Grid-like hexadirectional modulation of human entorhinal theta oscillations

Shachar Maidenbaum[a], **Jonathan Miller**[a], **Joel M. Stein**[b], **and Joshua Jacobs**[a,1]

[a]Department of Biomedical Engineering, Columbia University, New York, NY 10027; and [b]Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104

Edited by Gyorgy Buzsáki, NYU Neuroscience Institute, New York, New York, and approved September 7, 2018 (received for review March 22, 2018)

The entorhinal cortex contains a network of grid cells that play a fundamental part in the brain's spatial system, supporting tasks such as path integration and spatial memory. In rodents, grid cells are thought to rely on network theta oscillations, but such signals are not evident in all species, challenging our understanding of the physiological basis of the grid network. We analyzed intracranial recordings from neurosurgical patients during virtual navigation to identify oscillatory characteristics of the human entorhinal grid network. The power of entorhinal theta oscillations showed six-fold modulation according to the virtual heading during navigation, which is a hypothesized signature of grid representations. Furthermore, modulation strength correlated with spatial memory performance. These results demonstrate the connection between theta oscillations and the human entorhinal grid network and show that features of grid-like neuronal representations can be identified from population electrophysiological recordings.

spatial memory | theta oscillations | navigation | intracranial electrocorticography | grid cells

During navigation, entorhinal grid cells activate when one crosses a series of locations that are arranged in a hexagonal lattice that tiles our surrounding environment (1). These cells represent our current location in space to support path integration (2) and memory (3). Entorhinal grid-like coding patterns also represent other behaviorally relevant information beyond location in physical space, such as visual space (4, 5), sensory information (6), and abstract concepts (7). Given their importance, researchers have probed the physiological basis of entorhinal grid representations, finding that neuronal oscillations, particularly in the theta band (5 to 8 Hz), have a pivotal role in rodents (8–12). However, studies reported that navigation-related theta oscillations in bats and humans differ from the signals measured in rodents—including having a slower frequency and duration (13, 14)—which suggests that the link between oscillations and entorhinal grid representations may not be preserved across species. We examined this issue in humans with the use of rare direct recordings of oscillations from the entorhinal cortex (EC). We use these recordings to test whether human EC oscillations have properties indicating that they relate to grid-like representations of the spatial environment.

Whereas much research on the contribution of the EC to spatial navigation focused on the activity of individual grid cells, an emerging body of work with fMRI showed that grid-like representations are also visible in aggregate signals across neuronal populations. When a subject navigates, the fMRI signal from the EC is elevated for movements that are oriented near each of six equally spaced (60°) heading directions (3)—a phenomenon termed "hexadirectional modulation." The hexadirectional modulation of population EC activity is a robust phenomenon, as it was replicated in many settings (4, 5, 7) and shown to correlate with navigation performance and with indications of neurological disease (15, 16). The common view in this body of work is that the headings that elicit elevated fMRI activity correspond to the six primary axes of the representations of the underlying grid cells, which also have a hexadirectional structure (3). Although the single-neuron basis of the population hexadirectional signal has not been definitively identified (see *Discussion*), the existence of this signal is important because it suggests that one can measure properties of the entorhinal grid code from mesoscale neural recordings.

Building from the fMRI work, we hypothesized that we would observe hexadirectionally modulated patterns in population electrical signals from the EC. Therefore, we measured intracranial electroencephalographic (iEEG) recordings from neurosurgical patients as they performed a virtual navigation task. We then tested whether the power of iEEG oscillations was hexadirectionally modulated according to the subject's heading, using analogous methods to those used with fMRI (3). Going beyond fMRI work, because iEEG data have a higher temporal resolution, we measured the temporal dynamics of this signal to identify a potential functional role in spatial grid representations for entorhinal oscillations in the high-theta range and other bands.

Results

Hexadirectional Modulation of Entorhinal Theta Oscillations. We recorded iEEG signals from neurosurgical patients with electrodes in their EC ($n = 20$ subjects) as they performed a virtual-reality spatial navigation and memory task (17, 18) (Fig. 1*D* and *SI Appendix*, Fig. S1). Subjects accurately navigated and

Significance

The entorhinal cortex plays a critical role in allowing organisms to navigate and represent spatial memories using grid-like representations. Given the importance of spatial processing for everyday life, we examined the patterns of neuronal oscillations in the entorhinal cortex, which are thought to underlie grid cells, in humans using intracranial recordings from neurosurgical patients as they navigated in virtual reality. We show that the power of entorhinal theta oscillations shows a distinctive six-way symmetric directional modulation, suggesting they correlate with grid representations, and that this signal correlates with spatial memory performance. Our findings thus show that the human entorhinal grid network is associated with theta oscillations and indicate that it is possible to measure properties of grid-like neural representations by recording oscillations.

