encoding the visual cue. Hence the direction reversal here seems more interesting and is novel. The scope of the

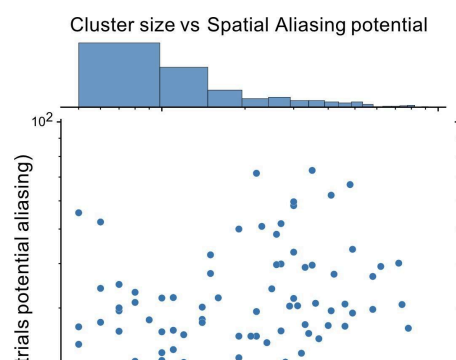
directional changes according to behavior/cognition measured --from majority of the human cortex intracranially-- is a major advance as well (not to mention the aliasing analyses below, and other novel advances herein). It may be helpful to emphasize these distinctions from prior work more in the text.

We thank the reviewer for their point about the reversal of traveling wave directions prior to free recall as a particularly novel and important distinction from previous work. In agreement with the reviewer, we have addressed this by elaborating on why this finding provides greater insight into the role of oscillations in supporting the two distinct active cognitive processes of memory encoding and retrieval by reversing directions (Lines 199-212).

The new rigorous assessment of spatial aliasing is also a welcome and novel methodological addition; I found this to be reassuring in general for my concerns regarding coarse spatial resolution. The illustrations are helpful, but the potential variability in some of the phase lag illustrations in Supplementary Figure 1 raises the question whether issues of spatial undersampling could be exacerbated by using fewer and fewer electrodes (hence data points for modeling) in an electrode cluster. The authors set a minimum of only five electrodes per cluster (might seem low for reliable two-dimensional phase modeling of traveling waves). While this is unlikely to be a major issue in light of the newly added aliasing approaches, it may be helpful to add a simple check to the paper of whether the number of electrodes in an oscillation cluster is predictive of the cluster having bidirectional traveling waves.

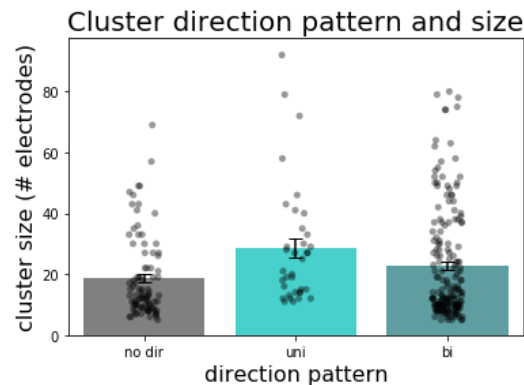
The reviewer brings up an interesting question of whether the number of channels that an oscillation cluster is composed of would affect our measurement of spatial aliasing and thus bidirectionality. It is unlikely that fewer electrodes would exacerbate spatial aliasing since phase differences are calculated between each pair of adjacent electrodes and each electrode's local propagation direction is calculated using the phases of electrodes in its immediate neighborhood. Thus a smaller cluster would have fewer "neighborhoods", but each local direction measurement would rely on a similar number of phase measurements.

Even so, to confirm that small cluster sizes do not exacerbate the impact of spatial aliasing on our measurements, we first performed an analysis of the percent of trials that could be susceptible to spatial aliasing as a function of cluster size. As seen below in Response Figure 1, we did not find evidence that smaller cluster sizes were more susceptible to spatial aliasing ($p = 0.99$, Spearman's one-tailed test of negative correlation), which we now report in the manuscript (Line 390-391).



Caption for Revision Figure 1: The percent of encoding trials that are susceptible to spatial aliasing on each cluster plotted as a function of that cluster's size measured by the number of electrodes showing the same oscillation frequency.

To then check whether cluster size related to our measurements of bidirectionality, we then performed an analysis of the size of clusters showing non-directional, unidirectional, and bidirectional patterns. This analysis showed that the bidirectional clusters were smaller than unidirectional clusters (Kruskal-Wallis, $h=11.8$, $p=0.002$). Together, these results indicate that the traveling waves that change direction may occur across smaller areas of the cortex compared with unidirectional waves, which we now mention on Page 9.



Caption for Revision Figure 2: Cluster size measured by the number of electrodes in an oscillation cluster grouped by the general directional pattern measured on each cluster.

