SPACE IN THE BRAIN
HIPPOCAMPAL SIGNALS UNDERLYING NAVIGATION

PLACE CELLS
Wilson & McNaughton (1993)

HIPPOCAMPUS

THETA OSCILLATION (~8 Hz)
K. Diba

DIFFERENCES FROM ANIMALS?
ROLE IN EPISODIC MEMORY?
Figure 4. Micro-electrode splay in vivo and ex vivo. (A) Post-operative axial MRI of depth electrodes shown in figure 2. (B) Cartoon example of optimal and sub-optimal micro-electrode splay patterns and staggered micro-wire lengths. (C), (D) Thin sliced post-operative CTs of the posterior (C) and the anterior (D) depth electrodes. (E), (F) Benchtop tests of micro-wire splay patterns using pre-implantation induction of micro-electrode splay (E) and simply implanting the naïve micro-electrode (F).

Recording sessions within these 11 patients, 125 single units and 39 multi-units were successfully identified. An example of unit activity recorded from the patient presented in figures 2 and 4 is provided in figure 5. For the 11 patients presented, four had two depth electrodes, three had three depth electrodes and four had four depth electrodes. Single neurons were recorded as far as 2 weeks post-implantation but on average recordings persisted for 7 ± 3 days with 50% of recording limits by the clinical decision to proceed with resection. On average, each BFD–IWB (8 micro-wires) recorded a maximum of 2.1 ± 0.9 single neurons. Before failure modes were identified and workaround protocols were developed, the average single neuron yield per depth electrode was 1.4 ± 0.5 (n = 3) single neurons per depth. After recordings were optimized to avoid the identified failure modes, the yield nearly doubled to 2.7 ± 0.8 (n = 3) single neurons per depth electrode. All patients had at least one multi/single unit during the last recording prior to deplantation.

Direct brain stimulation (Jacobs et al., Neuron, 2016).


Traveling waves (Zhang et al., Neuron, 2018).

Direct brain stimulation (Jacobs et al., Neuron, 2016).
Electrocorticography (ECoG)

- Each electrode records ~400,000 neurons.
- A higher-resolution version of EEG.

Microelectrodes

- Record individual action potentials.
TESTING ENVIRONMENT
Patients learn locations of four visible objects.

Navigate between the locations with the objects hidden.

JACOBS ET AL., 2013, NATURE NEUROSCIENCE
Significant grid cells identified by computing spatial autocorrelation of firing rate map, computing 6-way symmetry ("gridness") score, and performing a shuffling procedure.
REGIONAL DISTRIBUTION OF GRID CELLS

<table>
<thead>
<tr>
<th>Region</th>
<th>% grid cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC</td>
<td>12</td>
</tr>
<tr>
<td>H</td>
<td>8</td>
</tr>
<tr>
<td>PHG</td>
<td>4</td>
</tr>
<tr>
<td>A</td>
<td>2</td>
</tr>
<tr>
<td>CC</td>
<td>12</td>
</tr>
<tr>
<td>Cx</td>
<td>6</td>
</tr>
</tbody>
</table>

REGION KEY:
EC, ENTORHINAL CORTEX;
PHG, PARAHIPPOCAMPAL GYRUS;
CC, CINGULATE CORTEX.
LINEAR-TRACK ‘GRID’ CELLS

A. Two dimensional firing rate map for epochs of clockwise movement.
B. Linearized firing rate map for epochs of clockwise movement.
C. Firing rate as a function of distance from the beginning of the side, plotted separately for each side of the environment.

Bottom Row:
A. Activity of a cell in patient 2’s entorhinal cortex during counter clockwise movement.
B. Activity of a cell in patient 5’s cingulate cortex during counter clockwise movement.
C. Activity of a cell in patient 2’s entorhinal cortex during clockwise movement.
D. Activity of a cell in patient 4’s cingulate cortex during clockwise movement.
E. Activity of a cell in patient 5’s entorhinal cortex during clockwise movement.
F. Activity of a cell in patient 12’s entorhinal cortex during counterclockwise movement.

Figure 2: Examples of path equivalent cells.

Figure 3: The percent of spatially responsive cells in each region that exhibit path equivalent firing.

Jonathan Miller
(Miller et al., Current Biology, 2015)
DIRECTION ENCODING: ENTORHINAL “PATH CELLS”

(Jacobs et al., 2010, PNAS)
“Train” cued-recall task

cue

hold

movement

fixation

feedback

encoding

retrieval

v.t.

4 s

v.t.