Author contributions: S.M. and J.J. designed research; S.M. performed research; J.M. contributed new reagents/analytic tools; S.M. and J.M.S. analyzed data; and S.M., J.M., and J.J. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

[1]To whom correspondence should be addressed. Email: joshua.jacobs@columbia.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1805007115/-/DCSupplemental.

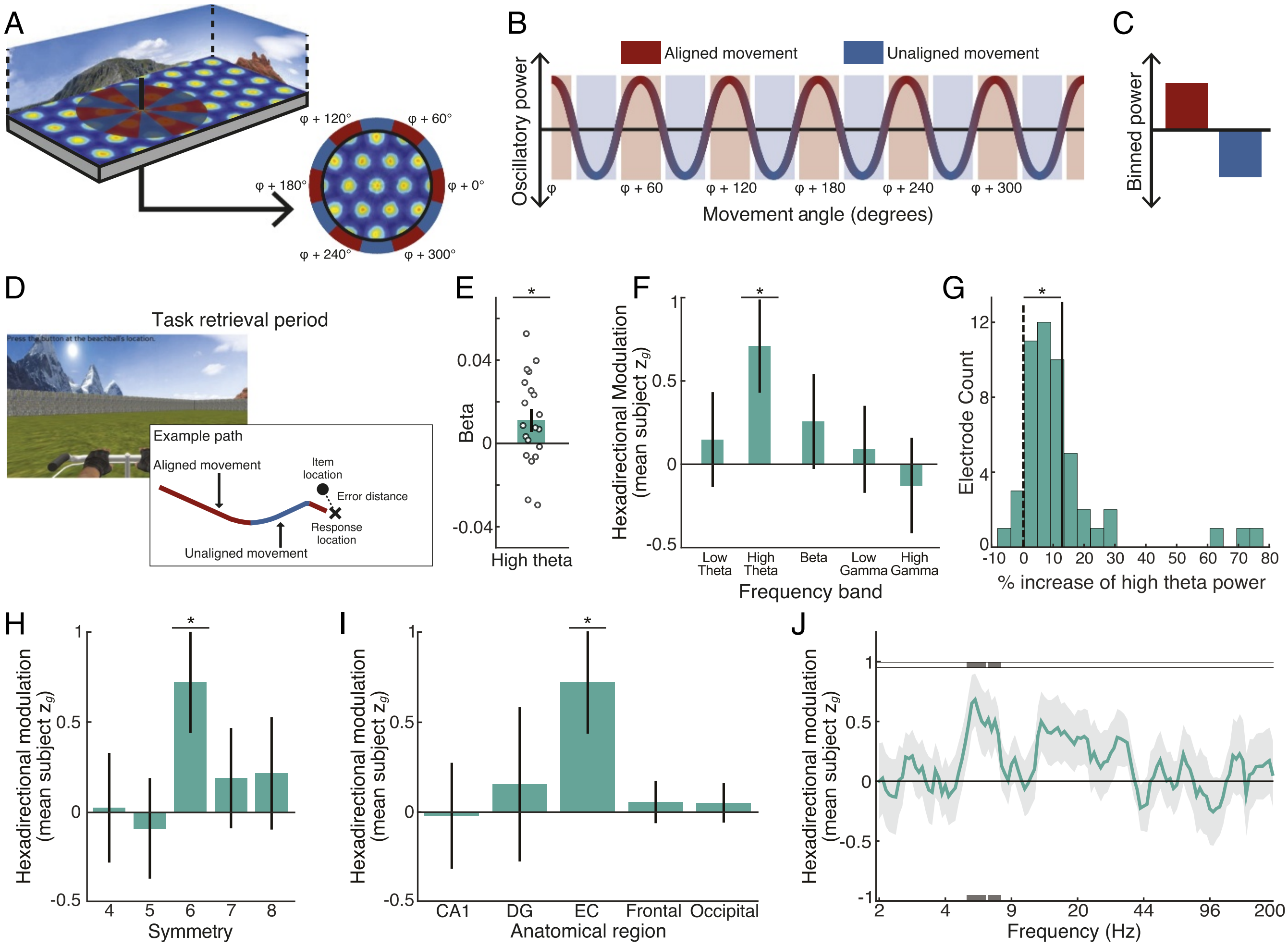

Fig. 1. Analyses of heading-related modulation of oscillatory power from the human EC. (*A*) Illustration of how grid representations could tile the environment in our virtual-reality task. *Inset* shows that the six-way symmetric pattern of grid fields predicts that mean neuronal activity will be hexadirectionally modulated by the subject's heading. (*B* and *C*) Prediction of a model based on grid-by-direction cells (3), showing that movement at headings aligned with the grid orientation will produce greater mean neuronal activity (red) compared with movement at unaligned headings (blue). (*D*) Screen image of the task and an illustration of a subject's path on a single trial. Path is color-coded according to the grid field shown in *A*. (*E*) The uncorrected beta scores for hexadirectional modulation of oscillatory power in the high-theta band. Individual dots represent individual subjects. Error bars denote 95% confidence intervals. (*F*) Mean z_g scores across subjects with electrodes in their EC, separately computed for five predefined different frequency bands: low theta (1 to 4 Hz), high theta (5 to 8 Hz), beta (12 to 30 Hz), low gamma (40 to 60 Hz), and high gamma (60 to 100 Hz). Error bars denote 95% confidence intervals. (*G*) Population data on the magnitude of hexadirectional modulation of high-theta power. Bars in the histogram indicate the number of electrodes showing each percentage of oscillatory power increase between unaligned and aligned time points. (*H*) Mean subject z_g scores for different heading symmetry patterns. (*I*) Mean subject z_g across brain regions. CA1, hippocampal region CA1; DG, dentate gyrus; EC, entorhinal cortex. Frontal and occipital denote the corresponding lobes. (*J*) Mean group level z_g score for 120 log-spaced frequencies from 2 to 200 Hz. Gray bars indicate significance at $*p < 0.05$. Error regions denote 95% confidence intervals. $*p < 0.05$.

remembered the locations of objects in the task, as indicated by their mean spatial memory score of 0.81 (see *SI Appendix*, *SI Methods*), which was reliably above chance ($p < 0.01$). Across trials, subject trajectories in the task were distributed broadly across the environment (*SI Appendix*, Fig. S2).

To identify iEEG correlates of grid representations, we analyzed how the power of oscillations related to each subject's instantaneous heading during movement in a hexadirectional fashion. At each electrode, we measured for every time point throughout virtual movement the oscillatory power at each of five predefined frequency bands. We then measured the degree to which the oscillatory power on each electrode at a given frequency was hexadirectionally modulated by the subject's instantaneous heading, which we quantified as the β from a general linear model (see *SI Appendix*). To measure the statistical reliability of each electrode's hexadirectional representation at each frequency, we calculated z_g, which is the z score of the p value for each β, as estimated with a permutation procedure.

