UC Davis
UC Davis Previously Published Works

Title

Oscillations Go the Distance: Low-Frequency Human Hippocampal Oscillations Code Spatial Distance in the Absence of Sensory Cues during Teleportation

Permalink

https://escholarship.org/uc/item/8q60x4qp

Journal

Neuron, 89(6)

ISSN

0896-6273

Authors

Vass, Lindsay K
Copara, Milagros S
Seyal, Masud
et al.

Publication Date

2016-03-01

DOI

10.1016/j.neuron.2016.01.045

Peer reviewed

Oscillations go the distance: Low frequency human hippocampal oscillations code spatial distance in the absence of sensory cues during teleportation

Lindsay K. Vass[1], **Milagros S. Copara**[1], **Masud Seyal**[2], **Kiarash Shahlaie**[3], **Sarah Tomaszewski Farias**[2], **Peter Y. Shen**[4], and **Arne D. Ekstrom**[1,5,6]

[1]Center for Neuroscience, University of California, Davis, 1 Shields Avenue, Davis, CA 95618, USA

[2]Department of Neurology, University of California Davis Medical Center, 4860 Y Street, Suite 0100, Sacramento, CA, 95817, USA

[3]Department of Neurological Surgery, University of California Davis Medical Center, 4860 Y Street, Suite 0100, Sacramento, CA, 95817, USA

[4]Department of Radiology, University of California Davis Medical Center, 4860 Y Street, Suite 3100, Sacramento, CA, 95817, USA

[5]Department of Psychology, University of California, Davis, 1 Shields Avenue, Davis, CA 95618, USA

Summary

Low-frequency (delta/theta band) hippocampal neural oscillations play prominent roles in computational models of spatial navigation but their exact function remains unknown. Some theories propose they are primarily generated in response to sensorimotor processing while others suggest a role in memory-related processing. We directly recorded hippocampal EEG activity in patients undergoing seizure monitoring while they explored a virtual environment containing teleporters. Critically, this manipulation allowed patients to experience movement through space in the absence of visual and self-motion cues. The prevalence and duration of low-frequency hippocampal oscillations were unchanged by this manipulation, indicating that sensorimotor processing was not required to elicit them during navigation. Furthermore, the frequency-wise pattern of oscillation prevalence during teleportation contained spatial information capable of classifying the distance teleported. These results demonstrate that movement-related sensory information is not required to drive spatially informative low-frequency hippocampal oscillations during navigation and suggest a specific function in memory-related spatial updating.

Introduction

A consistent observation across studies of spatial navigation is the presence of low-frequency oscillations in the hippocampal local field potential (LFP) (for a review, see Buzsaki, 2005). Despite the presence of these oscillations in multiple mammalian species (see Jutras and Buffalo, 2010), including humans (Ekstrom et al., 2005, Watrous et al., 2011) and rodents (Vanderwolf, 1969, McFarland et al., 1975, Czurko et al., 1999), the animal model in which they are most commonly studied, the functional significance of these oscillations remains unclear, with multiple theoretical frameworks put forth to account for their presence during navigation (for a review, see Ekstrom and Watrous, 2014). One set of models hypothesizes that these oscillations are related to sensorimotor processing, a position consistent with the observation that low-frequency power is modulated by running speed (McFarland et al., 1975, Czurko et al., 1999). According to these models, low-frequency oscillations are present either because they serve to coordinate sensory input in service of producing the correct motor output (Bland and Oddie, 2001) or because neural activity becomes entrained to the rhythmicity of sensory or motor information when actively processing stimuli (Komisaruk, 1970, Jutras et al., 2013, see also Schroeder et al., 2010).

A second set of models, which emphasize the mnemonic role of these oscillations, hypothesize that low-frequency oscillations organize the firing of neural ensembles related to encoding and retrieval of memories (Hasselmo et al., 2002, Buzsaki, 2006, Jacobs, 2014). Although there is evidence that low-frequency power differs as a function of mnemonic success in non-spatial tasks (for a review, see Nyhus and Curran, 2010), little is known about how these oscillations might contribute to memory during navigation. A third idea recently put forth hypothesizes that the hippocampal LFP recorded during navigation contains signals associated with both bottom-up movement-related processing and top-down memory-related processing, but that these signals may manifest at different frequencies (Ekstrom and Watrous, 2014, Jacobs, 2014).

