Human hippocampal theta power indicates movement onset and distance travelled

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Theta frequency oscillations in the 6- to 10-Hz range dominate the rodent hippocampal local field potential during translational movement, suggesting that theta encodes self-motion. Increases in theta power have also been identified in the human hippocampus during both real and virtual movement but appear as transient bursts in distinct high- and low-frequency bands, and it is not yet clear how these bursts relate to the sustained oscillation observed in rodents. Here, we examine depth electrode recordings from the temporal lobe of 13 presurgical epilepsy patients performing a self-paced spatial memory task in a virtual environment. In contrast to previous studies, we focus on movement-onset periods that incorporate both initial acceleration and an immediately preceding stationary interval associated with prominent theta oscillations in the rodent hippocampal formation. We demonstrate that movement-onset periods are associated with a significant increase in both low (2–5 Hz)- and high (6–9 Hz)-frequency theta power in the human hippocampus. Similar increases in low- and high-frequency theta power are seen across lateral temporal lobe recording sites and persist throughout the remainder of movement in both regions. In addition, we show that movement-related theta power is greater both before and during longer paths, directly implicating human hippocampal theta in the encoding of translational movement. These findings strengthen the connection between studies of theta-band activity in rodents and humans and offer additional insight into the neural mechanisms of spatial navigation.

theta | hippocampus | navigation | spatial memory | intracranial EEG

The rodent hippocampal local field potential (LFP) is dominated by 6- to 10-Hz theta oscillations during translational movement (1, 2). Both the power (1, 3) and frequency (3–6) of theta are positively correlated with running speed. Theta oscillations might therefore encode self-motion information and contribute to the generation of spatially modulated firing patterns (7–9). A critical concern for contemporary neuroscience is to establish whether this hypothesis can be translated across species. During navigation, intracranial recordings from depth electrodes in the human hippocampus have shown that theta is more prevalent during movement than during stationary periods (10–12) and that theta power increases with movement speed (13). In addition, increases in movement-related theta power are seen across the neocortex (10, 11, 14). These findings support the hypothesis that human theta oscillations might encode self-motion information. However, it has also been demonstrated that human theta-band activity typically occurs in transient bursts distributed throughout movement, in contrast to the continuous high-amplitude oscillation observed in the rodent (15, 16). Moreover, these studies identified movement-related oscillations within both higher and lower frequency theta bands (17–20). Hence, it is not yet clear how theta oscillations in the human hippocampus relate to those observed in the rodent.

To address this question, we examine intracranial recordings from the temporal lobe of presurgical epilepsy patients performing a self-paced spatial memory task (21). In contrast to previous studies, we focus on analyzing changes in oscillatory power around movement onset in the virtual environment. In the rodent hippocampal formation, theta power increases are observed during the stationary period immediately before movement initiation in both the membrane potential oscillations of single neurons (22) and in the LFP (1, 2, 23–26). In addition, magnetoencephalographic (MEG) recordings in healthy human participants have identified a transient increase in theta power around virtual movement onset that is correlated with subsequent spatial memory performance, although the source of this oscillation could not be localized (27). Here, we demonstrate that movement onset is associated with a significant increase in both low and high theta power across the human hippocampus and lateral temporal lobe that persists throughout the remainder of movement. Moreover, we find that increases in movement-related theta power are greater for longer paths, directly implicating human hippocampal theta in the encoding of translational movement. These findings support the translation of hypotheses regarding movement-related theta from rodent models and provide additional insight into the mechanisms of human spatial navigation.

Significance

Rodent hippocampal theta-band oscillations are observed throughout translational movement, implicating theta in the encoding of self-motion. Interestingly, increases in theta power are particularly prominent around movement onset. Here, we use intracranial recordings from epilepsy patients navigating in a desktop virtual reality environment to demonstrate that theta power is also increased in the human hippocampus around movement onset and throughout the remainder of movement. Importantly, these increases in theta power are greater both before and during longer paths, directly implicating human hippocampal theta in the encoding of translational movement. These findings help to reconcile previous studies of rodent and human hippocampal theta oscillations and provide additional insight into the mechanisms of spatial navigation in the human brain.