The other analytical justifications and methodology details in the text related to my comments are expanded and improved.

Reviewer #5:

Remarks to the Author:

In this work, the authors analyze intracranial recordings from human clinical patients during a memory encoding and recall task. The authors detect alpha-, theta-, and beta-band oscillations and then analyze traveling waves across the electrode array. They find the

direction of the theta and alpha traveling waves changes when subjects are encoding memories versus recalling them.

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First, there is not enough information provided to accurately assess many technical details of the analysis. The authors state that their detection of oscillation clusters finds well-isolated narrowband peaks in the PSD. It would be really important, however, to have evidence documenting this. For example, showing the PSD for specific instances and for the average over all trials included in the analysis would be important in establishing that the oscillations analyzed are in fact well-formed peaks in the power spectrum. In looking for this information, I also noted that there are no units for power given in Table S3.

We thank the reviewer for their important point about isolating narrowband peaks in the power spectra. To demonstrate that we did in fact analyze oscillations based on established peaks, we added inset power spectra in both Figures 1 and 3 and Supplementary Figure 7 (more examples). We have also added units to power in Table 3.

Second, the method for quantifying propagation direction is much more complicated than what is normally used. Propagation direction is normally calculated by the gradient of phase (Rubino et al., Nature Neuroscience, 2006; Alexander et al., PLoS Comp Biol, 2019). The fitting procedure used here is much more complicated than what is used in previous work. Because propagation direction is the central focus of the present manuscript, it is unclear why a method that is so much more complicated than the straightforward calculation of phase gradient would be used. Lastly, it's not clear how the preferred propagation directions are aligned to anatomical landmarks when comparing across all subjects. If the alignment is done in Talairach coordinates, could this introduce any confound?

The reviewer noted an important change in our methodology for calculating propagation direction from our previous work. We recognized that patterns of traveling waves across the cortex are often complex and heterogeneous, so we built upon our previous method to be able to capture phase gradients that are not solely uniform across the entire oscillation cluster. Consistent with directional measurements from our earlier work, our improved method measures direction utilizing a gradient of phases. To specifically measure a local propagation

direction at a specific channel's location, we instead use the phases measured on channels immediately surrounding the channel. This higher resolution of propagation direction across a cluster is particularly important because our grids often span large regions of the cortex across which direction is rarely consistent. This allows us to identify when nonplanar traveling wave patterns are occurring and observe complex patterns at these times. The previous method that measured direction with a phase gradient across the entire oscillation cluster would not be able to reliably fit a single plane to phases from all channels of the oscillation cluster if the wave was not planar. Thus, the improved method allows us to capture complex traveling waves that would otherwise be missed with the more straightforward calculation. Additionally, by calculating direction at each channel, we were also able to rule out directional consistency across the cluster, or planarity of a wave, as a factor related to memory.

We thank the reviewer for their comment concerning the anatomical alignment of propagation directions. All directional measurements, including the preferred direction, were aligned to anatomical landmarks using the Talairach coordinates from all channels in an oscillation cluster. The use of Talairach coordinates to align propagation directions to anatomical landmarks would not introduce a confound to our main results because we calculate a comparison for each subject and oscillation cluster between behavioral conditions for which electrode locations remain the same. Electrode locations measured with Talairach coordinates are not aligned to individual subjects' anatomical landmarks, but rather to the overall shape of the brain. Since we see traveling wave directions change between opposite directions on clusters located on regions across the brain with distinct brain curvatures, we believe that our main findings of broad directional shifts are not due to anatomical surface differences. We calculated propagation directions in each of the three dimensions and visualized these directions in the sagittal plane of the brain. Future studies may further explore methods to capture the propagation of oscillations across gyri and sulci using an inflated brain surface of the cortex model as we explain on Lines 269-273.

Third, how does Figure 4B show an increase in the rate of successful memory encoding? The manuscript text mentions that the rate of success nearly doubled if waves are propagating in the preferred direction and points to Fig. 4B; however, the y-axis for Fig. 4B reads "normalized % in preferred direction", with around 10% increase. The calculation here appears to be related to the propagation direction, and not to the rate of success. For example, the cluster-based permutation test is related to the propagation direction. No other details, either in the main text or Methods, provide more about the increase in behavioral performance, which is really the critical feature here. Lastly, the baseline normalization for each cluster is unclear - what does it mean to normalize "the observed percent of TWs propagating in the preferred

encoding direction relative to the cluster's non-memory baseline"? Does this involve dividing a percentage in one condition by a percentage in another?