To better understand the conditions that elicit low-frequency hippocampal oscillations during navigation, we directly recorded hippocampal EEG activity from human patients while they navigated a virtual environment containing teleporters. Critically, this manipulation allowed us to test whether low-frequency oscillations are present when sensory feedback has been removed and explicit motor signals are absent. If sensorimotor processing is the primary driver of low-frequency hippocampal oscillations, then they should be disrupted or greatly attenuated during virtual teleportation. In contrast, if this oscillatory signal is important for memory-related spatial coding, then low-frequency oscillations should persist during teleportation.

Results

Prevalence of Low-Frequency Oscillations is Not Reduced by Removal of Visual and Self-Motion Cues

To test our primary hypothesis that hippocampal oscillations are sustained during virtual movement in the absence of visual and self-motion cues (e.g., optic flow, vestibular input, and proprioception), we recorded intracranial hippocampal EEG activity in three human

patients undergoing seizure monitoring while they navigated a virtual plus (+) maze (Figure 1). During navigation, patients were instructed to find one of four different stores, each of which was located at the end of one of four different arms of the maze. After finding the target store, participants entered one of two kinds of teleporters (short or long distance), which transported them to the center of the maze. Critically, teleportation allowed patients to experience movement to a known location in space in the absence of any sensory feedback because they remained seated on a hospital bed and viewed a black screen during this time.

Inspection of the raw hippocampal traces provided clear evidence that low-frequency oscillations are indeed sustained during teleportation (Figure 2A, Figure 4). To confirm this observation, we quantified the proportion of time oscillations were present immediately before, during, and immediately after teleportation using $P_{Episode}$ (see Experimental Procedures). Because patients were actively navigating toward the teleporter in the pre-teleportation (Pre) period (mean speed, 13.7 ± 0.3 units/s) but were moving slowly (patient 2 [P2], mean speed, 3.3 ± 0.2 units/s) or were stationary (patients 1&3 [P1&3], mean speed, 0.1 ± 0.03 units/s) during the post-teleportation (Post) period when they were reading the cue for the next trial, this analysis allowed us to compare activity during teleportation (Tele) to that during both active and still periods with full visual cues.

Consistent with the raw traces, these analyses revealed that low-frequency $P_{Episode}$ during teleportation was similar to that during active navigation (Figure 2B, Figure S1), an effect present independently in all 3 patients (Table S2, Figure S2). Low-frequency oscillations on 38/42 electrodes did not significantly change when patients transitioned from navigating to teleporting. Only 4/42 electrodes showed significant decreases in Delta-Theta (< 8 Hz) $P_{Episode}$ upon entering the teleporter (Pre > Tele Wilcoxon Signed Rank test), a proportion which was not higher than that expected by chance ($p_{corrected} = 0.6$). In fact, we tended to observe *higher* low-frequency $P_{Episode}$ during teleportation relative to the still period after teleportation (Tele > Post Wilcoxon Signed Rank test; 6/42 electrodes, $p_{corrected} = 0.07$), but this effect was only observed in electrodes from one patient (Table S2). Although low-frequency oscillatory activity across the population of electrodes was largely unaffected by entering and exiting the teleporter, higher frequency oscillations in the gamma band (> 30 Hz) were sensitive to this manipulation, exhibiting significantly higher $P_{Episode}$ upon entering (7/42 electrodes, $p_{corrected} = 0.02$) and exiting (8/42 electrodes, $p_{corrected} = 0.002$) the teleporter. Thus, these data suggest that low-frequency oscillations were not significantly attenuated by teleportation.

As a positive control, we confirmed attenuation of low-frequency oscillations when participants viewed a black screen but did not experience virtual movement. We measured low-frequency oscillations immediately after patients completed the free exploration portion of the experiment and immediately after patients completed the final spatial memory trial. During these time periods, participants viewed a black screen as they did during teleportation, but memory and movement-related processing were minimal. Thus, we would expect reduced low-frequency oscillations during these control periods relative to teleportation and navigation. Consistent with predictions, when patients viewed a black screen but did not experience virtual movement, low-frequency oscillations were significantly attenuated compared to both teleportation (Wilcoxon Signed Rank $Z = -4.6$,

p$_{corrected}$ 0.001) and visually-guided navigation (Z = −4.6, p$_{corrected}$ 0.001) (Figure S2). These findings further support the idea that memory and/or movement-related processing can sustain hippocampal low-frequency oscillations in the absence of visual and self-motion cues.

