nature portfolio

Peer Review File

Thalamic oscillations distinguish natural states of consciousness in humans

Corresponding Author: Professor Tobias Staudigl

Version 0:

Decision Letter:

5th September 2025

Dear Professor Staudigl,

Thank you once again for your manuscript, entitled "Thalamic oscillations distinguish natural states of consciousness in humans", and for your patience during the peer review process.

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

In particular, Reviewer #1 questions whether the thalamic gamma-band signal observed here can be concluded to be either thalamic in origin or causally related to consciousness. We believe that it will be important to directly address these concerns with additional analyses and/or new data.

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

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

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

With your revision, please:

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

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

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

Link Redacted

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

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

Sincerely,

[redacted]

[redacted]
Nature Human Behaviour

REVIEWER COMMENTS:

Reviewer #1 (Remarks to the Author):

Review of the manuscript "Thalamic oscillations distinguish natural states of consciousness in humans" by Chowdhury et al.

This is a very well-executed and clearly written study that provides novel and important insights into the role of thalamic activity across different natural states of consciousness in humans. The work stands out for its clarity, methodological rigor, and the careful description of a rare and valuable intracranial dataset. Despite the limited number of participants, the characterization of the patients is detailed and appropriate for the type of analysis performed.
The most striking and novel finding is the identification of a gamma-band thalamic activity that is selectively present during wakefulness and phasic REM sleep, but absent during NREM sleep. This pattern suggests that such activity might alternate with sleep spindles, potentially reflecting another manifestation of the same thalamic generator. This insight opens up exciting possibilities in our understanding of the thalamus's role in modulating conscious states.
However, I have several comments and suggestions that I believe should be addressed or discussed further in order to strengthen the manuscript and refine the conclusions:

Major Concerns:
Link between gamma activity and consciousness: While the gamma activity is well characterized, the conclusion that it is directly linked to consciousness remains speculative. The manuscript would benefit from a more cautious interpretation of these findings. For instance, is there any clinical or behavioral evidence (e.g., changes in vigilance, sleep patterns, neuropsychological testing) from these patients during or after DBS that could support this link more directly? The fact that modulating this activity changes behavior will be a real evidence of the link between this activity and consciousness or arousal. Some DBS electrodes allow registration also after implantation, is it your case?

Causal attribution to thalamic origin: The claim that this gamma activity originates in the thalamus rather than cortex could be supported more robustly. The authors might consider using directionality index associated to connectivity to test thalamo cortical directionality, especially since similar gamma peaks are visible in frontal scalp electrodes (extended data fig 2 frontal and REM). There is no other simultaneous iEEG sampling from neocortex in this dataset, limiting the assumption of this activity being exclusively coming from thalamus. This should be discussed.

Interpretation of common generator for gamma and spindles: The hypothesis that gamma and spindle activity may reflect different manifestations of a common generator is intriguing, but currently based only on similar features and alternation. Further clarification or discussion of this point is warranted, including its limitations and whether there are anatomical or functional data to support it.

Patient variability and epilepsy context: The manuscript does not adequately address the fact that the data come from pharmacoresistant epilepsy patients, many of whom may have disturbed sleep, widespread interictal activity, and structural abnormalities. Although epileptic discharges are carefully excluded, a discussion is needed on how pathological thalamocortical dynamics might differ from those in healthy individuals.
Are there differences in gamma activity or spindles related to seizure frequency, type of epilepsy, or medication?
Could the presence or absence of gamma activity in the three non-included patients be related to individual pathology? There is a patient in particular excluded as he/she has a " reduced vigilance", it could be indeed interesting to compare to support your hypothesis…

In the Discussion, it would be valuable to elaborate briefly on why some patients did not show thalamic gamma activity, and what factors (anatomical, clinical, technical) might account for this absence.

Stage specificity of NREM: NREM sleep is heterogeneous. The analysis does not clearly separate stage N1, N2, or N3, which may each have distinct thalamic dynamics. Have the authors considered this? Differences in spindle and gamma rates across these sub-stages would be highly informative.

Electrode localization and nuclear specificity: The manuscript would benefit greatly from an image or schematic showing the precise locations of the 17 thalamic electrodes. Current analyses are based on distance from the "central thalamus", but activity may be more accurately interpreted relative to specific thalamic nuclei explored. I guess you should have a lot of data

specific of ANT for example. Moreover, do also spindle rates vary depending on proximity to the central thalamus?

Detection thresholds and spike rate: In lines 416–420, the authors describe an envelope amplitude threshold of 5× the baseline. Considering that thalamic spikes are often of low amplitude, could this threshold be too conservative? Can you provide some visual confirmation made by an epileptologist? Furthermore, providing the thalamic spike rate across states (NREM, REM, wake) would help interpret whether spiking may contribute to the observed gamma detection rates or might modify this "background" activity.

DBS montage and interpretation: The bipolar montage used may span different thalamic nuclei. When bipolar electrodes included contacts in distinct nuclei, how were these cases handled?

Conclusion:
In conclusion, this is a novel study that provides important evidence for oscillatory dynamics in the human thalamus during natural states of consciousness. The work is solid in its methodology, well written, and has significant clinical and theoretical relevance. However, some of the key interpretations, particularly those linking gamma activity to consciousness and possible DBS efficacy, require more cautious framing or additional data to be fully substantiated.

Reviewer #2 (Remarks to the Author):

General comment:
1) The submitted study investigates oscillatory activity in the thalamus (and EEG) during NREM, REM and wakefulness. This was done using field potential recordings from depth electrodes targeted to the (anteroventral) thalamus in epilepsy patients. These are rare recordings, which is a major plus for the study. The study identified fast oscillations (20-45Hz) in the thalamus during REM sleep and wakefulness. This finding is consistent with published animal studies over past decades. In addition, the study reports fast oscillations correlated with eye movements (detected from the EEG) and phasic REM. This finding seems a little at odds, with respect to frequency changes in phasic REM, with a previous human study recording from the anterior thalamus (Simor et al., 2021, Journal of Neuroscience 41: 5677). Although Simor et al. was cited as an example of human thalamic recordings during sleep, surprisingly, I didn't find a discussion of the similarities and differences between Simor et al. and the submitted study. Moving on, there are a number of methodological and analysis issues that should be addressed, to allow a better evaluation of the data. Specific comments on these and other issues below.

Specific comments:
2) RE: Fig. 1, and line 69: "the figure shows the ubiquitous presence of a faster oscillation (≈ 28 Hz) during both wakefulness and REM sleep that, to the best of our knowledge, has not been reported before." Please contextualize / clarify that this fast oscillation during wakefulness and REM has been previously reported in thalamus (and cortex) of animals, e.g., Steriade et al., 1996, Journal of Neuroscience, 76:2788; Steriade et al., 1996, Journal of Neuroscience, 76:392; Steriade et al., 1991, Proc Natl Acad Sci U S A 88:4396.

3) RE: Fig. 2, Extended Data Table 1, and line 103: "rate of oscillatory activity during wakefulness and REM sleep is significantly higher than in NREM sleep ($p< 2 \times 10–4$ 104 for both cases, subject-level paired Wilcoxon Rank Test with 14 subjects)." However, in the methods, it states that "our main analysis is carried out on a total of 17 patients", and "For all patients (but one, see note c), the number of bipolarly rereferenced contacts is 6 (3 on each hemisphere)". Please show the location of the thalamic electrodes in the 3 patients without the high-frequency oscillatory activity vs the 14 patients with the high-frequency oscillatory activity?

4) RE: line 62 and 111. From line 62: "We obtained the thalamic field potential by bipolarly rereferencing the voltages recorded in neighboring contacts of the DBS electrodes, obtaining a total of 105 channels." and from line "54 thalamic contacts where we detected the fast oscillatory activity." Please show the location of the 54 thalamic electrodes with the high-frequency oscillatory activity vs the 49 thalamic electrodes without the high-frequency oscillatory activity?

5) RE: Fig. 3. The methods state that "We used the bipolar derivative F7-F8 as a substitute for horizontal EOG" giving rise to a "mean rapid EM frequency of 8 +/- 5 per minute". To estimate the reliability of this approach, there was a "comparison with events detected in a standard horizontal EOG setup, we used data of 11 healthy participants from an independent study where reliable EOG measurements during REM sleep were available simultaneously with standard 64-channel scalp EEG." While this comparison in healthy participants is appreciated, it would be useful to show in the epilepsy patients that your methods detect saccades at known frequencies (3 per second) during wakefulness. This would help validate your eye movement detection method further.

6) RE: Fig. 4c. Is it possible that the amplitudes are correlated because they are derived from the same electrode with the same impedance and other factors, rather than fast oscillations and spindles being derived from the same mechanism?

7) RE: Fig 4d. If I have understood correctly, all the pink circles derive from one subject. Without this subject, it is not clear how strong the correlation would be. What is the correlation without this subject?

8) RE: line 215. “Our findings that sleep spindles during NREM sleep and the faster oscillatory during wakefulness and REM sleep reported here show remarkable similarity in their properties thus indicates a common mechanistic origin for both.” It isn’t clear that this necessarily follows (also see comments 6 and 7 above). Evidence suggests different mechanisms contribute to spindles and REM fast oscillations in the thalamus: for instance, brainstem cholinergic inputs give rise to fast thalamic oscillations in REM, but these inputs do not seem necessary for spindles (Steriade et al., 1991, Proc Natl Acad Sci U S A 88:4396; Durkin and Aton, 2019, Annu Rev Vis Sci. 5:295). To help the reader evaluate your results, please include this past evidence which suggest differences in the mechanisms giving rise to spindles and fast oscillations.

9) RE: Fig. 5. The distances marked by black dots in panels b and c make it difficult for the reader to assess exactly where the fast oscillations were recorded in the thalamus. Please add each electrode contact position to panel a, color coding each contact based on whether it was associated with fast oscillations. This would help the reader assess the localization of fast oscillations in REM to particular thalamic nuclei (the goal of section 2.4).

10) line 711 of methods. “An important consideration for the analysis of detection probabilities is the fact that all analyses of thalamic field potentials were done on bipolar derivatives of neighbouring channels; any activity detected on a bipolar derivative could arise due to the proximity of either of the two contacts to the source of the signal. In our analysis, we dealt with this issue in an assumption-free way by assigning the signal to both contacts that went into the bipolar channel.” If I have understood correctly, this approach, in a sense, artificially doubles the number of values that contribute to the regression analyses? A more appropriate approach might be to assign the bipolar-derived channel to a location midway between the two contacts, then perform the analyses.

11) Line 246 and Extended Data Fig. 2: “We found that only 4 out of the 14 patients showed clear evidence for a Wake- and REM sleep- specific oscillations at least one scalp electrode in a frequency range that overlapped with the frequency range of thalamic activity” and “The figure illustrates the lack of a clear oscillatory peak, as is seen in the thalamic contacts, during either wakefulness or REM sleep in any of the scalp EEG electrodes.” If there is no clear EEG oscillation in the frequency of interest (i.e., frequency of fast oscillation in the thalamus), then how to interpret the phase lag index?

12) RE: Discussion, paragraph starting line 328. While it is interesting to speculate that the thalamus may be “involved in a simulation of actions and their consequences during REM sleep”, I think that given the study’s data (which doesn’t provide evidence for this speculation), there are other interpretations that should be discussed. For example, the thalamus may simply be responding during eye movements (not necessarily performing a simulation) as in the oculomotor thalamus experiments from Schlag and Schlag-Rey (e.g., review by Tanaka and Kunimatsu, 2011, Eur J Neurosci 33:2046).

13) RE: Discussion. The findings in the submitted study seem somewhat different, with respect to frequency changes in phasic REM, etc, compared with a previous human study recording from the anterior thalamus (Simor et al., 2021, Journal of Neuroscience 41: 5677). Please discuss these differences and similarities in the manuscript.

14) RE: Methods, line 423. Please include far more detail on sleep staging. The only text currently seems to be: “4.4 Sleep Staging. We carried out sleep staging using standard procedures53. Sleep stages N2 and Slow Wave Sleep (SWS) were combined into NREM epochs.”

Reviewer #2 (Remarks on code availability):

I had a brief look at what was shared. I did not go through code line by line.

Reviewer #3 (Remarks to the Author):

The authors present a highly interesting analysis based on a unique dataset, including thalamic recordings from 17 epilepsy patients undergoing deep brain stimulation (DBS). Their work reveals state-specific oscillatory activity in the central nucleus of the thalamus, particularly prominent during wakefulness and REM sleep, and especially during the phasic stage of REM (when ocular activity is maximal).
While the identification of fast-frequency bursting activity is not entirely without precedent, prior studies have primarily investigated such phenomena at the scalp level. The finding that the central thalamus is involved in wake- and REM-specific oscillations opens promising new directions for research and holds strong potential to advance our understanding of arousal, consciousness, and the functional roles of REM sleep. The observed relationship between sleep spindles and fast-frequency bursts is also intriguing, and the authors employ a variety of analytic techniques to characterize these oscillatory phenomena.

I believe this is a valuable contribution to the field; however, I have several questions and comments that I recommend the authors address before publication.

Introduction:

(…) such oscillations are hypothesized to selectively activate various brain networks required for cognitive processes – this sentence is somewhat simplified, I recommend the authors to briefly specify the brain networks and cognitive processes they refer to.

The rationale for focusing on the fast frequency range (20–45 Hz) is not clearly articulated in the introduction. The authors do not cite previous studies that highlight the relevance of this oscillatory activity, and the introduction lacks a theoretical framework justifying the detailed examination of this frequency band. Is the interest in this range motivated by its association with arousal, its proposed role in cognitive processes, its relation to recently described iota oscillations, or perhaps findings on REM-specific beta tufts? I recommend that the authors briefly contextualize their focus by providing a theoretical basis for investigating this specific frequency range during REM sleep.

Studies that bear relevance:

Snipes, S. (2025). Iota oscillations (25–35 Hz) during wake and REM sleep in children and young adults. Journal of Neurophysiology, 134(1), 1-9.

Ujma, P. P. et al. (2017). The sleep EEG spectrum is a sexually dimorphic marker of general intelligence. Scientific reports, 7(1), 18070.

Methods

I am not familiar with the authors' statistical approach but as far as I understand, statitsitcal significance was defined across contacts, patients and states, however it is not fully clear to me how the nested nature of the data was handled. For instance, measurements in different pairs of electrodes within patients cannot be considered independent for the correlational analyses between spindle and fast frequency parameters.

Related to this point, the authors may verify whether the correlation between spindle and fast freq. parameters is specific to these oscillatory phenomena, or such correlations may also arise between other oscillations or frequency-specific activity measured by the same electrodes in the same patient.

Results

It is surprising that in some patients, fast frequency bursts in the central thalamus were not detected. What might be the reason for the lack of thalamic bursts in some of the patients?

Were the 4 patients that showed bursting activities also at the level of the scalp different from the other patients with respect to thalamic fast frequency bursts?

Eye movements in REM sleep seem to show intense bursting activities in a periodic manner, see for instance: Ktonas, P., Nygren, A., & Frost Jr, J. (2003). Two-minute rapid eye movement (REM) density fluctuations in human REM sleep. Neuroscience letters, 353(3), 161-164.

Interestingly, sleep spindles were also shown to peak periodically (See: Lecci, S., Fernandez, L. M., Weber, F. D., Cardis, R., Chatton, J. Y., Born, J., & Lüthi, A. (2017). Coordinated infraslow neural and cardiac oscillations mark fragility and offline periods in mammalian sleep. Science Advances, 3(2), e1602026.)

Did the authors identify any periodicity in the appearance of centrothalamic fast-frequency bursts?

During wakefulness, were the detected fast-frequency bursts associated with eye movements? The authors might consider analyzing whether these oscillations were more prominent during eye movements or under eyes-open vs. eyes-closed conditions. Such comparisons may offer additional insights into the relationship between centrothalamic fast-frequency bursts, REM phasic activity, and the functional role of these oscillations.

Typo

For example, during Non-Rapid Eye Movement (NREM) sleep, thalamocortical sleep spindles at 11-17 Hz are generated via a mechanism driven by inhibitory neurons in the thalamic reticular nuclues – typo (nucleus)

Overall, I find this to be a valuable and promising study with the potential to make a significant contribution to our understanding of thalamocortical dynamics in REM sleep and wakefulness. I encourage the authors to consider these points to strengthen the theoretical and methodological clarity of the manuscript.

Version 1:

Decision Letter:

Our ref: NATHUMBEHAV-25073202A

8th January 2026

Dear Dr. Staudigl,

Thank you for submitting your revised manuscript "Thalamic oscillations distinguish natural states of consciousness in

humans" (NATHUMBEHAV-25073202A). It has now been seen by the original referees and their comments are below.

As you can see, the reviewers find that the paper has improved in revision. We will therefore be happy in principle to publish it in Nature Human Behaviour, pending minor revisions tocomply with our editorial and formatting guidelines.

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

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

Sincerely,

[redacted]

[redacted]
Nature Human Behaviour

Reviewer #1 (Remarks to the Author):

I thank the authors for their careful and detailed responses to all my remarks. The revised manuscript satisfactorily addresses my concerns.

Reviewer #2 (Remarks to the Author):

My comments have been satisfactorily addressed. I think the dialogue in the response to reviewers would be very helpful for readers to contextualize the results. So I highly encourage the authors to opt in to transparent peer review and publish the reviewers' comments and authors' responses.

Reviewer #3 (Remarks to the Author):

The authors have addressed all of my comments and also provided new analyses to answer some of my questions, which is highly appreciated.

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The images or other third party material in this Peer Review File are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.
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We thank the reviewers for their detailed and constructive comments. In the revised manuscript, we have addressed all of the reviewer comments and questions. We provide below responses to individual reviewer comments, also indicating relevant parts of the manuscript that have now been revised (all such changes have been highlighted in the revised version). We also added a file with Supplementary Information, providing supporting figures and text; none of the text and figures in the file were part of the original manuscript. Note that we have also modified the format of reporting statistics such that they are in line with journal guidelines.

Reviewer #1

Review of the manuscript "Thalamic oscillations distinguish natural states of consciousness in humans" by Chowdhury et al.

