RAPID COMMUNICATION

A Comparative Study of Human and Rat Hippocampal Low-Frequency Oscillations During Spatial Navigation

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ABSTRACT: Rhythmic oscillations within the 3–12 Hz theta frequency band manifest in the rodent hippocampus during a variety of behaviors and are particularly well characterized during spatial navigation. In contrast, previous studies of rhythmic hippocampal activity in primates under comparable behavioral conditions suggest it may be less apparent and possibly less prevalent, or even absent, compared with the rodent. We compared the relative presence of low-frequency oscillations in rats and humans during spatial navigation by using an oscillation detection algorithm ("P-episode" or "BOSC") to better characterize their presence in microelectrode local field potential (LFP) recordings. This method quantifies the proportion of time the LFP exceeds both a power and cycle duration threshold at each frequency, characterizing the presence of (1) oscillatory activity compared with background noise, (2) the peak frequency of oscillatory activity, and (3) the duration of oscillatory activity. Results demonstrate that both humans and rodents have hippocampal rhythmic fluctuations lasting, on average, 2.75 and 4.3 cycles, respectively. Analyses further suggest that human hippocampal rhythmicity is centered around ~3 Hz while that of rats is centered around ~8 Hz. These results establish that low-frequency rhythms relevant to spatial navigation are present in both the rodent and human hippocampus, albeit with different properties under the behavioral conditions tested. © 2013 Wiley Periodicals, Inc.

KEY WORDS: rodent; human; hippocampus; delta; theta; spatial navigation

Previous studies have demonstrated the existence and functional relevance of the rodent hippocampal theta (3–12 Hz) rhythm, relating it to arousal, movement, spatial navigation, and memory (Green and Arduini, 1954; Vanderwolf, 1969; Winson, 1978). Theta amplitude correlates with movement speed (McFarland et al., 1975), abolishing the rodent theta rhythm impairs spatial memory (Winson, 1978), and hippocampal place cells systematically vary their firing relative to theta oscillations (O'Keefe and Recce, 1993) to encode spatial location (Jensen and Lisman, 2000). During movement, theta activity typically manifests in rodents as a continuous voltage fluctuation that persists until the cessation of movement (Vanderwolf, 1969). Although the exact relationship between the theta rhythm and behavior is still being delineated (Buzsaki, 2005), there is little debate that the rodent theta rhythm exists and has functional relevance to spatial memory and navigation.

In contrast, there has been only mixed evidence for hippocampal theta in nonhuman primates (Green and Arduini, 1954; Stewart and Fox, 1991; Skaggs et al., 2007). Stewart and Fox observed 7–9 Hz theta activity in anesthetized monkeys along with "considerable amounts of low-frequency electroencephalography (EEG)" activity, which likely included oscillations in the delta band and lower theta band. In addition, these authors and others (Robinson, 1980) made the qualitative observation that theta activity in primates typically occurs in shorter "bouts" of activity compared with the more continuous rodent theta rhythm. Together, these difficulties in consistently identifying a continuously observable, frequency specific primate homologue to the rodent hippocampal theta rhythm have led to questions about the existence of theta oscillations in the nonhuman primate, and, by extension, humans altogether (Skaggs et al., 2007).

This view stands in contrast to early evidence from human hippocampal depth recordings from clinical populations that have demonstrated oscillatory activity in the 3–12 Hz range (Brazier, 1968; Halgren et al., 1978b; Arnolds et al., 1980), although the behavioral correlates and relation to rodent theta in some reports is more controversial (Halgren et al., 1978b; Robinson, 1980). Similar to rodents, human hippocampal/medial temporal lobe (MTL) low-frequency oscillations have been associated with sleep (Bodizs et al., 2001; Cantero et al., 2003), spatial navigation (Ekstrom et al., 2005; Cornwell et al., 2008; Watrous et al., 2011), and memory (Lega et al., 2011). These studies have found that delta (1–4 Hz) and theta (4–8 Hz) oscillations increase during exploration, such as real (Arnolds et al., 1980) and virtual movement (Ekstrom et al., 2005; Watrous et al., 2011), and that

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theta coordinates the timing of hippocampal neurons (Jacobs et al., 2007) during memory encoding (Rutishauser et al., 2010). These parallels between humans and rodents suggest that theta activity may serve a similar functional role in both species.