An alternative explanation for the observation that low-frequency oscillations were unaffected by teleportation, however, is that the low-frequency oscillations just prior to entering the teleporter were themselves different from those elicited during normal uninterrupted navigation. For example, this time period could involve anticipation and predictions about the teleportation event, which could reduce its validity as a comparison condition. To more completely explore whether low-frequency oscillations before, during, and after teleportation differed from those elicited during uninterrupted navigation, we created three epochs of equal duration during the preceding part of the trial when patients were in the correct arm of the maze and actively navigating to the target store (see Figure 1). We then tested whether P$_{Episode}$ was higher during these epochs than during the matched teleportation epochs. Consistent with the previous results, 0/42 electrodes showed a significant difference in the Delta-Theta band during the pre-teleportation period (Teleportation Epoch 1 vs. Navigation Epoch 1), and only 1 electrode showed significantly lower P$_{Episode}$ in this frequency band during teleportation (Teleportation Epoch 2 vs. Navigation Epoch 2) (Figure 2C), providing further evidence that activity during teleportation was similar to that during visually-guided active navigation. A significant proportion of electrodes (10/42, p$_{corrected}$ < 0.001) did show significantly lower Delta-Theta P$_{Episode}$ during the *post*-teleportation epoch (Teleportation Epoch 3 vs. Navigation Epoch 3), an effect that was also observed in the Alpha band (8–12 Hz) (8/42 electrodes, p$_{corrected}$ = 0.004), and which was present for 2/3 patients (Table S2). Because movement speed was reduced during the post-teleportation epoch, this reduced oscillatory activity is consistent with previous work showing lower Delta-Theta activity during still compared to movement periods in the human hippocampus (Ekstrom et al., 2005, Watrous et al., 2011). Thus, these results are consistent with previous data suggesting a sense of movement is important for driving hippocampal low-frequency oscillations. When patients received full visual cues but were stationary, low-frequency oscillations were overall less prevalent than during active navigation. In contrast, when patients received no visual cues but "moved" via teleportation, low-frequency oscillations were similar to those elicited during visually-guided active navigation.

Low-Frequency Oscillations Do Not Attenuate or Reset After Removal of Visual and Self-Motion Cues

Although we did not observe a decrease in the prevalence of low-frequency oscillations during teleportation, it is still possible that ongoing oscillations attenuated and/or reset when entering the teleporter. To test whether oscillations attenuated after entering the teleporter, we first identified oscillations that crossed the time point of teleporter entry (or an artificially-imposed boundary during active navigation, see Figure 1, Figure 2A). We then tested whether the post-entry oscillation duration was reduced in the teleporter relative to a matched uninterrupted navigation epoch. No electrodes (0/35) exhibited significantly attenuated Delta-Theta oscillation durations during teleportation relative to active navigation

(mean duration of navigation oscillations, 528 ± 25 ms; mean duration of teleportation oscillations, 518 ± 15 ms), indicating that the removal of visual information did not disrupt ongoing low-frequency oscillations (Figure 3).

To test whether entering the teleporter induced a phase reset, we performed Rayleigh tests for phase consistency at each time point in the first 500 ms after teleporter entry and defined a phase reset event as significant phase consistency at all samples throughout a two-cycle interval at a given frequency (Rizzuto et al., 2003). Although we observed some evidence of phase reset events at higher frequencies, we did not observe any instances of significant phase reset in the Delta-Theta frequency band in any electrode (Figure S3). Taken together, these findings suggest that Delta-Theta oscillations were not interrupted or reset by teleportation.

Frequency-Wise Pattern of Low-Frequency Oscillation Prevalence During Teleportation Provides Classification of Spatial Distance

Because the prevalence and duration of Delta-Theta oscillations did not change as a result of teleportation, one possible explanation is that they carried no navigationally relevant information. An alternative possibility is that they may have carried spatial information that could potentially support spatial updating (Watrous et al., 2011) during teleportation. To adjudicate between these two possibilities, we tested whether the frequency-wise pattern of low-frequency $P_{Episode}$ could distinguish between short- and long-distance teleportation events. Because the teleporters were in fixed locations and always transported the patient to the same position on every trial, patients were able to predict the distance they would travel (either short or long; see Figure 1). Importantly, because we randomly varied the duration of the teleportation events (1830 ms or 2830 ms), patients could not predict when they would exit the teleporter. This manipulation thus disentangled spatial distance from temporal duration and velocity, ensuring that knowledge about spatial distance did not derive from time in the teleporter or perceived velocity.