This is a very well-executed and clearly written study that provides novel and important insights into the role of thalamic activity across different natural states of consciousness in humans. The work stands out for its clarity, methodological rigor, and the careful description of a rare and valuable intracranial dataset. Despite the limited number of participants, the characterization of the patients is detailed and appropriate for the type of analysis performed.
The most striking and novel finding is the identification of a gamma-band thalamic activity that is selectively present during wakefulness and phasic REM sleep, but absent during NREM sleep. This pattern suggests that such activity might alternate with sleep spindles, potentially reflecting another manifestation of the same thalamic generator. This insight opens up exciting possibilities in our understanding of the thalamus's role in modulating conscious states.
However, I have several comments and suggestions that I believe should be addressed or discussed further in order to strengthen the manuscript and refine the conclusions:

We thank the reviewer for these constructive comments. We address below the comments and suggestions by the reviewer, providing new analysis and data wherever possible. These have now helped us make our findings more robust and their interpretations clearer. Most notably, we are pleased to report here that in two of the patients in the current cohort, where we had simultaneous video-based eyetracking data available, we find a **clear correlation between the pupil diameter, a frequently-used marker of arousal level, and the burst rate of the fast thalamic oscillation reported in this work.**

Comment R1.1

Link between gamma activity and consciousness:While the gamma activity is well characterized, the conclusion that it is directly linked to consciousness remains speculative. The manuscript would benefit from a more cautious interpretation of these findings. For instance, is there any clinical or behavioral evidence (e.g., changes in vigilance, sleep patterns, neuropsychological testing) from these patients during or after DBS that could support this link more directly? The fact that modulating this activity changes behavior will be a real evidence of

the link between this activity and consciousness or arousal. Some DBS electrodes allow registration also after implantation, is it your case?

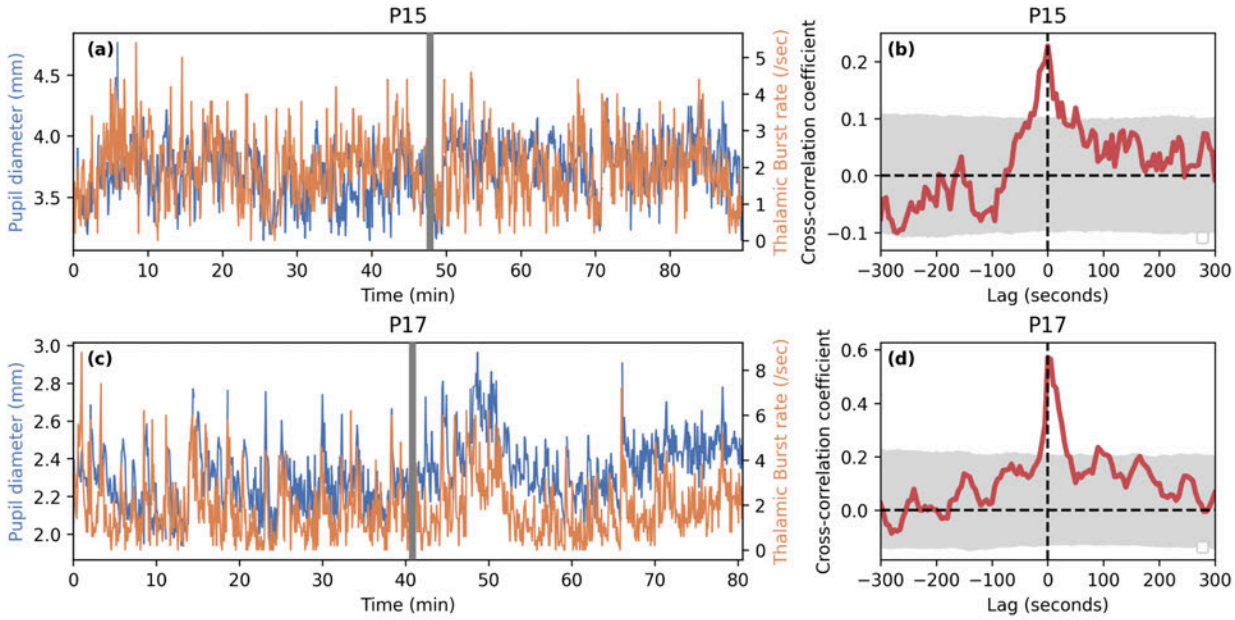
We entirely agree with the reviewer that a direct link between consciousness and the fast thalamic oscillatory activity reported in this work can only be speculated at this point. What our current data supports is a link between the *global states* of consciousness and the oscillatory activity in the human thalamus, rather than a more general link with the broad phenomenon of consciousness. We have now modified the last paragraph of the discussion to explicitly state this (lines 370-375). The modified sentences are as follows:

> While our study establishes that thalamic oscillations are correlated with different states of consciousness and provides evidence that the fast thalamic oscillations reported in this work are related to arousal levels in wake, it is important to note that the connection of the oscillation to the broader phenomenon of consciousness, specifically with contents of consciousness (Koch et al. 2015, Whyte et al. 24) remains an open issue. Future experiments specifically designed to address this important open issue would be of much interest.

The reviewer's question of whether there is a link between the potential effects of the DBS in these patients and our findings here is very interesting. In general, DBS of the Anterior Thalamus for epilepsy has been reported in the literature to be well tolerated (e.g., Kaufmann et al., 2024, Epilepsia). Although interestingly, there has indeed been an open question about its impact on the sleep architecture with conflicting findings (e.g., Voges et al., 2015, Epilepsia; Buenzli et al., 2023, Epilepsia). A systematic study of such effects could be of much interest to both understanding the thalamus' contribution to global states of consciousness as well as for clinical considerations. We also agree with the reviewer that stimulating the specific DBS contacts of the patients where we find this fast oscillation and studying its effect on the arousal levels or consciousness would be a way to understand causality. However, we feel that gathering results for this next step would require significant effort, time, and ethical considerations. We thus feel that these constitute significant endeavors that would be well beyond the scope of the current work. We note that the recordings for the cohort in the current study are based on implantations at the LMU Hospital over the last 13 years. Given the rarity of direct recordings from the human thalamus, we feel that the discovery reported in this manuscript can be of much immediate interest.

Finally, for two of the most recent patients in our current cohort, we had obtained video-based eyetracking data for a separate, unrelated project. These data allowed us to directly study the connection between the fast thalamic oscillations and pupil dilation, a commonly used behavioural readout for arousal levels (see e.g., Grujic et al., 2024, Neuron, for a review). For each of these two patients, **we find a significant correlation** ($p<10^{-4}$, comparison against shuffled distributions, see Methods in revised manuscript) **between the rate of thalamic bursts and pupil diameter.** Despite the analysis being limited to two patients, the clear correlation provides tentative evidence that the fast thalamic oscillations are related to arousal levels. We

note that we also checked for a correlation between the burst rates and saccade rates in the same two patients over the same duration of recording with eye-tracking data available. However, we found no significant correlation ($p>0.05$) between the burst rates and saccade rates in the time period that shows a significant correlation between the burst rates and pupil diameter. We have now included the results of this analysis in the revised version of our manuscript (Extended Data Figure 3, Methods lines 825-860 and Discussion in lines 270-275).



Extended Data Figure 3: Correlation between pupil diameter and burst rate of the fast thalamic oscillations in two patients. Panels **(a)** and **(c)** show the pupil diameter (in blue) and the thalamic burst rate (in orange) as a function of time. The gray vertical bands show the separation between the two discrete sessions over which the data were acquired (see Methods in revised manuscript). Panels **(b)** and **(d)** show the cross-correlation coefficient as a function of lag between the pupil diameter and the thalamic burst rates. The gray shaded regions indicate the 95% confidence interval on the cross-correlation coefficients, obtained via a shuffling procedure (see Methods). For both patients, a significant peak in the cross-correlation can be seen at zero lag ($p<10^{-4}$).

Comment R1.2

Causal attribution to thalamic origin:The claim that this gamma activity originates in the thalamus rather than cortex could be supported more robustly. The authors might consider using directionality index associated to connectivity to test thalamo cortical directionality, especially since similar gamma peaks are visible in frontal scalp electrodes (extended data fig 2 frontal and REM). There is no other simultaneous iEEG sampling from neocortex in this dataset, limiting the assumption of this activity being exclusively coming from thalamus. This should be discussed.

We have now incorporated both the reviewer's suggestions.

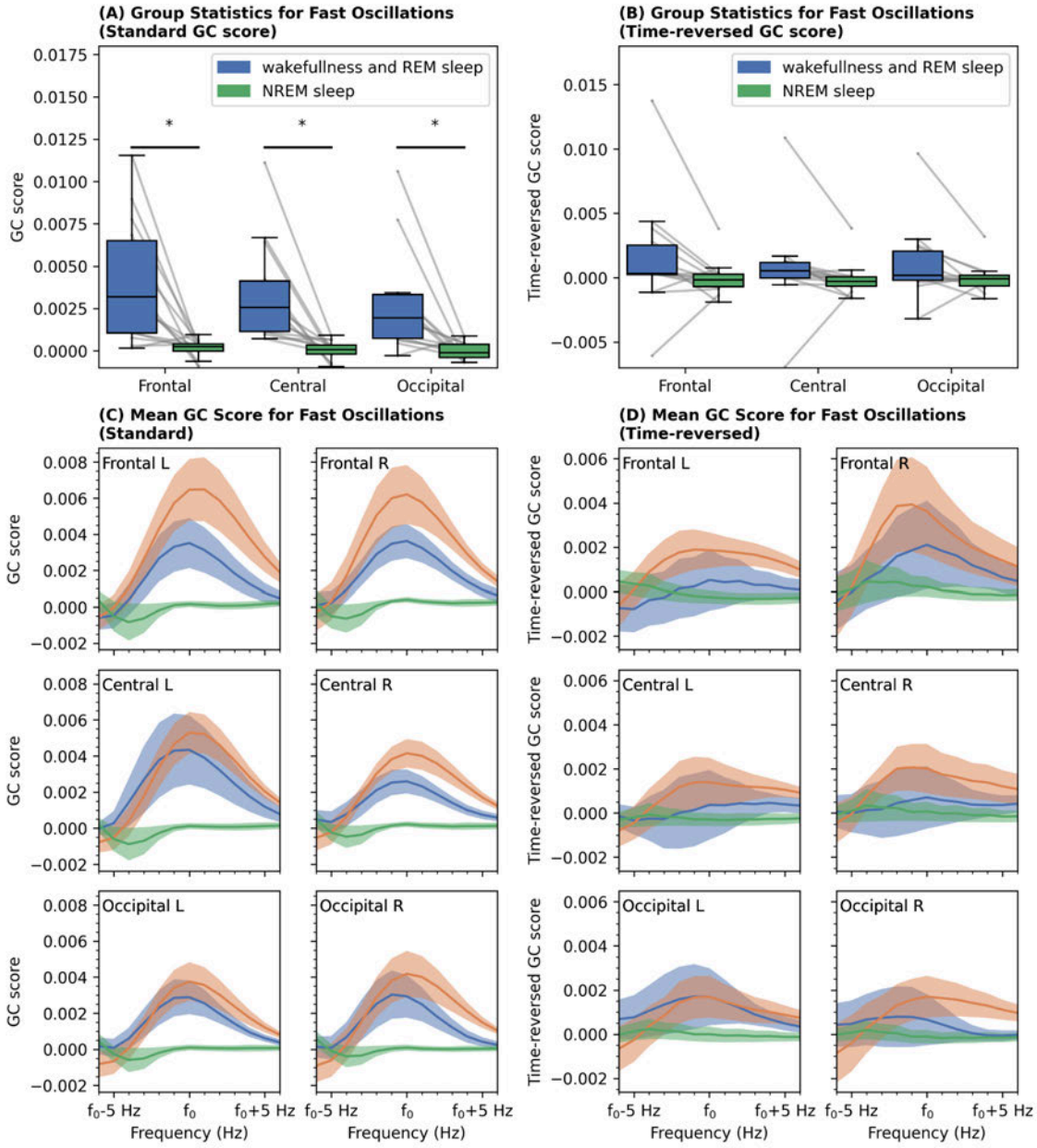
First, we have now clearly discussed the difficulty of assigning an exclusive thalamic origin to the signal. We agree that it is possible that the oscillatory signal we report in this work is thalamocortical in nature. Indeed, our original intent was not to claim this as a signal that can exclusively be found in the Thalamus. We had only intended to claim the specificity of the signal to the Central Thalamus as compared to other thalamic nuclei, based on the data. We have now carefully gone through the manuscript and made sure that this point is clarified. However, we would also like to emphasize here the specificity of the signal to the central thalamus, and that such a signal in humans has not been reported as being widely seen before, despite iEEG recordings in the cortex being much less of a rarity than thalamic recordings; these are potentially indicative of a key role of the thalamus, specifically the central thalamus. We have now clarified this point with the following sentences in the Discussion (lines 300-306):

> The distance to the Central Thalamus significantly predicted the detection probability of Wake- and REM sleep- specific oscillatory bursts. This was not the case for any of the other thalamic regions that were sampled by our data (AV, Mediodorsal medial, Ventral Anterior, or Ventral Lateral Thalamus). However, it is important to note that the specificity of the signal to the Central Thalamus does not necessarily implicate the region as the source of the oscillation. For example, the generation or sustenance of the oscillation may depend on thalamocortical networks.

We have also followed the reviewer's suggestion to use a connectivity index that can provide some information about directionality. For this, we computed the frequency-resolved Granger Causality score between simultaneously recorded thalamic and scalp EEG. Supplementary Figure 1 (shown below) shows the subject-level average Granger Causality score (GC for thalamus to scalp minusscalp to thalamus), as a function of frequency relative to the peak frequency of the fast oscillations (similar to the analysis for wPLI in Extended Data Figure 2 of the original manuscript). We clearly see a positive peak in the Granger Causality score, consistent with the primary drive of the fast oscillations being the thalamus**.**

We also investigated this further by correcting for the Granger Causality score by subtracting a time-reversed GC score from the scores in Supplementary Figure 1(a). This technique is thought to minimize the effect of correlated noise on the standard GC scores (Vinck et al. 2015, NeuroImage). Supplementary Figure 1(b) below shows the time-reversal corrected GC scores. The evidence of directionality that the standard GC scores show (Panels a and c of Supplementary Figure 1) is no longer significant in the time-reversal corrected scores. It is unclear why the time-reversal correction has this effect on the GC scores; potential causes could be (a) the much lower signal-to-noise ratio of the scalp EEG compared to the thalamic iEEG, leading to difficulty in computing GC scores for scalp-to-thalamus connectivity, and (b) the presence of bidirectional connectivity between the scalp and thalamic channels, which makes the interpretation of the time-reversal correction non-trivial (e.g., Chvosteková et al., 2021, Entropy). A clearer understanding of the connectivity would potentially require simultaneous

thalamic and cortical iEEG, providing high signal-to-noise ratio recordings in both the thalamus and cortex (we state this in both the original submission and the revised manuscript, lines 372-376). However, such recordings in humans are even rarer.
We have now added these analyses and the above discussion to the revised manuscript (Supplementary Information Section 1).



Supplementary Figure 1: Granger Causality between the Thalamic iEEG Contacts and Scalp EEG Electrodes. The figure shows the averaged Granger causality scores (subject-level) between simultaneously recorded thalamic contacts and scalp electrodes in the frequency range of the fast thalamic oscillations during REM sleep and wakefulness. Panel **(a)** shows the

Granger Causality score [$GC_{Thalalmus->Scalp}$ - $GC_{Scalp->Thalamus}$] in the frequency range of fast thalamic oscillations for all three regions of scalp electrodes. Panel **(b)** shows the same, but with the scores now having a time-reversal correction (Winkler et al., 2016, IEEE Transactions on Signal Processing). The corrected score is defined as [($GC_{Thalalmus->Scalp}$ - $GC_{Scalp->Thalamus}$)-($GCTR_{Thalalmus->Scalp}$ - $GCTR_{Scalp->Thalamus}$)] where GCTR are the GC scores obtained after flipping the time axes of both the thalamic and the scalp time series. Panels~(c) and (d) show, for visualization purposes, the frequency-resolved average wPLI, after aligning to the peak frequency of the thalamic fast oscillations separately for each group of scalp electrodes (L: Left Hemisphere, R: Right Hemisphere), for the standard GC score and the time-reversed GC scores, respectively. While a clear peak can be seen at the corresponding peak frequencies for the standard GC score, implying a thalamus to cortex drive, this is diminished after applying the time-reversal correction. (* p_{corr}< 0.004, group-level paired Wilcoxon Rank Test with 14 subjects, corrected for 3 comparisons using the Bonferroni method.)

Comment R1.3

Interpretation of common generator for gamma and spindles:The hypothesis that gamma and spindle activity may reflect different manifestations of a common generator is intriguing, but currently based only on similar features and alternation. Further clarification or discussion of this point is warranted, including its limitations and whether there are anatomical or functional data to support it.

Based on the comments above, as well as those of other reviewers (comments R2.7-2.9, R3.2), we now now revised this part of our analysis and their interpretation: (i) the width correlation is not robust enough at the group-level (Comment R2.7), and (ii) as the reviewer points out, the interpretation of a common generator based only on the feature similarity is speculative. We have thus moved this analysis to the Supplementary Information now (lines 50-104) and have modified the associated discussion to reflect this (lines 300-319).

> The distance to the Central Thalamus significantly predicted the detection probability of Wake- and REM sleep- specific oscillatory bursts. This was not the case for any of the other thalamic regions that were sampled by our data (AV, Mediodorsal medial, Ventral Anterior, or Ventral Lateral Thalamus). However, it is important to note that the specificity of the signal to the Central Thalamus does not necessarily implicate the region as the source of the oscillation. For example, the generation or sustenance of the oscillation may depend on thalamocortical networks. In this context, it is interesting to note that research with model animals (specifically cats) shows that thalamocortical networks can produce fast oscillations, both *in vivo* and *in vitro* (Pinault & Deschenes, 1992, Neuroscience; Pedroarena & Llinas, 1997, PNAS). The typical frequencies of the oscillatory activities, as well as their brain-state specificity (Steriade et al. 1996a, 1996b, Journal of Neuroscience), are similar to the oscillatory activity we detect in the human

thalamus. Interestingly, these studies indicate that the thalamocortical networks that maintain sleep spindles can switch to sustaining faster rhythms depending on the type of ion channels that were activated (Steriade et al. 1993, Science; Crunelli et al. 2018, Nature Reviews Neuroscience) and different neuromodulatory conditions, e.g., driven by cholinergic input from the brain stem (Steriade et al. 1991, PNAS). Further, computational modeling of thalamocortical networks also produces similar transitions in dominant oscillatory activity from spindle-like oscillations under neuromodulatory conditions of NREM sleep to faster oscillations in the beta-gamma frequency ranges under conditions of wakefulness (Li et al. 2017, PLoS Computational Biology). Indeed, it is interesting to note that we find the amplitudes of NREM sleep spindles and the wake- and REM- specific fast oscillations to be correlated across contacts and patients, indicative of an underlying relationship between these oscillations (see Supplementary Figure 2).

Comment R1.3

Patient variability and epilepsy context:The manuscript does not adequately address the fact that the data come from pharmacoresistant epilepsy patients, many of whom may have disturbed sleep, widespread interictal activity, and structural abnormalities. Although epileptic discharges are carefully excluded, a discussion is needed on how pathological thalamocortical dynamics might differ from those in healthy individuals.

Are there differences in gamma activity or spindles related to seizure frequency, type of epilepsy, or medication?

We thank the reviewer for pointing this out. We agree with the reviewer on the difficulty of generalizing studies in cohorts of pharmacoresistant epilepsies, as is often done in cognitive neurosciences, to healthy populations. We have now followed all of the reviewers' suggestions to understand this issue better and have included all the additional analyses in the revised manuscript.