5 s

v.t.
“Train” task

Learn four objects

Retrieve a target object
Place cells in train

Green line indicates location of cued object
Object-trace cells

Green line indicates location of cued object
Characteristics of object-trace cells

- **% Responsive Cells**
  - Area: A, H, EC, C
    - A: Low, H: Low, EC: High, C: High
  - EC area has significantly more responsive cells compared to A and H

- **# of Fields**
  - Pos. Relative to Object (VR-bins)
    - Object
      - Significant increase in responsive cells around the object

Graphs illustrate the distribution and percentage of responsive cells in different areas and positions relative to the object.
Correlated firing between hold and retrieval

Memory Trace (a.u)

Hold Phase F.R. (z)

Correlation (R)

PDF

Hold Phase F.R. (z)

Control

*
NEXT-GENERATION TASK: TREASURE HUNT

“Gamified” high-speed location-object memory task.
Do you remember where to find the... **shield**?

- **YES!** win a lot / lose a lot
- **MAYBE** win some / lose some
- **NO...** win a little / lose a little

press (X) to select
Place-like cells in Treasure Hunt

**Navigation**

**Recall**

Melina Tsitsiklis
Goal-position cells

Left EC

FR by goal position

FR by subject position

Right EC

FR by goal position

FR by subject position

Firing rate

Melina Tsitsiklis
Memory-related oscillations

Red coloring denotes increased power for successful memory encoding

Miller et al., 2018, *Nature Communications*
Memory- vs. navigation-related theta

- Recalled vs. Not Recalled
- Navigation vs. Baseline

Statistical significance:
- *: p < 0.05
- **: p < 0.01
Slow theta oscillations in verbal memory

Single hippocampal electrode

(Similar results at group level.)
“Train” task

Learn four objects

Retrieve a target object

Variable movement speeds across trials
Oscillations along the hippocampus

Goyal et al., in prep
Single- and dual-theta networks
Fast theta correlates with speed

A

Subject 6, right hippocampus: $r = 0.35$, $p = 0.02$

% electrodes with significant speed/frequency correlation

% along A-P axis
THE HUMAN NAVIGATIONAL SYSTEM

SIMILARITIES TO RODENTS

Hippocampus encodes specific locations.

Entorhinal cortex supports coarser representations.

~8-Hz theta oscillations in navigation.

DISTINCTIVE FEATURES

Grid cells in cingulate.

~3-Hz theta oscillations in anterior hippocampus support memory.

Remapping from memory demands.

Flexible targeting of remote locations.
THETA TRAVELING WAVES

Different “time zones” throughout the hippocampus.

Alpha and theta oscillations in neocortex?

Work with my post-doc Honghui Zhang.

Lubenov & Siapas, 2009
HUMAN TRAVELING THETA WAVE

ZHANG & JACOBS, J. NEUROSCI., 2015
THETA PHASE SHIFT ACROSS THE HIPPOCAMPUS

Referenced Phase (degree) vs. Y Coordinates (mm)

POSTERIOR

ANTErior
**Method:**
Identify contiguous electrode clusters with narrowband oscillations within 2 Hz.

Assess significance with Moran’s I, a test for spatial autocorrelation (p<0.001).
NEOCORTICAL 8-HZ TRAVELING WAVE
CIRCULAR STATISTICS FOR IDENTIFYING TRAVELING WAVES

• **Problem:** Oscillatory phase is circular (i.e., $0=2\pi$).

• **Solution:** We built a framework based on circular statistics (Fisher, 1995).
1. Find clusters of electrodes with oscillations at the same frequency.

2. Identify single-trial phase gradients.

3. Measure directional consistency across trials.
EXAMPLE TRAVELING WAVES

8.8 Hz

5.9 Hz
FREQUENCY DISTRIBUTION OF TRAVELING WAVES

Temporal Frequency (Hz)

Frontal  Temporal  Occipital-parietal

Propagation direction
TRAVELING WAVES AND TASK PERFORMANCE

$F(2, 137) = 4.46, p = 0.013$

Median split based on reaction time.
Models of traveling waves (Ermentrout and Kleinfeld, 2001)

Figure 6: Models of traveling theta waves. A. Illustration of a single-oscillator model of theta traveling waves. According to this theory there is a single theta oscillator in the medial septum, which has projections along the length of the hippocampus. Each projection’s synaptic delay ($\Delta D$) is proportional to its length $x$, which produces the appearance of a traveling theta wave.

B. Coupled oscillator model of theta propagation. According to this model there are a series of weakly coupled theta oscillators along the length of the hippocampus. Each oscillator has a particular connection weight and an intrinsic frequency. This model predicts that traveling waves appear in the hippocampus when an oscillation begins in the medial septum and gradually propagates through the hippocampus via a series of coupled oscillators. Figures from Panels A & B were obtained and modified with permission from Ermentrout and Kleinfeld (2001).

C. Spatial propagation of a traveling theta wave at 8 Hz following a single oscillator model. Plot indicates theta phase as a color, plotted as a function of position along hippocampus and time.