We extracted trial-wise $P_{Episode}$ values at each frequency in the Delta-Theta band during short- and long-distance teleportation epochs (Figure 4, left and center panels) and submitted these values to binary classification with a linear support vector machine (Figure 4, right panels). We found that the pattern of low-frequency $P_{Episode}$ provided significant classification of distance teleported in far more electrodes than would be expected by chance (Short Duration Trials Model: 11/23 electrodes, $p_{corrected} < 0.001$; Long Duration Trials Model: 9/23 electrodes, $p_{corrected} < 0.001$; All Trials Model: 8/23 electrodes, $p_{corrected} < 0.001$), and in each individual patient (Table S2). This ability to classify distance was likely due to overall higher $P_{Episode}$ during long relative to short distance events (Long Distance: $16.2 \pm 1.2\%$; Short Distance: $14.8 \pm 1.1\%$), an effect that was present across the group of electrodes exhibiting significant classification (Wilcox Signed Rank Test: $Z = 2.6$, $p_{corrected} = 0.006$) as well as the entire population of electrodes ($Z = 4.3$, $p_{corrected}$ 0.001). Thus, even though patients were looking at a blank screen during teleportation and therefore received no visual or idiothetic cues about their virtual movement, hippocampal low-frequency oscillatory activity reliably varied according to the distance teleported. Because the classifier was trained to generalize over multiple starting positions (i.e., 2 short-distance

and 2 long-distance teleporters) and because we randomly varied the temporal duration of the teleportation events (1830 ms vs. 2830 ms), these decoding results cannot be explained by representations of teleporter position, time spent in the teleporter, or perceived velocity. Instead, our results suggest that higher prevalence of low-frequency oscillations during the long vs. short distance teleportation events may have related to the updating of position during teleportation.

To explore in more detail the idea that patients remained spatially oriented during teleportation and successfully updated their position, we analyzed patients' behavior immediately upon exiting the teleporter. Specifically, we tested whether patients turned the optimal direction to face the next target store upon exiting the teleporter (i.e., a 90° turn rather than 270° turn), which would be consist ent with the idea that they remained oriented upon exiting the teleporter. Note that there were no external cues to indicate the optimal turn direction; only the patient's knowledge about their current position and orientation could support this behavior. For this analysis, we excluded trials for which the target landmark was straight ahead (1/3 of trials) and "error" trials in which the patient first went down an incorrect arm of the maze, indicating a cue-landmark association retrieval error (% of "error" trials: P1, 34%; P2 Session 1, 11%; P2 Session 2, 0%; P3 Session 1, 2%; P3 Session 2, 0%). All patients turned the optimal direction more often than the suboptimal direction (overall selection of correct turn direction across patients: 75%; P1, 59%; P2 Session 1, 73%; P2 Session 2, 70%; P3 Session 1, 80%; P3 Session 2, 91%), consistent with the idea that patients correctly maintained their expected position and orientation during teleportation.

Discussion

The principal finding of this study is that low-frequency hippocampal oscillations elicited during navigation are sustained when humans experience virtual movement to a known location in space in the absence of visual and idiothetic cues. Furthermore, the low-frequency oscillations elicited under these conditions carried meaningful spatial information, as demonstrated by our ability to decode the distance traveled. These results therefore demonstrate that movement-related sensory information is not required to drive spatially informative low-frequency oscillations in the human hippocampus during navigation. Overall, our findings support the idea that low-frequency oscillations in humans do not require sensory input during navigation and still carry important memory-related signals in the absence of visual or idiothetic cues.

Our first main result is that low-frequency hippocampal oscillations are sustained during virtual movement even when sensory feedback is not available. Previous studies in rodents have measured navigation-elicited oscillations when some, but not all, forms of sensory feedback are eliminated and have largely implicated proprioceptive cues in driving these low-frequency oscillations. Hippocampal oscillations are present when rodents navigate in total darkness (Gavrilov et al., 1996, Chen et al., 2011) or when they navigate in a head-fixed recording device (thereby eliminating vestibular cues) (Chen et al., 2013), but are significantly reduced when animals are wrapped in a towel and passively moved through space (Foster et al., 1989, Chen et al., 2011) or passively view movement through a virtual

environment (Chen et al., 2013). Although these proprioceptive cues seem to be important for driving oscillations in the rodent hippocampus, the same cannot be true for humans, as low-frequency hippocampal oscillations have been observed in multiple virtual navigation paradigms (Ekstrom et al., 2005, Watrous et al., 2011), none of which involve meaningful proprioceptive or vestibular feedback because the patient is confined to his or her hospital bed. Thus, in these tasks, patients primarily use visual cues to navigate and build spatial representations. Although the available set of cues during virtual navigation is impoverished compared to real-world navigation (Taube et al., 2013), it is perhaps not surprising that visual cues can drive human hippocampal oscillations because such cues are critically important for successful human navigation, whereas they seem to be less important for rodent navigation (Ekstrom, 2015). Here, we show for the first time that even when these visual cues are removed, low-frequency hippocampal oscillations persist when humans experience virtual movement through space. This strongly suggests that, at least in humans, internally generated spatial memory representations are sufficient to drive this oscillatory activity and that sensorimotor processing is not required. This result is broadly consistent with theories that implicate hippocampal oscillations in the encoding and retrieval of spatial and non-spatial information in memory (Hasselmo et al., 2002, Buzsaki, 2006) and with recent work in rodents indicating that internally-generated memory processing can drive sequential firing within an ensemble of neurons even when sensory cues are held relatively constant (Wang et al., 2015).

