

# Multisecond Periodicities in Basal Ganglia Firing Rates Correlate With Theta Bursts in Transcortical and Hippocampal EEG

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**Allers, Kelly A., David N. Ruskin, Debra A. Bergstrom, Lauren E. Freeman, Leyla J. Ghazi, Patrick L. Tierney, and Judith R. Walters.** Multisecond periodicities in basal ganglia firing rates correlate with theta bursts in transcortical and hippocampal EEG. *J Neurophysiol* 87: 1118–1122, 2002; 10.1152/jn.00234.2001. Multisecond oscillations in firing rate with periods in the range of 2–60 s (mean, 20–35 s) are present in 50–90% of spike trains from basal ganglia neurons recorded from locally anesthetized, immobilized rats. To determine whether these periodic oscillations are associated with similar periodicities in cortical activity, transcortical electroencephalographic (EEG) activity was recorded in conjunction with single- or dual-unit neuronal activity in the subthalamic nucleus (STN) or the globus pallidus (GP), and the data were analyzed with spectral and wavelet analyses. Multisecond oscillations in firing rates of 31% of the STN neurons and 46% of the GP neurons with periodicities significantly correlated with bursts of theta (4–7 Hz) activity in transcortical EEG. Further recordings of localized field potentials in the hippocampus and frontal or parietal cortices simultaneously with GP unit activity showed field potentials from the hippocampus, but not from the frontal or parietal cortices, exhibited bursts of theta rhythm that were correlated with GP firing rate oscillations. These results demonstrate a functional connectivity between basal ganglia neuronal activity and theta band activity in the hippocampus.

## INTRODUCTION

Multisecond oscillations in firing rate with periods in the range of 2–60 s, and averaging 20–35 s, are present in 50–90% of spike trains from neurons in basal ganglia nuclei [subthalamic nucleus (STN), globus pallidus (GP), entopeduncular nucleus and substantia nigra pars reticulata] recorded from locally anesthetized, immobilized rats (Allers et al. 2000; Ruskin et al. 1999). Similar oscillations have also been observed in spike trains recorded from the basal ganglia of awake monkeys (Wichmann et al. 2000). Oscillations in rate with periods in this time range appear too slow to be involved in the fine aspects of motor control, but pharmacological studies have hinted that they may play a role in processes such as those involved in synaptic plasticity or attentional state (discussed in Allers et al. 2002). Stimulants such as cocaine, methylphenidate, and amphetamine increase the frequency of these oscillations within GP spike trains (Ruskin et al. 2001a,b), while general anesthesia virtually eliminates them (Allers et al. 2000;

Ruskin et al. 1999, 2001b). The fact that dopamine receptor stimulation affects the frequencies of these oscillations in a similar manner in all the basal ganglia nuclei studied (Allers et al. 2000; Ruskin et al. 1999) suggests that there may be a considerable degree of coherence in oscillations in this time range in the basal ganglia. This idea is supported by additional studies which have shown that ~30% of simultaneously recorded pairs of basal ganglia neurons, with individual neurons located in either the same or different basal ganglia nuclei, show firing rate multisecond oscillations with matching periods (Allers et al. 1999).

These observations have led to the hypothesis that multisecond oscillations could act to organize the propagation and synchronization of faster oscillatory activity in distributed circuits. This study combines single- and dual-unit recordings studies in the basal ganglia with transcortical electroencephalography (EEG) and depth electrode recordings in the frontal and parietal cortices and hippocampus to examine the relationship between multisecond oscillations in the basal ganglia and synchronized activity at higher frequencies in the cortex and hippocampus. The results indicate that multisecond oscillations in STN and GP firing rates can be correlated with bursts of theta rhythm activity (4–7 Hz) in transcortical EEG recordings, which appear to reflect synchronized activity in the theta range in the hippocampus.

## METHODS

Recordings of spontaneously active STN and GP neurons were conducted in male Sprague-Dawley rats (250–350 g) as previously described (Allers et al. 2000; Ruskin et al. 1999). All experiments were conducted in strict accordance with the *Guide for Care and Use of Laboratory Animals* from the National Institutes of Health and approved by the National Institute of Neurological Disorders and Stroke Animal Care and Use Committee. Because general anesthetics eliminate multisecond oscillations in basal ganglia nuclei, rats were locally anesthetized, artificially respired, and gallamine immobilized during the recording period. Rats were maintained under halothane anesthesia during all surgical procedures.