Although there appear to be functional parallels between human and rodent low-frequency hippocampal oscillations, important distinctions remain. Human intracranial (Mormann et al., 2008; Rutishauser et al., 2010; Lega et al., 2011) and magnetoencephalography (de Araujo et al., 2002) studies have identified prominent behavior-related hippocampal and MTL activity centered at ~3 Hz, lying at the interface of the canonical delta and theta frequency bands. Other studies, though, have observed changes in both delta and theta bands in the human hippocampus (Ekstrom et al., 2005; Mormann et al., 2008; Watrous et al., 2011). Together, these findings are consistent with the observation that low-frequency oscillations occur at a lower peak frequency in larger animals (Robinson, 1980; Miller, 1991; Penttonen and Buzsaki, 2003). Another potential difference between rat and human low-frequency oscillations is the qualitative observation that human oscillations often occur in short bursts (Cantero et al., 2003) rather than as a nearly continuous signal in rodents (Vanderwolf, 1969), although intracranially recorded raw traces from the hippocampus (Ekstrom et al., 2005; Watrous et al., 2011) and MTL (Watrous et al., in press) typically show oscillations lasting several cycles. Thus, previous observations indicate that there may be differences in both the frequency and duration of human low-frequency oscillations compared with rodents, though this issue has yet to be addressed systematically.

We sought to clarify this issue by comparing human hippocampal activity during virtual navigation and rodent hippocampal activity during Barnes Maze exploration. One challenge in conducting such inter-species comparisons deals with comparing real and virtual navigation. Rodent virtual navigation experiments have demonstrated hippocampal place cell activity, theta oscillations, and phase precession (Harvey et al., 2009) in the absence of vestibular motion inputs (Chen et al., 2013), supporting the idea that virtual navigation can be used as an experimental proxy for studying navigation related neural activity. Consistent with this, we have identified the behavioral correlates of the human data reported here previously (Watrous et al., 2011), finding behavior-related low-frequency power modulations associated with changes in virtual movement speed, spatial view, and task demands.

In this report, we assessed recordings of human and rodent local field potential (LFP) data quantitatively using a validated oscillatory detection algorithm (known as either P-episode or BOSC) (Caplan et al., 2003; Hughes et al., 2012) to better characterize and compare rodent and human theta oscillations. Briefly, this algorithm performs time-frequency decomposition using wavelets to estimate power values, regresses out the background $1/f$ signal, and then subjects the remaining signal for each epoch of interest to power and duration threshold criteria. Values exceeding these power criteria for a minimum duration are marked as oscillatory events and the resulting dependent measure is the proportion of recording time oscillatory events are observed (P-episode) (van Vugt et al., 2007). The method thus accounts for background noise, allowing more direct comparisons between different frequency bands, and allows direct quantification of the duration (number of cycles) of an ongoing oscillation.

We analyzed a total of 284 human hippocampal recordings from seven patients with pharmacologically intractable epilepsy, excluding data from all electrodes implanted in subsequently resected tissue. Details regarding the general recording procedures and navigation tasks used in each species have been published previously (Fedor et al., 2010; Watrous et al., 2011). The current results are novel as they are based on P-episode/BOSC. We also analyzed 30 recordings from 5 adult male Sprague-Dawley rats with implanted hippocampal CA3/CA1 bipolar fissure microelectrodes similar to our human recordings (i.e., Fried-Behnke electrodes).