The reviewer brings up an important difference between the two methods used to capture the main effect. Our statement that the rate of success nearly doubled refers to an odds ratio calculated using recall rates between the trials where waves were propagating in preferred versus non-preferred directions. We have further clarified the terminology to indicate that we are reporting odds throughout the text. To respond to the reviewer's request for more information about the behavior performance here, we have added Supplemental Figure 12 which measures the odds ratio of memory performance when waves are propagating in the preferred encoding direction compared to the recall direction.

We made the decision to present the timing-related results as "Normalized % waves in preferred direction" in order to show a comparable measure between both encoding and recall conditions. This would not have been possible to plot a measure comparing successful and unsuccessful behavior for the recall condition because all recalled words are inherently successful.

In response to the reviewer's last point here, we have further clarified our method of normalization in the main text where we now explain that the data are presented by subtracting the percent of waves going in the preferred direction for during unsuccessful encoding from successful encoding and then the percent change was calculated relative to the baseline (the percent of waves going in the preferred direction in the absence of task-related behavior). For recall conditions, we normalized the percent of waves going in the preferred direction relative to the baseline.

Fourth, the observed propagation speeds could be inconsistent with the central hypothesis in the paper. The propagation speeds are reported in Table S3 to be approximately 0.5 m/s for theta and 0.9 m/s for alpha. If we take the example in Figure 2C, where a traveling wave moves across 6-7 electrodes and about 5-6 cm of cortex (considering an inter-electrode distance of 1 cm), then the temporal offset would be 120 ms for theta across these areas. The white-matter fibers connecting these regions, however, have axonal conduction speeds in the range of 2-8 m/s. Spikes conducting along the myelinated fiber network at this speed would travel across the same distance in 30 ms, at least four times faster. If these traveling waves are in fact organizing neural activity, then the activity along the traveling waves would be traveling at the wrong speed to interact with other regions, posing a contradiction to the central hypothesis. There are several possibilities why the true wave speed could be different from what's reported here, including the possibility that temporal smoothing from the filter or spatial smoothing from the estimation of phase gradient could artifactually reduce the estimate of

propagation speed. At the same time, however, this contradiction may pose a strong concern for the central hypothesis of this work.

There is no theoretical reason why the speed of traveling wave propagation should match the speed of axonal conduction. An extreme example of why these speeds need not match is the situation where oscillations at two sites are synchronized with zero-phase difference, which would appear to have an infinite conduction speed.

To better explain this point in the paper, we edited the text on Page 10 to explain that in many models of traveling waves, such as Kuramoto's weakly coupled oscillator model (Ermentrout & Kleinfeld, 2001), the apparent speed of wave propagation does not match the axonal conduction speed because the oscillation's propagation is paced by additional factors such as the local intrinsic oscillation frequency at each site and the coupling between oscillators. In fact, in the coupled oscillator model, the strongest determinant of the apparent traveling wave propagation speed is the difference in the intrinsic oscillation frequencies between sites, rather than the axonal propagation speed itself. Thus, whereas axonal conduction delays are generally fixed on the order of ~2–8 m/s, it is likely that oscillatory traveling waves will sometimes appear to move slower or faster. Therefore, as we now explain in this section, although traveling wave propagation speeds may vary, it is actually expected that wave propagation speed will vary independently of the speed of axonal conduction.

To clarify this issue further, we have edited the terminology throughout the paper to use the more precise term "phase velocity" when describing the rate of oscillation propagation, which is the distance a phase of an oscillation travels in a period of time. We hope that this new term will minimize potential confusion with axonal conduction speed, rather than the word "speed" that was used previously.

Decision Letter, first revision:

20th December 2023

Dear Dr. Jacobs,

Thank you for your patience as we've prepared the guidelines for final submission of your Nature Human Behaviour manuscript, "The direction of theta and alpha traveling waves modulates human memory processing" (NATHUMBEHAV-23072294A). Please carefully follow the step-by-step instructions provided in

the attached file, and add a response in each row of the table to indicate the changes that you have made. Please also check and comment on any additional marked-up edits we have proposed within the text. Ensuring that each point is addressed will help to ensure that your revised manuscript can be swiftly handed over to our production team.