We performed this analysis for each electrode and then aggregated the results by calculating the mean z_g for each subject and region of interest (averaging across electrodes for subjects with multiple contacts in a region). Using these values, we found a significant grid-like hexadirectional modulation of entorhinal oscillatory power in the high-theta band (5 to 8 Hz). This modulation was significantly positive across subjects when calculated both for the raw β values (mean $\beta = 0.01 \pm 0.004$; t test $p < 0.018$, Fig. 1*E*) and for the z_g values (mean $z = 0.72 \pm 0.27$, t test $p < 0.008$, Fig. 1*F*). Fig. 1*G* shows this result in a different fashion, by showing that entorhinal theta power increases by an average of 13% for movements at grid-aligned directions compared with unaligned headings. Analyzing the data by comparing the power of aligned and unaligned bins instead of via a cosine predictor (as done in ref. 15) led to equivalent results ($r = 0.95$).

To assess the specificity of this hexadirectional modulation, we repeated this analysis for entorhinal signals at other predefined frequency bands. However, we did not find that β or z_g were significantly positive in any other bands (Fig. 1*F* and *SI Appendix*, Fig. S3). We also measured this effect with a higher spectral resolution (Fig. 1*J*), and this analysis confirmed that hexadirectional modulation was significant only in the high-theta band and more specifically at 5.4 to 7.5 Hz with a peak value at 6.1 Hz ($p < 0.002$). Entorhinal theta power was significantly hexadirectionally modulated when measured separately in each of the left and right hemispheres (ps< 0.05; *SI Appendix*, Fig. S4), indicating that the hexadirectional modulation of entorhinal theta power is a bilateral effect.

In addition to these group-level analyses, we also assessed whether individual electrodes showed reliable hexadirectional modulation. These analyses showed that many individual electrodes had robust hexadirectional patterns (e.g., Fig. 2 and *SI Appendix*, Fig. S5). In the theta band, 30% of the 50 entorhinal electrodes showed significant ($p < 0.05$) hexadirectional modulation, which was substantially more than the 5% expected by chance ($p < 10^{-8}$, binomial test). Overall, 55% of the 20 subjects had at least one such electrode, and 25% of subjects individually had a statistically significant proportion of entorhinal electrodes that showed this effect ($p < 0.002$, binomial test) (*SI Appendix*, Fig. S6).

As a control analysis, we next examined whether our results specifically reflected hexadirectional symmetry rather than other types of directional patterns. To do this, we used our main statistical model to test for modulation of oscillatory power according to other rotational symmetries instead of six-fold hexadirectional modulation. We did not find significant modulation of entorhinal power for any other control symmetry type (ps > 0.3 and mean z_gs < 0.21 for four-, five-, seven-, and eight-way symmetries; Fig. 1*H*). We then tested if the hexadirectional modulation was specific to the EC. Repeating our main analysis across regions, significant hexadirectional modulation of theta power was only found in the EC and not in other nearby control regions roughly matched for size and electrode coverage (Fig. 1*I*), such as the dentate gyrus ($z_g = 0.15$, $p = 0.7$) and hippocampal region CA1 ($z_g = -0.02$, $p = 0.9$), nor was it found in larger areas such as the occipital ($z_g = 0.05$, $p = 0.6$) and frontal lobes ($z_g = 0.04$, $p = 0.9$).