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Results

Behavioral Data. Nineteen presurgical epilepsy patients with depth electrodes implanted in the temporal lobe performed a spatial memory task in a virtual reality (VR) environment (Fig. 1*A*) (21, 27, 28). Temporal lobectomy patients have been shown to be impaired on a similar task (29), and performance of this task has been related to increases in hippocampal activity in previous fMRI studies (21, 27). Briefly, during encoding, patients were asked to navigate toward and memorize the location of four visible objects. During retrieval, patients were cued with an image of one object and then placed back in the environment and asked to navigate toward the remembered location of that (now invisible) object and make a response. This provides a continuous measurement of distance error, Δd, between the location at which the patient made a response and the true location of the object in each retrieval trial. The object then appeared in its correct location to provide patients with feedback on their performance and allow further learning. The feedback period ended when patients navigated to the location of the now-visible object.

Three patients did not complete the task due to technical difficulties, one patient could not perform the task, and two patients failed to produce sufficient stationary periods due to continuous movement. For the remaining 13 patients (see Tables S1 and S2 for details), mean $\Delta d = 28.7 \pm 14.4$ virtual meters (vm)
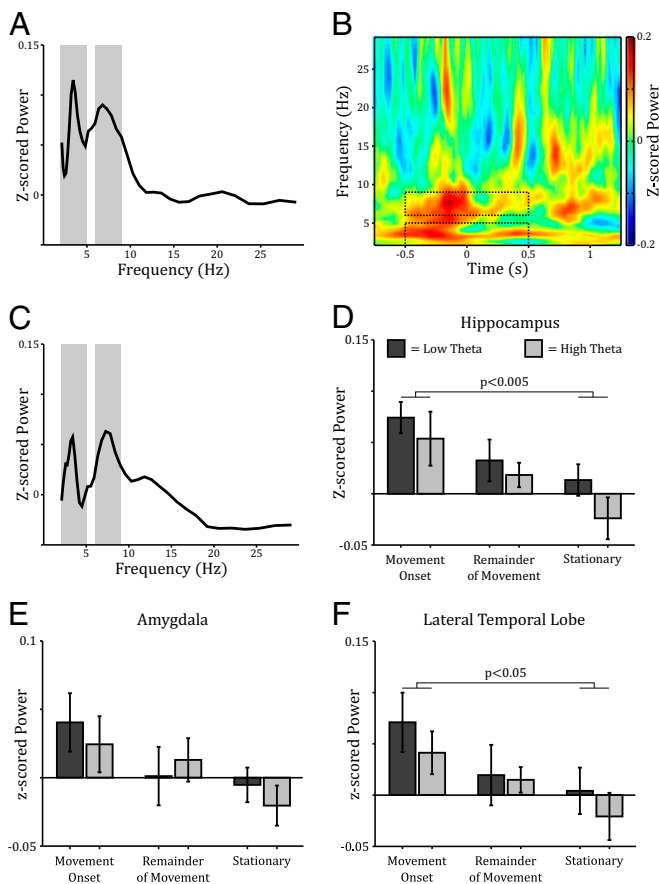
(range, 10.5–49.6 vm), which is smaller than chance performance [∼49.4 vm, $t(12) = -5.19$, $P < 0.001$, Cohen's $d = 1.44$] (Fig. 1 *B* and *C*). In addition, there was a significant reduction in Δd for each object across retrieval trials [$t(12) = -2.25$, $P < 0.05$, $d = 0.62$] (Fig. 1*D*), suggesting that the feedback provided at the end of each trial led to an improvement in patient's performance. These results indicate that patients could successfully perform the task.