Our second main result confirms that spatial representations, in some form, are indeed elicited when patients experience virtual teleportation: the pattern of low-frequency hippocampal oscillations present during teleportation was sufficient to distinguish short- and long-distance teleportation events, and these oscillations were significantly attenuated when patients viewed a blank screen with no task-related memory demands. Previous efforts to identify spatial codes in the human hippocampus have largely focused on the activity of single neurons and have revealed representations of position, direction, and other spatial variables (Ekstrom et al., 2003, Jacobs et al., 2010, Jacobs et al., 2013). In contrast, past studies of hippocampal LFPs, which represent the summation of the activity of thousands of neurons, have struggled to identify a clear behavioral correlate of low-frequency oscillations during navigation (Buzsaki, 2005). Recent evidence indicates that rodent hippocampal LFPs contain information sufficient to decode spatial position (Agarwal et al., 2014) and human hippocampal LFPs can distinguish between the retrieval of spatial and temporal information (Watrous et al., 2013). In contrast to this previous work, which has leveraged the spatial distribution of LFP activity using either multielectrode recordings (Agarwal et al., 2014) or the coherence in LFP activity between multiple recording sites (Watrous et al., 2013), here we show that the pattern of oscillatory activity recorded at a single macroelectrode can distinguish between short and long distances.

What kind of neural code could give rise to the distance decoding we observed? Though there is to date little evidence in humans for an oscillatory neural code in the "strong" sense (e.g., modulation of neural firing via ephaptic coupling), previous work using stimulation paradigms that artificially impose oscillations suggests that they may indeed contribute to neural representations (Polania et al., 2012, Wimber et al., 2012). We speculate that the ability of these low-frequency oscillations to distinguish between short and long distances

may reflect differences in the degree of spatial updating required, with more spatial updating inducing more persistent oscillations. This explanation is consistent with our behavioral analysis of patient turn preference upon exiting the teleporter, which showed that patients remained spatially oriented after teleportation. We do not believe that the distance decoding can be explained by other variables (e.g., duration, velocity) that are often highly correlated with distance in real world environments because we specifically designed the virtual environment and experimental paradigm to disentangle these variables. Although more work will be needed to determine the precise neural codes supported by low-frequency hippocampal oscillations during navigation, the 3 fold decrease in low-frequency oscillations when patients viewed a black screen with no task-related memory demands strongly links the prevalence of these oscillations to cognitive processing in support of memory during navigation.

In sum, we have shown that human hippocampal low-frequency oscillations elicited during navigation can be sustained when visual and idiothetic cues are removed and the only available spatial information is internally generated from memory. We have further shown that the frequency-wise pattern of these oscillations was sufficient to decode the distance traveled under these conditions. Thus, these results expand our understanding of the conditions necessary to generate low-frequency hippocampal oscillations in humans and highlight the need for future research that characterizes the precise types of information coded by this oscillatory activity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

Agarwal G, Stevenson IH, Berenyi A, Mizuseki K, Buzsaki G, Sommer FT. Spatially distributed local fields in the hippocampus encode rat position. Science. 2014; 344:626–630. [PubMed: 24812401]

Bland BH, Oddie SD. Theta band oscillation and synchrony in the hippocampal formation and associated structures: the case for its role in sensorimotor integration. Behav Brain Res. 2001; 127:119–136. [PubMed: 11718888]

Buzsaki G. Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. Hippocampus. 2005; 15:827–840. [PubMed: 16149082]

Buzsaki, G. Rhythms of the Brain. Oxford, U.K: Oxford University Press; 2006.

