Spatially Distributed Local Fields in the Hippocampus Encode Rat Position

Gautam Agarwal,1 Ian H. Stevenson,2+ Antal Berényi,2+ Kenji Mizuseki,2+ György Buzsáki,2++ Friedrich T. Sommer2++

Although neuronal spikes can be readily detected from extracellular recordings, synaptic and subthreshold activity remains undifferentiated within the local field potential (LFP). In the hippocampus, neurons discharge selectively when the rat is at certain locations, while LFPs at single anatomical sites exhibit no such place-tuning. Nonetheless, because the representation of position is sparse and distributed, we hypothesized that spatial information can be recovered from multiple-site LFP recordings. Using high-density sampling of LFP and computational methods, we show that the spatiotemporal structure of the theta rhythm can encode position as robustly as neuronal spiking populations. Because our approach exploits the rhythmicity and sparse structure of neural activity, features found in many brain regions, it is useful as a general tool for discovering distributed LFP codes.

Two qualitatively different types of electric signals can be detected extracellularly, action potentials (spikes) and local field potentials (LFPs) (1–5), and these signals are regarded as complementary readouts of information about neuronal computation (5, 6). As a rat moves through its environment, hippocampal pyramidal cells spike at specific locations (place cells) (7). In contrast, the LFP maintains rhythmic (8 to 9 Hz) theta oscillations, independent of the rat’s position (8, 9). We hypothesized that the theta rhythm also contains information about the rat’s position, since it is
Rats were implanted with 32-, 64-, or 256-site silicon probes in the hippocampus to monitor both LFP and unit firing (Fig. 1A) while they traversed a linear track (Fig. 1B), open field, or a T maze (11). When mapped onto electrode space, the theta rhythm showed spatiotemporal variations (Fig. 1A) that changed gradually over multiple cycles (movie S1). By analogy to radio communication, we defined the theta oscillation to be a carrier wave whose modulation contains information. This information was extracted from the theta rhythm using a demodulation operation (fig. S1).

First, the theta-band-filtered oscillatory activity of each electrode was converted to a complex-valued signal, representing its instantaneous phase and amplitude (Fig. 1D). The carrier signal, identified by principal component analysis, was highly coherent across electrodes (Fig. 1D, lower trace). The demodulation operation then removed the phase of the theta carrier from each electrode, resulting in a spatiotemporal pattern of relative phase and amplitude that covaried smoothly (Fig. 1, E and F) with the rat’s position.

The position of the rat during navigation was estimated from the demodulated LFP (Fig. 2 and fig. S2) and compared to spike-based decoding (1, 7, 12, 13). Although the cross-validated accuracy of the two decoders was comparable [optimal linear estimator (OLE) median error 6.7 ± 0.2 cm (LFP) and 9.2 ± 0.2 cm (spiking)] (Fig. 2G and fig. S2), they had distinct velocity and position dependence (Fig. 2, B and D). Accurate decoding of the theta rhythm depended on demodulation, as well as preserving the high dimensionality of the signal, even though the variance of the multielectrode signal was largely concentrated in a low-dimensional subspace (Fig. 2C), visible in the strong correlations in the LFP recorded at different electrodes (Fig. 1, C and D). Whitening and Bayesian decoding methods further improved accuracy, especially in the open field (120 by 120 or 180 by 180 cm²) (Fig. 2G).

Because position encoding is sparse, a theoretical result (14) based on compressed sensing (15) suggests that unsupervised learning can discover position-dependent sparse structure in the LFP without explicit knowledge of the rat’s position. We tested this prediction by examining the evolving spatiotemporal distribution of the theta-filtered LFP using independent component analysis (ICA) (16, 17). A subset of the components (termed feature-tuned field potentials [FFPs]) showed selective activation at specific positions along one direction of motion (Fig. 3A and figs. S3 and S4) and comprised the major portion of the signal variance (53%, 69%, and 79% of total variance for n = 3 rats). When FFPs were projected back onto the anatomical space, they were distributed across the entire surface of the electrode array (Fig. 3B and movie S2).