We first compared the peak frequency exhibited by human and rodent hippocampal LFPs during the spatial navigation tasks (humans, virtual navigation; rats, Barnes maze). Visual inspection of raw traces from each individual (5 rodents and 7 humans) showed rhythmic voltage fluctuations from ~3 to 8 Hz, with recordings from the human hippocampus (Fig. 1A) exhibiting lower frequency oscillations compared with rodents (Figs. 1B,C). We confirmed this impression by first calculating P-episode (cycle duration criteria ≥ 1) for each species and electrode and identified the frequency at which each electrode showed maximal activity (Fig. 1D; black lines and dots indicate peak detected frequency at each electrode in humans and rodents, respectively). The largest proportion of human recordings showed maximal activity at 3.4 Hz, consistent with numerous other studies showing prominent activity at this frequency (Brazier, 1968; Huh et al., 1988; Bodizs et al., 2001; Zaveri et al., 2001; Jacobs et al., 2007; Lega et al., 2011). In contrast, none of the rodent recordings showed maximal activity at this frequency (Fig. 1D). Instead, the largest proportion (50%) of rodent recordings showed maximal oscillatory activity at 8 Hz, consistent with the notion of Type I (atropine-resistant) theta during rodent locomotor behavior (Vanderwolf, 1969; Kramis et al., 1975). None of the human recordings showed maximal activity at 8 Hz, leading to a significant difference in the distribution of peak frequencies between species (Fig. 1E; $P < 0.001$ two-sample Kolmogorov-Smirnov test). These results confirm the presence of human hippocampal theta activity and suggest that the majority of low-frequency oscillatory activity in humans manifests at a lower peak frequency compared with rodents during spatial navigation.

While the data demonstrates a difference in peak frequency, it is also important to assess transient vs. sustained oscillatory bouts of theta activity. To this end, we calculated P-episode for each hippocampal recording and varied the duration criteria for identifying oscillatory activity. To do this, we investigated oscillatory activity lasting from 1 to 10 cycles (as shown in Figs. 2A,B, 10 cycles appeared to be the upper limit, in our data set, for detecting oscillations). Figure 2A shows the
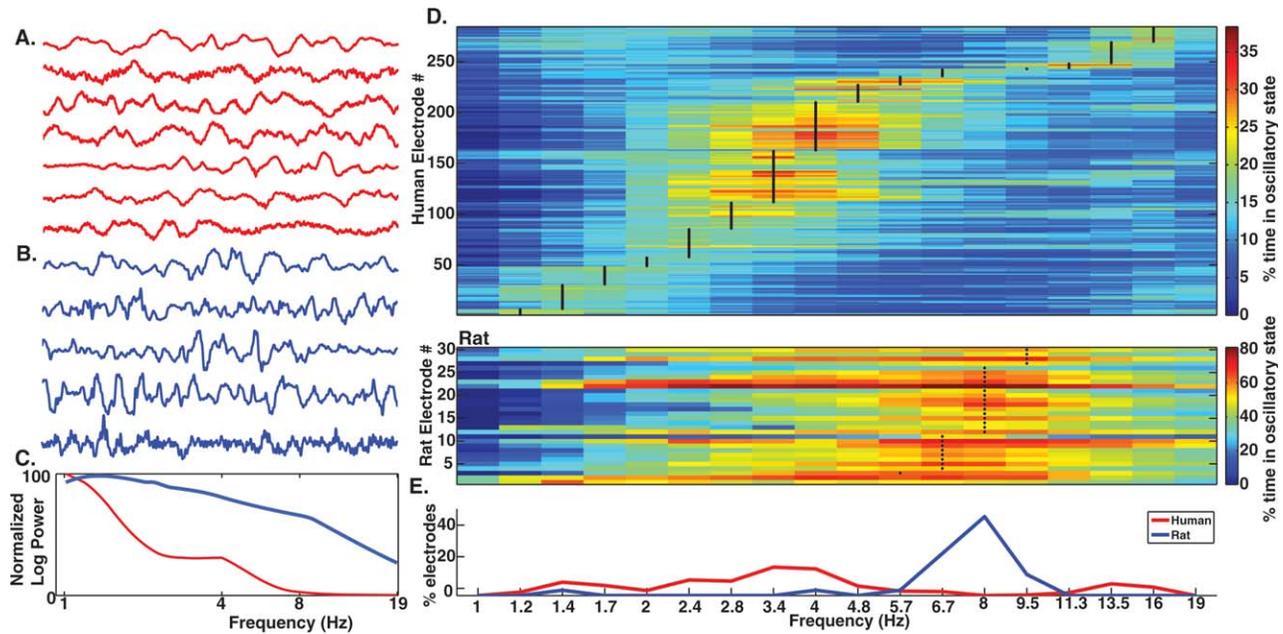
FIGURE 1. **Theta is present in humans at a lower frequency compared with rodents during spatial navigation. A: Examples of human hippocampal raw LFP traces, each from a separate patient, during virtual navigation, showing prominent low-frequency oscillations. B: Examples of raw LFP traces, each from a different rat, during the Barnes Maze, also showing prominent low-frequency oscillations. C: Example power spectral density plots for a human electrode (red) and a rodent electrode (blue) during navigation.** **D: Proportion of time oscillatory activity was detected as a function of frequency for 284 human hippocampal recordings (top) and 30 rodent recordings (bottom). Black vertical lines (humans) and dots (rats) indicate the peak frequency at which oscillatory activity was detected for each recording. Note the difference in color scale for humans and rodents. E: Proportion of electrodes with peak activity at each frequency. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]**