Increased Hippocampal Theta Power Around Movement Onset. In the rodent hippocampal formation, significant increases in theta power have been observed during the stationary period immediately before movement onset (1, 2, 22–26). To establish whether similar increases in theta power could be observed in the human hippocampus, we focused our analysis on a 1-s period centered on movement onset that includes both the initial period of acceleration and an immediately preceding stationary interval (*Materials and Methods*). We began by comparing low-frequency oscillatory power on hippocampal electrode contacts during these movement-onset periods with periods of complete immobility across encoding and retrieval phases [excluding all trials that contained interictal spike (IIS) artifacts; see Table S3 for trial counts]. The resultant power spectrum exhibits two peaks centered around ∼3.5 Hz and 7 Hz, respectively (Fig. 2 *A* and *B*), consistent with previous human intracranial studies that have described distinct task-related changes in separate low- and high-frequency theta bands (17–20). No significant event-related potentials (ERPs) were observed around movement onset, suggesting that these power increases reflect induced oscillations (Fig. S1). In addition, a comparison of power spectra for the remainder-of-movement and stationary periods also revealed peaks in the low- and high-frequency theta bands (Fig. 2*C*; see Fig. S2 for separate power spectra from each condition).

To further characterize these changes, we extracted mean z-scored power values from 3-Hz windows around the observed peaks in the low- and high-frequency theta band (i.e., 2–5 Hz and 6–9 Hz, respectively) for all movement periods. A repeated-measures ANOVA with levels of frequency band (low- versus high-frequency theta band), task phase (encoding versus retrieval), and movement period (movement onset versus remainder of movement versus stationary) revealed a main effect of movement period on hippocampal theta power [$F(2,16) = 10.1$, $P = 0.001$, $\eta_p^2 = 0.56$] but no effect of frequency band or task phase and no interactions (all $P > 0.17$) (Fig. 2*D*). Subsequent analyses indicated that this arose from an increase in theta power during movement-onset compared with stationary periods [$t(8) = 4.78$, $P < 0.005$, d = 1.59], consistent with previous rodent studies and our prior hypothesis (2, 26). We also note a trend toward greater theta power during movement-onset compared with remainder-of-movement periods [$t(8) = 2.16$, $P = 0.06$, $d = 0.72$] and during remainder-of-movement compared with stationary periods [$t(8) = 2.24$, $P = 0.06$, $d = 0.75$], although neither of these contrasts reached statistical significance. Moreover, z-scored theta power was greater than zero (i.e., from mean power in that frequency band across the entire recording, including task and nontask periods) during both movement-onset [$t(8) = 3.56$, $P < 0.01$, $d = 1.19$] and remainder-of-movement [$t(8) = 2.51$, $P < 0.05$, $d = 0.84$] but not during stationary [$t(8) = -0.33$, $P = 0.75$, $d = 0.11$] periods. Subsequent analysis indicated that these findings were not affected by differences in clinical characteristics among the patient population (*Supporting Information*).

These results demonstrate that a large but transient increase in both low and high human hippocampal theta power accompanies the onset of movement in a VR environment, analogous to the increase in rodent hippocampal theta power immediately before the onset of physical movement (1, 2, 22–26). Importantly, this effect may have been overlooked by previous paradigms that

Fig. 1. Behavioral data. (*A*) Schematic of the spatial memory task. Participants navigate freely in a square VR environment, 100 vm per side, with distal cues for orientation. Participants memorize the location of one of four objects across 20 encoding trials (five for each object). Encoding is followed by a 30-s break period during which participants are instructed to focus on memorizing object locations. Each of 20 retrieval trials (five for each object) begins with a 3-s cue period, during which an image of one object is presented on screen. Participants are then placed back at one of four starting locations and are instructed to navigate to the remembered location of that object and make a response. Following this response, the object appears in its correct location to provide feedback on their performance in each trial. (*B*) Heat map of all responses for the object location in session one with the largest mean error across patients. The true object location is marked with a yellow star. (*C*) Histogram of Δds across all objects and patients. Chance performance is marked with a red dashed line. (*D*) Change in mean Δd for all objects across retrieval trials. Linear fits to each patient's performance are marked with a light gray line, and the average is marked with a thick red line.