Chen CY, Yang CC, Lin YY, Kuo TB. Locomotion-induced hippocampal theta is independent of visual information in rats during movement through a pipe. Behav Brain Res. 2011; 216:699–704. [PubMed: 20888366]

Chen G, King JA, Burgess N, O'Keefe J. How vision and movement combine in the hippocampal place code. Proc Natl Acad Sci U S A. 2013; 110:378–383. [PubMed: 23256159]

Czurko A, Hirase H, Csicsvari J, Buzsaki G. Sustained activation of hippocampal pyramidal cells by 'space clamping' in a running wheel. Eur J Neurosci. 1999; 11:344–352. [PubMed: 9987037]

Ekstrom AD. Why vision is important to how we navigate. Hippocampus. 2015 [PubMed: 25800632]

Ekstrom AD, Caplan JB, Ho E, Shattuck K, Fried I, Kahana MJ. Human hippocampal theta activity during virtual navigation. Hippocampus. 2005; 15:881–889. [PubMed: 16114040]

Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, Fried I. Cellular networks underlying human spatial navigation. Nature. 2003; 425:184–188. [PubMed: 12968182]

Ekstrom AD, Watrous AJ. Multifaceted roles for low-frequency oscillations in bottom-up and top-down processing during navigation and memory. Neuroimage. 2014; 85(Pt 2):667–677. [PubMed: 23792985]

Foster TC, Castro CA, McNaughton BL. Spatial selectivity of rat hippocampal neurons: dependence on preparedness for movement. Science. 1989; 244:1580–1582. [PubMed: 2740902]

Gavrilov VV, Wiener SI, Berthoz A. Whole-body rotations enhance hippocampal theta rhythmic slow activity in awake rats passively transported on a mobile robot. Ann N Y Acad Sci. 1996; 781:385–398. [PubMed: 8694429]

Hasselmo ME, Bodelon C, Wyble BP. A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. Neural Comput. 2002; 14:793–817. [PubMed: 11936962]

Jacobs J. Hippocampal theta oscillations are slower in humans than in rodents: implications for models of spatial navigation and memory. Philos Trans R Soc Lond B Biol Sci. 2014; 369:20130304. [PubMed: 24366145]

Jacobs J, Kahana MJ, Ekstrom AD, Mollison MV, Fried I. A sense of direction in human entorhinal cortex. Proc Natl Acad Sci U S A. 2010; 107:6487–6492. [PubMed: 20308554]

Jacobs J, Weidemann CT, Miller JF, Solway A, Burke JF, Wei XX, Suthana N, Sperling MR, Sharan AD, Fried I, Kahana MJ. Direct recordings of grid-like neuronal activity in human spatial navigation. Nat Neurosci. 2013; 16:1188–1190. [PubMed: 23912946]

Jutras MJ, Buffalo EA. Synchronous neural activity and memory formation. Curr Opin Neurobiol. 2010; 20:150–155. [PubMed: 20303255]

Jutras MJ, Fries P, Buffalo EA. Oscillatory activity in the monkey hippocampus during visual exploration and memory formation. Proc Natl Acad Sci U S A. 2013; 110:13144–13149. [PubMed: 23878251]

Komisaruk BR. Synchrony between limbic system theta activity and rhythmical behavior in rats. J Comp Physiol Psychol. 1970; 70:482–492. [PubMed: 5418472]

McFarland WL, Teitelbaum H, Hedges EK. Relationship between hippocampal theta activity and running speed in the rat. J Comp Physiol Psychol. 1975; 88:324–328. [PubMed: 1120805]

Nyhus E, Curran T. Functional role of gamma and theta oscillations in episodic memory. Neurosci Biobehav Rev. 2010; 34:1023–1035. [PubMed: 20060015]

Polania R, Nitsche MA, Korman C, Batsikadze G, Paulus W. The importance of timing in segregated theta phase-coupling for cognitive performance. Curr Biol. 2012; 22:1314–1318. [PubMed: 22683259]

Rizzuto DS, Madsen JR, Bromfield EB, Schulze-Bonhage A, Seelig D, Aschenbrenner-Scheibe R, Kahana MJ. Reset of human neocortical oscillations during a working memory task. P Natl Acad Sci USA. 2003; 100:7931–7936.

Schroeder CE, Wilson DA, Radman T, Scharfman H, Lakatos P. Dynamics of Active Sensing and perceptual selection. Curr Opin Neurobiol. 2010; 20:172–176. [PubMed: 20307966]

Taube JS, Valerio S, Yoder RM. Is navigation in virtual reality with FMRI really navigation? J Cogn Neurosci. 2013; 25:1008–1019. [PubMed: 23489142]

Vanderwolf CH. Hippocampal electrical activity and voluntary movement in the rat. Electroencephalogr Clin Neurophysiol. 1969; 26:407–418. [PubMed: 4183562]

Wang Y, Romani S, Lustig B, Leonardo A, Pastalkova E. Theta sequences are essential for internally generated hippocampal firing fields. Nat Neurosci. 2015; 18:282–288. [PubMed: 25531571]

Watrous AJ, Fried I, Ekstrom AD. Behavioral correlates of human hippocampal delta and theta oscillations during navigation. J Neurophysiol. 2011; 105:1747–1755. [PubMed: 21289136]