percentage of time oscillatory activity was detected at each frequency and duration criteria averaged across our human recordings. Comparing this to a similar plot derived from our rodent recordings (Fig. 2B) demonstrated two quantitative species differences in LFP oscillations. First, at the 1-cycle duration criteria, significantly more oscillatory activity was detected at the rodent peak frequency of 8 Hz compared with the human peak frequency of 3.4 Hz ($P < 0.001$, Mann-Whitney test). Second, when increasing the number of cycles used in our duration cutoff, the amount of detectable oscillatory activity decreased more rapidly in human recordings compared to those of the rodent (Fig. 2C). This suggests that rat low-frequency oscillations lasted a greater number of cycles than human low-frequency oscillations. This result is visually evident by looking at the "color spread" along the vertical axis in Figures 2A,B and was quantitatively evaluated in two ways. The slope of these functions across all sampled recordings was significantly more negative (steeper) in humans (Fig. 2C; $P < 0.001$, Mann-Whitney test) and the average P-episode duration criteria at which half of the maximum activity was detected was lower in humans than in rodents ($P < 0.001$, Mann-Whitney test, 3.2 and 5.8, respectively). These findings indicate a more rapid decline in detected activity at increasing cycles criteria in humans compared with rats, suggesting that human low-frequency oscillations lasted fewer numbers of cycles on average.

To approach this same issue with a slightly different analysis, we also calculated the average number of cycles for each detected oscillatory event across electrodes using a minimal duration criteria of at least 1 cycle. Human oscillatory activity lasted significantly fewer cycles compared with rodents (Fig. 2D, $P < 0.002$ at each frequency, Mann-Whitney test). Whereas human activity lasted 2.75 cycles at the peak-detected frequency of 3.4 Hz, rodent 8 Hz activity lasted 4.3 cycles. It is important to note that rodent low-frequency oscillations lasted greater numbers of cycles across all frequency bands from 1 to 19 Hz although this difference was most pronounced at the peak preferred frequencies, as shown in Figure 2D. Thus, both analyses confirmed the presence of human hippocampal low-frequency oscillations at a lower peak frequency and indicate that human activity is less continuous compared with rodents.