D. Spatial propagation of a traveling theta wave at 8 Hz following the coupled oscillator model.

E. Spatial propagation of a 2-Hz traveling theta wave following the single-oscillator model. Here the speed of propagation (slope of colored lines) is the same as Panel C, demonstrating that speed is not frequency dependent.

F. Spatial propagation of a 2-Hz traveling theta wave following the coupled oscillator model. Slope changes compared to Panel D demonstrates a change in the speed of theta’s propagation.
Coupled oscillator model of traveling waves (Ermentrout and Kleinfeld, 2001)

- Distinguishing features:
  - Propagation from fast to slow oscillators.
  - Propagation speed correlates with frequency.
TRAVELING WAVE PROPAGATION SPEED

A
\[ \Delta t = 28 \text{ ms}, \Delta d = 32 \text{ mm} , \text{ speed} = 1.14 \text{ m/s} \]

B
\[ \Delta t = 44 \text{ ms}, \Delta d = 33 \text{ mm}, \text{ speed} = 0.75 \text{ m/s} \]

\text{Propagation speed (m/s)}

\text{Frequency (Hz)}

\[ r = 0.53, p < 0.001 \]
Next steps: Multiple traveling waves in different directions?
Conclusions

- Commonly observed theta and alpha oscillations are really traveling waves.
  - 47% of all electrodes.
  - Bands of spiking activity moving across the brain?
- Propagation of information across the cortex?
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Memory Enhancement and Deep-Brain Stimulation of the Entorhinal Area

Nanthia Suthana, Ph.D., Zulfi Haneef, M.D., John Stern, M.D., Roy Mukamel, Ph.D., Eric Behnke, B.S., Barbara Knowlton, Ph.D., and Itzhak Fried, M.D., Ph.D.

Claim: Entorhinal Stimulation Improves Spatial Memory By 64% (Suthana et al., 2012).
The Restoring Active Memory (RAM) Project

• A multi-center approach to study the neuro-physiological and behavioral effects of brain stimulation.

• Eight clinical centers around the U.S. use our standardized memory testing and stimulation platform.
Memory tasks optimized for stimulation

- **Spatial task**: Virtual-reality, high-speed version of Morris's (1984) water maze.
- **Verbal task**: Delayed free recall with 12-item lists of words.
- **Stimulation**: 50-Hz stimulation throughout encoding of some items.
- **Targets**: Hippocampus and entorhinal cortex.
- Stimulation monitored by neurologists in case of afterdischarges.
You are now beginning trial 42 of 48. The new object is a trashcan.

Press the button to be driven to the trashcan.
Spatial memory performance

Good memory, Memory score ~1

Poor memory, Memory score <1
Distinctive task features

- 48 observations per session (6x more).
- 49 patients.
- Identical behavior between stim and non-stim.
- Hidden target location:
  - More-sensitive error measure.
  - Eliminates visual strategies.
Entorhinal stimulation and memory

** denotes p<0.01, rank-sum test

MS=1, perfect performance. MS=.5, chance.
Spatial memory impairment from stimulation

Subject 44
entorhinal stimulation

Subject 5
entorhinal stimulation

Subject 6
entorhinal stimulation

Subject 26
entorhinal stimulation
Verbal memory task

- Delayed free recall task, with ‘stim’ (80%) and ‘non-stim’ lists.
- Stim lists have stimulation applied on half of the items.
Stimulation also impairs verbal memory

Subject 48
entorhinal stimulation

Subject 38
hippocampal stimulation

Subject 11
hippocampal stimulation

Subject 14
hippocampal stimulation
Conclusions

• 50-Hz stimulation in hippocampus and entorhinal cortex impairs memory!

• Left and right hemispheres.

• Stronger impairment for weaker memory items.

• MTL involvement in spatial and verbal memory.

• Refinements necessary for stimulation to improve memory.
Macroscopic measure of human grid cells

Evidence for grid cells in a human memory network

Christian F. Doeller1,2, Caswell Barry3,4 & Neil Burgess1,2

Potential mechanism:
Alignment of grid-by-direction cells to grid axes
Hexadirectionally modulated EC oscillations (Maidenbaum et al., in press)

Population analysis

Frequency

Hexadirectional Modulation (mean subject z)

Low Theta  High Theta  Beta  Low Gamma

Frequency band

Symmetry

Hexadirectional modulation (mean subject z)

Region

Hexadirectional modulation (mean subject z)

CA1  DG  EC  Frontal  Occipital

Anatomical region

* p<0.05

Frequency

% increase of high theta power

Electrode Count

-10  0  10  20  30  40  50  60  70  80

0  4  8  12
Example electrodes

A

B
Hexadirectional theta modulation correlates with spatial memory accuracy