First, we tested whether the rate of thalamic bursts, both fast oscillations during Wake and REM sleep, as well as spindles during NREM sleep, correlates with the seizure frequency. For this, we used a baseline total seizure frequency measurement one month before the DBS implantation surgery, and hence, the date of recording of the data presented in this work. We found no significant correlation between the baseline seizure rate and the rate of thalamic fast oscillations, nor between the seizure rate and the rate of spindles in the same thalamic contacts (Supplementary Figure 4, also shown below, panels a and b, Spearman correlation, $p>0.45$).

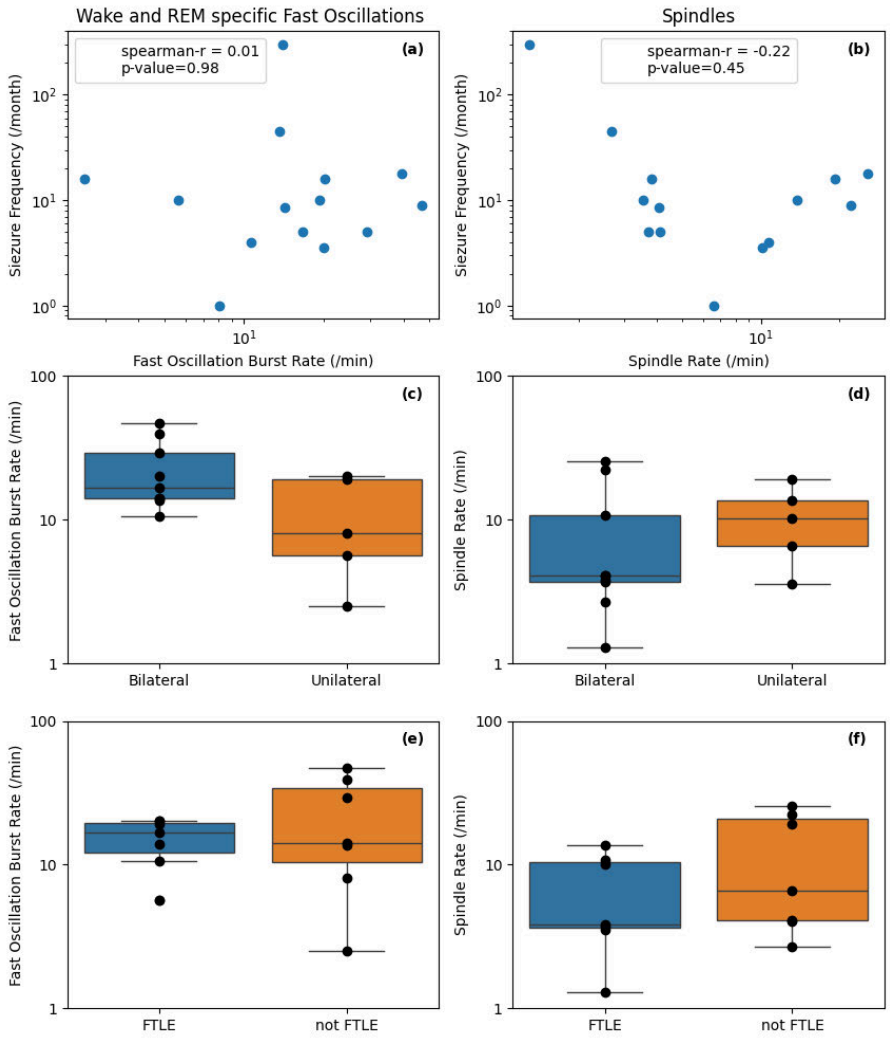
Next, we studied differences in the rates of either fast oscillations or spindles based on epilepsy types. We note that the epilepsy types for the patients in our cohort are very diverse, with different focuses and etiologies (Extended Data Table 1). It is thus unlikely that the presence of

the oscillation itself is due to a network pathology. Further, after consulting with an epileptologist (E.K.), we classified the cohort of patients using different criteria: (i) unilateral epilepsies vs. bilateral epilepsies and (ii) Fronto-Temporal Lobe Epilepsies (FTLE) or other types. We then tested whether either the rate of fast oscillations in Wake and REM sleep or the rate of spindles in NREM sleep is different between these different cohorts. For both classifications, we did not find any significant differences in the rates (Supplementary Figure 4 below, panels c-f, Mann-Whitney U test, $p>0.11$ in all four cases).

Finally, while we acknowledge that anti-seizure medications (ASM) are known to affect the sleep architecture (e.g, Liguori et al., 2021, Sleep Medicine Reviews), the heterogeneity of ASMs that were administered (listed in Extended Data Table 1) makes it unlikely that these had a systematic effect on the findings reported in the current manuscript. Indeed, the large heterogeneity prevents a meaningful separation of the cohort into different groups based on the ASMs they were administered.

We have now added all of the above analyses and discussions to our revised manuscript (Supplementary Information, lines 105-125). The discussion added to the main text of the manuscript (lines 355-365) is as follows:

> A potential limitation of the study is the possibility of abnormalities in thalamocortical structural connectivity (Zhang et al., 2020, Brain Research), which have been described previously for such cohorts with pharmacoresistant epilepsies. Further, administration of anti-seizure medication (ASM) is also known to have an impact on sleep architecture (Liguori et al., 2021, Sleep Medicine Reviews). As with any study that utilizes intracranial data from such cohorts, the extent to which the results generalize to healthy populations remains an open question. However, multiple factors, such as (i) the relatively large size of our cohort (compared to similar studies), (ii) the use of group-level statistics throughout the study, (iii) the heterogeneity of epilepsy types (see Extended Data Table 1), (iv) the lack of correlation between thalamic burst rates and seizure rates as well as between the burst rates and epilepsy type (see Supplementary Figure 4), and (v) the heterogeneity of ASM regimes (see Extended Data Table 1), makes it unlikely that the main findings of this work are driven by pathology.



Supplementary Figure 4: Relationship between fast oscillation (spindle) rates in the thalamic contacts and pathological properties. Panels (a) and (b) show the baseline seizure frequency, measured one month before the DBS implantation surgery, as a function of the rate of the fast oscillation in Wake and REM sleep (Panel a) and that of the rate of spindles in NREM sleep (Panel b), for the 14 patients where we detected the thalamic fast oscillation. The data in both panels are consistent with there being no correlations between either the rate of fast oscillations or that of spindles and the baseline seizure rate (Spearman-r=0.01, p>0.98 for fast oscillations and Spearman-r=-0.22, p>0.45 for spindles). Panels (c) and (d) show the rates of fast oscillations and spindles, respectively, for patients diagnosed with unilateral epilepsies and bilateral epilepsies. Panels (e) and (f) show the same, but now dividing the cohort based on whether they had Fronto-Temporal Lobe Epilepsies (FTLE) or not. We did not find any statistically significant differences between the two cohorts for either of the two classifications, for both fast oscillation rates and spindles (Mann-Whitney U test, p>0.11 in all four cases). Note that the rates of both fast oscillations and spindles were consistently computed from thalamic iEEG contacts where the fast oscillation was detected.

Comment R1.4

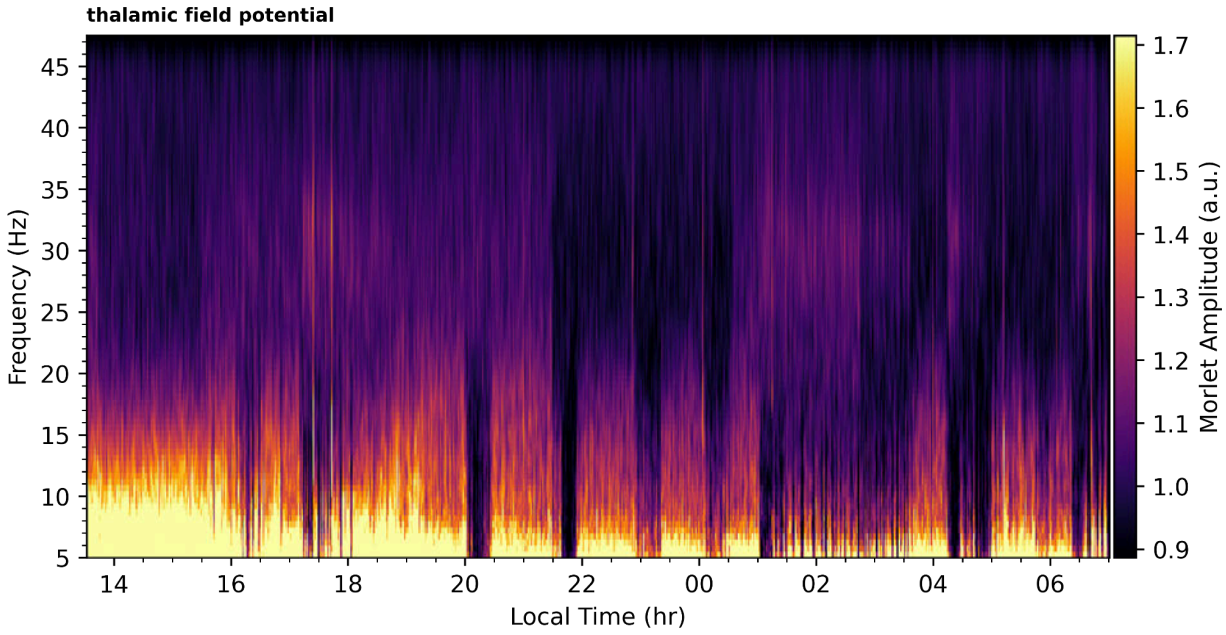
Could the presence or absence of gamma activity in the three non-included patients be related to individual pathology? There is a patient in particular excluded as he/she has a " reduced vigilance", it could be indeed interesting to compare to support your hypothesis…

This is indeed a very interesting question. We would like to first reiterate below our exclusion criteria (lines 402-408 of Methods) and emphasize that these patients had not entered the primary analysis (i.e., they were not part of the 17 patients in the cohort).

> We excluded 7 patients from the main analysis due to various reasons. These exclusions can be broadly classified into four categories: (i) one patient with reduced vigilance, (ii) two patients due to excessive Epileptic Spiking in the scalp electrodes and the inability to confidently classify sleep stages, (iii) three patients due to very short duration of REM sleep (<10 minutes) in the only night of recording that was available, and (iv) one patient with clear recording system malfunction during the night of recording. Overall, our main analysis is carried out on a total of 17 patients.

For the one patient with reduced vigilance, we could not find clear signatures of different sleep stages when inspecting the scalp EEG. Further, the thalamic field potentials also showed no clear sign of spindles in the ~16 hr of data that was recorded from the patient (see Figure below). While we did not see a clear indication of the presence of a fast thalamic oscillation in this patient, the thalamic field potential (shown in the figure below) does show some switching between slow oscillation-dominated epochs and epochs with some enhancement in higher frequency power. However, the inability to unambiguously classify sleep stages based on scalp EEG makes it difficult to draw any conclusions. We have now mentioned the above discussion in the revised manuscript (lines 412-419 in Methods).

For the patients in category (ii), i.e., those with excessive spiking in the scalp electrodes, we were again unable to confidently sleep stage the data. This also meant that it was not possible to identify the fast oscillations using the approach used in our manuscript. Finally, for the patients with very little REM sleep (category iii above), there was indeed some indication of a similar oscillation in wakefulness, but we did not include them in the primary analysis due to the inability to make a claim about wake *and* REM specificity of the signal. It was also not clear if the short REM epochs in these patients were indications of a disrupted sleep architecture in general or if it was specific to the nights of recording in the clinic.

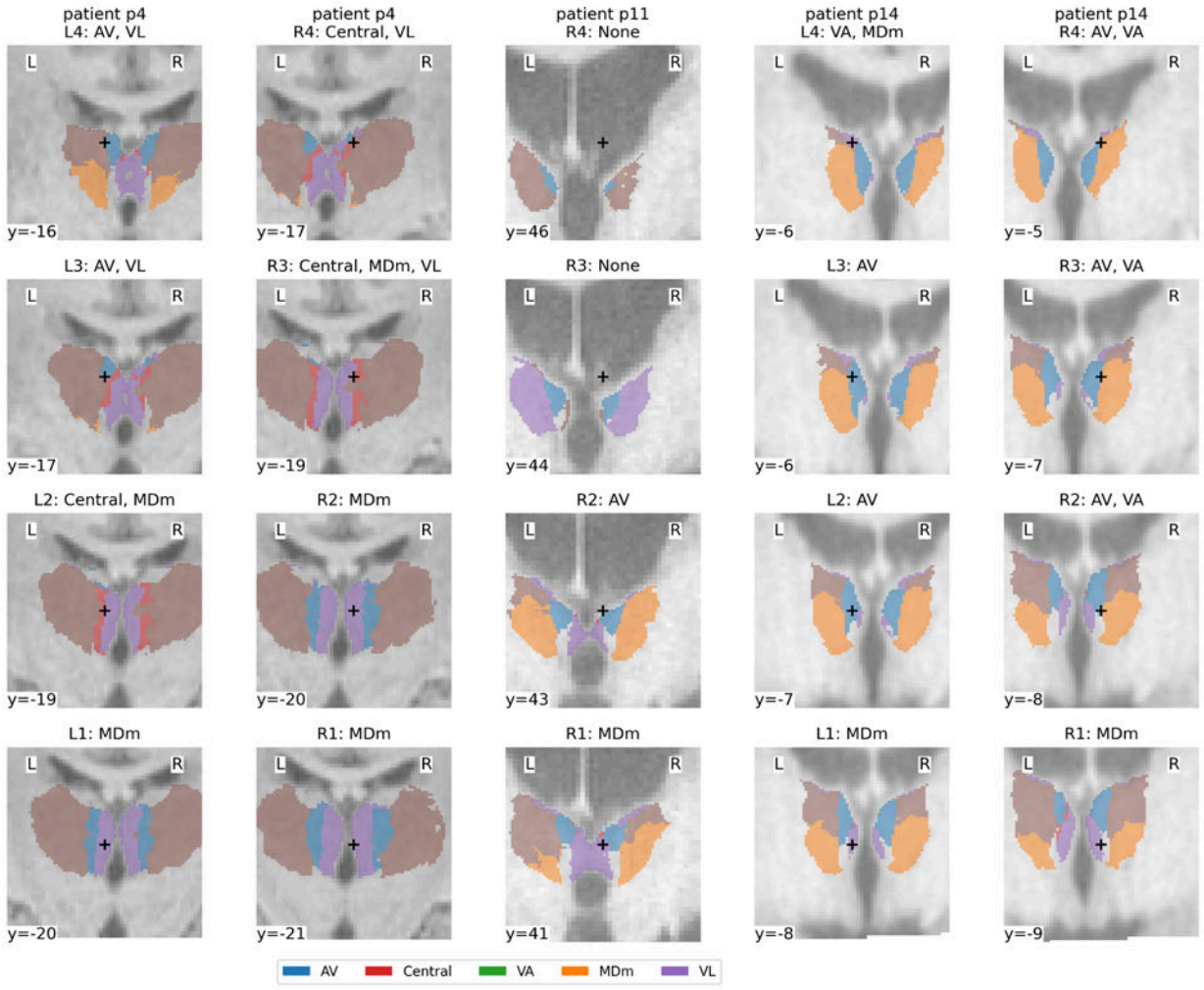


Morlet Spectrogram of the excluded patient with reduced vigilance. Note that we could not reliably sleep score the data using the scalp EEG data for the duration of recording. The field potential above shows an absence of a well-defined oscillatory band in the sleep spindle range (see, for example, Figure 1 of the main text for examples of well-defined spindle bands that were ubiquitously seen throughout our patient cohort)

Comment R1.5

In the Discussion, it would be valuable to elaborate briefly on why some patients did not show thalamic gamma activity, and what factors (anatomical, clinical, technical) might account for this absence.

We thank the reviewer for pointing this out. We did not find the fast thalamic oscillation in 3 of the 17 patients in our cohort. Supplementary Figure 11 (also shown below) shows the native space localizations for these three patients. As can be seen from the figure, two patients did not have any contacts in the Central Thalamus (note that this includes patient p11, where we had access to recordings from a single hemisphere only). It could thus be that the location of the DBS contacts affected the detectability of the fast oscillations (specially for p11, where all the contacts were very anterior, with 2 of the 4 not being in the thalamus). The reason for not detecting the fast oscillation in p4 remains unclear, given that the patient had DBS contacts in the Central Thalamus. It is difficult to conclusively establish why this was the case, but one possibility is that the signal is intrinsically much weaker in the particular patient.



Supplementary Figure 11: Localization of contacts for patients for whom we did not detect the wake and REM- sleep- specific thalamic oscillations. Each row shows a particular DBS contact in a particular patient. Note that for p11, we did not have access to the recording from the left hemisphere and have thus shown here only the relevant right electrode. The black cross indicates the location of the contact on the sagittal slice of the native-space patient T1-weighted MRI (for a view of all three slices, see Supplementary Figures 18, 19, 34, 39, 40). The filled contours indicate the segmentation obtained from the Freesurfer algorithm (Iglesias et al. 2018, NeuroImage). The labels on top of each slice also indicate the thalamic region(s) that the contact was localized to; note that we have taken into account here the 1 mm length of the contacts.

We have now added the above figure in the revised manuscript (Supplementary Figure 11) and the following discussion to the main text of the paper (lines 205-213):

> We investigated whether the anatomical localizations for the DBS contacts of the 3 out of 17 patients in our cohort where we did not detect the Wake- and REM- sleep- specific thalamic oscillations, were systematically not in the Central Thalamus. Indeed, for two of these patients, there were no contacts localized to the Central Thalamus (see Supplementary Figure 11). It could thus be that the location of the DBS contacts affected

the detectability of the fast oscillations in these two patients. The reason for not detecting the fast oscillation in the other patient remains unclear, given that the patient had DBS contacts in the central thalamus. It is difficult to conclusively establish why this was the case, but one possibility is that the signal is intrinsically much weaker in the particular patient.