Extracellular single- or dual-unit activity of spontaneously firing STN and GP neurons was recorded with single-barrel glass microelectrodes filled with 1% Pontamine sky blue dye in 2 M NaCl. The electrode tips were broken back to a diameter of 1–2  $\mu\text{m}$  providing in

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vitro impedances between 3.0 and 6.0 M $\Omega$  (at 135 Hz). Recordings started 10–20 min after halothane was removed. Baseline activity was recorded for  $\geq 5$  min per neuron, and recordings were typically stable for periods of 20 min or more. Signal-to-noise ratios were  $>2:1$  for all neurons studied and often 4:1. Eighty-nine rats were studied in these experiments; activity of one neuron per rat was recorded in most cases (87). Biphasic action potentials were passed through a high-input impedance amplifier and monitored on an oscilloscope and an audio monitor. Signals were collected using CED 1401 hardware and Spike2 software (Cambridge Electronic Design, Cambridge, UK). Dual units in the STN were discriminated off-line using Spike2 software.

Skull screws for transcortical EEG recordings were placed above frontal motor and occipital cortices in the ipsilateral hemisphere, with a reference electrode placed into the bone above the olfactory cavity. In a separate series of experiments, field potentials were recorded from concentric conical-tip bipolar electrodes (300  $\mu\text{M}$  OD; FHC, Bowdoinham, ME) placed in the frontal or parietal cortices and the hippocampus. EEG and field potential signals were passed through a Grass amplifier. For analysis of theta activity, EEG and field potential signals were digitally filtered (4–7 Hz), rectified, and binned (200 ms bins); peaks from these rectified EEG signals were voltage-discriminated and used for cross-correlation analyses with STN or GP spike trains.

Oscillatory characteristics of interspike interval data from spike trains and rectified EEG were assessed for significant periodicity ( $P < 0.05$ ) using the method of Kaneoke and Vitek (1996), with the modification that power spectra were taken from rate histogram data instead of autocorrelograms. Multisecond oscillations in spike trains and EEG were considered to have matching periods if differences between periods of spectral peaks were  $\leq 5\%$ . These cases were further analyzed by cross-correlation. Time versus frequency representations of oscillatory power were produced from raw EEG data with windowed fast Fourier transforms (FFT) (Spike 2 software) and in raw EEG and spike train data with Morlet wavelet scalograms from the Time-Frequency Toolbox (<http://www-syntim.inria.fr/fractales/Software/TFTB>) (wavelet half length: 1.9 s at 2 Hz scale) with Matlab 5.3.1 (The MathWorks, Natick, MA).

## RESULTS

Eight dual- and 35 single-unit recordings from STN neurons and 40 single-unit recordings from GP neurons were performed in conjunction with simultaneous transcortical EEG recordings. Visual inspection of wavelet scalograms and windowed FFT (FFT data not shown) demonstrated that multisecond oscillations in STN and GP spike trains were most clearly correlated with changes in transcortical EEG theta (4–7 Hz) power (Fig. 1, 2) as compared with other frequency bands (2–4, 7–30 Hz). Of the STN neurons exhibiting multisecond oscillations within the 2–60 s range ( $n = 26$ ; mean period:  $23.3 \pm 3.2$  s), eight (31%) exhibited firing rate oscillations (2 from a dual-unit recording as shown in Fig. 1 and 6 from single-unit recordings) that were correlated with bursts of theta activity in the transcortical EEG (Fig. 1). Of the GP neurons with spike trains exhibiting multisecond oscillations within the 2–60 s range ( $n = 35$ ; mean period:  $25.2 \pm 2.5$  s), firing rate oscillations of 16 neurons (46%) were correlated with bursts of theta in the transcortical EEG (Fig. 2). STN and GP neurons showing oscillations correlated with transcortical theta activity were not localized to any particular subarea of these nuclei. Phase relationships between multisecond oscillations in STN and GP firing rates and theta oscillations in the transcortical EEG varied considerably: Fig. 1 shows an example of near synchrony of slow oscillations of two STN neurons and EEG

theta, while the GP neuronal oscillation/EEG theta pair in Fig. 2 is near antiphase. Intermediate phase relationships were also observed. There was no evident concentration of power in the 4–7 Hz frequency range within most GP or STN spike trains (Figs. 1C and 2C), although a small number of STN neurons had autocorrelograms with weak periodicities in the theta range.