We would hope to receive your revised paper, with all of the requested files and forms within two-three weeks. Please get in contact with us if you anticipate delays.

When you upload your final materials, please include a point-by-point response to any remaining reviewer comments.

If you have not done so already, please alert us to any related manuscripts from your group that are under consideration or in press at other journals, or are being written up for submission to other journals (see: <https://www.nature.com/nature-research/editorial-policies/plagiarism#policy-on-duplicate-publication-for-details>).

Nature Human Behaviour offers a Transparent Peer Review option for new original research manuscripts submitted after December 1st, 2019. As part of this initiative, we encourage our authors to support increased transparency into the peer review process by agreeing to have the reviewer comments, author rebuttal letters, and editorial decision letters published as a Supplementary item. When you submit your final files please clearly state in your cover letter whether or not you would like to participate in this initiative. Please note that failure to state your preference will result in delays in accepting your manuscript for publication.

In recognition of the time and expertise our reviewers provide to Nature Human Behaviour's editorial process, we would like to formally acknowledge their contribution to the external peer review of your manuscript entitled "The direction of theta and alpha traveling waves modulates human memory processing". For those reviewers who give their assent, we will be publishing their names alongside the published article.

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If you have any further questions, please feel free to contact me.

Best regards,
Abbey Ford
Editorial Assistant
Nature Human Behaviour

On behalf of

Giacomo Ariani
Editor
Nature Human Behaviour

Reviewer #4:

Remarks to the Author:

The authors have once again put in high quality work into this interesting paper, and they have addressed my concerns.

While at first glance their phrasing in the most recent rebuttal text, “It is unlikely that fewer electrodes would exacerbate spatial aliasing” sounds like the anti-thesis of sampling theorem, they clarify that their clusters rely only on “adjacent” electrodes. I see their point, therefore, since regardless of cluster size the distances of spatially contiguous would be generally consistent as alluded in the main text. The relevant new finding that smaller (spatially contiguous) clusters are more likely to have bidirectionality may actually be quite important in the long run, since human high density ECoG/micro-ECoG is an emerging technology (e.g. Duraivel et al 2023, Nat Commun) and such complex local patterns are likely to be seen increasingly with this spatial detail.

I would support this paper and its novel and important contributions to the field for publication.

Reviewer #5:

Remarks to the Author:

In this revised manuscript, the authors have introduced updates to address the points raised in review. Many points remain unclear, however, and the revision does not adequately address the concerns raised in the previous round.

Concerning the first point, the additional power spectra in Figures 1 and 3 are presented only after removal of the $1/f$ component. This is not a standard way of plotting the PSD, and it still leaves open the point of whether these are well-formed peaks in the PSD. To be specific, presenting only the spectra after this step makes it difficult to assess the height of the peak relative to the background signal.

Concerning the second point, the additions do not clarify why a more complicated method than phase gradient would be useful. The authors state that "to specifically measure a local propagation direction at a specific channel's location, we instead use the phases measured on channels immediately surrounding the channel". This is exactly the information that would be used in a numerical implementation of the gradient. Without a clear reason why this is preferable, or a demonstration that it recovers the same information as the gradient, both the motivation and the soundness of this method remain unclear.

Concerning the fourth point, it may be mathematically possible for waves to travel at speeds different from the axonal conduction speed. The key point, however, is the neurophysiology: if the propagation speeds are indeed an order of magnitude slower than the axonal conduction speed, then how are forward and backward waves coordinating activity across multiple cortical regions, as the authors suggest? The actual circuit mechanism here still remains unclear.

The key point of this manuscript is to link a circuit phenomenon (forward and backward traveling waves) with a cognitive process (memory storage) in the human. To establish this link, the paper must have a clear mechanism through which these dynamics enable this process. Without a clear and definite mechanism, it remains difficult to see how alpha and theta traveling waves (and their direction of travel) could work to enable memory storage.

Author Rebuttal, first revision:

Point by point response to comments from Reviewer 4:

Reviewer #4:

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sampling theorem, they clarify that their clusters rely only on “adjacent” electrodes. I see their point, therefore, since regardless of cluster size the distances of spatially contiguous would be generally consistent as alluded in the main text. The relevant new finding that smaller (spatially contiguous) clusters are more likely to have bidirectionality may actually be quite important in the long run, since human high density ECoG/micro-ECoG is an emerging technology (e.g. Duraivel et al 2023, Nat Commun) and such complex local patterns are likely to be seen increasingly with this spatial detail.