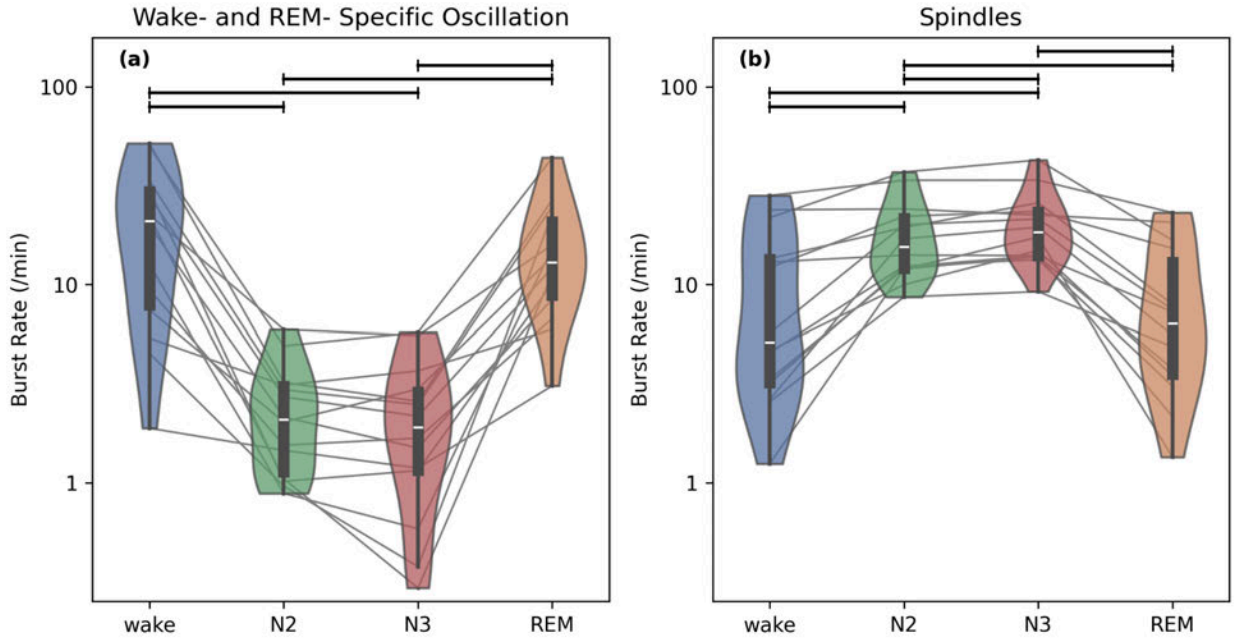
Comment R1.6

Stage specificity of NREM:NREM sleep is heterogeneous. The analysis does not clearly separate stage N1, N2, or N3, which may each have distinct thalamic dynamics. Have the authors considered this? Differences in spindle and gamma rates across these sub-stages would be highly informative.

We thank the reviewer for this interesting suggestion. We have now also checked and divided NREM sleep into N2 and N3, and tested if the rates are different between these. We note that we did not include N1 because of the very little data that is often available for the light sleep stage and the general difficulty of confidently classifying N1, in particular in clinical settings as ours. Supplementary Figure 5 (also below) shows the burst rates of both oscillations as a function of sleep stages, with NREM divided into N2 and N3. For both oscillations, the figure shows the trends expected from our main findings: (i) the burst rate of the thalamic fast oscillations in each of wake and REM is significantly higher than in both N2 and N3 (Wilcoxon Rank Test at the group level, N=14, $p_{cor}<0.002$ for all four comparisons, Bonferroni corrected for a total of 12 pair-wise comparisons) and (ii) the burst rate of spindles is significantly higher in each of N2 and N3 than in both wake and REM (Wilcoxon Rank Test at the group level, N=14, $p_{cor}<0.003$ for all four comparisons). Further, for the fast oscillations, we find no statistically-significant difference in the rates between N2 and N3 (Wilcoxon Rank Test at the group level, N=14, $p_{cor}>0.05$).

Interestingly, for sleep spindles, we find that the rate in N3 is significantly higher than in N2 (Wilcoxon Rank Test at the group level, N=14, $p_{cor}=0.036$). While there is some consensus that spindle rates are higher in N2 than in N3 in the human cortex (e.g., Purcell et al. 2017), the relationships of the rates in the thalamus are unclear. In the few studies that use direct iEEG recordings from the Thalamus (Mak-McCully et al., 2017; Bastuji et al., 2020; Schreiner et al., 2022), the rate of sleep spindles between N2 and N3 is either consistent or the rate is found to be significantly higher in N3 than in N2 (similar to our findings here). We note that these papers also studied different regions of the thalamus (e.g., the Pulvinar in Mak-McCully et al., 2017, ANT and MD in Schreiner et al., 2022). The prior studies, along with our findings here, are indicative that the relative rates of spindles in N2 and N3 are different in different parts of the brain (and potentially between different parts of the thalamus). In the future, it would indeed be very interesting to carry out further investigations of NREM sleep oscillations in the thalamus, both as a function of NREM microstates as well as thalamic nuclei.

In the revised version, we have now included the figure as well as the above discussion (Supplementary Figure 5).



Supplementary Figure 5: The rate of Wake- and REM- specific Oscillations and NREM Spindles in Thalamic iEEG contacts, as a function of sleep stages, with NREM sleep divided into N2 and N3. Significant differences in burst rates (Wilcoxon Rank Test at the group level, N=14, p_{corr}<0.05, after correcting for multiple comparisons) between pairs of brain states are indicated with horizontal lines on the top. For the Wake- and REM- sleep specific fast oscillations, shown in Panel (a), the burst rate is significantly higher in REM and wake compared to both N2 and N3, with no differences in the rates between N2 and N3. For the NREM sleep spindles, shown in Panel (b), the rates in N2 and N3 are significantly higher than in both wake and REM sleep. Further, the rate of spindles in the thalamic contacts is significantly higher in N3 than in N2.

Comment R1.7

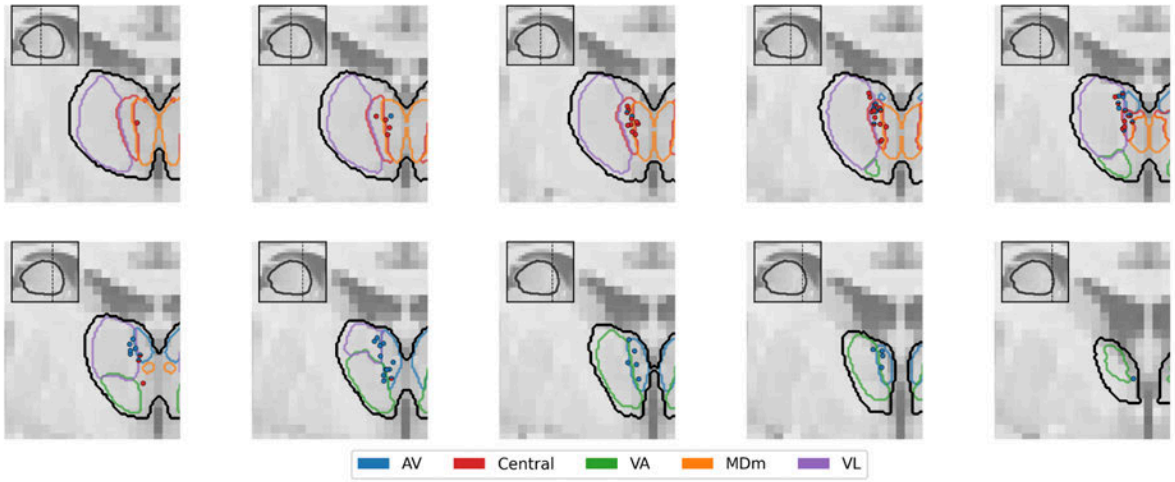
Electrode localization and nuclear specificity:The manuscript would benefit greatly from an image or schematic showing the precise locations of the 17 thalamic electrodes. Current analyses are based on distance from the “central thalamus”, but activity may be more accurately interpreted relative to specific thalamic nuclei explored. I guess you should have a lot of data specific of ANT for example. Moreover, do also spindle rates vary depending on proximity to the central thalamus?

We thank the reviewer for the comments and have now followed all of the suggestions above. We would first like to emphasize here a few critical issues when working with macroelectrode recordings in the human thalamus and the anatomical specificity of such recordings.

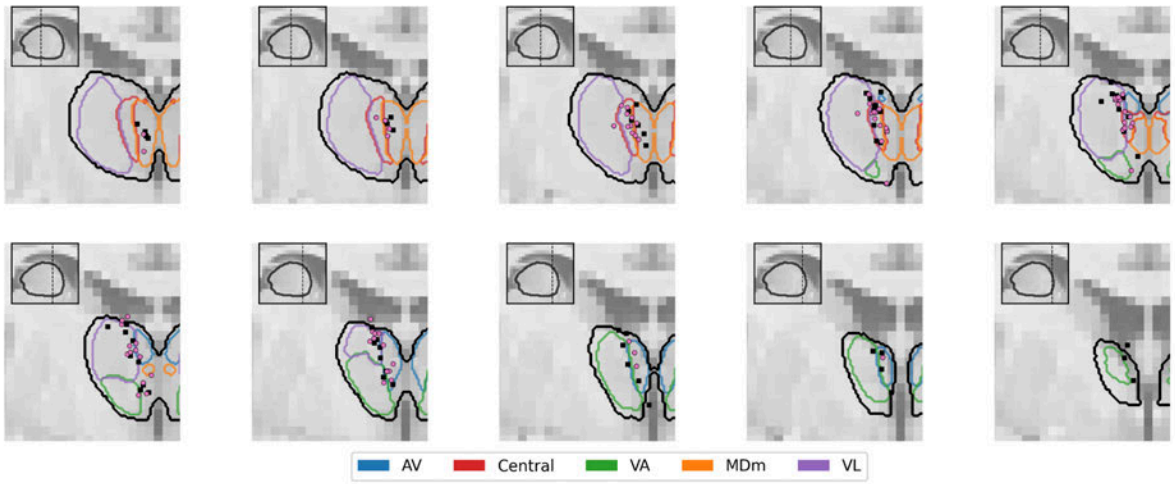
The segmentation of the human thalamus from T1-weighted MRI images is quite challenging, with a large number of segmentation algorithms that are available, each of which is based on a different approach and ground-truth database (e.g., Saranathan et al., 2021, Nature Scientific data and references therein). There are only a few anatomical landmarks that are typically available in MRI images to clearly delineate the boundaries between different thalamic nuclei, implying the exact boundaries of the nuclei in individual patients may not be entirely accurate (see, for example, Lehtimäki et al. 2016, Brain Stimulation, for a discussion on the difficulty of targeting the ANT due to the high individual variability in the location and size of the nucleus). However, the algorithms are indeed designed to ensure that the segmentation boundaries are, *on average*, correct.

We had chosen to use the Iglesias et al. (2018, NeuroImage et al.) thalamic segmentation algorithm, as implemented in FreeSurfer, because it performs a native space segmentation. In our testing, we found native space segmentations to be far superior to an MNI-space atlas (such as those typically used with the standard LeadDBS workflow), as it entirely avoids the native-to-MNI coregistration process, an additional step that adds to the localization error. Note that patient brains are prone to asymmetries that are particularly problematic when converting from native to MNI space. While our approach makes the localization more accurate, it makes it impossible to accurately visualize all contacts on a single MRI. We have thus provided with this revised manuscript the localization for each of the 136 thalamic contacts on the native-space MRI of the 17 individual patients (Supplementary Figure 12-46).

However, we entirely agree with the reviewer that an overview plot would be very useful. We have thus also done so by performing the additional step of native-to-MNI space coregistration. We emphasize again that the results thus obtained do not reflect the native-space localization. For example, we show the MNI-space coordinates of the contacts that were localized in the native space to the Anterior thalamus and the Central Thalamus in Supplementary Figure 9 (also shown below), with the MNI space atlas overlaid on it. The figure clearly shows that the localization in the MNI space inaccurately depicts the native-space localization in the native space of the patients. With this declaimer stated, we also used a similar approach to help visualize the location of all iEEG contacts that were used in this work, with color coding to indicate the contacts where we detected the fast thalamic oscillation versus those where we did not do so (Supplementary Figure 10, also shown below).



Supplementary Figure 9: Thalamic Segmentation in MNI Space. The figure shows different coronal slices on an MNI brain, with the plane of the slices shown in the top-left insets. The contours show the MNI space boundaries of the different nuclei in the Iglesias et al. (2018, NeuroImage) atlas. The MNI-coordinates of the electrode contacts of all 17 patients in our cohort, which were classified in the native patient space as being in the AV are shown with blue-filled circles and those in the Central Thalamus with red-filled circles. Note that we transformed all coordinates to the left hemisphere for a clearer visualization. The contacts shown with half red and blue fillings are those that lie within 1 mm of both the AV and the Central Thalamus. Note that 1 mm is similar to the length of the DBS contacts as well as the typical resolution of MRI. The figure illustrates that transforming patient MRIs to the MNI space introduces additional errors that lead to inaccuracies in localization. See Supplementary Figures 12-46 for the individual native-space localizations of all contacts for the 17 patients in our cohort.



Supplementary Figure 10: Visualization of contact localizations in the MNI Space. The same as in Supplementary Figure 9, but now with the MNI coordinates of all 132 contacts from the 17 patients being plotted. The contours show the MNI space boundaries of the different nuclei in the Iglesias et al. (2018, NeuroImage) atlas. Note that this figure is for visualization purposes only and that the plot does not accurately reflect the native space localizations (See Supplementary Figure 9). The magenta points indicate the contacts where the Wake- and REM Sleep- specific oscillation was detected. Note that the oscillation was detected with bipolar montages, and we thus indicated both contacts that were part of

a bipolar montage with a magenta circle. The black squares indicate contacts where we did not detect the oscillation. See Supplementary Figures 12-46 for the individual native-space localizations of all contacts for the 17 patients in our cohort.

The other critical issue in understanding anatomical specificity comes from the fact that we are recording with macroelectrodes (a standard for most iEEG papers that do not have microwire recordings for single units). The size of each of the macroelectrode contacts is 1.5 mm in length and 1.27 mm in diameter, implying that in some cases the contact itself might be at the boundary of two nuclei and thus pick up signals from both. This issue is further complicated by the use of bipolar rereferencing, which, while necessary to derive spatially confined mesoscale field potentials, could imply that each of the contacts lies in two different thalamic nuclei. Bipolar rereferencing is widely used in human iEEG studies and is also widely believed to be the best approach to get a handle on local activity. However, it is likely that, when using a macroelectrode channel, the probability of detecting a neural signal from a given nucleus of origin remains non-zero outside the exact boundary of the nucleus, with the probability dropping with the distance of the contact to the nucleus.

The above issues, in both the thalamic segmentation itself and the specificity of macroelectrode recordings, informed our current analysis methodology, where we pooled all the contacts together to analyze if the detection probability of the wake- and REM- specific oscillations varied with distance from a particular nucleus. Such an approach takes into account the nature of the data we worked with, making the outcome robust against the above uncertainties in the specificity of an individual contact. We are confident that this approach is more accurate and avoids binary language used by atlas-based approaches, which usually imply that a contact “lies in” a region or not.

We have now added the above discussion and Figures R6, R7 to the revised manuscript (Supplementary Information, lines 210-252)

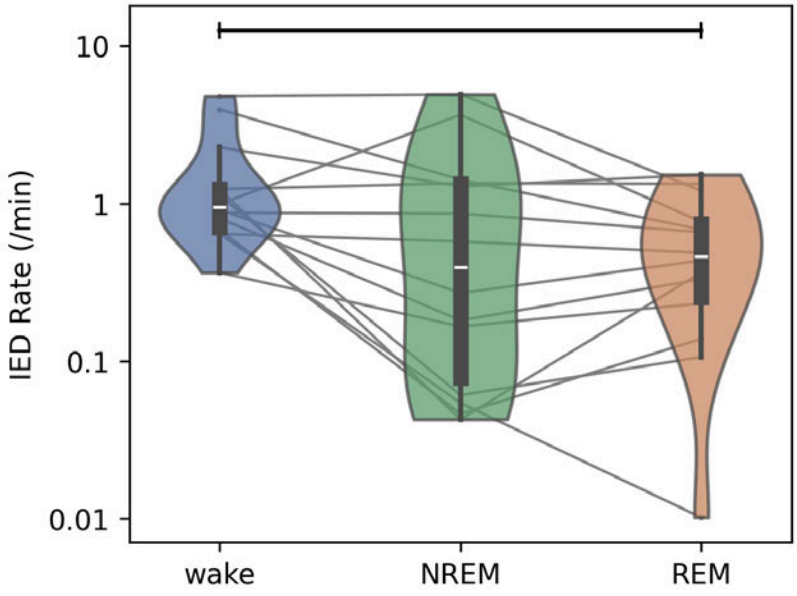
Finally, as suggested by the reviewer, we also checked if the spindle rates correlated with distance from the Central Thalamus. We found no correlation between the spindle rates and the distance to the central thalamus (Spearman-r = 0.11; $p>0.8$). We note that we detect spindles ubiquitously in nearly all thalamic contacts and thus could not repeat the analysis of Figure 4 (of the revised manuscript) for the spindles. The ubiquity of sleep spindles throughout the thalamus is consistent with sleep spindles generally being detectable throughout the brain.

Comment R1.8

Detection thresholds and spike rate:In lines 416–420, the authors describe an envelope amplitude threshold of 5× the baseline. Considering that thalamic spikes are often of low amplitude, could this threshold be too conservative? Can you provide some visual confirmation made by an epileptologist? Furthermore, providing the thalamic spike rate across states (NREM, REM, wake) would help interpret whether spiking may contribute to the observed gamma detection rates or might modify this “background” activity.

As suggested by the reviewer, two epileptologists (E.K. and J.R.) have now visually looked at a random selection of epochs, pooled from all the patients in our cohort, with a mix of those that were marked as bad by our algorithm and those that were not. The classification of the epochs by the algorithm was blinded. While the clear spikes were identified as such by both raters, a high variability in the classification was observed for the remaining epochs - well in line with the previously described high interrater variability for the classification of single-channel EEG epochs and reflecting the individual thresholds to exclude IED-like events (e.g., Jing et al. 2019, JAMA Neurology). However, despite this, an epoch marked as containing an epileptic spike by *either* of the raters was also classified as such by the algorithm in over 90% of the cases. Indeed, our algorithm tended to be very aggressive, leading to the exclusion of a large number of epochs that the human expert raters reported as not containing an epileptic spike. While such false positive rates are not optimal either, our long recordings ensure that the removal of more data than is strictly necessary does not affect the key results of the paper. Thus, while we agree with the reviewer that the choice of threshold is debatable, our detection algorithm ensures that the data we used for our analysis is predominantly free of epileptic spikes.

We have now also computed the IED rates as a function of brain states (Supplementary Figure 6, shown below). We did group-level paired Wilcoxon Rank Tests on all possible pairs to find that the IED rate is significantly lower in REM sleep than in Wake (p_{corr}=0.0007). While the lower IED rate in REM sleep is broadly consistent with findings in the literature (e.g., Conrad et al., 2023, Epilepsia), we note that the difference in brain regions and epilepsy types could contribute differently to IED rates. We have now included this figure in the revised manuscript (Supplementary Figure 6).



Supplementary Figure 6: IED rates as a function of brain states. We find that the rate of IEDs in REM sleep is significantly less than in wake (p_{corr}<0.0007, group-level paired Wilcoxon Rank Test with 14 subjects, corrected for the three comparisons).

Comment R1.9

DBS montage and interpretation:The bipolar montage used may span different thalamic nuclei. When bipolar electrodes included contacts in distinct nuclei, how were these cases handled?