Finally, we assessed how low-frequency activity varied during movement. In our human recordings, we calculated the percent time oscillatory activity was detected between 1 and 10 Hz during the top and bottom quartile of virtual movement speed (referred to as fast and slow movement, respectively). In our rat recordings, we compared the same measures during a period in which movement was restricted in the start box with active exploration of the Barnes maze. This analysis was conducted on all rodent data and a subset of the human data ($n = 240$ electrodes) for which we had data in both conditions. In both data sets, we detected greater oscillatory activity at
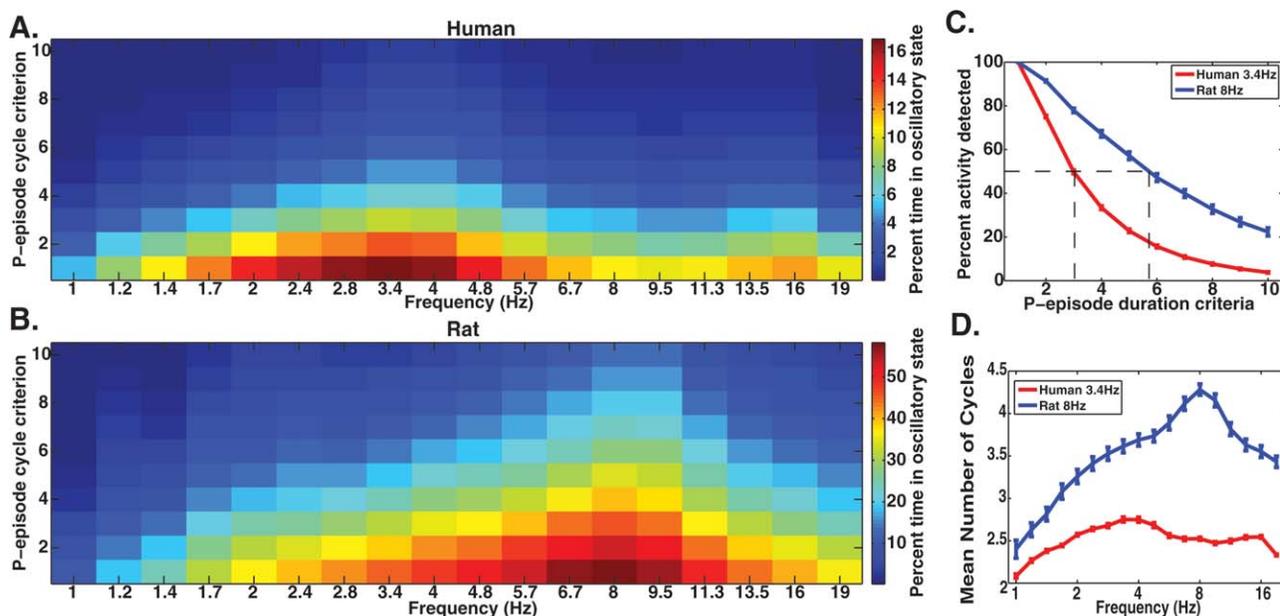
FIGURE 2. Human theta is less continuous compared with rodent theta. A: Proportion of time each frequency was detected averaged across all 284 human recordings and at increasing P-episode duration criteria. B: Similar to (A), but for 30 rodent recordings. C: Proportion of time oscillatory activity was detected at the human peak frequency of 3.4 Hz and the rodent peak frequency of 8 Hz. Gray dashed lines correspond to the half-maximum P-episode duration criteria at the human and rodent peak frequency. D: Average number of cycles for each detected oscillatory event for humans and rodents. Error bars indicate the standard error of the mean across electrodes. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

higher frequencies during movement compared with either slow or still periods, suggesting that movement resulted in increased oscillatory activity at higher frequencies. In humans, a 2 × 14 condition by frequency analysis of variance (ANOVA) revealed main effects of frequency and condition and a frequency by condition interaction (each $F(1,6718) > 5$, and all $P < 0.001$). These results are consistent with previous findings that have shown oscillatory power increases with movement speed (Ekstrom et al., 2005; Watrous et al., 2011) and qualitative observations, based on raw traces, that movement results in a frequency increase (Ekstrom et al., 2005). For the rodent data, a 2 × 14 condition by frequency ANOVA revealed main effects of frequency and condition and a frequency by condition interaction (each $F(1,938) > 2.85$, and all $P < 0.001$). These findings are also consistent with previous rodent studies demonstrating increases in running speed result in both increases in theta power and frequency (McFarland et al., 1975; Czurko et al., 1999; Geisler et al., 2007; Mitchell et al., 2008).

Using a novel computational method to better characterize oscillatory activity in humans and rats during spatial navigation tasks, we find that oscillations in the human hippocampus occur at a lower frequency (∼3.4 Hz as compared with ∼8 Hz) and are less continuous than rodent theta. These findings are consistent with qualitative observations suggesting such frequency (Miller, 1991; Lega et al., 2011) and continuity (Arnolds et al., 1980; Stewart and Fox, 1991) differences between rodents and primates. While previous reports have

suggested such differences, no previous study has directly compared recordings between species. Although our results assessing hippocampal low-frequency activity is potentially confounded by studying patients with epilepsy, our results are consistent with previous research investigating the spectral properties of the MTL invasively in clinical populations (Brazier, 1968; Huh et al., 1988; Zaveri et al., 2001) and noninvasively in healthy participants (de Araujo et al., 2002; Cornwell et al., 2008). Additionally, we only analyzed electrodes drawn from areas that did not show epileptogenic activity and thus would be more likely to be directly involved in behavior.