Since we collected the data from patients with intractable epilepsy, we avoided data collection from within 2 h of a seizure event. However, we also confirmed in a control analysis that our main effect of hexadirectionally modulated theta power persisted after excluding the sites and time points that showed evidence of potential epileptiform activity ($z_g = 0.83$, $p < 0.05$; see *SI Appendix, SI Methods*). After performing this exclusion, the data analyses showed the same pattern of hexadirectional activity across frequencies, spatial symmetry types, and anatomical regions, which confirmed that our main effects were not related to epileptiform activity.

Hexadirectional Modulation and Behavior. Given the hypothesized role of grid representations in memory (3), we next measured the correlation between memory performance and hexadirectional modulation of theta power (as measured with z_g). Mean memory scores positively correlated with z_g across subjects ($r = 0.55$, $p < 0.011$; Fig. 3*A*). Fig. 3*B* shows the relation between task performance and hexadirectional representations across frequencies, showing a significant peak in the theta band only for good-performing subjects, where the effect is significantly greater than in bad-performing subjects. This supports the view that hexadirectional theta representations are behaviorally relevant, as they were more prominent in patients with the best task performance. For analyses of the relation of hexadirectional modulation to subject demographics, see *SI Appendix*, Fig. S7.

Hexadirectional Modulation Within Other Frequencies. Although we observed the strongest hexadirectional modulation for local field potential (LFP) power in the theta band, there were indications of similar effects at other frequencies for some electrodes and subjects, including within the beta and gamma bands. *SI Appendix*, Fig. S6 shows the number of electrodes that individually showed statistically significant effects at each frequency, and Fig. 2 and *SI Appendix*, Fig. S5 show additional examples in other bands. Significant hexadirectional modulation of beta oscillations is also evident at the group level for the best

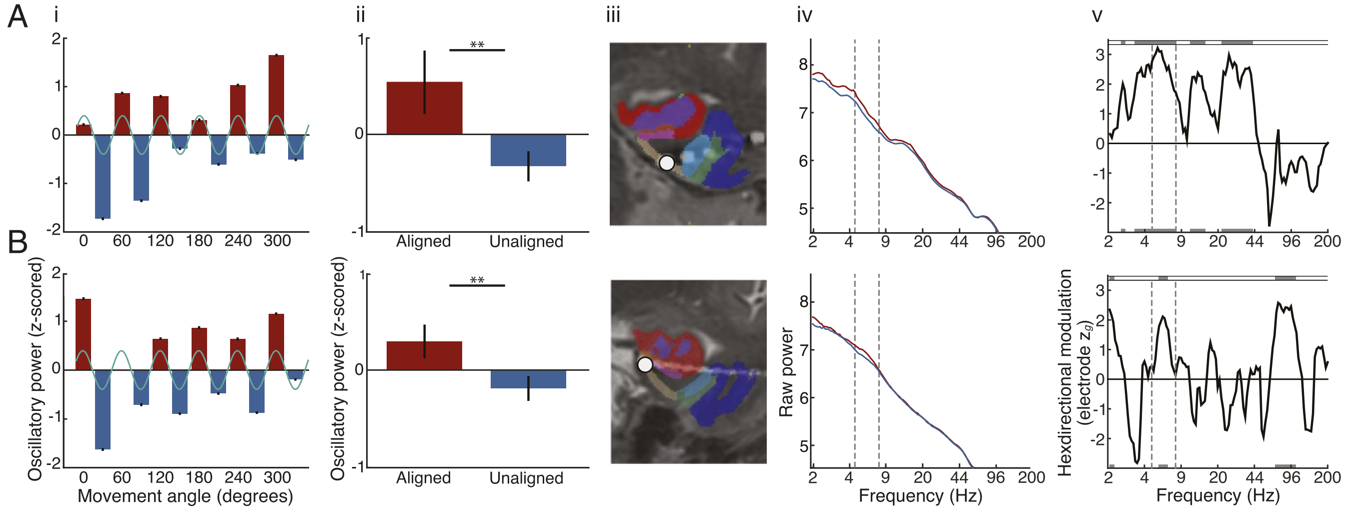

Fig. 2. Example electrodes that exhibit significant hexadirectional heading modulation of theta power (5 to 8 Hz). (*A*) An electrode from patient 14's left EC, and (*B*) an electrode from patient 2's entorhinal cortices. (*i*) Mean theta power as a function of adjusted heading. Bars denote observed power in each bin; green line indicates the prediction of the cosine model (Fig. 1*B*). (*ii*) Mean theta power for aligned and unaligned headings. $^{**}p < 0.01$. (*iii*) fMRI-CT overlay of the subject's medial temporal lobe with subregions segmented in different colors (resolution of 0.5 × 0.5 mm per voxel). The circle denotes the location of the recording electrode. Tan coloring denotes EC. (*iv*) Mean power spectra for aligned (red) and unaligned (blue) movement. (*v*) Group-level z_g values on a wider frequency spectrum. Shading at top indicates statistical significance at $p < 0.05$.