The issue raised by the reviewer is indeed an important one. As discussed in response to comment R1.7, the detection of a signal on a bipolar montage could indeed indicate a source that is close to either of the contacts. This, along with the other issues discussed in our response to comment R1.7, motivated us to use our current approach of avoiding hard classifications of contacts being in certain nuclei and instead using the distance of the contacts to the specific nuclei as the independent variable (as in Figure 4 of the revised manuscript). Further, as also discussed in response to reviewer comment R2.9, our analysis yields the same result independent of whether we use the distance from each of the two contacts in the bipolar rereference or the distance from the midpoint of the two contacts.

Comment R1.10

Conclusion:
In conclusion, this is a novel study that provides important evidence for oscillatory dynamics in the human thalamus during natural states of consciousness. The work is solid in its methodology, well written, and has significant clinical and theoretical relevance. However, some of the key interpretations, particularly those linking gamma activity to consciousness and possible DBS efficacy, require more cautious framing or additional data to be fully substantiated.

We again thank the reviewer for these detailed comments that have now helped improve the quality and clarity of our manuscript. As outlined above in our responses, we have followed all of the reviewer's suggestions, adding both new data and new analyses to the revised version of the manuscript.

Reviewer #2 (Remarks to the Author):

Comment R2.1

General comment:
1) The submitted study investigates oscillatory activity in the thalamus (and EEG) during NREM, REM and wakefulness. This was done using field potential recordings from depth electrodes targeted to the (anteroventral) thalamus in epilepsy patients. These are rare recordings, which is a major plus for the study. The study identified fast oscillations (20-45Hz) in the thalamus during REM sleep and wakefulness. This finding is consistent with published animal studies over past decades. In addition, the study reports fast oscillations correlated with eye movements (detected from the EEG) and phasic REM. This finding seems a little at odds, with respect to frequency changes in phasic REM, with a previous human study recording from the anterior thalamus (Simor et al., 2021, Journal of Neuroscience 41: 5677). Although Simor et al. was cited as an example of human thalamic recordings during sleep, surprisingly, I didn't find a discussion of the similarities and differences between Simor et al. and the submitted study. Moving on, there are a number of methodological and analysis issues that should be addressed, to allow a better evaluation of the data. Specific comments on these and other issues below.

We thank the reviewer for the detailed comments. We have now incorporated all of the reviewer's suggestions in the revised version of the manuscript.

We thank the reviewer for pointing to the Simor et al. (2021) study; the rarity of studies in the human thalamus indeed makes it important to discuss the similarities and differences across different studies. We have now included a full paragraph discussing Simor et al. and also elaborated on the differences between our and their analyses (lines 320-334 in the revised manuscript):

> We note that Simor et al. (2021, Journal of Neuroscience) also used DBS electrodes in the thalamus of patients with pharmacoresistant epilepsy to study differences in power spectra between tonic and phasic REM sleep. However, a direct comparison between their and the results of this work is made difficult by the very different focuses of their study and this work; the primary being (i) Simor et al. focused on the overall power spectrum in the two REM microstates, after averaging across subjects, while we focused primarily on oscillatory power across multiple brain states (NREM, wake, tonic and phasic REM) at the individual subject level; our burst detection technique to differentiate between oscillatory power and aperiodic power allowed us to detect patient-specific frequency bands with elevated oscillatory power and (ii) Simor et al. investigated the power spectra in the anterior thalamus only, while we included all available thalamic contacts, and found that the probability of detecting the oscillatory activity depends on the distance to the Central Thalamus but not the Anterior Thalamus.

Comment R2.2

Specific comments:
2) RE: Fig. 1, and line 69: “the figure shows the ubiquitous presence of a faster oscillation (≈ 28 Hz) during both wakefulness and REM sleep that, to the best of our knowledge, has not been reported before.” Please contextualize / clarify that this fast oscillation during wakefulness and REM has been previously reported in thalamus (and cortex) of animals, e.g., Steriade et al., 1996, Journal of Neuroscience, 76:2788; Steriade et al., 1996, Journal of Neuroscience, 76:392; Steriade et al., 1991, Proc Natl Acad Sci U S A 88:4396.

We have now made the sentence clearer to make it specific to the human thalamus. The revised sentences now read as follows:

> the figure shows the ubiquitous presence of a faster oscillation (≈ 28 Hz) during both wakefulness and REM sleep that, to the best of our knowledge, has not been reported in the human thalamus before.

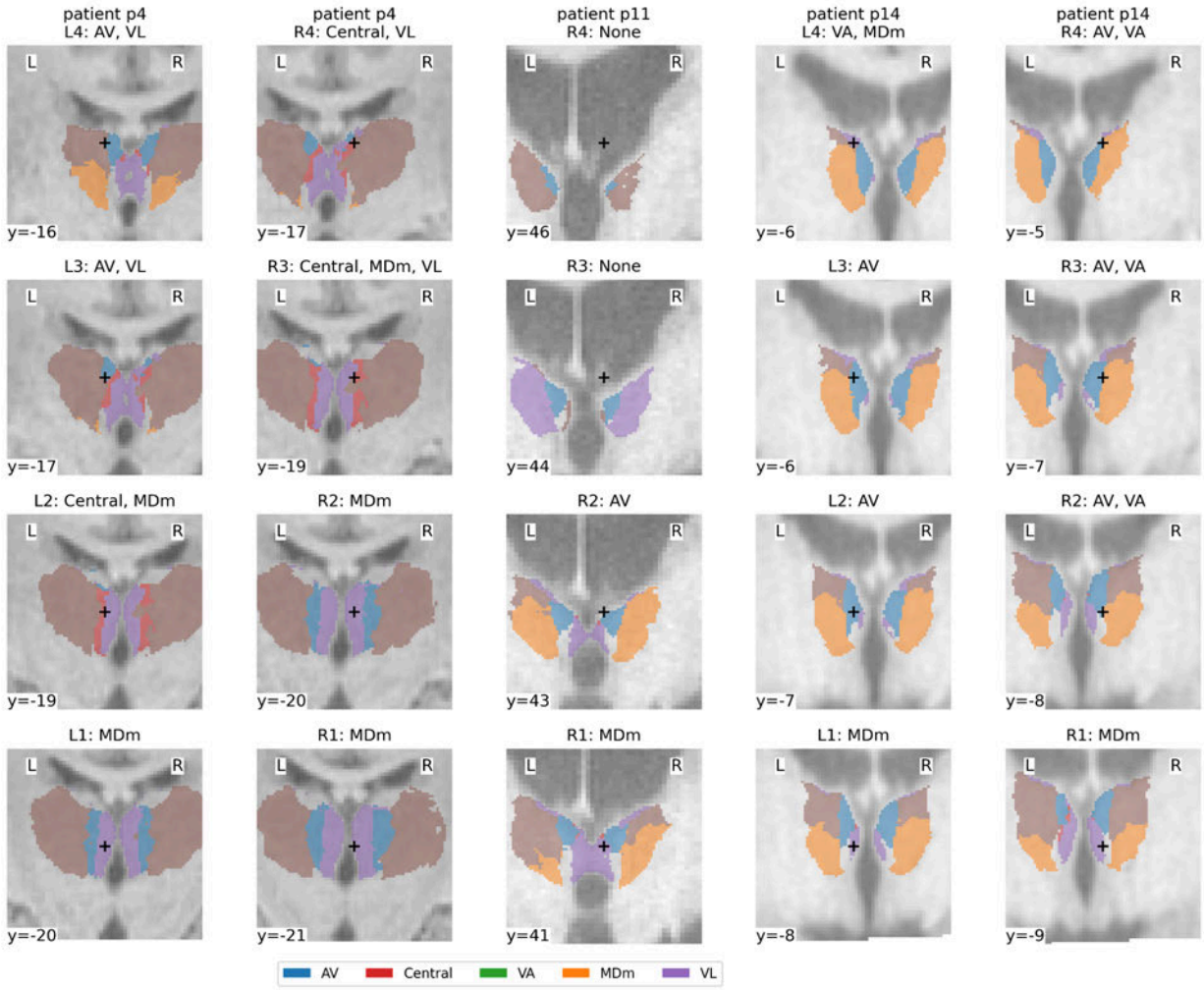
Further, a detailed discussion of the potential similarity of the oscillation reported in this paper to those found in the studies of the thalamus of cats by Steriade et al. was included in the original manuscript. We have now updated the same to also include a discussion of possible generation mechanisms for the oscillations, based on the same body of work (based on comment R2.9 by the reviewer).

> In this context, it is interesting to note that research with model animals (specifically cats) shows that thalamocortical networks can produce fast oscillations, both *in vivo* and *in vitro* (Pinault & Deschenes, 1992, Neuroscience; Pedroarena & Llinas, 1997, PNAS). The typical frequencies of the oscillatory activities, as well as their brain-state specificity (Steriade et al. 1996a, 1996b, Journal of Neuroscience), are similar to the oscillatory activity we detect in the human thalamus. Interestingly, these studies indicate that the thalamocortical networks that maintain sleep spindles can switch to sustaining faster rhythms depending on the type of ion channels that were activated (Steriade et al. 1993, Science; Crunelli et al. 2018, Nature Reviews Neuroscience) and different neuromodulatory conditions, e.g., driven by cholinergic input from the brain stem (Steriade et al. 1991, PNAS). Further, computational modeling of thalamocortical networks also produces similar transitions in dominant oscillatory activity from spindle-like oscillations under neuromodulatory conditions of NREM sleep to faster oscillations in the beta-gamma frequency ranges under conditions of wakefulness (Li et al. 2017, PLoS Computational Biology). Indeed, it is interesting to note that we find the amplitudes of NREM sleep spindles and the wake- and REM- specific fast oscillations to be correlated across contacts and patients, indicative of an underlying relationship between these oscillations (see Supplementary Figure 2).

Comment R2.3

3) RE: Fig. 2, Extended Data Table 1, and line 103: “rate of oscillatory activity during wakefulness and REM sleep is significantly higher than in NREM sleep ($p< 2 \times 10-4$ 104 for both cases, subject-level paired Wilcoxon Rank Test with 14 subjects).” However, in the methods, it states that “our main analysis is carried out on a total of 17 patients”, and “For all patients (but one, see note c), the number of bipolarly rereferenced contacts is 6 (3 on each hemisphere)”. Please show the location of the thalamic electrodes in the 3 patients without the high-frequency oscillatory activity vs the 14 patients with the high-frequency oscillatory activity?

We note that we used the thalamic segmentation algorithm in FreeSurfer (Iglesias et al. 2018, NeuroImage) to compute a segmentation in the native space of the patients. This avoids the additional step of coregistering native space MRIs to a template MNI-space brain, and thus avoids the associated additional uncertainty that comes from such transformations. Note that patient brains are prone to asymmetries that are particularly problematic when converting from native to MNI space. As requested by reviewer #1 above, we have now provided figures showing the localization, in the native space MRI, for each of the DBS contacts for all 17 patients (Supplementary Figures 12-46). The thalamic contacts where we detected the oscillation, as well as those where we did not, are labelled in the Supplementary Figures.



Supplementary Figure 11: Localization of contacts for patients for whom we did not detect the wake and REM- sleep- specific thalamic oscillations. Each row shows a particular DBS contact in a particular patient. Note that for p11, we did not have access to the recording from the left hemisphere and have thus shown here only the relevant right electrode. The black cross indicates the location of the contact on the sagittal slice of the native-space patient T1-weighted MRI (for a view of all three slices, see the Supplementary Figures 18, 19, 34, 39, 40). The filled contours indicate the segmentation obtained from the Freesurfer algorithm (Iglesias et al. 2018, NeuroImage). The labels on top of each slice also indicate the thalamic region(s) that the contact was localized to; note that we have taken into account here the 1 mm length of the contacts.

We have shown above (and also in response to comment R1.5) the native-space localizations of the three patients that did not show the wake and REM- specific fast thalamic oscillation. We have now added to the revised manuscript the above figure (Supplementary Figure 11) and the following discussion (lines 205-213) on potential reasons for not detecting the oscillation in the three patients:

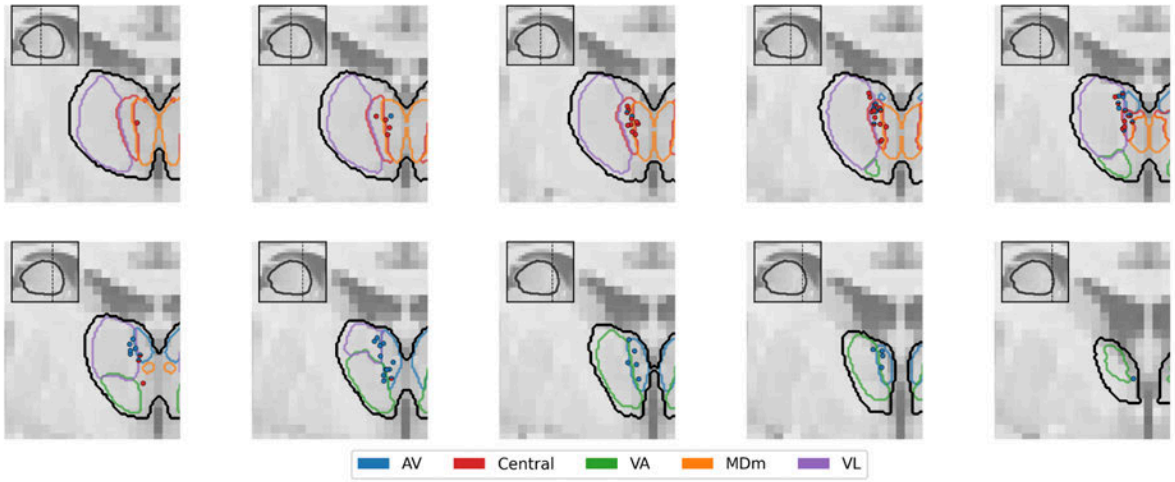
> We investigated whether the anatomical localizations for the DBS contacts of the 3 out of 17 patients in our cohort where we did not detect the Wake- and REM- sleep- specific

thalamic oscillations, were systematically not in the Central Thalamus. Indeed, for two of these patients, there were no contacts localized to the Central Thalamus (see Supplementary Figure 11). It could thus be that the location of the DBS contacts affected the detectability oscillations in these two patients. The reason for not detecting the fast oscillation in the remaining patient remains unclear, given that the patient had DBS contacts in the central thalamus. It is difficult to conclusively establish why this was the case, but one possibility is that the signal is intrinsically much weaker in the particular patient.

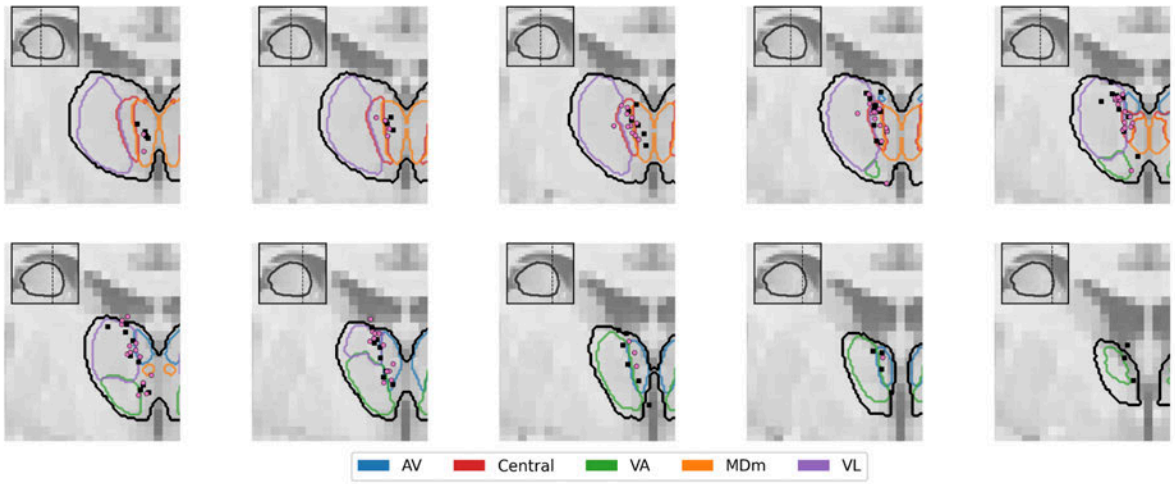
Comment R2.4

4) RE: line 62 and 111. From line 62: “We obtained the thalamic field potential by bipolarly rereferencing the voltages recorded in neighboring contacts of the DBS electrodes, obtaining a total of 105 channels.” and from line “54 thalamic contacts where we detected the fast oscillatory activity.” Please show the location of the 54 thalamic electrodes with the high-frequency oscillatory activity vs the 49 thalamic electrodes without the high-frequency oscillatory activity?

As discussed above (and also in Response R1.7), the native-space segmentation and localization make it impossible to accurately depict the coordinates of all contacts in a single brain MRI. However, we agree with the reviewer that such a visualization would be useful. We have thus, purely for visualization purposes, also coregistered the individual MRIs to a common template brain in MNI space. However, as discussed above (and also in response to comment R1.7), this introduces significant errors in the localization. For example, Supplementary Figure 9 (also below) shows the MNI-space coordinates of the thalamic contacts, which, according to native space segmentation, lie in the anterior thalamus and the central thalamus. The figure clearly illustrates the problems with such a visualization: the figure does not accurately reflect which contact lies in each nucleus based on the native space segmentations. With this caveat stated, we have plotted all DBS contacts of the 17 patients in our cohort in Supplementary Figure 10 (also below), with color-codes indicating whether the wake- and REM Sleep- specific signal was (i) detected in any of the bipolar channels including the contact (magenta circles), (ii) was not detected in the contact.



Supplementary Figure 9: Thalamic Segmentation in MNI Space. The figure shows different coronal slices on an MNI brain, with the plane of the slices shown in the top-left insets. The contours show the MNI space boundaries of the different nuclei in the Iglesias et al. (2018, NeuroImage) atlas. The MNI-coordinates of the electrode contacts of all 17 patients in our cohort, which were classified in the native patient space as being in the AV are shown with blue-filled circles and those in the Central Thalamus with red-filled circles. Note that we transformed all coordinates to the left hemisphere for a clearer visualization. The contacts shown with half red and blue fillings are those that lie within 1 mm of both the AV and the Central Thalamus. Note that 1 mm is similar to the length of the DBS contacts as well as the typical resolution of MRI. The figure illustrates that transforming patient MRIs to the MNI space introduces additional errors that lead to inaccuracies in localization. See Supplementary Figures 12-46 for the individual native-space localizations of all contacts for the 17 patients in our cohort.