To explore the source of the synchronized activity producing the transcortically recorded theta signal, localized field potentials in the ipsilateral hippocampus and frontal or parietal cortices were recorded simultaneously with GP unit activity. Dorsal hippocampal field potentials (6 of 7) recordings exhibited bursts of theta that correlated with multisecond oscillations in GP firing rates (Fig. 3). Frontal (1 of 7) and parietal (0 of 3) cortical field potentials rarely showed this correlation.

## DISCUSSION

This study demonstrates a relationship between slow periodicities in firing rate of STN and GP neurons and transcortically recorded EEG theta (4–7 Hz) activity. Of STN and GP spike trains exhibiting multisecond oscillations in firing rate, 31 and 46%, respectively, had multisecond oscillations with periods that correlated with oscillatory periods detected in transcortically recorded theta activity. Similar correlations between GP spike train oscillations and bursts of theta recorded from depth electrodes in the hippocampus, but not the frontal or parietal cortex, indicate that the transcortically recorded EEG theta activity is highly likely to be volume conducted from the hippocampus. Theta frequency, per se, is not prominent in the individual basal ganglia spike trains; rather it is the slower periodic fluctuations in firing rate that correlate with changes in theta power in transcortical EEG and hippocampal field potentials.

Previous studies have shown that these multisecond oscillations are not present in the basal ganglia of rats systemically anesthetized with chloral hydrate, ketamine, or urethan (Allers et al. 2000; Ruskin et al. 1999, 2001b). In contrast, oscillations in the 1 Hz range are prominent in recordings from many brain regions in ketamine- or urethan-anesthetized rats. Correlated oscillations in this 1 Hz frequency range were originally observed in thalamocortical circuits (Steriade 2001) but have also been found in the globus pallidus, subthalamic nucleus, and cortex of ketamine- or urethan-anesthetized rats (Magill et al. 2000) as well as in the nucleus accumbens and hippocampus (Goto and O'Donnell 2001). These observations indicate that mechanisms exist for the wide spread propagation of both slow (1 Hz) and ultraslow oscillatory activity throughout basal ganglia, thalamocortical, and limbic areas, although it is not clear how similar the mechanisms involved in generation and propagation of these different oscillations may be.

A number of studies have focused on the time-limited emergence of correlated multisecond (ultraslow) oscillations in neural activity in early postnatal development and their potential role in the establishment of activity-based synaptic connectivity (Feller 1999). The mature organism, however, also clearly maintains mechanisms for generating correlated multisecond periodicities, as evidenced by the present observations, which join data showing that oscillations in this frequency range modulate a number of processes including heart rate (Cooley et