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Fig. 2. Theta power changes during virtual movement across the temporal lobe. (A) Average power spectrum for movement-onset periods, baseline corrected by mean power at each frequency during stationary periods, for electrode contacts in the hippocampus. Power is increased in both low (2–5 Hz) and high (6–9 Hz) theta bands (marked in gray). (B) Spectrogram of power around virtual movement onset, baseline corrected by mean power at each frequency during stationary periods, for electrode contacts in the hippocampus. Black dashed regions indicate the low- and high-frequency theta bands for the 1-s period around movement onset. (C) Average power spectrum for remainder of movement periods, baseline corrected by mean power at each frequency during stationary periods, for electrode contacts in the hippocampus. Peaks in the low- and high-frequency theta bands (marked in gray) are visible but are less pronounced than during movement onset. (D–F) Mean z-scored power in the low (2–5 Hz) and high (6–9 Hz) theta bands during movement-onset, remainder-of-movement, and stationary periods in the hippocampus (D), amygdala (E), and lateral temporal lobe (F). Both low and high theta power are significantly increased during virtual movement onset, compared with stationary periods, on electrode contacts in the hippocampus and lateral temporal lobe but not on those located in the amygdala. In addition, mean z-scored power in the low- and high-frequency theta bands is greater than zero during movement onset on electrode contacts in the hippocampus and lateral temporal lobe and during the remainder of movement on electrode contacts in the hippocampus.

have compared "pure" movement and stationary periods (10–12, 14). Although theta power is strongest around movement onset, it does not differ statistically from the remainder of movement ($P < 0.06$) and remains elevated above baseline levels throughout both periods. Additional analyses indicate that theta power increases are specific to translational movements, as no analogous changes in low-frequency power are observed during the onset or remainder of purely rotational movement (Fig. S3). Interestingly, we also found no evidence for a difference in the magnitude of theta power increases around movement onset between encoding and retrieval periods. These findings are

consistent with sensor-level MEG recordings using a similar paradigm (27) and suggest that the hippocampus may be one source of that observed signal, although other potential sources cannot be ruled out.

Increased Theta Power in the Lateral Temporal Lobe Around Movement Onset. Next, we asked whether movement-related theta oscillations were restricted to hippocampal electrode contacts or were also present in other temporal lobe regions. In rodents, theta has been observed in the amygdala during emotional arousal (30, 31) and in pre- and infralimbic cortices during spatial memory tasks (32, 33). In humans, theta oscillations appear to be widespread across the neocortex during navigation in VR environments (10, 11, 14) as well as during short- and long-term memory tasks (28, 34, 35). We therefore analyzed changes in z-scored theta power between movement periods across patients with depth electrode contacts located in the amygdala ($n = 12$ patients) and lateral temporal lobe ($n = 12$ patients; for complementary analysis of $n = 8$ patients with electrode contacts in all three regions, see *Supporting Information*).

For electrode contacts located in the amygdala, we note a trend toward a main effect of movement period [$F(2,22) = 3.09$, $P = 0.07$, $\eta_p^2 = 0.22$] but no other main effects or interactions (Fig. 2E; see Table S4 for trial counts). In addition, mean z-scored power values across both task phases and frequency bands were not different from zero during any movement period (all $P > 0.09$). Electrode contacts located in the lateral temporal lobe showed a main effect of movement period [$F(2,22) = 3.77$, $P < 0.05$, $\eta_p^2 = 0.26$] but no other main effects or interactions (all $P > 0.19$) (see Fig. 2F and Table S5 for trial counts). Subsequent analyses demonstrated that, as in the hippocampus, this arose from an increase in theta power during movement-onset periods compared with stationary periods [$t(11) = 2.35$, $P < 0.05$, $d = 0.68$], while there was no difference in theta power between movement-onset and remainder-of-movement periods [$t(11) = 1.74$, $P = 0.11$, $d = 0.50$] or between remainder-of-movement and stationary periods [$t(11) = 1.24$, $P = 0.24$, $d = 0.36$]. Moreover, mean z-scored theta power was greater than zero during movement-onset [$t(11) = 2.48$, $P < 0.05$, $d = 0.72$] but not during remainder-of-movement or stationary periods (both $P > 0.27$). Again, these findings were not affected by differences in clinical criteria among the patient population (*Supporting Information*).