Supplementary Figure 10: Visualization of contact localizations in the MNI Space. The same as in Supplementary Figure 9, but now with the MNI coordinates of all 132 contacts from the 17 patients being plotted. The contours show the MNI space boundaries of the different nuclei in the Iglesias et al. (2018, NeuroImage) atlas. Note that this figure is for visualization purposes only and that the plot does not accurately reflect the native space localizations (See Supplementary Figure 9). The magenta points indicate the contacts where the Wake- and REM Sleep- specific oscillation was detected. Note that the oscillation was detected with bipolar montages, and we thus indicated both contacts that were part of

a bipolar montage with a magenta circle. The black squares indicate contacts where we did not detect the oscillation. See Supplementary Figures 12-46 for the individual native-space localizations of all contacts for the 17 patients in our cohort.

We would like to further emphasize here the challenges in delineating the human thalamus into different nuclei based on T1-weighted MRIs. While this is a common approach used across studies, not all thalamic nuclei have clearly identifiable markers in a T1-weighted MRI. Thalamic segmentation algorithms that work in the native patient space, like the one we use here (Iglesias et al. 2018, NeuroImage), try to identify a few clear boundaries and then attempt to extrapolate that to other nuclei. This means that while on average the segmentation is broadly correct, individual localizations may sometimes be unreliable. Our approach in the manuscript is thus based on pooling all the data together to determine whether proximity to a nucleus correlates with the detection probability of the wake- and REM- specific oscillation.

We have now added both of these figures as well as a detailed discussion on the issue of determining signal specificity in Supplementary Information (lines 210-252).

Comment R2.5

5) RE: Fig. 3. The methods state that “We used the bipolar derivative F7-F8 as a substitute for horizontal EOG” giving rise to a “mean rapid EM frequency of 8 +/- 5 per minute”. To estimate the reliability of this approach, there was a “comparison with events detected in a standard horizontal EOG setup, we used data of 11 healthy participants from an independent study where reliable EOG measurements during REM sleep were available simultaneously with standard 64-channel scalp EEG.” While this comparison in healthy participants is appreciated, it would be useful to show in the epilepsy patients that your methods detect saccades at known frequencies (3 per second) during wakefulness. This would help validate your eye movement detection method further.

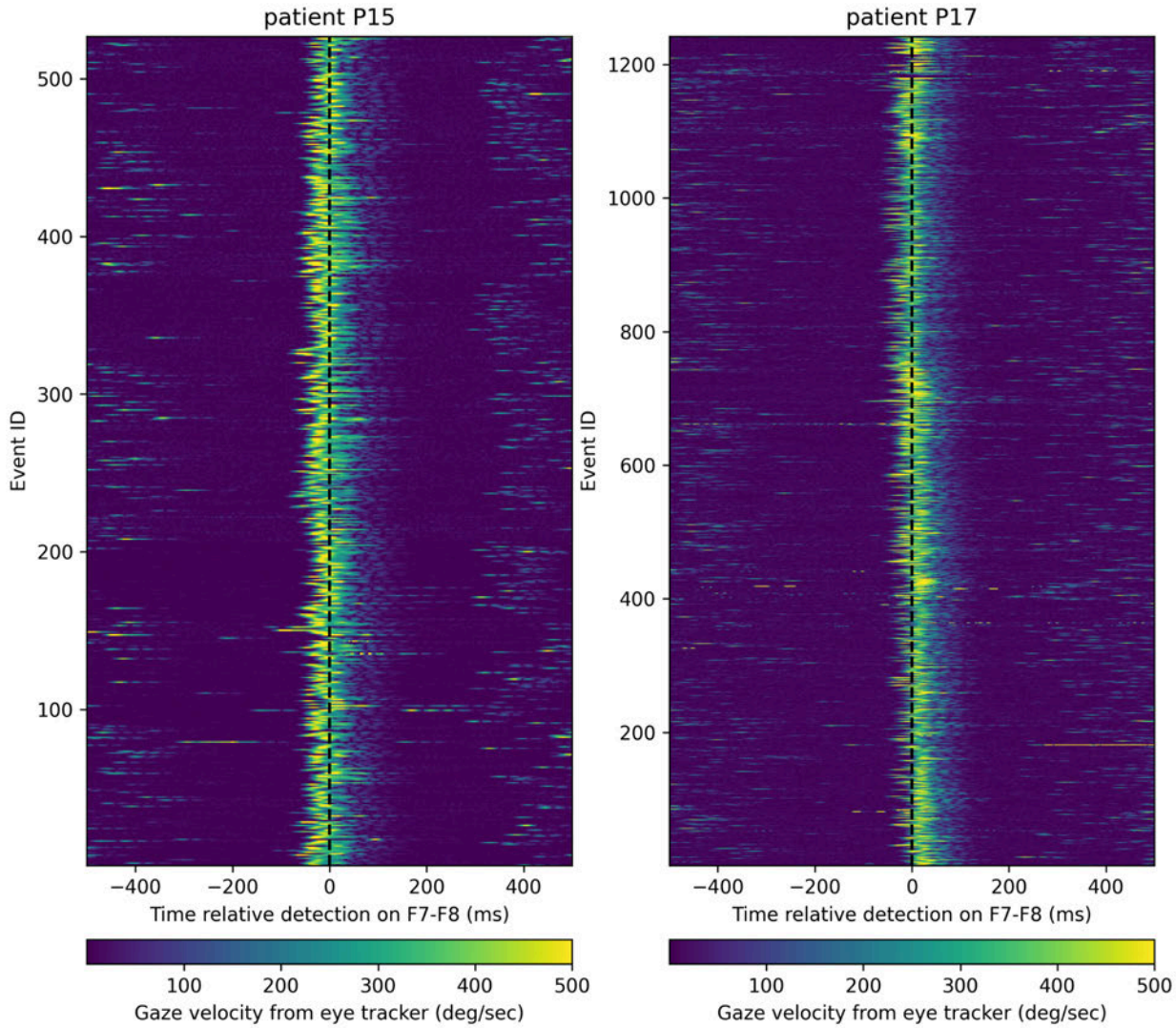
We thank the reviewer for the interesting suggestion. We have now computed the frequency of eye movements detected by our algorithm during wake to find an average of 0.3 ± 0.1 events per second, clearly lower than the typical 2-3 per second.

This lower event detection rate in wake could be due to a few different reasons. The primary reason is that our choice of thresholds in the algorithm was driven by an effort to minimize false detections, such that we could be highly confident of the events we detected as genuine eye movements. This would naturally lead to a bias towards detecting only the relatively large eye movements. Further, there might be periods of closed-eye wakefulness in the data, which could substantially affect the computation of the mean saccade rate during wake.

To further investigate this issue, we have now made use of video-based eyetracking data that is available for two of the patients in our cohort (whose pupil data were used for the analysis in

response to comment R1.1). The two patients had performed an unrelated task, with a total duration of ~80-100 min per patient, where we had simultaneous eye-tracker data at 600 Hz, recorded with the Tobii Pro Eyetracker.

For this analysis, we first ran the same EEG-based eye-detection technique on the data from these sessions. Next, we computed the eye velocity from the eye tracking data. Extended Data Figure 6 (also below) shows the eye velocity data for the two patients, aligned to the events detected by our algorithm from the scalp-based data for which valid eye-tracker data were available (527 events in patient 1 and 1242 in patient 2). The figure shows that using the scalp derivative F7-F8 lets us reliably detect eye movements, as is evident from the increase in eye velocity around the epoch of detection, as measured with the video-based eyetracker. We have now included the figure in the revised manuscript (Extended Data Figure 6).



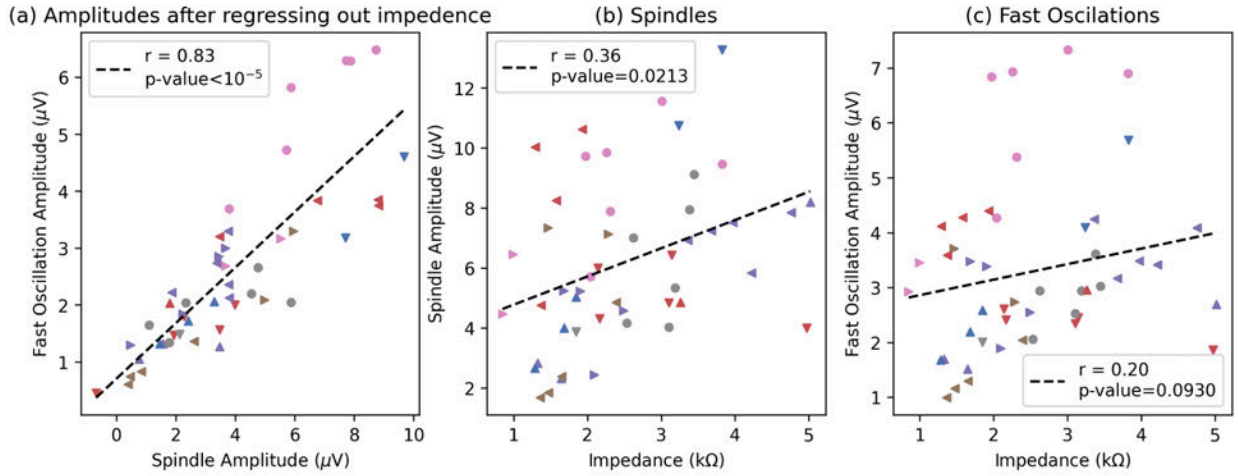
Extended Data Figure 6: Gaze velocity measurement using a video-based eyetracker locked to the eye-movement events detected in F7-F8. The plot shows a clear enhancement

in the gaze velocity, as measured by the video-based eyetracker, around the epoch of events detected on the EEG derivative F7-F8.

Comment R2.5

6) RE: Fig. 4c. Is it possible that the amplitudes are correlated because they are derived from the same electrode with the same impedance and other factors, rather than fast oscillations and spindles being derived from the same mechanism?

This is indeed an important consideration, and we thank the reviewer for pointing it out. We have now computed the amplitude correlation after regressing out the effect of the impedance of each contact. In this analysis, we used measurements of bipolar impedances on each pair of contacts that were made at the time of activating the patient's stimulators; this was typically done 3 weeks after the implantation. These measurements were available for all but one patient in our cohort. We used a partial correlation analysis to regress out the effect of impedance, treating it as a covariate. Supplementary Figure 3(a) shows the amplitudes of the two oscillations after subtracting out the effect of impedances on both the amplitudes of NREM sleep spindles and of the fast oscillations (the individual regressions are shown in panels (b) and (c)). We find a statistically significant correlation between the amplitudes of the two oscillations even after regressing out the effect of impedances ($r=0.833 \pm 0.042$; $p<10^{-5}$, Block bootstrapping with N=13 patients). The analysis shows that impedance variability across contacts and electrodes is not the primary driver of the high correlation between the amplitudes of the two oscillations ($r=0.841 \pm 0.039$, see Supplementary Figure 2). We note that DBS contact impedances are known to drift slowly over time (see e.g., Satzer et al. 2014, Stereotactic and Functional Neurosurgery); however, this is not expected to affect the conclusions of this analysis due to the short gap of only approximately 3 weeks between our iEEG recordings and the impedance measurements.



Supplementary Figure 3: Effect of contact impedances on the correlation between the average burst amplitudes of NREM sleep spindles and fast oscillations in REM sleep and

wakefulness. Panel (a) shows, after regressing out the effect of impedances, the amplitudes of the two oscillations on each bipolar contact. The regression lines used to subtract out the effect of impedances are shown in panels (b) and (c). Note that the negative amplitudes in panel (a) are an effect of subtracting out the regression lines of panels (b) and (c) from the individual amplitude values. We find that the amplitudes of the two oscillations are significantly correlated even after regressing out the effect of contact impedances ($p<10^{-5}$). All statistics were done at the group-level with N=13, using block bootstrapping. In both panels, each unique combination of colors and symbols represents measurements from a patient.

We also carried out an additional analysis to further understand the issue. A high electrode impedance of an EEG contact leads to high noise levels on the channel (Kappenman et al., 2010, Psychophysiology). If electrode impedances drive the correlation, this is likely to also cause a related anti-correlation between the amplitudes and the rates of the bursts. For example, an electrode contact with a relatively good impedance should lead to a better detection threshold (in microVolts). The detections of a larger number of weaker events would lead to a higher event rate and a lower average event amplitude. An impedance-based explanation of the amplitude correlation should thus lead to an anticorrelation between mean amplitudes and event rates. We thus tested whether the spindle rates and the average spindle amplitudes are correlated. We found no statistically significant correlation between these two measures (pearson-r=0.19±0.14, p=0.083, Block Bootstrapping at the group-level with N=14). We also repeated this for fast oscillations to find a significant correlation instead of an anti-correlation between these measures (Pearson-r=0.64±0.20, p=0.009, Block Bootstrapping at the group-level with N=14).
The results of the above analyses demonstrate that the amplitude correlation is unlikely to arise purely due to an impedance effect. However, we agree with the reviewer that the correlated amplitudes alone do not necessarily indicate that the two oscillations have similar origins. We have thus chosen to move this part of the analysis to the supplementary information in the revised manuscript, where we now also explicitly state the issue of impedances (Supplementary Information lines 50-104).

Comment R2.6

7) RE: Fig 4d. If I have understood correctly, all the pink circles derive from one subject. Without this subject, it is not clear how strong the correlation would be. What is the correlation without this subject?

The correlation indeed becomes non-significant if we drop the patient that was shown in pink circles. We thank the reviewer for pointing this out and apologize for not having spotted this ourselves. Given this lack of robustness of the width correlation, we have now chosen to remove it entirely from the manuscript. We have also accordingly modified the related discussions for the mechanistic origin of the signal and have incorporated the reviewer's other comment below (comment R2.7).

Comment R2.7

8) RE: line 215. “Our findings that sleep spindles during NREM sleep and the faster oscillatory during wakefulness and REM sleep reported here show remarkable similarity in their properties thus indicates a common mechanistic origin for both.” It isn’t clear that this necessarily follows (also see comments 6 and 7 above). Evidence suggests different mechanisms contribute to spindles and REM fast oscillations in the thalamus: for instance, brainstem cholinergic inputs give rise to fast thalamic oscillations in REM, but these inputs do not seem necessary for spindles (Steriade et al., 1991, Proc Natl Acad Sci U S A 88:4396; Durkin and Aton, 2019, Annu Rev Vis Sci. 5:295). To help the reader evaluate your results, please include this past evidence which suggest differences in the mechanisms giving rise to spindles and fast oscillations.

We entirely agree with the reviewer’s comment, especially in light of the changes to our manuscript based on the reviewer’s other comments (R2.5 and R2.6 above). We have now removed the above sentence on the common origin and modified the discussion for the mechanistic origin, taking into account the reviewer’s comment. The modified version is as follows (lines 306-319):

> In this context, it is interesting to note that research with model animals (specifically cats) shows that thalamocortical networks can produce fast oscillations, both *in vivo* and *in vitro* (Pinault & Deschenes, 1992, Neuroscience; Pedroarena & Llinas, 1997, PNAS). The typical frequencies of the oscillatory activities as well as their brain-state specificity (Steriade et al. 1996a, 1996b, Journal of Neuroscience), are similar to the oscillatory activity we detect in the human thalamus. Interestingly, these studies indicate that the thalamocortical networks that maintain sleep spindles can switch to sustaining faster rhythms either under a different neuromodulatory tone, driven by the type of ion channels that were activated (Steriade et al. 1993, Science; Crunelli et al. 2018, Nature Reviews Neuroscience) or under different conditions of cholinergic input from the brain stem (Steriade et al. 1991, PNAS). Further, computational modeling of thalamocortical networks also produces similar transitions in dominant oscillatory activity from slow spindle-like oscillations under neuromodulatory conditions of NREM sleep to faster oscillations in the beta-gamma frequency ranges under conditions of wakefulness (Li et al. 2017, PLoS Computational Biology).

Comment R2.8

9) RE: Fig. 5. The distances marked by black dots in panels b and c make it difficult for the reader to assess exactly where the fast oscillations were recorded in the thalamus. Please add each electrode contact position to panel a, color coding each contact based on whether it was associated with fast oscillations. This would help the reader assess the localization of fast oscillations in REM to particular thalamic nuclei (the goal of section 2.4).

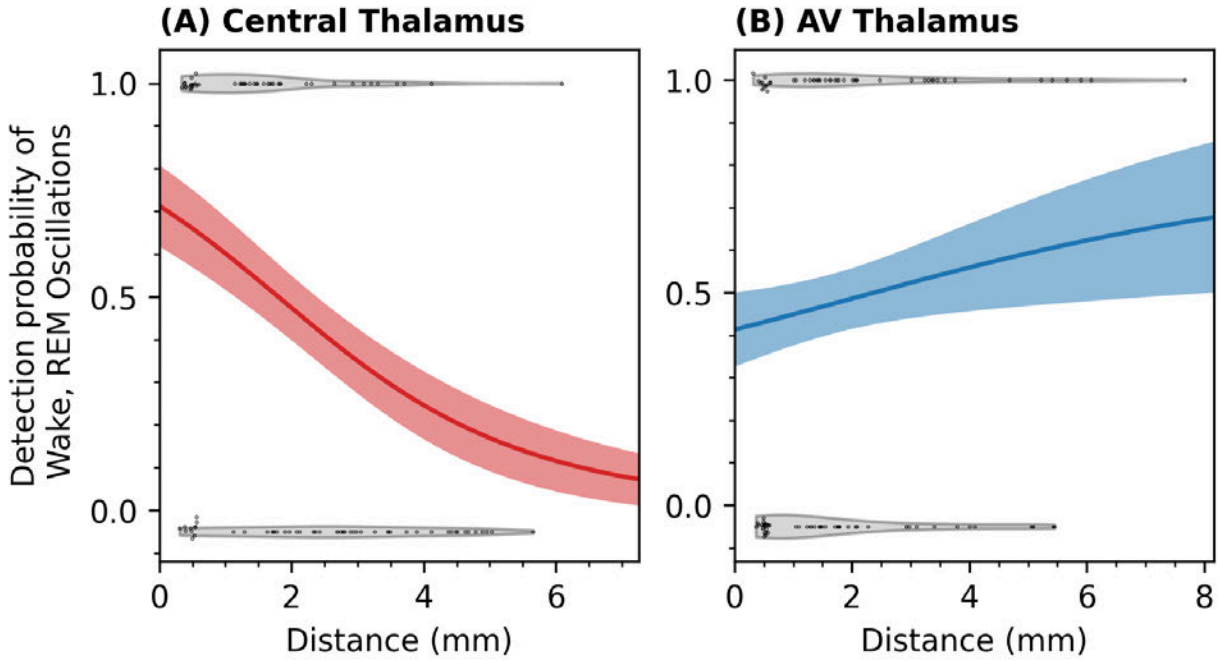
We thank the reviewer for this suggestion. We entirely agree that showing an overview of the localization would be a very helpful visual aid. However, as stated in response to comments R2.3, R2.4, and R1.7, our patient space segmentations do not allow for an accurate visualization in a single plot. We have thus provided the localization for each of the individual contacts in Supplementary Figures 12-46. In addition, we've also provided an approximate overview of the localizations in MNI space (Supplementary Figure 10).