We next asked whether the sparse structure of the broadband LFP (4 to 80 Hz) is also position dependent by training a convolutional sparse coding algorithm (18), which models signals as...
a sparse superposition of spatiotemporal features. Despite differences in the analysis method and training data, the broadband components activated at single positions were spaced along the whole track, similar to the theta-band components (Fig. 3D and fig. S5). Each broadband feature exhibited the sawtooth waveform characteristic of hippocampal theta, with unique spatial variations in attributes such as onset and peak time (Fig. 3C). Broadband features, similar to theta-band FFPs, remained largely silent outside a small range of preferred positions, each activating briefly at theta frequency (Fig. 3D).

The entire population of FFPs in a given session uniformly tiled the linear track (Fig. 4A). The phase of each demodulated FFP showed progressive advancement as the rat traversed the corresponding place field (Fig. 4A), reminiscent of the theta-phase precession of place cell spikes (19), and suggesting that the theta-rhythm arises largely from a population of phase-precessing neurons (10). The distribution of the place fields of pyramidal cells was more irregular than that of the FFPs (Fig. 4B and fig. S6), consistent with the performance of the corresponding decoders (Fig. 2). Unlike FFPs, pyramidal cells had multiple place fields in one or both directions of travel, leading to distinct pairwise activity profiles of the populations (Fig. 4C and fig. S6). We also examined FFPs as the rat performed a spatial alternation memory task (20) in a T maze with a 10-s delay period in a large waiting area (Fig. 4D). Recordings from two 256-electrode arrays (11) contained ~50 FFPs that together covered the entire maze (Fig. 4D). About half of all FFPs densely tiled the two-dimensional (2D) waiting area (Fig. 4D). Most 2D place fields occupied largely similar positions independent of whether the rat came from a leftward or rightward journey (fig. S7). Accurate LFP decoding and identification of FFPs could also be performed on recording sites within the dendritic layers (fig. S8), excluding somatic layers where spikes were detected.

To understand how properties of FFPs relate to the activity of the underlying neuronal population, a simulation was constructed in which the LFP was modeled as the superimposed activity generated by numerous place-modulated synaptic inputs (fig. S9). Although individual electrodes showed weak place-tuning, their collective activity could nonetheless be decoded. Furthermore, ICA identified a large number of learned FFPs tuned to very specific locations of the track, consistent with theory (fig. S10) (14). However, as the trial-by-trial variability of neuronal activity was increased, ICA identified a decreasing number of FFPs. For noisy populations, FFP width increased in proportion to, but never exceeded, the tuning width of the underlying population’s place fields.

We demonstrated that the rat’s location is encoded by spatial variations of the hippocampal LFP. An often-assumed limitation of the LFP is that each electrode subsamples (pools) the activity of a large population of neurons. In topographically

---

**Fig. 2. Decoding of position by demodulated LFP and spikes.** (A) Decoding of rat position on a linear track by LFP and spikes. Lines indicate actual trajectory, while dots indicate OLE estimate of position (y axis) at each time point (x axis). (B) LFP-based decoder performs best at high velocities, unlike spike-based decoder. The lower histogram shows the time spent at different speeds. (C) Variance is largely explained by PC1 (~85% of total variance, falling outside of plotted range), and accurate, cross-validated decoding depends on a large number of PC dimensions. (D) Histogram of decoder predictions; dark squares indicate high-probability events. Decoders trained on subsets of LFP channels (right) degrade uniformly, whereas those trained on spikes from subsets of neurons (left) degrade in a patchy manner. (E) Decoding of rat position in a 2D open field using a Bayesian filter-based decoder. Lines indicate actual trajectory in x and y coordinates; dots indicate decoder estimates. (F) Bird’s eye view of actual (black) and estimated (color) position at different time points. Ellipses indicate ±1 SD confidence regions. (G) Median error of decoders as a function of the number of (random) channels used. Data is from rat ec014, with 64 electrodes straddling the cornu ammonis 1 (CA1) pyramidal layer. Identical color codes are used for (A), (B), (E), and (G).
Fig. 3. Sparse decompositions of oscillatory features in multielectrode data. (A) ICA of the signal reveals components, termed FFPs, that activate selectively at particular locations. (B) Each FFP exhibits a unique phase-amplitude relationship across the recorded area. For display purposes, FFPs are mean-subtracted to reveal differences (see supplementary materials). (C) Sparse decomposition of the broadband signal (4 to 80 Hz) reveals components that activate at corresponding locations and have distinctive broadband structure, consisting of diverse onsets and peaks. Individual traces are colored according to their corresponding electrodes in (B). (D) Broadband sparse components activate sequentially on the track, also exhibiting theta periodicity; components that activate in the reverse direction (black lines) remain silent. (Inset) Mean power spectrum of component activations. Data was recorded by a 64-electrode array implanted in CA1.