Watrous AJ, Tandon N, Conner CR, Pieters T, Ekstrom AD. Frequency-specific network connectivity increases underlie accurate spatiotemporal memory retrieval. Nat Neurosci. 2013; 16:349–356. [PubMed: 23354333]

Wimber M, Maass A, Staudigl T, Richardson-Klavehn A, Hanslmayr S. Rapid memory reactivation revealed by oscillatory entrainment. Curr Biol. 2012; 22:1482–1486. [PubMed: 22795695]

Highlights

- Novel paradigm that intermittently removes all sensory cues during navigation

- Hippocampal low-frequency oscillations persist without sensorimotor processing

- Low-frequency oscillations can discriminate short- and long-distance displacement

- More spatial updating is associated with more persistent low-frequency oscillations
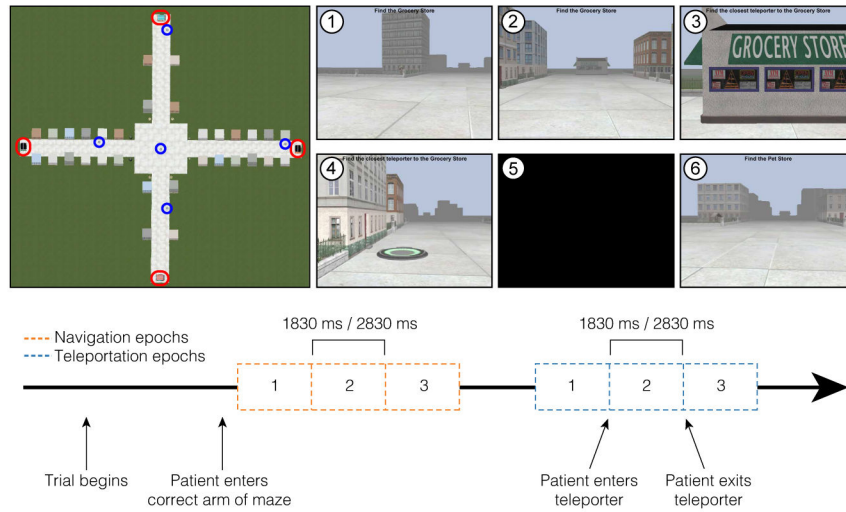
Figure 1.