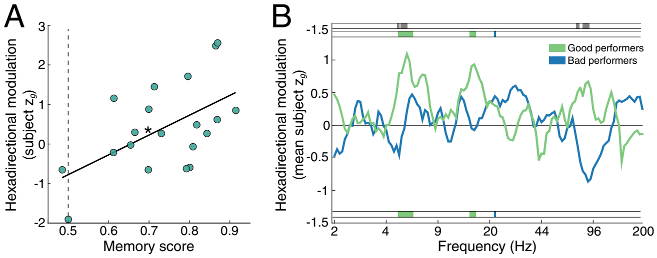

Fig. 3. Relation between task performance and hexadirectional modulation. (*A*) Plot indicates subject memory scores versus hexadirectional modulation (z_g) of entorhinal theta ($R = 0.55$, $p < 0.011$). Dotted line denotes chance level for memory scores. (*B*) Spectrum of entorhinal mean group-level z_g across 2 to 200 Hz as in Fig. 1*J*. We separated the subjects into good and bad performers via a median split on memory scores. Shading indicates statistical significance at $p < 0.05$: gray indicates a significant difference between the two groups; green and blue shading indicates that the good and bad groups, respectively, are significantly different from zero.

performing subjects (Fig. 3*B*). Further, using a different analysis technique based on circular–linear modeling (see *SI Appendix*), we replicated our main findings and also showed significant hexadirectional modulation within the beta band across the entire population (*SI Appendix*, Fig. S8). Together, these results suggest that hexadirectional modulation of the entorhinal LFP may extend to other frequencies beyond the high-theta band.

Grid Orientations Are Consistent for Each Subject but Differ Across Subjects. To examine the consistency of grid representations, we compared the orientations of hexadirectional representations across electrodes. First, we compared grid orientations between separate electrodes from each individual as well as across subjects (see *SI Appendix*). Analyzing the individuals who had multiple entorhinal electrodes ($n = 11$), we found that grid orientations were similar between contacts within a subject ($p < 0.001$; Fig. 4 *A* and *B*). However, across subjects, mean grid orientations were not clustered to any specific direction ($p = 0.6$, Rayleigh test; Fig. 4*C*). The finding that grid orientations were uniformly distributed relative to the environment is consistent with the finding in rodents that grid-cell representations are randomly oriented for rectangular environments (4, 19, 20). Furthermore, this suggests that the grids were not coupled to the environment's landmarks, which were separated by 90°.

We next examined the possibility that the observed hexadirectionally modulated theta correlated with subject movement in the task. Some subjects showed tendencies to move in particular directions during the task (*SI Appendix*, Fig. S2), perhaps due to unique orienting strategies for visual landmarks. However, we measured each subject's most common movement direction and found that this heading was uncorrelated with the mean preferred angle of the subject's hexadirectional modulation (circular–circular correlation, $\rho = 0.08$, $p = 0.7$). Thus, there is no evidence to indicate that the hexadirectionally modulated theta we observed was an artifact of subject movement patterns.

Analyzing subjects who had electrodes in both the left and right entorhinal cortices ($n = 7$), we found similar grid orientations across both hemispheres (v test, $v = 3.9$, $p < 0.01$; Fig. 4 *D* and *E*). These results support the view that humans have a stable grid representation that is coherent within and across both hemispheres but that varies across individuals even when representing the same environment.

To examine the stability of these signals, we compared grid orientations for the subjects ($n = 9$) who performed separate sessions of the task on different days. Grid orientations were stable across sessions ($v = 5$, $p < 0.008$; Fig. 4 *F* and *G*), indicating that the entorhinal representation of an environment is preserved over time.

Replication. To verify the reliability of the hexadirectional modulation of entorhinal theta power, we next preregistered (Open Science Framework, https://goo.gl/Z9GamB) and tested our main result on a separate dataset. In this dataset, 15 subjects with 22 entorhinal electrodes performed the "Treasure Hunt"