Fig. 4. Population properties of FFPs and neuronal spikes during a single session. (A) FFPs uniformly tile the length of the track. The spatial extent and spacing of different FFPs is largely homogeneous across the track (middle). FFPs exhibit phase precession with respect to PC1 (bottom). (B) Pyramidal cells have place fields that are more variable in extent and distribution. (C) The overlap of FFP activations is largely restricted to neighbors, unlike that for pyramidal cells [grayscale range of P(Overlap) = 0 to 0.1]. (D) Activation of FFPs in a T maze. Waiting area is enclosed in a red box. Right panels show close-up of activations in waiting area, separated by direction of entry. Asterisks mark activations that are entry-direction selective. Each point represents a time bin where FFP activation exceeds a threshold, its size indicating the magnitude of activation. In (A) and (B), place-field hues are assigned based on location of maximal activation; in (D), hues are assigned to distinguish neighbors. Data for (A), (B), and (C) are collected by a 64-electrode array; (D) was from 2- by 256-electrode arrays.
organized brain regions, this limitation is less hampering, because the electrode conveys the activity of similarly tuned neurons (21, 22). In contrast, because cell positions in the hippocampus are distributed without topographic ordering (23), the LFP measured at any single location exhibits only weak place-modulation (fig. S9). However, compressed sensing methods can recover sparse signals even from mixed and subsampled measurements (15). During movement, population activity in the hippocampus is largely determined by a single (i.e., highly sparse) cause: the rat’s current position. Therefore, distributed messages can be discovered by unsupervised learning methods such as ICA (14). Our experimental and simulation results show that the ICA-derived FFPs exhibit several properties reminiscent of place cells: They have smooth, localized place fields, exhibit phase precession, and show considerable trial-by-trial variability (24). Building on earlier work (e.g., (25)), these findings show how large-scale recordings of LFP can help in understanding the organization of activity in other brain regions, as well as developing robust decoders for brain-computer interfaces.

References and Notes
18. A. Khosrowshahi et al., Exploring the Statistical Structure of Large-Scale Neuronal Recordings Using a Sparse Coding Model (Canyon, Salt Lake City, UT, 2010).
26. K. Mizuseki, A. Sirota, E. Pastalkova, K. Diba, G. Buzsáki, Multiple single unit recordings from different rat hippocampal and entorhinal regions while the animals were performing multiple behavioral tasks (2013); available at http://crcns.org/data-sets/hc-3.

Acknowledgments: This work was supported by NIH National Research Service Award fellowship no. 1F32MH093048 (G.A.); NSF CIF-D-018 no. 0937060 (I.H.S.); Marie Curie FP7-PEOPLE-2009-IDF grant no. 254780, EU-ERP-ENC2013-Starting grant no. 337075, and the Lendräl program of the Hungarian Academy of Sciences (A.B.); Japan Society for the Promotion of Science’s Research Fellowship for Research Abroad (K.M.); NIH nos. NS-034949, MH-54671, and NS074015, NSF SBE no. 0542013, and the J. D. McDonnell Foundation (G.B.); NSF nos. 0855272 and 1219212 (F.S.). We thank D. Kaufman and J. Wolfe for advice on movies; C. Thanaporn for suggesting the Kuramoto model for rendering; K. D. Harris for suggestions about modeling; A. Khosrowshahi, J. Guelppe, C. Cadien, and B. Olhausen for convolutional sparse coding; Walter Freeman for feedback; and members of the Buzsáki laboratory and the Redwood Center for discussions. All data collected from 32- to 64-electrode arrays is available in the nc-3 data set at crcns.org (W2).