Environment layout and example trial structure. Top left, top-down view of the plus maze, with target stores circled in red and teleporters circled in blue. This view is for schematic purposes only and was not shown to patients. Top right, views from one example trial. Each trial starts in the central plaza (1) where patients first find the landmark associated with the target store, which is visible in the distance, but whose identity is obscured by fog. Patients proceed down the arm of the maze (2) until reaching the target store (3). They then proceed to the nearest teleporter (4), at which point the display fades to black (5) and they teleport to the central plaza (6) to begin the next trial. Example trial shown is a short teleportation distance. Bottom, schematic of the relative timing of navigation and teleportation epochs. Teleportation epochs were time-locked to the moments of teleporter entry and exit, and were either 1830 ms or 2830 ms in duration. Navigation epochs started after the patient entered the correct arm of the maze and were matched in duration to the upcoming teleportation epochs.
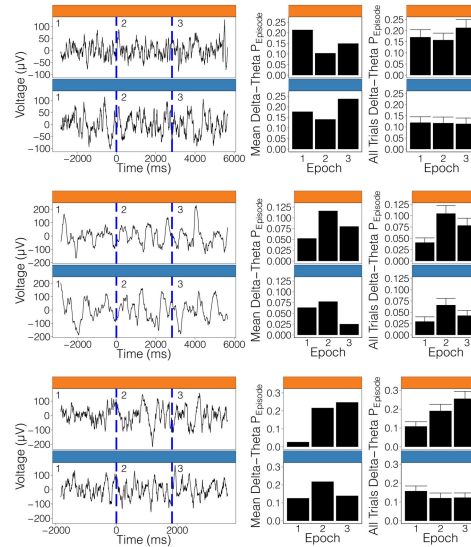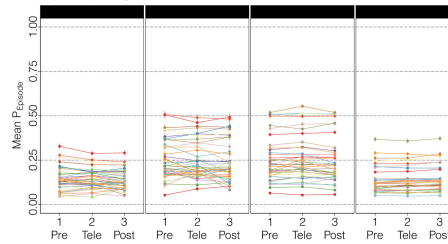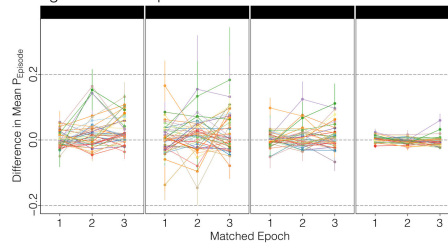
Figure 2.
Oscillatory activity by time point and condition. A) Example recordings during navigation and teleportation in three electrodes. Raw traces (left) show iEEG activity over time for the three teleportation epochs (1, 2, 3; dashed blue lines represent teleporter entry and exit) and their matched navigation epochs (1, 2, 3; dashed blue lines represent artificially imposed boundaries). Center, mean Delta-Theta $P_{Episode}$ for each epoch of the example trial. Right, mean Delta-Theta $P_{Episode}$ averaged across all trials for that electrode. B) Mean $P_{Episode}$ values for each epoch for each frequency band. Each line represents one electrode. Overall, low-frequency $P_{Episode}$ does not differ across epochs. C) Difference in mean $P_{Episode}$ between active navigation and teleportation for each pair of matched epochs (1, 2, 3, as in A). A significant proportion of electrodes show reduced Delta-Theta and Alpha $P_{Episode}$ post-teleportation (Epoch 3), likely because navigation speed is much slower during this time. Data shown as mean ± SEM. See also Figures S1 and S2, Tables S1 and S2.
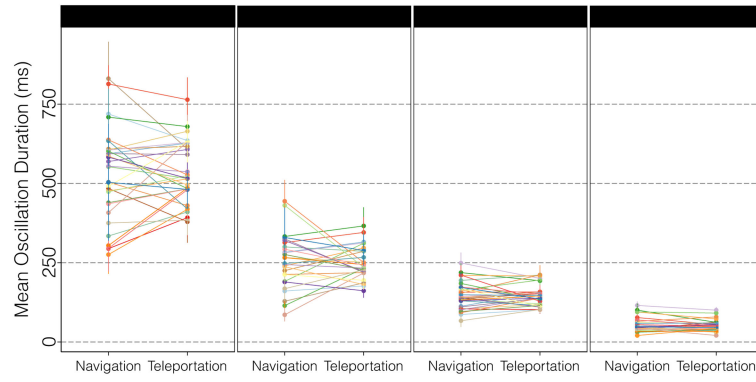
Figure 3.
Oscillatory episode duration for navigation and teleportation. Each line is an electrode and indicates the mean (± SEM) duration of oscillatory episodes that cross either the time point of teleporter entry or an artificially imposed boundary during navigation (see Figure 2A). Duration refers to the length of time the oscillation persisted after entering the teleporter or crossing the artificial boundary. No electrodes exhibited a significant difference in Delta-Theta oscillatory episode duration, indicating that entering the teleporter did not disrupt ongoing oscillations. See also Figure S3.
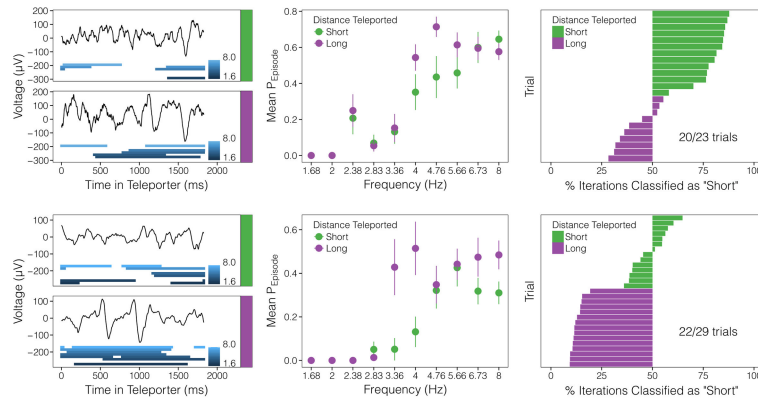
Figure 4.
Successful classification of distance teleported using low-frequency $P_{Episode}$. Left, raw traces from two example electrodes showing individual short-distance (top) and long-distance (bottom) teleportation events. Colored bars below each trace indicate periods of significant oscillatory episodes for each frequency. Color scale at right indicates frequencies in Hz. In both electrodes, there is greater low-frequency oscillatory activity during the long-distance teleportation event. Center, for the same electrodes, mean $P_{Episode}$ at each frequency during short-distance and long-distance teleportation trials. Right, for the same electrodes, classification results for each trial across iterations. Perfect classification over all iterations would be characterized by all purple bars at 0% and all green bars at 100%. Text at right indicates the number of trials that achieved correct classification for >50% of iterations. For display purposes, we show the classification of individual trials across iterations; however, statistical analyses were performed on the mean classification across trials for each iteration.