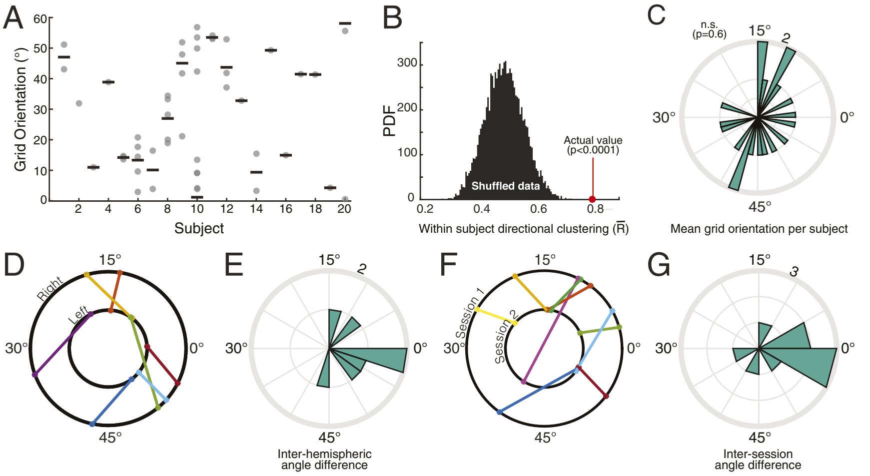

Fig. 4. Analysis of grid orientation. (*A*) Grid orientations (modulus 60°) of individual entorhinal electrodes (gray circles), by subject. Black lines indicate each subject's circular mean. (*B*) Analysis of within-subject grid orientation stability. $\bar{R}$ is the within-subject mean similarity between electrode orientations as calculated by the mean circular resultant vector length, averaged across subjects. It is compared with a surrogate distribution computed by randomly assigning the associations between subject labels and individual electrode orientations and then reperforming the same procedure. Red line indicates the actual mean directional clustering score; black bars indicate the distribution of scores expected by chance. (*C*) Distribution of mean grid orientation across subjects does not reveal a significant clustering (Rayleigh test, $p = 0.6$). (*D*) Grid orientation by hemispheres, for subjects with bilateral entorhinal electrodes. Each circle denotes one of the hemispheres, with colored lines connecting the orientations from individual subjects. (*E*) Distribution of differences in grid orientation across hemispheres (*V* test, $p < 0.01$). This circular difference histogram matches the data presented in *D*. (*F*) Grid orientation across sessions. Each circle denotes one of the sessions, with colored lines connecting the orientations from individual subjects. (*G*) Differences in grid orientation across sessions (*V* test, $p < 0.008$). This circular difference histogram matches the data presented in *F*.

task (task described in ref. 21; see *SI Appendix*). We found the same pattern of results: The power of entorhinal theta oscillations was hexadirectionally modulated with a similar magnitude as in our main dataset. This pattern was not found at other frequency bands, brain regions, or organizational symmetries (*SI Appendix*, Fig. S9). This replication thus supports the view that our findings are robust.

Discussion

We show that theta oscillations in the human EC show six-way-symmetric hexadirectional modulation according to the direction of movement in an environment. This hexadirectional oscillatory modulation was robust at the group level and for many electrodes individually. This type of hexadirectional modulation of a large-scale neural signal is commonly interpreted as a signature of grid cells (3), which suggests that recordings of entorhinal oscillations may be used to assess certain properties of grid representations. By measuring the correlation between patients' navigation performance and the robustness of their hexadirectional theta modulation, we found that this pattern was strongest in the subjects who showed good navigation performance. Practically, this result is useful because it suggests that one can use measurements of hexadirectional activity to predict when someone is disoriented. Further, this indicates that our population results could be underreporting the theoretical capabilities of this method because its apparent statistical robustness is diminished due to weaker scores from poorly navigating subjects.

The predominant view from several studies is that the hexadirectional modulation of population neural signals from the EC reflects the spatial representations of underlying grid cells (3–5, 7, 15, 16), although this link has not yet been proven directly. However, as described by Doeller et al. (3), there are theories of how the aggregate activity across populations of entorhinal cells would produce hexadirectional modulations of the group activity that are aligned with the spatial firing patterns of individual grid cells. Both of these explanations rely on the known similarity of grid-cell orientations across the EC (1). One way that population hexadirectional modulation could occur is due to the summed activity of conjunctive grid-by-direction cells (22), which are theta-modulated (23) and have preferred directions that are preferentially aligned to the primary axes of the underlying spatial grid representations [Doeller et al. (3); Fig. 1*C*]. Owing to this alignment, the mean population activity of the network of grid-by-direction cells would be hexadirectionally modulated, such that there would be greater neuronal activity overall during movements at grid-aligned headings. A second potential mechanism for hexadirectional modulation of population activity involves the phenomena of repetition enhancement and suppression (24). When a subject moves through an environment at an angle aligned with the main axis of the entorhinal grid, it will cause a relatively small set of neurons to activate repeatedly because the firing fields of individual grid cells are spaced more tightly when measured at orientations parallel to the grid's main axis. Inversely, movements at misaligned directions would activate a broader group of grid cells because their firing fields are more broadly spaced at these headings. In conjunction with repetition enhancement and suppression, in which neurons change firing rates nonlinearly when activated repeatedly, the differing spacing of individual grid fields between aligned and misaligned headings would cause variations in the population signal.