These results demonstrate that changes in movement-related theta power within the amygdala and lateral temporal lobe show the same general pattern as those in the hippocampus, although these differences reach significance only on lateral temporal lobe electrode contacts. In light of this, we asked whether theta oscillations recorded on medial and lateral electrode contacts were the product of independent sources or a single theta generator. To answer this question, we examined the phase offset between theta band oscillations on all pairs of electrode contacts in the hippocampus and lateral temporal lobe during movement-onset periods. We found that the distribution of phase lags across patients was unimodal with zero mean in both the low (circular V = 8.30, $P < 0.001$) and high (circular V = 8.89, $P < 0.001$) theta bands. Similarly, distributions of trial-by-trial phase lags across all electrode pairs in the low- and high-frequency theta band for each individual patient were also unimodal with zero mean (all circular V > 54.1, all $P < 0.001$). Next, we examined the relationship between trial-by-trial variations in power within each region during movement-onset periods. We found that trial-by-trial power in the hippocampus and lateral temporal lobe were highly correlated in both the low [$t(8) = 10.36$, $P < 0.001$, $d = 3.45$] and high [$t(8) = 8.05$, $P < 0.001$, $d = 2.68$] theta bands. Each of these results is consistent with the influence of a single theta generator on both regions. Further analyses indicated that theta oscillations recorded on lateral temporal lobe contacts were

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unlikely to arise as a result of volume conduction from the hippocampus (*Supporting Information*) (36). Hence, it appears that theta oscillations across the temporal lobe are actively driven by a single source. Although these data are insufficient to determine the location of that source, we note that theta synchrony across the hippocampal formation in rodents is thought to be driven by common input from the medial septum (26).

Movement-Related Theta Power Is Greater During Longer Paths. Having established that movement-onset and, to a lesser extent, remainder-of-movement periods were accompanied by a transient increase in theta power across the hippocampus and lateral temporal lobe, we asked whether theta amplitude during these periods had any behavioral correlates. Previous human intracranial EEG studies have demonstrated that theta power correlates with movement speed (13) and is greater when navigating more complex trajectories (15, 37). In our task, movement in the virtual environment accelerated quickly to a fixed top speed. However, we were able to examine whether theta power varied with distance traveled during each translational movement by separating movement-onset and remainder-of-movement periods for each patient according to whether the distance traveled was longer or shorter than their median path length.

In the hippocampus, a repeated-measures ANOVA with levels of frequency band (low- versus high-frequency theta band), movement period (movement onset versus remainder of movement), and path length (long versus short) showed a main effect of path length on theta power [$F(1,8) = 8.28$, $P < 0.05$, $\eta_p^2 = 0.51$] in addition to the expected main effect of movement period described above [$F(1,8) = 9.63$, $P < 0.05$, $\eta_p^2 = 0.55$] but no other main effects or interactions (all $P > 0.65$). Subsequent analyses demonstrated that this resulted from higher theta power both before and during longer paths [$t(8) = 2.88$, $P < 0.05$, $d = 0.96$] (Fig. 3 *A* and *B*). Importantly, z-scored power was also greater than zero both before and during long [$t(8) = 4.12$, $P < 0.005$, $d = 1.37$] but not short [$t(8) = 0.77$, $P = 0.46$, $d = 0.26$] paths.

Data from lateral temporal lobe contacts revealed similar results: a significant main effect of path length [$F(1,11) = 29.37$, $P < 0.001$, $\eta_p^2 = 0.73$] but no other main effects or interactions (all $P > 0.06$), which resulted from increased theta power before and during long, compared with short, paths [$t(11) = 5.42$, $P < 0.001$, $d = 1.56$] (Fig. 3 *C* and *D*), with z-scored theta power being greater than zero before and during long [$t(11) = 4.32$, $P < 0.005$, $d = 1.18$] but not short [$t(11) = 1.34$, $P = 0.22$, $d = 0.20$] paths (for complementary analysis of eight patients with electrode contacts in all regions, see *Supporting Information*). In both cases, we note that changes in movement-related oscillatory power between short and long paths were not restricted to the low- and high-frequency theta band but could be observed across a broad range of frequencies (<30 Hz) (Fig. 3 *B* and *D*). While this may be partly accounted for by spectral leakage from peaks in the low- and high-frequency theta band, the modulation of oscillatory power in other frequency bands might be addressed by future studies. Again, these results were generally unaffected by differences in clinical characteristics among the patient population (*Supporting Information*). In addition, we found no evidence for differences in movement-related theta power according to the duration of the stationary period preceding movement, when spatial orienting may occur, or between trials with high and low performance on electrode contacts in any region (all $P > 0.12$) (*Supporting Information*).