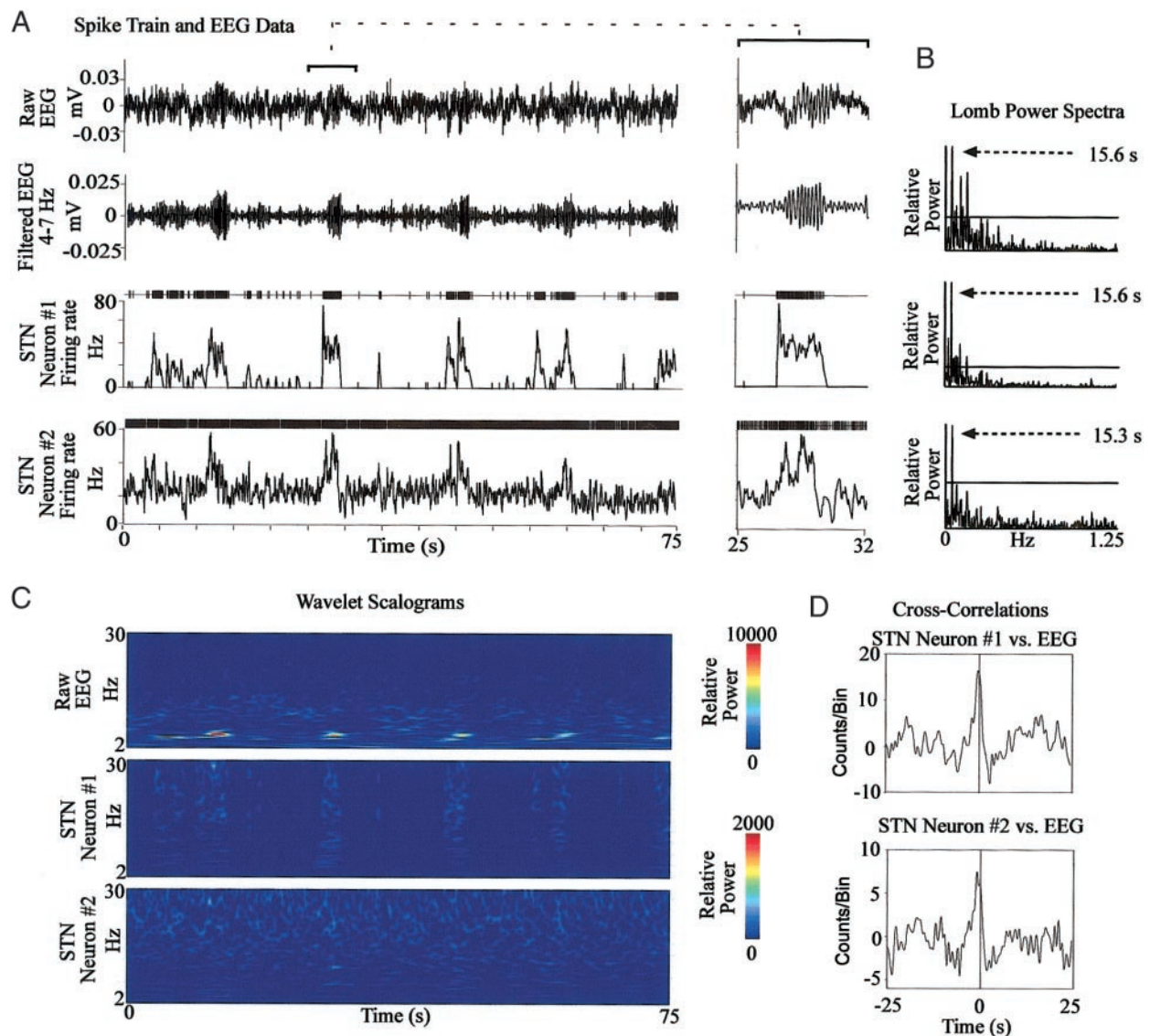


FIG. 1. Correlated oscillations in 2 subthalamic nucleus (STN) spike trains and transcortical electroencephalogram (EEG). *A*: raw and filtered EEG tracings with spike trains from 2 simultaneously recorded STN neurons (displayed as rasters and mean frequency plots with 200 ms bins) are shown. These spike trains have periodic increases in firing rate that correlate with short bursts of the theta rhythm in the transcortical EEG. *B*: Lomb power spectra indicate that the periods of STN neuronal firing rate oscillations and recurrent bursts of theta activity in the EEG are identical. Spectral peaks above the significance level (at  $P < 0.05$ ) are considered statistically significant; the period of the strongest spectral peak is indicated. *C*: corresponding wavelet scalograms demonstrate that within the EEG recording, the 4–7 Hz band has the greatest spectral power in the 2–30 Hz range shown and that there is relatively little 4–7 Hz activity within the STN spike trains. Note that the scalogram of the EEG recording is scaled to a maximum 5 times that of the spike train scalograms. *D*: shuffle-corrected cross-correlations between each STN spike train and EEG theta indicate phase relationships near  $0^\circ$ . Maximal peak-to-trough differences closest to the origin were 6.1 times the SD of the bin values for STN neuron 1 and 5.4 SD for STN neuron 2. A peak-to-trough difference  $>2.5$  times the SD was considered significant.