Comment R2.9

10) line 711 of methods. "An important consideration for the analysis of detection probabilities is the fact that all analyses of thalamic field potentials were done on bipolar derivatives of neighbouring channels; any activity detected on a bipolar derivative could arise due to the proximity of either of the two contacts to the source of the signal. In our analysis, we dealt with this issue in an assumption-free way by assigning the signal to both contacts that went into the bipolar channel." If I have understood correctly, this approach, in a sense, artificially doubles the number of values that contribute to the regression analyses? A more appropriate approach might be to assign the bipolar-derived channel to a location midway between the two contacts, then perform the analyses.

We thank the reviewer for the comments. While it is true that our choice of assigning the signal to both contacts introduces correlated measurements for the regression analysis, our choice of doing statistics at the group-level by randomly drawing surrogate cohorts ensures that the correlated measurements do not affect the statistical outcome of the analysis.

We have also repeated the analysis, now following the reviewer's suggestion of using midpoints for each bipolar montage. Extended Data Figure 7 (also below) shows the outcome of this analysis. We find that the distance to the Central thalamus is correlated with the detection probability of the wake- and REM- specific oscillations (logistic regression slope= -0.53±0.18, p=0.00036), but the distance to the AV thalamus is not (logistic regression slope= 0.15±0.14, p=0.9, block Bootstrapping). This is entirely consistent with the outcome of the analysis presented in the manuscript. We have now also included this analysis in the revised manuscript (Extended Data Figure 7).



Extended Data Figure 7: Logistic regression analysis using distance to the midpoint of bipolar contacts. The panels show, for each of (a) Central Thalamus and (b) AV thalamus, the probability of detecting the Wake- and REM sleep- specific oscillations as a function of distance from the thalamic subregions. The solid curves in each plot show the logistic regression curve, with the shaded area indicating the standard error on it. The black dots indicate our measurements; a y-axis value near 1.0 would imply that the Wake- and REM sleep- specific oscillatory signal was detected in the contact, while a y-axis value close to 0.0 would imply no detection. The points clustered around 0.5~mm on the x-axis are those where the midpoint of the pair of electrode contacts was inside the subregion (see Methods); we added a scatter to these points to aid visualization. Note that all DBS contacts for all 17 patients entered the analysis of this figure. The plot shows that the detection probability of the signal is strongly dependent on the distance of the midpoint of the contact to the Central Thalamus (logistic regression slope= -0.53±0.18, p=0.00036, group-level statistic using block Bootstrapping with N=17 patients, see Methods) but not on the distance of the midpoint of the contacts to the AV (logistic regression slope= 0.15±0.14, p=0.9, block Bootstrapping).

Comment R2.10

11) Line 246 and Extended Data Fig. 2: “We found that only 4 out of the 14 patients showed clear evidence for a Wake- and REM sleep- specific oscillations at least one scalp electrode in a frequency range that overlapped with the frequency range of thalamic activity” and “The figure illustrates the lack of a clear oscillatory peak, as is seen in the thalamic contacts, during either wakefulness or REM sleep in any of the scalp EEG electrodes.” If there is no clear EEG oscillation in the frequency of interest (i.e., frequency of fast oscillation in the thalamus), then how to interpret the phase lag index?

Indeed, coherence (which we calculate using the phase lag index) has been shown to depend on power and phase-locking in the sender, and connectivity (Schneider et al., 2021, Neuron). Assuming that the thalamus is the sender in our case, coherence can be found without an increase in power in the receiver (the cortex). This could happen, for example, if the signal is only weakly detectable in the scalp EEG, and the phase information from the thalamic signal helps boost its detectability when computing coherence.

We are careful not to imply neuronal communication between the thalamus and the cortex, which would be currently premature. Instead, we describe coherence between thalamus and scalp electrodes using a conservative connectivity metric, the weighted phase lag index, that controls for many confounds that can artificially drive coherence, like volume conduction.

We have now added the following discussion to our manuscript (lines 248-254):

> We note that coherence measures such as wPLI have been shown to depend on power and phase-locking in the sender, as well as connectivity between the two regions. (Schneider et al., 2021, Neuron). Assuming that the thalamus is the sender in our case, coherence could be found without an increase in power in the receiver (the cortex). This could happen, for example, if the signal is only weakly detectable in the scalp EEG, and the phase information from the thalamic signal helps boost its detectability when computing coherence. However, we would like to emphasize that coherence between two regions does not necessarily imply neuronal communication between them.

We have now also included a Granger Causality analysis, where we find some evidence for the thalamus being the driver (see response to comment R1.2 and Supplementary Information lines 11-47). However, these results are not entirely conclusive, and a definitive statement on the directionality of the signal might only be possible with simultaneous cortical and thalamic iEEG in humans or with experiments in model animals.

Comment R2.11

12) RE: Discussion, paragraph starting line 328. While it is interesting to speculate that the thalamus may be “involved in a simulation of actions and their consequences during REM sleep”, I think that given the study’s data (which doesn’t provide evidence for this speculation), there are other interpretations that should be discussed. For example, the thalamus may simply be responding during eye movements (not necessarily performing a simulation) as in the oculomotor thalamus experiments from Schlag and Schlag-Rey (e.g., review by Tanaka and Kunimatsu, 2011, Eur J Neurosci 33:2046).

We note that we were not referring to the possibility that the thalamus by itself is simulating action or that the thalamic bursts are themselves causally involved with the simulation. We were referring to the broad hypothesis about REM sleep: “the brain is involved in a simulation of

actions and their consequences during REM sleep". Our speculation here was that the bursts indeed have something directly to do with the eye movements themselves, in terms of transmitting efference copies of the saccades. However, we had indeed missed the possibility that the thalamus plays a role in the *generation* of eye movements themselves. We thank the reviewer for pointing this out. We have now added the following sentences to the paragraph of Discussion:

> In addition, the Central Thalamus has regions that overlap with the "occulomotor thalamus" which is known to play a role in the generation of eye movements in animals (Tanaka and Kunimatsu, 2011, European Journal of Neuroscience). It is thus possible that these oscillations are also related to the generation of eye movements during REM sleep.

In addition, it is interesting to note that the data from the 2 patients in our cohort with simultaneous video-based eyetracking available shows that the burst rate is strongly correlated with pupil diameter rather than saccade rate (Extended Data Figure 3 in the revised manuscript), making it unlikely that the bursts are responses to the eye movements themselves. However, this would need to be conclusively established with controlled experiments in larger cohorts.

Comment R2.12

13) RE: Discussion. The findings in the submitted study seem somewhat different, with respect to frequency changes in phasic REM, etc, compared with a previous human study recording from the anterior thalamus (Simor et al., 2021, Journal of Neuroscience 41: 5677). Please discuss these differences and similarities in the manuscript.

As stated in the response to the reviewer's earlier comment (R2.1), we have now added the following discussion to our revised manuscript (lines 323-334):

> We note that Simor et al. (2021, Journal of Neuroscience) also used DBS electrodes in the thalamus of patients with pharmacoresistant epilepsy to study differences in power spectra between tonic and phasic REM sleep. However, a direct comparison between their results and of this work is made difficult by the very different focuses of their study and this work; the primary being (i) Simor et al. focused on the overall power spectrum in the two REM microstates, after averaging across subjects, while we focused primarily on oscillatory power across multiple brain states (NREM, wake, tonic and phasic REM) at the individual subject level; our burst detection technique to differentiate between oscillatory power and aperiodic power allowed us to detect patient-specific frequency bands with elevated oscillatory power and (ii) Simor et al. looked at the power spectra in the anterior thalamus only, while we included all available thalamic contacts, and found

that the probability of detecting the oscillatory activity depends on the distance to the Central Thalamus but not the Anterior Thalamus.

Comment R2.13

14) RE: Methods, line 423. Please include far more detail on sleep staging. The only text currently seems to be: “4.4 Sleep Staging. We carried out sleep staging using standard procedures53. Sleep stages N2 and Slow Wave Sleep (SWS) were combined into NREM epochs.”

We have now added additional details on sleep staging. The modified version of Section 4.4 (lines 459-472) is as follows:

> We carried out sleep staging using standard procedures (Iber et al., The American Academy of Sleep Medicine Manual, 2017), with sleep stages N2 and N3 or Slow Wave Sleep (SWS) combined into NREM. The sleep staging was carried out visually in standard 30-second segments by looking only at activity on the scalp EEG channels. The thalamic iEEG channels were not used to sleep score to avoid potential confounds and confirmation biases. The standard AASM guidelines on looking for characteristic oscillations in different sleep stages were followed (spindles, K-complexes in N2 sleep, the presence of slow oscillations in N3 sleep for more than 20% of the 30s epochs in N3 sleep, and signatures of eye rolling and reduction in alpha power for N1). Signatures of eye blinks on the scalp EEG were further used as an indicator for wakefulness. We also note that special attention was paid to ensure that the classification of REM sleep is highly reliable, and that there is no misclassification of REM stages with periods of arousals or NREM sleep; specifically, we ensured that REM epochs overlapped with periods of clear eye-movement-related activity on the frontal contacts, that no characteristic NREM specific oscillations (spindles or K-complexes) were present, and that there were no indications of eye blinks on the frontal scalp electrodes throughout the entire epoch.

Reviewer #3:

The authors present a highly interesting analysis based on a unique dataset, including thalamic recordings from 17 epilepsy patients undergoing deep brain stimulation (DBS). Their work reveals state-specific oscillatory activity in the central nucleus of the thalamus, particularly prominent during wakefulness and REM sleep, and especially during the phasic stage of REM (when ocular activity is maximal).
While the identification of fast-frequency bursting activity is not entirely without precedent, prior studies have primarily investigated such phenomena at the scalp level. The finding that the central thalamus is involved in wake- and REM-specific oscillations opens promising new directions for research and holds strong potential to advance our understanding of arousal, consciousness, and the functional roles of REM sleep. The observed relationship between sleep spindles and fast-frequency bursts is also intriguing, and the authors employ a variety of analytic techniques to characterize these oscillatory phenomena.

I believe this is a valuable contribution to the field; however, I have several questions and comments that I recommend the authors address before publication.

We thank the reviewer for the constructive and positive comments. We have now incorporated all of the reviewer's suggestions in the revised version.

Comment R3.1

Introduction:
(…) such oscillations are hypothesized to selectively activate various brain networks required for cognitive processes – this sentence is somewhat simplified, I recommend the authors to briefly specify the brain networks and cognitive processes they refer to.

We have now added the following sentence, referring to the systems consolidation hypothesis for memory formation as an example of a cognitive process that depends on oscillations:

> Indeed, sleep spindles form a crucial part of the systems memory consolidation hypothesis that depends on oscillations-mediated communication between the thalamus, the hippocampus, and the cortex (Klinzing et al. 2019, Nature Neuroscience).

Comment R3.2

The rationale for focusing on the fast frequency range (20–45 Hz) is not clearly articulated in the introduction. The authors do not cite previous studies that highlight the relevance of this

oscillatory activity, and the introduction lacks a theoretical framework justifying the detailed examination of this frequency band. Is the interest in this range motivated by its association with arousal, its proposed role in cognitive processes, its relation to recently described iota oscillations, or perhaps findings on REM-specific beta tufts? I recommend that the authors briefly contextualize their focus by providing a theoretical basis for investigating this specific frequency range during REM sleep.

Studies that bear relevance:

Snipes, S. (2025). Iota oscillations (25–35 Hz) during wake and REM sleep in children and young adults. Journal of Neurophysiology, 134(1), 1-9.

Ujma, P. P. et al. (2017). The sleep EEG spectrum is a sexually dimorphic marker of general intelligence. Scientific reports, 7(1), 18070.

We were guided by the discovery of a wake-and-REM specific oscillation in this frequency range in the human thalamus (Figures 1b, 2b of the manuscript). As we stated in the Introduction, we aimed to characterize thalamic oscillations across global brain states in a cohort of patients without disorders of consciousness. The most relevant previous works for us were studies on the Central Thalamus in non-human primates and single case studies in humans that indicate the importance of the Central Thalamus for states of consciousness.

Given the unique opportunity to investigate long-duration thalamic iEEG recordings (median duration: ~40 h per patient) in a very rare sample of patients, we used a methodological approach that we specifically developed to avoid a priori selection of frequency ranges of interest (Sections 4.5 and 4.6 in Methods). Our approach allowed us to identify at the individual contact level, frequency ranges with enhanced burst probabilities in each of the three global brain states (e.g., Figure 2b). We emphasize that this is different from starting out with a frequency range to focus on. We discussed the results from this analysis in detail in the first section of our Results. The analysis showed a clear enhancement in oscillatory activity in the frequency range 19-45 Hz (i.e., above the typical 11-19 Hz frequencies of NREM spindles). We then choose to focus on this oscillation for the rest of the paper.

While we did not pre-select the frequency range, we agree with the reviewer that the frequency range where we found the thalamic oscillation is indeed very interesting in the context of certain cortical oscillations that have been reported before. We also agree on the necessity of a discussion of our results in the context of these cortical oscillations, some of which have indeed been hypothesized to be thalamocortical in nature. We have thus now expanded on the existing discussion on this issue to a dedicated paragraph. The expanded version is the following (lines 366-376 in the revised manuscript):

> An important question for future research would be to understand how the thalamic oscillations reported here compare with cortical oscillatory activities reported at similar frequencies that researchers have hypothesized to be thalamocortical in nature. Specifically, the thalamic oscillations bear interesting resemblances to 40 Hz oscillations

detected in MEG during REM sleep (Llinas and Ribary, 1993), beta-band power enhancements (Uchida et al., 1992, Sleep) as well as beta oscillations in REM sleep (Vijayan et al., 2017, eLife, Ujma et al., 2017, Scientific Reports), beta bursts during wake (Lundqvist et al., 2024, Trends in Cognitive Sciences), and narrowband EEG oscillations at 25-35 Hz in children and young adults (Snipes, 2025, Journal of Neurophysiology). We note that while our current results show a clear modulation of brain-state-specific functional connectivity at the frequencies of thalamic oscillations, the low-density and sparse coverage of the simultaneously recorded scalp EEG was a limitation of our study. A full understanding of the connection with cortical activity may only be possible with simultaneous intracranial cortical and central thalamic recordings.

Comment R3.3

Methods

I am not familiar with the authors' statistical approach but as far as I understand, statitsitcal significance was defined across contacts, patients and states, however it is not fully clear to me how the nested nature of the data was handled. For instance, measurements in different pairs of electrodes within patients cannot be considered independent for the correlational analyses between spindle and fast frequency parameters.

Related to this point, the authors may verify whether the correlation between spindle and fast freq. parameters is specific to these oscillatory phenomena, or such correlations may also arise between other oscillations or frequency-specific activity measured by the same electrodes in the same patient.

The statistics for nearly all analyses in this study were done at the group-level, typically by generating surrogate cohorts via block bootstrapping (as detailed in Methods) or at the level of *individual* contacts. Note that the latter does not involve pooling together data across different subjects and thus constitutes a statistical replication of the results for each patient separately. Both of these approaches ensure that the statistical outcomes of our analyses are robust. We provide below a list summarizing the statistical approach in different parts of the manuscript:

1. The detection of bands with significant oscillatory bursts in the different sleep stages was done separately for each bipolar contact (as detailed in Methods, lines 473-582).
2. The statistics to test for the difference in detection probability of a frequency band with significant oscillatory activity above the typical spindle frequencies (19-45 Hz) were done at the group level using block Bootstrapping.
3. The statistics to test for differences in burst rates or connectivity metrics as a function of brain states (as in Figure 2d, Figure 2F, Extended Data Figure 2a,b, Supplementary

Figure 1a,b, Supplementary Figure 5, and Supplementary Figure 6) were all done at the group-level using paired Wilcoxon Rank Test.

4. The statistics on the correlation between burst probabilities and rapid EMs were done for each contact separately, with the results shown in Figure 3(D). Note that this panel displays the robustness of the effect: we found statistically significant correlations in each contact without any averaging across either contacts or patients.
5. The statistics on the correlation between distance to different nuclei and the detection probability of the bursts (Figure 5) were done at the group level using block bootstrapping.
6. The statistics on the cross-correlation analysis between the pupil diameter and the thalamic burst rate were done separately for each of the two patients.

The only exception to the above was in the correlational analysis for the spindle and fast oscillation parameters. We had initially done this because the measurements of the parameters in different electrodes were different, as would be expected from different signal properties in different anatomical regions. However, we entirely agree with the reviewer that for this particular analysis, the approach has the risk of the correlation being driven by a few subjects. We thus repeated the statistical analysis, but now using block bootstrapping where either all or none of the contacts from a given subject were included in a surrogate cohort, to find that while the amplitude correlation is also significant at the subject level ($p<10^{-5}$), the width correlation is not ($p=0.085$). We also found the width correlation to not be robust at the group-level, based also on reviewer #2's comment (comment R2.6). We apologize for having missed the lack of robustness of the width correlation in our original manuscript. Based on the above issues and also those raised by reviewers 1 and 2 (comments R1., R2.5, R.6), we have thus now chosen to move this part of the analysis to the supplementary information, with statistics done at the group-level, and with a clear discussion on the potential limitations of such an analysis (Supplementary Information, lines 50-104).