Hence, theta power increases across the temporal lobe during both movement-onset and remainder-of-movement periods are most pronounced for longer paths across the virtual environment but do not appear to covary with task performance. These results are consistent with movement-related theta oscillations mediating spatial processing rather than necessarily determining memory
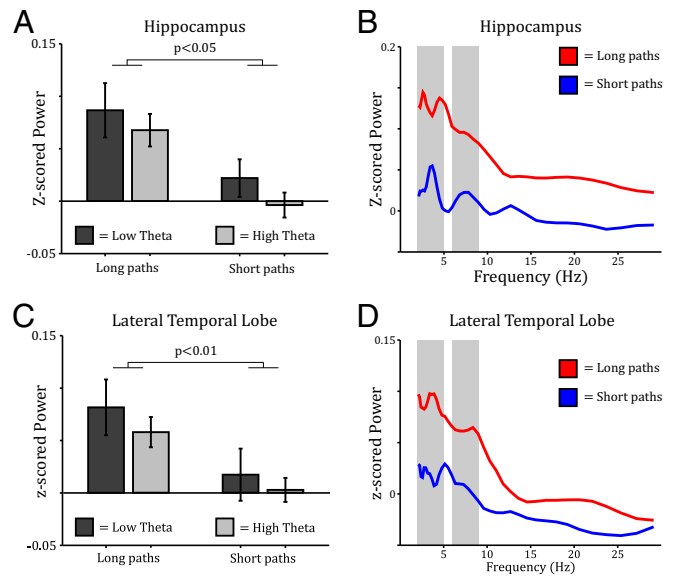
Fig. 3. Theta power changes with path length in the hippocampus and lateral temporal lobe. (*A* and *C*) Mean z-scored power in the low (2–5 Hz) and high (6–9 Hz) theta bands averaged across movement-onset and remainder-of-movement periods for long and short paths across the virtual environment on hippocampal (*A*) and lateral temporal lobe (*C*) electrode contacts. In each region, both low and high theta power are significantly increased during long paths compared with short paths. (*B* and *D*) Power spectra averaged across movement-onset and remainder-of-movement periods for long and short paths across the virtual environment in the hippocampus (*B*) and lateral temporal lobe (*D*). In both regions, broadband low-frequency oscillatory power is increased during long paths compared with short paths. Low (2–5 Hz) and high (6–9 Hz) theta bands are marked in gray.

performance during encoding or retrieval: Theta power is increased immediately before and throughout translational movements, and the magnitude of that power increase indicates the distance traveled. Moreover, these findings implicate theta oscillations in spatial updating during both the planning and execution of translational movements (2).

Discussion

We have demonstrated that both low and high theta power in the human hippocampus and lateral temporal lobe are increased around movement onset in a virtual environment, compared with stationary periods. These theta power increases appear to peak during the stationary interval immediately before movement onset (Fig. 2*B*), although our movement-onset periods also incorporate an initial period of acceleration that may contribute to the observed effect. Analogous results have been obtained from the rodent hippocampus, in which theta power increases are seen immediately before the onset of translational movement in both the LFP (1, 2, 23–26) and in the membrane potential of single neurons (22). Hence, this finding strengthens the translational connection between studies of movement-related theta in human and rodent models. Importantly, this increase in theta power around movement onset may have been overlooked by previous human intracranial recording studies that have exclusively compared pure movement and stationary periods that tend to be of short duration (10–12, 14). Theta power increases are not specific to movement-onset periods, however: Both low and high theta power remained above baseline levels during the remainder of movement in the hippocampus and, to a lesser extent, in the lateral temporal lobe. These data are consistent with the rodent literature and several previous intracranial studies that have described an increased prevalence of theta band

oscillations in both the hippocampus and neocortex during movement compared with stationary periods (10–12).