al. 1998), EEG activity patterns in sleep (cyclic alternating pattern) (Terzano et al. 2000), and coherence in cortical fMRI signals (Biswal et al. 1995). The observed variability of phase relationships in the slow oscillations in EEG theta power and GP/STN firing rates noted in the present study and the absence of direct anatomical connections between the globus pallidus and the hippocampus suggest that mechanisms underlying the correlated oscillations in basal ganglia/hippocampal activity involve a complex pattern of connectivity. Buzsáki and co-workers (Penttonen et al. 1999) have demonstrated multisecond (ultra slow) periodicities in hippocampal excitability in the

range of 0.025 Hz, evident in recordings from behaving, drug-free Sprague-Dawley rats, and point out that the network properties of the hippocampus may be capable of generating slow oscillations in excitability. It remains to be determined, however, whether the multisecond oscillations in basal ganglia activity observed in the present study and in previous investigations (Allers et al. 2000; Ruskin et al. 1999, 2001a,b) are driven by the hippocampus, generated in the basal ganglia themselves, or shaped by a common input.

Hippocampal theta activity has been linked to neuronal plasticity and long-term potentiation, as well as movement,



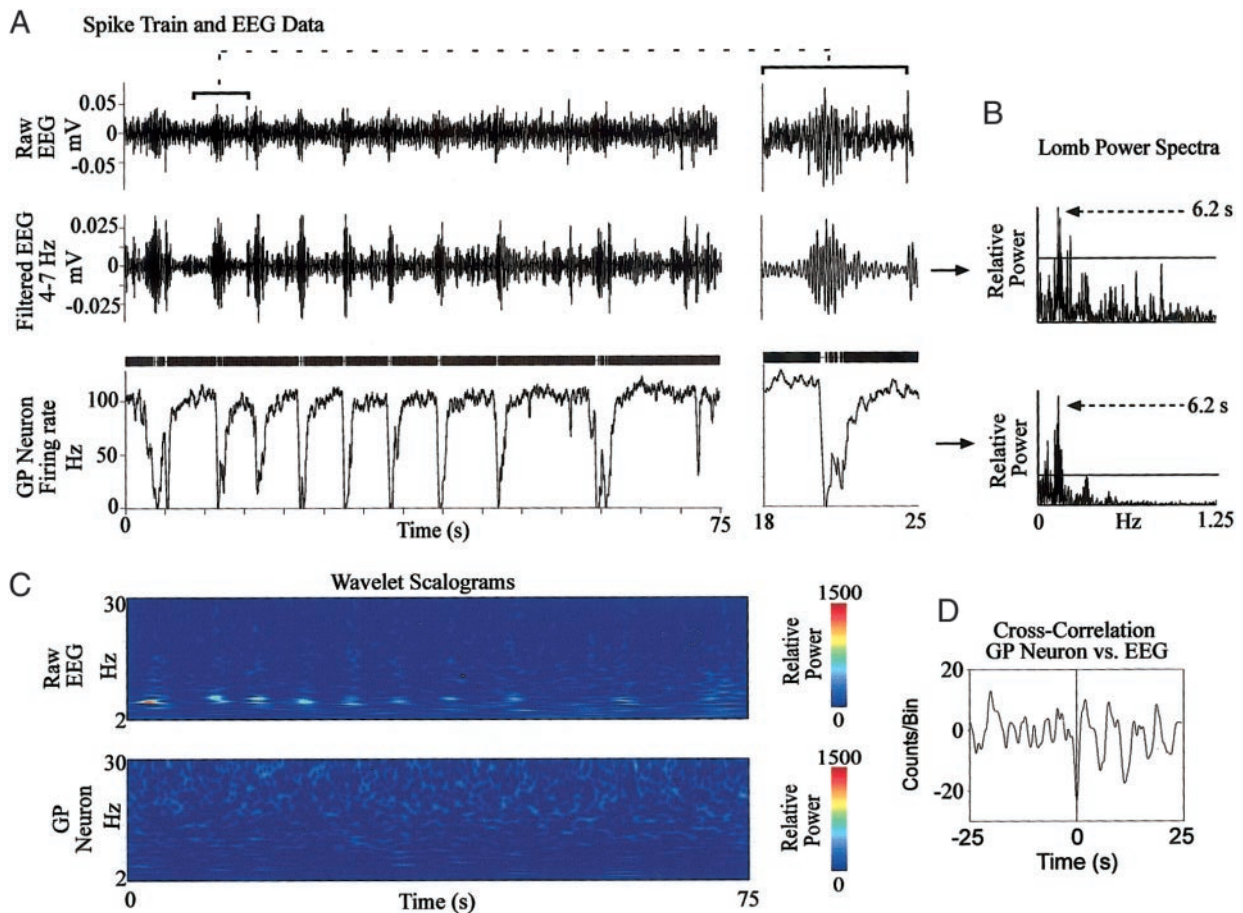


FIG. 2. Correlated oscillations in a globus pallidus (GP) spike train and transcortical EEG. *A*: this GP spike train, displayed as a raster and mean frequency plot (200 ms bins), has periodic decreases in firing rate that coincide with the appearance of short bursts of the theta rhythm in the transcortical EEG. *B*: Lomb power spectra indicate that the periods of GP neuronal firing