Because we did not record directly from individual grid cells in this dataset, we unfortunately cannot distinguish between these models, and moreover, as both of these models have been criticized, we cannot rule out the possibility that the hexadirectional activity we observed reflects a different phenomenon that is distinct from the activity of underlying grid cells. Nonetheless, we think it seems likely that hexadirectional population signals are related to the activity of underlying grid cells in light of the multiple studies that showed correspondences in features between the single-cell and aggregate measures of grid representations (3–5, 7, 15, 16). The connection between our results and the fMRI literature fit well with the previous finding that in the human EC the fMRI BOLD signal is more correlated with theta oscillations than with gamma as common in cortical regions (25).

Our findings have both practical and theoretical implications by showing that features of entorhinal grid representations are evident in large-scale recordings of neuronal oscillations. First, by demonstrating that oscillations in the 5 to 8 Hz band are most strongly correlated with the activity of the entorhinal grid network, it supports a role for high-theta oscillations in the entorhinal representation of space in humans, despite the fact that earlier work in humans showed mixed evidence for the presence and behavioral relevance of navigation-related high-theta signals (14, 26–28). This connection between theta and human entorhinal grid representations also supports the oscillation- and hybrid attractor-based models of grid cells developed based on rodent results, which had been challenged by the lack of clear oscillatory signals in humans and bats (8, 12, 13, 29, 30).

Practically, these results are important because they offer a way to measure population grid-like activity and characteristics with oscillations, expanding beyond single-cell and fMRI recordings. Our results generally support the studies showing that the human grid representations can be measured with fMRI, both by replicating the general method for identifying hexadirectional modulation patterns in population signals (31) and by replicating specific features of the fMRI results, such as demonstrating grid orientation stability within subjects and showing differences across subjects (4). The ability to measure properties of the grid network with oscillations, combined with the correlation of this signal with task performance, is useful because it could allow the development of techniques to decode, and possibly influence, one's orientation and memory state from mesoscale brain recordings (32). Single-neuron recordings of grid cells are indispensable for many purposes because they provide a more detailed kind of spatial information compared with the hexadirectional LFP signal. However, the LFP signal has advantages for certain purposes: In addition to directly revealing rhythmic features of this network, LFPs are easier to measure practically in humans, both in the EC and in other regions where single-cell recordings are not available. The ability to measure hexadirectional oscillations with LFPs, and in particular to predict whether someone is disoriented, opens avenues for future research.

More broadly, an intriguing feature of our findings is that, together with recent literature, they suggest that entorhinal theta oscillations could have a broad role in supporting various types of neural codes beyond location. There is evidence from single-cell recordings in animals that grid-like patterns represent various types of nonspatial variables in the EC (6). Similarly, in humans, grid-like entorhinal patterns have been demonstrated for nonspatial representations (7), and theta oscillations in the EC and surrounding areas are present and behaviorally relevant in various nonspatial tasks (33). Together with our results, this work suggests that theta oscillations may have a general role in supporting various types of entorhinal neuronal codes that also follow grid-like representational schemes.

Methods

We studied data from 20 neurosurgical patients who had electrodes implanted in their EC. During recordings, subjects performed a virtual-reality spatial navigation and memory task in which they had to encode the location of an object and then navigate to that same location from a different starting point. We analyzed the data to identify hexadirectional modulation of neural signals according to the subject's virtual heading during movement (3). We measured the power of oscillatory activity at various frequency bands and used a permutation procedure to identify sites that showed significant increases in oscillatory power when the subject faced in six equally spaced headings during movement in the environment. The study was approved by the Columbia University Institutional Review Board and all subjects provided their informed consent. For details on our methods, see *SI Appendix, SI Methods*.

ACKNOWLEDGMENTS. We thank the patients for participating in our study. We are grateful to Honghui Zhang and Uma Mohan for help with data analyses. This research was supported by the DARPA Restoring Active Memory (RAM) program (Cooperative Agreement N66001-14-2-4032), NIH Grants MH061975 and MH104606, and the National Science Foundation (BCS-1724243). The views, opinions, and/or findings expressed are those of the authors and should not be interpreted as representing the official views or policies of the Department of Defense or the US Government.