In addition, we have shown that movement-related power increases in low- and high-frequency theta bands are greater both before and during longer paths, but in neither band does power appear to correlate significantly with task performance or vary between periods of encoding and retrieval. These results suggest a role for theta oscillations in both the planning and execution of translational movements during an ethologically valid navigation task. This is consistent with several previous studies showing that theta oscillations are more prevalent during complex spatial navigation tasks (i.e., long versus short mazes) (15, 37), faster translational movements (13), and virtual teleportation over longer versus shorter distances in the absence of visual or self-motion cues (38). Importantly, this study also extends those results by focusing on changes in theta power, which can be more easily related to rodent data than the prevalence of theta oscillations, by examining active self-directed movements, which have greater ethological validity than periods of passive movement or teleportation, and by showing increased theta power before the onset of longer paths, supporting the hypothesis that theta oscillations are involved in spatial updating during the planning, as well as the execution, of translational movements (2).

Previous studies have highlighted two important differences between rodent and human movement-related theta oscillations (20). First, human theta oscillations appear in transient bursts that typically last several cycles, in contrast to the continuous rhythm in the rodent hippocampus (15, 16), and it is not clear whether these sporadic oscillations could encode continuous self-motion information (8, 20). However, it is possible that location estimates are updated intermittently during theta bursts, in accordance with the outcome of planned movements, rather than tracked continually throughout movement by an ongoing theta oscillation. Such a mechanism would be consistent with our observation that theta power was greater before movement onset and for longer translational movements. Alternatively, estimates of current location might be intermittently updated by tracking the relative location of visual landmarks during theta bursts, and distance traveled might be estimated by tracking the temporal duration of each translational movement. Further investigations using experimental paradigms that can dissociate the relative influence of temporal duration and visual input on estimates of distance traveled are required to address this issue (38).

Second, human movement-related theta oscillations apparently exist in two different frequency bands, one lower and closer to the traditional delta band and one higher and closer to the frequency of rodent hippocampal theta (10, 13, 20). It has been suggested that low theta may be the analog of rodent hippocampal theta, as it shows more prominent subsequent memory effects (17, 18); phase coupling with rhinal cortices (39); and modulates the firing rate of hippocampal cells during virtual navigation (40). Two distinct hippocampal theta oscillations have also been identified in rodents: type 1, which is typically modulated by translational movement and has a higher frequency, and type 2, which is typically modulated by anxiety and arousal and has a lower frequency, although still clearly above the delta band (41). However, the fact that both low and high theta power appear to be modulated by translational movement in our data, while no manipulations of anxiety or arousal were made, suggests that both correspond to rodent type 1 theta. In fact, we found no evidence for a functional distinction between low and high theta oscillations during any movement period, suggesting that these frequency bands might coexist to mediate human spatial processing. It is also possible that low and high theta do not reflect independent processes but instead are a single oscillation that varies dynamically over a broad frequency range (42, 43). This could explain the presence of spike-LFP phase coupling in single neurons within the human hippocampal formation in the absence of a strong fixed frequency baseline oscillation (40). Interestingly, the zero phase lag observed here between theta oscillations on hippocampal and lateral temporal lobe electrode contacts contrasts with previous reports of stable nonzero phase differences between theta oscillations in these regions during a nonspatial memory task (19). This might be accounted for by mnemonic function preferentially recruiting type 2 theta oscillations that are independently generated by separate hippocampal and cortical sources.