rate oscillations and recurrent bursts of theta activity in the EEG are identical. *C*: wavelet scalograms demonstrate that within the EEG recording, the 4–7 Hz activity has the greatest spectral power in the 2–30 Hz range shown and that there is very little 4–7 Hz activity within the GP spike train. The scalograms of the EEG and spike train are scaled to the same maximum. *D*: the shuffle-corrected cross-correlation between the GP spike train and the EEG theta indicates a phase relationship near 180°. The peak-to-trough difference closest to the origin was 5.3 SD.

orientation, and response to novel stimuli. A role for the basal ganglia in attention and learning, as well as movement and response to novel stimuli, has also long been suggested. Additionally, these functions are known to involve dopamine, a

robust modulator of slow oscillations in the basal ganglia (Allers et al. 2000; Ruskin et al. 1999, 2001a,b). The present study may provide insight into mechanisms underlying the overlap in functional roles of these brain regions by demon-

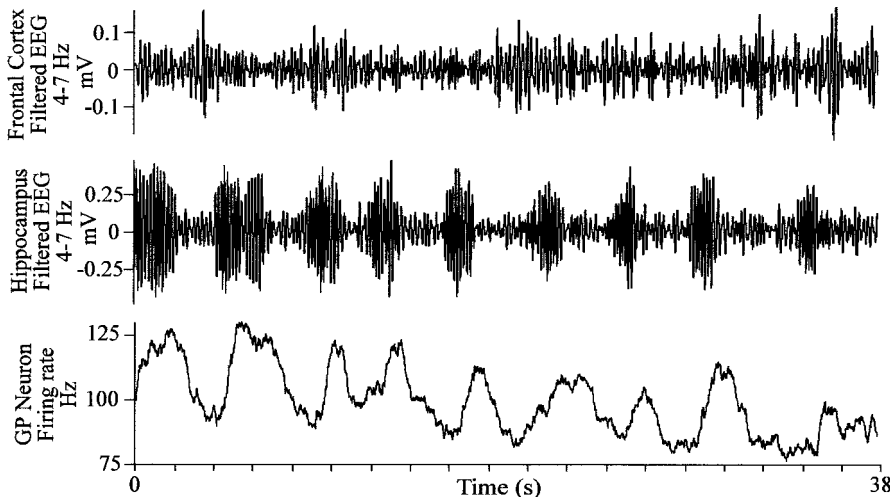


FIG. 3. Relationship between GP firing rate and hippocampal and cortical theta activity. *Top* and *middle* traces are digitally filtered (4–7 Hz) depth recordings from frontal cortex and hippocampus. *Bottom* trace is a mean frequency plot of a GP spike train. Note the multisecond periodicity of bursts of hippocampal theta rhythm power that correlate with a similar periodicity in firing of the GP neuron. Theta power in frontal cortex is variable, without apparent correlation to GP neuronal spiking rate.

strating a relationship between basal ganglia firing rates and hippocampal theta activity.

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