1. Hafting T, Fyhn M, Molden S, Moser MB, Moser EI (2005) Microstructure of a spatial map in the entorhinal cortex. *Nature* 436:801–806.
2. Gil M, et al. (2017) Impaired path integration in mice with disrupted grid cell firing. *Nat Neurosci* 21:81–91.
3. Doeller CF, Barry C, Burgess N (2010) Evidence for grid cells in a human memory network. *Nature* 463:657–661.
4. Julian JB, Keinath AT, Frazzetta G, Epstein RA (2018) Human entorhinal cortex represents visual space using a boundary-anchored grid. *Nat Neurosci* 21:191–194.
5. Nau M, Schröder TN, Bellmund JL, Doeller CF (2018) Hexadirectional coding of visual space in human entorhinal cortex. *Nat Neurosci* 21:188–190.
6. Aronov D, Nevers R, Tank DW (2017) Mapping of a non-spatial dimension by the hippocampal–entorhinal circuit. *Nature* 543:719–722.
7. Constantinescu AO, O'Reilly JX, Behrens TEJ (2016) Organizing conceptual knowledge in humans with a gridlike code. *Science* 352:1464–1468.
8. Burgess N (2008) Grid cells and theta as oscillatory interference: Theory and predictions. *Hippocampus* 18:1157–1174.
9. Koenig J, Linder A, Leutgeb J, Leutgeb S (2011) The spatial periodicity of grid cells is not sustained during reduced theta oscillations. *Science* 332:592–595.
10. Bonnevie T, et al. (2013) Grid cells require excitatory drive from the hippocampus. *Nat Neurosci* 16:309–317.
11. Domnisoru C, Kinkhabwala AA, Tank DW (2013) Membrane potential dynamics of grid cells. *Nature* 495:199–204.
12. Bush D, Burgess N (2014) A hybrid oscillatory interference/continuous attractor network model of grid cell firing. *J Neurosci* 34:5065–5079.
13. Yartsev M, Witter M, Ulanovsky N (2011) Grid cells without theta oscillations in the entorhinal cortex of bats. *Nature* 479:103–107.
14. Jacobs J (2014) Hippocampal theta oscillations are slower in humans than in rodents: Implications for models of spatial navigation and memory. *Philos Trans R Soc B: Biol Sci* 369:20130304.
15. Kunz L, et al. (2015) Reduced grid-cell–like representations in adults at genetic risk for Alzheimer's disease. *Science* 350:430–433.
16. Stangl M, et al. (2018) Compromised grid-cell-like representations in old age as a key mechanism to explain age-related navigational deficits. *Curr Biol* 28:1108–1115.
17. Jacobs J, et al. (2016) Direct electrical stimulation of the human entorhinal region and hippocampus impairs memory. *Neuron* 92:1–8.
18. Lee SA, et al. (2018) Electrophysiological signatures of spatial boundaries in the human subiculum. *J Neurosci* 38:3265–3272.
19. Krupic J, Bauza M, Burton S, Barry C, O'Keefe J (2015) Grid cell symmetry is shaped by environmental geometry. *Nature* 518:232–235.
20. Stensola T, Stensola H, Moser MB, Moser EI (2015) Shearing-induced asymmetry in entorhinal grid cells. *Nature* 518:207–212.
21. Miller J, et al. (2018) Lateralized hippocampal oscillations underlie distinct aspects of human spatial memory and navigation. *Nat Commun* 9:2423.
22. Sargolini F, et al. (2006) Conjunctive representation of position, direction, and velocity in entorhinal cortex. *Science* 312:758–762.
23. Brandon M, et al. (2011) Reduction of theta rhythm dissociates grid cell spatial periodicity from directional tuning. *Science* 332:595–599.
24. Henson R, Rugg MD, Shallice T, Dolan RJ (2000) Confidence in recognition memory for words: Dissociating right prefrontal rolesin episodic retrieval. *J Cogn Neurosci* 12:913–923.
25. Ekstrom A, et al. (2017) Correlation between BOLD fMRI and theta-band local field potentials in the human hippocampal area. *J Neurophysiol* 101:2668–2678.
26. Jacobs J, Kahana MJ, Ekstrom AD, Fried I (2007) Brain oscillations control timing of single-neuron activity in humans. *J Neurosci* 27:3839–3844.
27. Aghajan ZM, et al. (2016) Theta oscillations in the human medial temporal lobe during real world ambulatory movement. *Curr Biol* 27:3743–3751.
28. Bohbot VD, Copara MS, Gotman J, Ekstrom AD (2017) Low-frequency theta oscillations in the human hippocampus during real-world and virtual navigation. *Nat Commun* 8:14415.
29. Giocomo L, Zilli E, Fransen E, Hasselmo M (2007) Temporal frequency of subthreshold oscillations scales with entorhinal grid cell field spacing. *Science* 315:1719–1722.
30. Barry C, Ginzberg L, O'Keefe J, Burgess N (2012) Grid cell firing patterns signal environmental novelty by expansion. *Proc Natl Acad Sci USA* 109:17687–17692.
31. Kriegeskorte N, Storrs KR (2016) Grid cells for conceptual spaces? *Neuron* 92:280–284.
32. Ezzyat Y, et al. (2017) Direct brain stimulation modulates encoding states and memory performance in humans. *Curr Biol* 27:1251–1258.
33. Korotkova T, et al. (2018) Reconciling the different faces of hippocampal theta: The role of theta oscillations in cognitive, emotional and innate behaviors. *Neurosci Biobehav Rev* 85:65–80.