Three important caveats to the results presented here merit further discussion. First, contrasts between movement and stationary periods are confounded by the fact that patients must press a button to move across the VR environment but not to remain stationary. This raises the possibility that observed changes in theta power result from button pressing rather than from translational movement per se. However, our data show that button pressing in the absence of translational movement is not associated with changes in either low or high theta power (Fig. S4 and accompanying text), consistent with several previous studies showing no correlation between button pressing and theta power in the human hippocampus or neocortex (10, 11, 34, 36). Second, it is important to emphasize that patients do not physically locomote during the task. In rodents, both movement-related theta oscillations and the spatial modulation of neural firing patterns are weaker during passive movement through an environment (44, 45). Similarly, although LFP theta oscillations appear normal in rodent VR recordings (22, 46), the relationship between running speed and theta frequency is reduced (47). Hence, it is possible that the power, duration, and spectral fingerprint of movement-related theta in humans may differ during physical locomotion. Interestingly, recent depth electrode recordings taken from the hippocampi of a small number of patients hint at an increased prevalence of high-frequency theta oscillations during real-world ambulation (12). Finally, all human intracranial EEG studies must address the issue of extrapolating findings in epilepsy patients to the wider population. Reassuringly, the results presented here qualitatively replicate findings from a previous MEG study of healthy participants performing a similar task (27). The increase in theta power around movement onset observed in that study could not be localized, but the data presented here suggest the hippocampus as one candidate, although other potential sources cannot be ruled out. Further investigation with more advanced MEG source-localization techniques might elucidate this issue (48).

In summary, we have shown that movement onset is associated with a pronounced increase in both low and high theta power in the human hippocampus that also persists during the remainder of movement. Importantly, movement-related theta power is also greater both before and during longer translational paths. These findings strengthen the link between rodent and human hippocampal theta oscillations and provide additional insight into the mechanisms of human spatial navigation.

Materials and Methods

Nineteen patients with pharmaco-resistant epilepsy completed a spatial memory task used in several previous neuroimaging studies (Fig. 1A) (21, 27, 28) in which they were asked to remember object locations in the absence of direct cues, similar to the Morris water maze (49). Three of these patients were excluded due to technical difficulties, one patient could not perform the task, and two patients failed to produce a sufficient number of stationary trials as they moved continuously in the VR environment. This left 13 patients: six female, 11 right-handed, with a mean age ± SD of 29.3 ± 7.8 y (see Tables S1 and S2 for further details). Four patients completed one session of the task, and nine patients completed two sessions. The second session made use of the same environment but used four new objects in new locations.

Surgery and subsequent intracranial recordings were carried out at the National Hospital for Neurology and Neurosurgery, London. All patients had platinum Spencer probe depth electrodes (Severn Healthcare Technologies) inserted into the medial temporal lobe: in the right hemisphere in eight

Bush et al.

NEUROSCIENCE

patients, in the left hemisphere in four patients, and one bilateral implantation. Electrode locations were determined solely by clinical criteria, ascertained by visual inspection of postimplantation CT and/or MRI scans by R.R. and a consultant neurophysiologist (B.D.), and verified by an fMRI expert (J.A.B.). The presence of hippocampal damage was assessed, when histopathology was not available, by structural MRI at 3T including quantification of hippocampal volumes and T2 relaxation times. The study was approved by the National Health Service research ethics committee, and all patients gave written informed consent. Patients were seizure free for at least 24 h before participation.

Depth EEG was recorded continuously at a sample rate of 1,024 Hz (patients 4 and 10) or 512 Hz (all other patients) using either a NicoletOne long-term monitoring system (Natus Medical, Inc.) (patients 1–6) or Micromed SD long-term monitoring system (Micromed) (patients 7–13). Recordings made at a higher sampling rate were down-sampled to 512 Hz, to match those from the majority of patients, before any analyses were performed. Recordings made using the Micromed system were also subject to a 0.02-Hz digital high-pass filter. For each patient, a postimplantation CT image showing the implanted electrodes was coregistered with, and then overlaid upon, a preimplantation T1-weighted MR image. Candidate reference electrodes were chosen from contacts located in white matter by visual inspection of the overlaid images. EEG recordings from each candidate reference electrode were then visually inspected, and a single contact with little or no apparent EEG activity was chosen as the reference for all subsequent recordings. Audio triggers produced by the VR laptop were recorded on the monitoring system, allowing the EEG to be aligned with movement and task information sampled at 25 Hz.

Further information can be found in *SI Materials and Methods*.

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