Comment R3.4

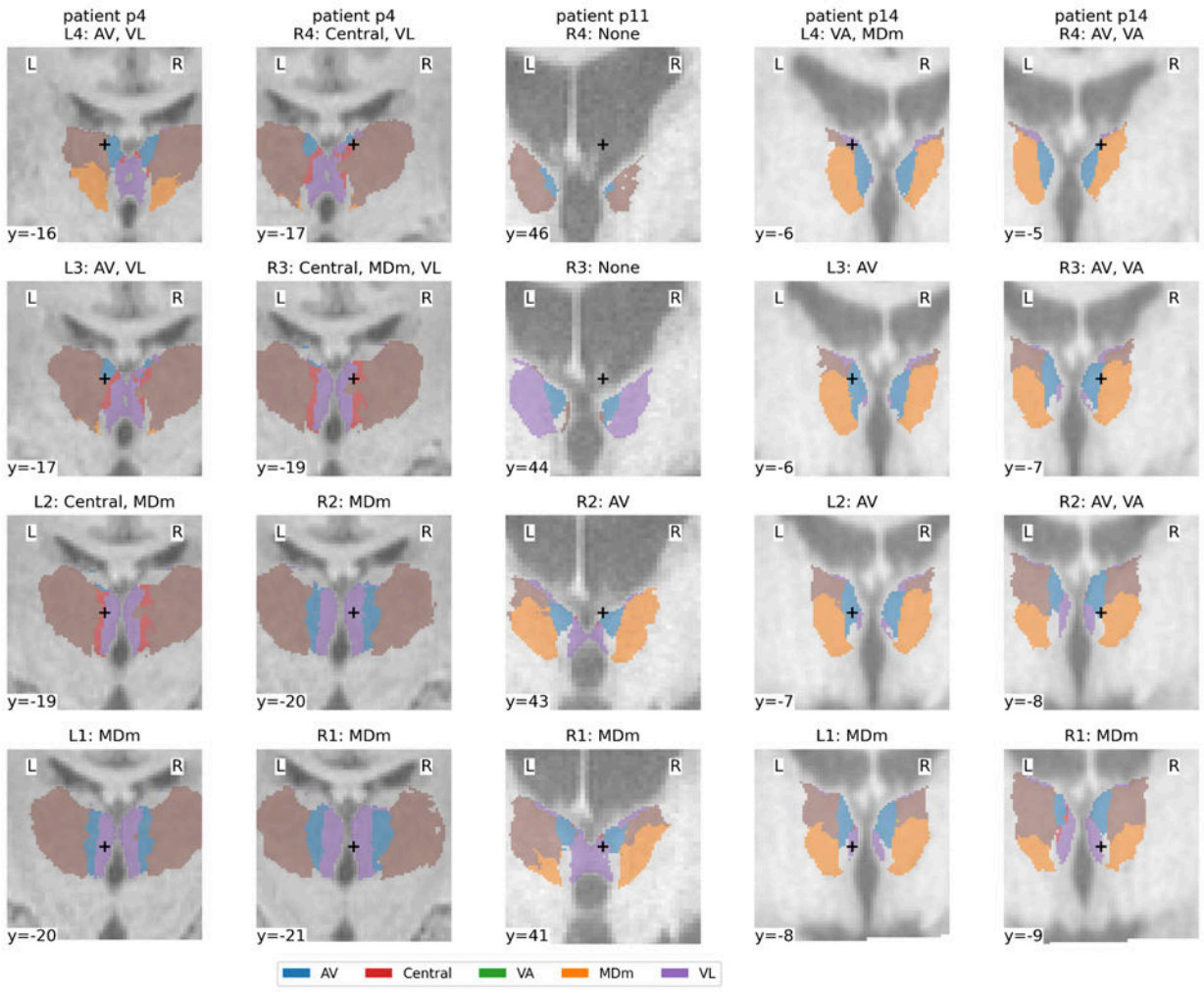
Results

It is surprising that in some patients, fast frequency bursts in the central thalamus were not detected. What might be the reason for the lack of thalamic bursts in some of the patients?

This is indeed an interesting question, that reviewers 1 and 2 also had (comments R1.5 and R2.4, responses therein, and Supplementary Figure 11, also shown below). We have now looked into this closely and have added the following paragraph discussing potential reasons (lines 205-213 of the main text):

> We investigated whether the anatomical localizations for the DBS contacts of the 3 out of 17 patients in our cohort where we did not detect the Wake- and REM- sleep- specific thalamic oscillations, were systematically not in the Central Thalamus. Indeed, for two of

these patients, there were no contacts localized to the Central Thalamus (see Supplementary Figure 11). It could thus be that the location of the DBS contacts affected the detectability of the fast oscillations in these two patients. The reason for not detecting the fast oscillation in the other patient remains unclear, given that the patient had DBS contacts in the central thalamus. It is difficult to conclusively establish why this was the case, but one possibility is that the signal is intrinsically much weaker in the particular patient.



Supplementary Figure 11: Localization of contacts for patients for whom we did not detect the wake and REM- sleep- specific thalamic oscillations. Each row shows a particular DBS contact in a particular patient. Note that for p11, we did not have access to the recording from the left hemisphere and have thus shown here only the relevant right electrode. The black cross indicates the location of the contact on the sagittal slice of the native-space patient T1-weighted MRI (for a view of all three slices, see the Supplementary Figures 18, 19, 34, 39, 40). The filled contours indicate the segmentation obtained from the Freesurfer algorithm (Iglesias et al. 2018, NeuroImage). The labels on

top of each slice also indicate the thalamic region(s) that the contact was localized to; note that we have taken into account here the 1 mm length of the contacts.

Comment R3.5

Were the 4 patients that showed bursting activities also at the level of the scalp different from the other patients with respect to thalamic fast frequency bursts?

This is indeed an intriguing issue. However, given the small number of patients who showed the thalamic burst at the same frequency in scalp electrodes, it would not be possible to statistically find differences between these four patients and the rest of the cohort. The oscillatory activity in these patients was strong enough in the cortex to be picked up by scalp EEG; this could be indicative of differences in thalamocortical connectivity. A clearer understanding of the thalamocortical connectivity of this oscillation might only be possible with high signal-to-noise recordings using simultaneous thalamic and cortical iEEG. This was not available for the patients in our cohort, who were bilaterally implanted with only the electrodes necessary for chronic DBS of the ANT. We note that access to simultaneous thalamic and cortical iEEG in humans is even rarer.

Comment R3.6

Eye movements in REM sleep seem to show intense bursting activities in a periodic manner, see for instance: Ktonas, P., Nygren, A., & Frost Jr, J. (2003). Two-minute rapid eye movement (REM) density fluctuations in human REM sleep. Neuroscience letters, 353(3), 161-164.

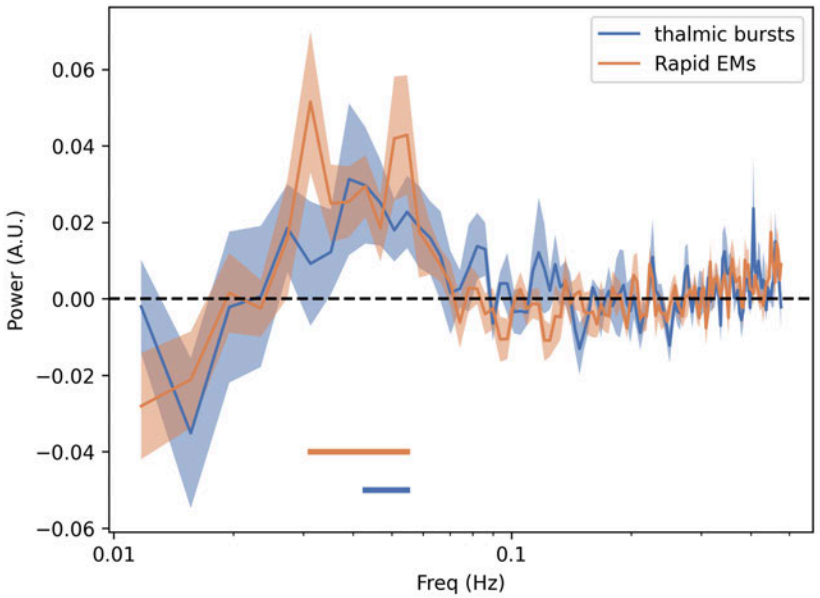
Interestingly, sleep spindles were also shown to peak periodically (See: Lecci, S., Fernandez, L. M., Weber, F. D., Cardis, R., Chatton, J. Y., Born, J., & Lüthi, A. (2017). Coordinated infraslow neural and cardiac oscillations mark fragility and offline periods in mammalian sleep. Science Advances, 3(2), e1602026.)

Did the authors identify any periodicity in the appearance of centrothalamic fast-frequency bursts?

We thank the reviewer for this very interesting suggestion. In order to check for the presence of an infraslow periodicity in the REM- and wake- specific thalamic bursts, we used the time stamps of the bursts detected by our burst-detection algorithm to get a burst rate as a function of time, in time bins of 0.5 seconds. Next, for each patient, we selected REM sleep segments that lasted for more than 5 minutes. We computed the power spectrum for each of these segments using the Welch method (with a FFT length of 512 samples), in the frequency range 0.008-0.5 Hz. For each patient, we combined all REM segments across all thalamic channels where we had detected the oscillation to get one burst-rate power spectrum per patient. We next

fitted a 1/f aperiodic component to this power spectrum, with a spectral knee, and subtracted it out to get a single power spectrum per patient.

Supplementary Figure 7 (also below) shows the average 1/f-subtracted power spectrum of the fast thalamic bursts in REM sleep (blue curve). We did a one-sided permutation cluster t-test to check for significantly enhanced oscillatory power to find a significant cluster in the range 0.043-0.054 Hz (p=0.036). Given our findings that the thalamic bursts during REM sleep are tightly correlated with epochs of rapid EMs, we also repeated the above procedure to compute a 1/f-subtracted power spectrum for the rate of rapid EMs (with identical choice of bin widths and parameters for the computation of the power spectrum). Supplementary Figure 7 also shows the power spectrum for the rapid EMs (orange curve). We again performed a one-sided permutation cluster t-test to find significantly enhanced power over the frequency range 0.031-0.055 Hz (p=0.0004). Thus, consistent with our findings that the thalamic bursts during REM sleep are tightly correlated with the bursts of rapid eye movements, we find an overlapping range of frequencies over which the power spectrum of both the thalamic burst rate and rate of rapid EMs is higher than what is expected from a purely aperiodic power spectrum. The frequency ranges where we find the significant enhancement correspond to time scales of ~20-30 seconds, shorter than the minute time scales reported in Ktonas et al. 2003. This could be due to a difference in the subject cohort for the two studies (five young and healthy subjects in Ktonas et al. vs. 14 epilepsy patients with a large variability in age in this study). A detailed analysis of such infraslow periodicities in rapid eye movement activity during REM sleep and how they relate to cohort properties would, however, be beyond the scope of the current study. We have now included the description and results of this analysis in the revised manuscript (Supplementary Information, lines 159-183).



Supplementary Figure 7: Infraslow oscillatory component (1/f-subtracted) power spectrum of the rate of thalamic bursts in REM sleep (blue curve) and the rate of rapid eye movements (orange curve). The curves show the subject-level means, while the shaded regions

indicate the standard errors on the mean. The horizontal bars indicate the frequency ranges with significant enhancements in oscillatory power (one-sided permutation cluster t-test, $p<0.05$). Both the rate of thalamic bursts and of rapid EMs show significant oscillatory power in an overlapping frequency range.

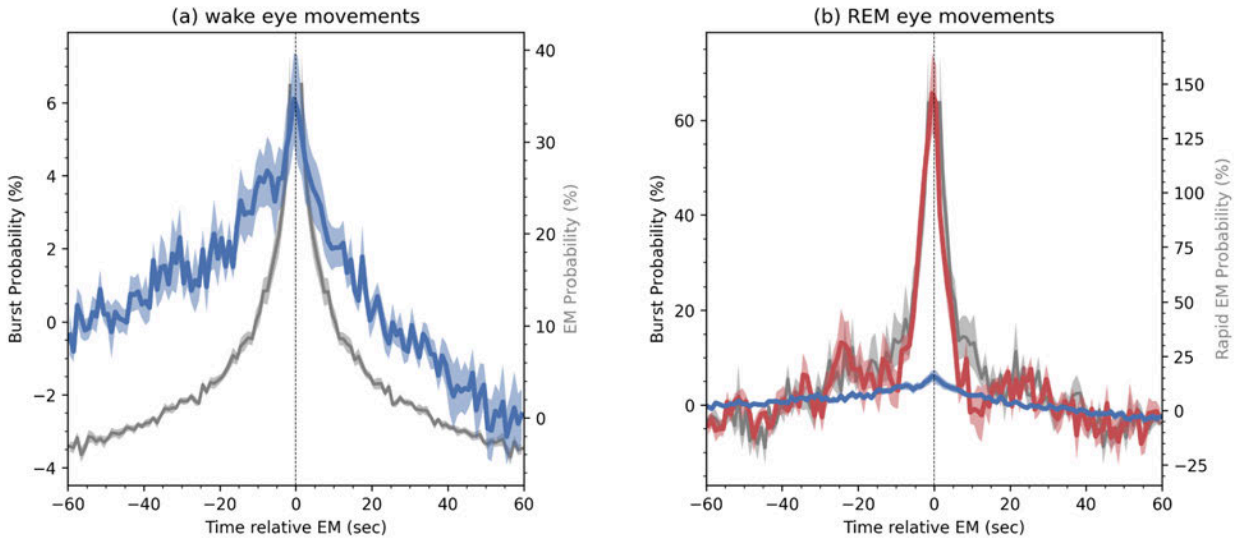
Comment R3.7

During wakefulness, were the detected fast-frequency bursts associated with eye movements? The authors might consider analyzing whether these oscillations were more prominent during eye movements or under eyes-open vs. eyes-closed conditions. Such comparisons may offer additional insights into the relationship between centrothalamic fast-frequency bursts, REM phasic activity, and the functional role of these oscillations.

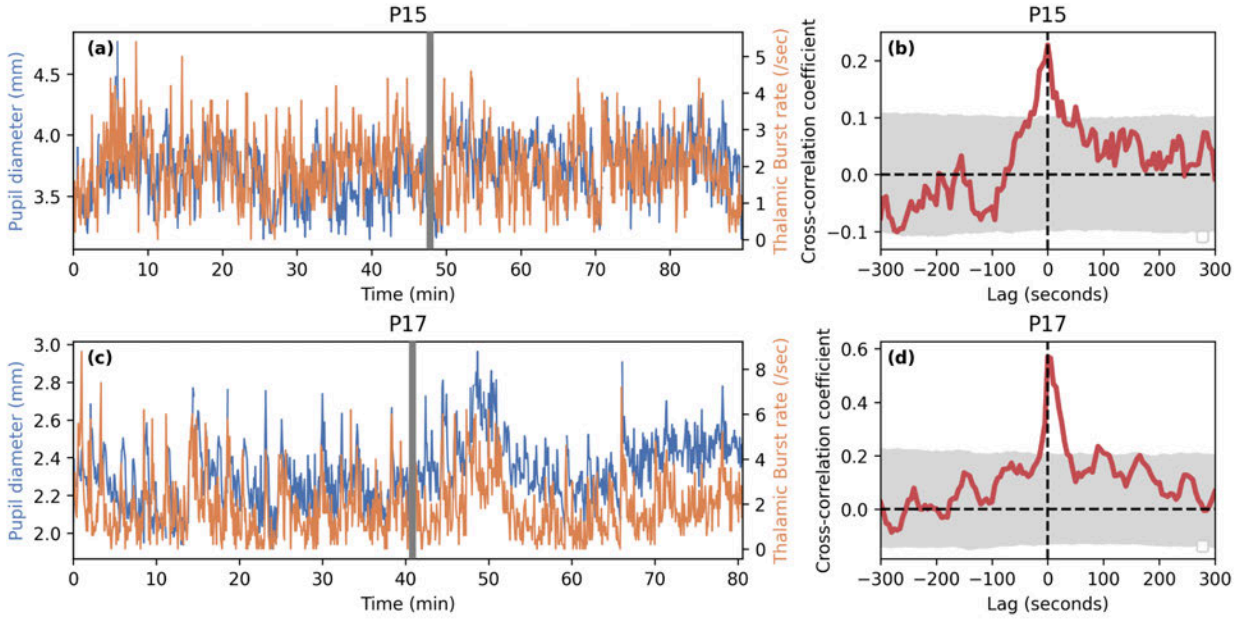
We entirely agree with the reviewer, but repeating our analysis with wake eye movements comes with multiple challenges. Unlike REM sleep, where eye movements occur in bursts with stereotyped durations, wakefulness can have very different occurrence rates of eye movements depending on the alertness levels and the activity being performed by the patient at the clinic. Further, there would be confounds between periods of open eye wakefulness and closed-eye wakefulness, which would be difficult to disentangle in the absence of video-based eyetracking.

Despite these challenges, we have followed the reviewer's suggestions and repeated the analysis we did with REM eye movements on wakefulness. Supplementary Figure 8(a) shows the peri-event histograms of the burst rates relative to the time of wake-eye movements as well as the eye movements themselves, for the same thalamic contacts where we detected a correlation between thalamic bursts and rapid EMs in REM sleep. The figure shows that while the peri-event histograms of the thalamic bursts during wakefulness are highly correlated with the peri-event histograms of the eye movements themselves ($r=0.84\pm0.02$), the enhancement in the burst-rates around the eye movements are both temporally less specific and much weaker compared REM sleep (see Supplementary Figure 8(b), peak modulation of $6\pm1\%$ over baseline in wake vs. $66\pm9\%$ over baseline in REM). There are at least two distinct possibilities for this difference (i) the thalamic activity is directly related to oculomotor activity but the continuous nature of eye movements in wakefulness leads to an elevated baseline level and hence a smaller modulation of the burst rates, and (ii) the thalamic bursts correlate with global states of the brain (such as arousal levels in wakefulness and phasic vs. tonic states in REM) rather than individual eye-movements.

We have now added additional data to the revised manuscript, where we had simultaneous video-based eye-tracking data for two of the patients in our current cohort (also see Response R1.1 and Extended Data Figure 3, also shown below). For these two patients, we find that the burst rate of the fast thalamic oscillations correlates significantly with pupil diameter, a widely used correlate of arousal level, but not with the saccade rate. These data thus tentatively support the hypothesis that the central thalamic wake- and REM- specific oscillations are tightly coupled with levels of arousal in wakefulness.



Supplementary Figure 8: Thalamic Bursts and Eye Movements in wake. Panel (a) shows, in blue, the average peri-event histogram of occurrence probability of thalamic bursts (in %) relative to the time of EMs, averaged over all 14 patients that showed the wake- and REM- specific fast oscillations. The grey curves indicate the probability distribution of other EMs relative to the current EM. Panel (b) shows the same, but for EMs in REM sleep (in red), with the peri-event histogram of bursts during wake also shown (in blue). Note that the curves for REM sleep in Panel (b) are the same as in Figure 3(E) of the main text. The enhancement of the burst probability at the time of EM, relative to baseline activity, is found to be much higher in REM sleep than in wake.



Extended Data Figure 3: Correlation between pupil diameter and burst rate of the fast thalamic oscillations in two patients. Panels **(a)** and **(c)** show the pupil diameter (in blue) and the thalamic burst rate (in orange) as a function of time. The gray vertical bands show the separation between the two discrete sessions over which the data were acquired (see Methods in revised manuscript). Panels **(b)** and **(d)** show the cross-correlation coefficient as a function of lag between the pupil diameter and the

thalamic burst rates. The gray shaded regions indicate the 95% confidence interval on the cross-correlation coefficients, obtained via a shuffling procedure (see Methods in revised manuscript). For both patients, a significant peak in the cross-correlation can be seen at zero lag ($p<10^{-4}$).

Comment R3.8

Typo

For example, during Non-Rapid Eye Movement (NREM) sleep, thalamocortical sleep spindles at 11-17 Hz are generated via a mechanism driven by inhibitory neurons in the thalamic reticular nuclues – typo (nucleus)

We thank the reviewer for pointing this out. We have now fixed the typo.

Comment R3.9

Overall, I find this to be a valuable and promising study with the potential to make a significant contribution to our understanding of thalamocortical dynamics in REM sleep and wakefulness. I encourage the authors to consider these points to strengthen the theoretical and methodological clarity of the manuscript.

We again thank the reviewer for these encouraging and constructive comments. As stated above, we have now considered all of the reviewer's suggestions, which have indeed helped strengthen and clarify various issues in our manuscript.