Supplementary Materials
www.sciencemag.org/content/344/6184/626/suppl/DC1 Materials and Methods
Figs. S1 to S10
Movies S1 and S2
References (G7, 28)
6 January 2014; accepted 14 April 2014
10.1126/science.1250444

Vascular and Neurogenic Rejuvenation of the Aging Mouse Brain by Young Systemic Factors

Lida Katsimpardi,1,2* Nadia K. Litterman,1,2 Pamela A. Schein,1,2 Christine M. Miller,1,2,3 Francesco S. Loffredo,1,2,4 Gregory R. Wojtkewicz,5 John W. Chen,5 Richard T. Lee,1,2,4 Amy J. Wagers,1,2,3 Lee L. Rubin1,2,*

In the adult central nervous system, the vasculature of the neurogenic niche regulates neural stem cell behavior by providing circulating and secreted factors. Age-related decline of neurogenesis and cognitive function is associated with reduced blood flow and decreased numbers of neural stem cells. Therefore, restoring the functionality of the niche should counteract some of the negative effects of aging. We show that factors found in young blood induce vascular remodeling, culminating in increased neurogenesis and improved olfactory discrimination in aging mice. Further, we find that GDF11 alone can improve the cerebral vasculature and enhance neurogenesis. The identification of factors that slow the age-dependent deterioration of the neurogenic niche in mice may constitute the basis for new methods of treating age-related neurodegenerative and neurovascular diseases.

In the adult brain, neural stem cells reside in a three-dimensional (3D) heterogeneous niche, where they are in direct contact with blood vessels and the cerebrospinal fluid. The vasculature can influence neural stem cell proliferation and differentiation by providing a local source of signaling molecules secreted from endothelial cells (1) as well as by delivering systemic regulatory factors (2). The hormone prolactin (3), dietary restriction (4), and an exercise/enriched environment (5) positively modulate neurogenesis, whereas increased levels of glycolcorticoids associated with stress have the opposite effect (6). In the aging niche, the vasculature deteriorates with a consequent reduction in blood flow (7), and the neurogenic potential of neural stem cells declines, leading to reduced neuroplasticity and cognition (8–10). Systemic factors can also affect these aging-associated events, either positively in which circulating monocytes enhance remyelination in aged mice (11, 12) or negatively in which the accumulation of chemokines in old blood can reduce neurogenesis and cognition in young mice (10).

To test whether the age-related decline of the neurogenic niche can be restored by extrinsic young signals, we used a mouse heterochronic parabiosis model. Our experiments reveal a remodeling of the aged cerebral vasculature in response to young systemic factors, producing noticeably greater blood flow, as well as activation of subventricular zone (SVZ) neural stem cell proliferation and enhanced olfactory neurogenesis, leading to an improvement in olfactory function. Furthermore, we tested GDF11, a circulating transforming growth factor-β (TGF-β) family member that reverses cardiac hypertrophy in aged mice (13), and found that it can also stimulate vascular remodeling and increase neurogenesis in aging mice. Thus, we have observed that age-dependent remodeling of this niche is reversible by means of systemic intervention.

1Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA 02138, USA. 2Harvard Stem Cell Institute, Cambridge, MA 02138, USA. 3Howard Hughes Medical Institute, Joslin Diabetes Center and the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging, Harvard Medical School, Boston, MA 02115, USA. 4Cardiovascular Division, Department of Medicine, Brigham and Women’s Hospital, Boston, MA 02115, USA. 5Center for Systems Biology and Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02115, USA.

*Corresponding author. E-mail: lee_rubin@harvard.edu (L.L.R.); lida_katsimpardi@harvard.edu (L.K.).

Downloaded from http://science.sciencemag.org/ on December 13, 2016
Spatially Distributed Local Fields in the Hippocampus Encode Rat Position
Science 344 (6184), 626-630. [doi: 10.1126/science.1250444]

Editor's Summary

Extracting Spatial Information
The location of a rat can be deciphered from hippocampal activity by detecting the firing of individual place-selective neurons. In contrast, the local field potential (LFP), which arises from the coherent voltage fluctuations of large hippocampal cell populations, has been hard to decode. Agarwal et al. (p. 626) worked out how to recover positional information exclusively from multiple-site LFP measurements in the rat hippocampus. The information was as precise as that derived from spiking place cells. The approach might also be applicable more generally for deciphering information from coherent population activity anywhere in the brain.