I would support this paper and its novel and important contributions to the field for publication.

We appreciate the reviewer's support of this work for publication and believe that their comments motivated us to think critically about our methodology and explain our methods more clearly.

Reviewer #5:

Remarks to the Author:

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Concerning the first point, the additional power spectra in Figures 1 and 3 are presented only after removal of the $1/f$ component. This is not a standard way of plotting the PSD, and it still leaves open the point of whether these are well-formed peaks in the PSD. To be specific, presenting only the spectra after this step makes it difficult to assess the height of the peak relative to the background signal.

We thank the reviewer for their point about visualizing well-formed narrowband peaks in the PSD. To demonstrate that we did in fact analyze oscillations based on well-formed peaks, we added additional inset power spectra prior to removing the $1/f$ component in both Figure 3 and Supplementary Figure 7 (now Extended Data Figure 7). We further explained the parameters used to facilitate reproducibility in our Methods (Lines 335-339).

Concerning the second point, the additions do not clarify why a more complicated method than phase gradient would be useful. The authors state that "to specifically measure a local propagation direction at a specific channel's location, we instead use the phases measured on channels immediately surrounding the channel". This is exactly the information that would be used in a numerical implementation of the gradient. Without a clear reason why this is preferable, or a demonstration that it recovers the same information as the gradient, both the motivation and the soundness of this method remain unclear.

We have expanded upon how we calculated direction and speed of traveling waves from phase gradients in our results (Lines 67-70), Figure 1 (caption), and we have further clarified the text in our Methods (Lines 349-358). In particular, we expand on our rationale in our methods: "By allowing each electrode to have its own propagation direction, this method has improved sensitivity to TWs with non-planar and complex propagation patterns, as well as to TWs that were present at only a subset of the electrodes in the cluster, which could otherwise not be detected reliably with a singular phase gradient across the entire oscillation cluster." We demonstrate the advantage of our improved method in examples in Supplementary Figure 7, where we were able to capture complex, non-planar wave patterns.

Concerning the fourth point, it may be mathematically possible for waves to travel at speeds different from the axonal conduction speed. The key point, however, is the neurophysiology: if the propagation speeds are indeed an order of magnitude slower than the axonal conduction speed, then how are forward and backward waves coordinating activity across multiple cortical regions, as the authors suggest? The actual circuit mechanism here still remains unclear.

We thank the reviewer for their attention to the neurophysiological mechanisms of traveling waves. To better describe the mechanisms by which traveling waves propagate and why their propagation velocity does not match axonal conduction speeds, we have expanded our discussion of traveling wave propagation velocities, mechanisms that may rely on a combination of synaptic and non-synaptic electrical activity, and the role of unmyelinated axons on the surface of the cortex. We have clarified in our discussion that traveling waves do not directly reflect axonal conduction speed but the phase velocity of traveling oscillations representing the flow of information across the cortex. (Lines 195-204).

The key point of this manuscript is to link a circuit phenomenon (forward and backward traveling waves) with a cognitive process (memory storage) in the human. To establish this link, the paper must have a clear mechanism through which these dynamics enable this process. Without a clear and definite mechanism, it remains difficult to see how alpha and theta traveling waves (and their direction of travel) could work to enable memory storage.

We agree with the reviewer that a circuit model demonstrating the mechanism behind this phenomenon is important in the field. Based on recent work (Shefrey et al. 2020 *Neurobiol Learn Mem.* and Sato 2022 *Scientific Reports*), we explore in our discussion the possible mechanisms by which oscillations may modulate the direction of information transfer in our discussion (Lines 233-244, 190-199). In our current follow-up studies, we are working to build computational models to show how traveling waves spontaneously modulate excitability in specific directions that are relevant for memory processing and how changes in direction are coordinated.

Final Decision Letter:

24th January 2024

Dear Dr Jacobs,

We are pleased to inform you that your Article "The direction of theta and alpha traveling waves modulates human memory processing", has now been accepted for publication in *Nature Human Behaviour*.

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With best regards,

Giacomo Ariani
Editor
Nature Human Behaviour