How might human and rodent hippocampal oscillations be interpreted given these differences? Previous analysis from our group (Watrous et al., 2011) and others (Bodizs et al., 2001; Jacobs et al., 2007; Lega et al., 2011) suggest functional parallels between human hippocampal low-frequency oscillations and rodent (Type I) theta. More broadly, numerous studies have shown the importance of human hippocampal activity at 3–8 Hz across a variety of behaviors (Brazier, 1968; Halgren et al., 1978a; Arnolds et al., 1980; Axmacher et al., 2010; Rutishauser et al., 2010). Within this band, the distinction between delta and theta activity is less clear, with some studies showing similar effects in these frequency bands (Jacobs et al., 2007; Watrous et al., 2011) and others functionally dissociating activity in these bands (Rutishauser et al., 2010; Lega et al., 2011). One possibility is that such distinctions only emerge during different behaviors, which could be tested by comparing human hippocampal activity in the delta and theta

band across multiple hippocampally dependent behaviors. Regardless of the resolution of these issues, our results indicate that navigation-related human hippocampal oscillations peak, in terms of prevalence, at or near 3 Hz, at least during a spatial navigation task similar to that used in rodents. This activity impinges on the classical boundaries of delta and theta and questions the utility of defining activity based upon these boundaries.

We also observed differences in the duration of oscillatory activity, in terms of number of detected cycles, between species. Oscillations in both species, however, lasted roughly comparable amounts of total time. Human oscillations at 3.4 Hz had a period of ∼290 ms and lasted an average of 2.75 cycles for a total duration of ∼800 ms while rodent oscillations at 8 Hz had a period of 125 ms and lasted an average of 4.3 cycles for a total duration of ∼540 ms. Although previous work suggested that the number of oscillatory cycles, rather than total duration, is the critical factor in determining the computational capacity of a given rhythm (discussed in van Vugt et al., 2007), our results do not allow us to determine which factor (cycle length or total duration) is most behaviorally relevant. Comparing oscillatory duration between species during correct versus incorrect behavior may be one way to address this issue as this would provide a more direct link to successful vs. unsuccessful computational processing in the hippocampal circuit.

To our knowledge, these results provide the first direct, quantitative comparison of human and rodent hippocampal activity during spatial navigation, a hippocampally dependent (Burgess, 2008; Mitchell et al., 2008) behavior known to elicit theta activity in each species (Kahana et al., 1999; Ekstrom et al., 2005; Watrous et al., 2011). One potential limitation with our study is that there are a number of differences between rats and humans that are difficult, if not impossible, to fully equate, including differences in body morphology, different visual and other sensory systems, different reliance on behavioral strategies (verbal vs. nonverbal), and differences in hippocampal connectivity. Of particular importance here, we tested our patients in virtual reality, due to constraints of the clinical testing environment, while rats freely explored the Barnes Maze. Theta oscillations are present during simulated movement and virtual reality (VR) in rodents (Terrazas et al., 2005; Harvey et al., 2009), although direct comparisons of real and VR navigation suggest an overall reduction in power and frequency (Chen et al., 2013). When compared with the frequency differences between species reported here, the decrease in rodent peak frequency during VR was relatively small (less than 1 Hz reduction) and the decrease in the theta index, a measure of power at the peak frequency, showed only a modest reduction between conditions. These differences thus would be unlikely to account for the observed decrease in peak frequency (∼5 Hz) and significantly lower cycle duration (∼2.8 vs. 4.3) we observed in our human compared with rat data. Future studies will aim to compare low-frequency oscillations during human real and VR navigation but based on the Chen et al. study, we expect that our results in VR would represent a lower bound for oscillatory activity detected during real navigation.

In conclusion, our results help better establish the existence of low-frequency oscillations during navigation in humans, a likely analogue of Type I theta in rats, and suggest important differences in how these manifest during behaviors in which they are consistently observed in rodents.

Acknowledgments

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