# Making space for memory: A fused function of the medial temporal lobe in mapping environments and events

Nicco Reggente | C-Examination | UCLA – Psychology Department | May 12, 2016

# Outline

## I. Space is everything

I. Purposeful movement is the most important thing we do.

## II. Neural systems that support spatial information

I. Our most archaic, and advanced, neural systems are those which represent space and navigation in the MTL.

## III. Repurposing for encoding events

I. By surpassing the breadth of its initial utility, the MTL's spatial processing framework, in the spirit of evolutionary conservation, spawned a mnemonic system capable of encoding.

## IV. Enhancement

I. By understanding the architecture of our processing systems, we can transform incoming information in a way that optimizes processing power.

# Space is Everything

Without an “organizing principle”, nothing has the ability to turn into information.

Space, according to Kant (1787), is the most important, integral, and effective organizing principle.

We think with space.

# Movement

If an organism it to achieve its primary objective (i.e. permanence of existence), then it must **acquire** the resources to persevere and **avoid** environmental stimuli associated with its demise.

The rudimentary component to accomplish this objective is **movement**—the act of changing one's physical location within a larger spatial construct

*clabelina moluccensis* digests its cerebral ganglion once identifying a suitable undersea perch to spend the rest of its existence.

Linas, 2001; Wolpert,2011;Dennett, 1993

# Movement

Disregarding the notion that being such a simple organism wouldn't permit for such advanced cognitive functioning, **imagine yourself as a small bundle of cells**, incapable of seeing or feeling as you try to slither around your rock towards some delicious nutrient treats.

How do you find food and avoid danger without a representation of space?

Random foraging?

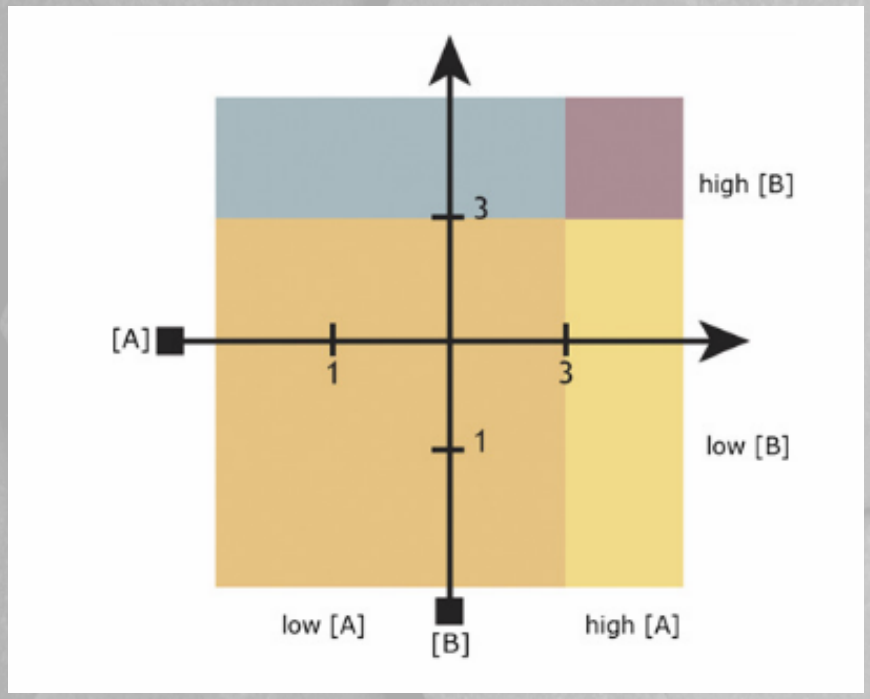
Prediction is the ultimate function of the mind.

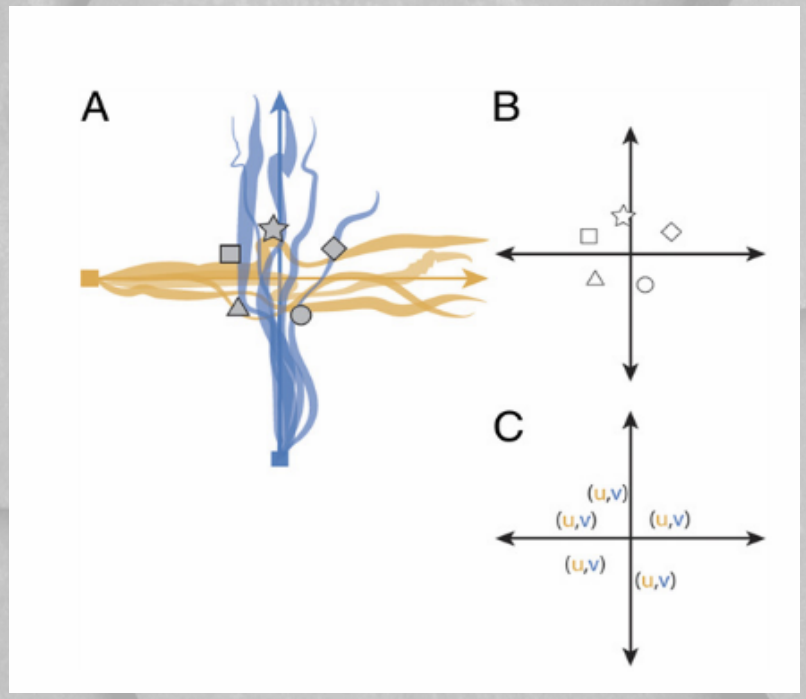
Llinas, 2002

# Chemotaxis

Chemical **gradients** afford sensing organisms with a **search-space** reduction.

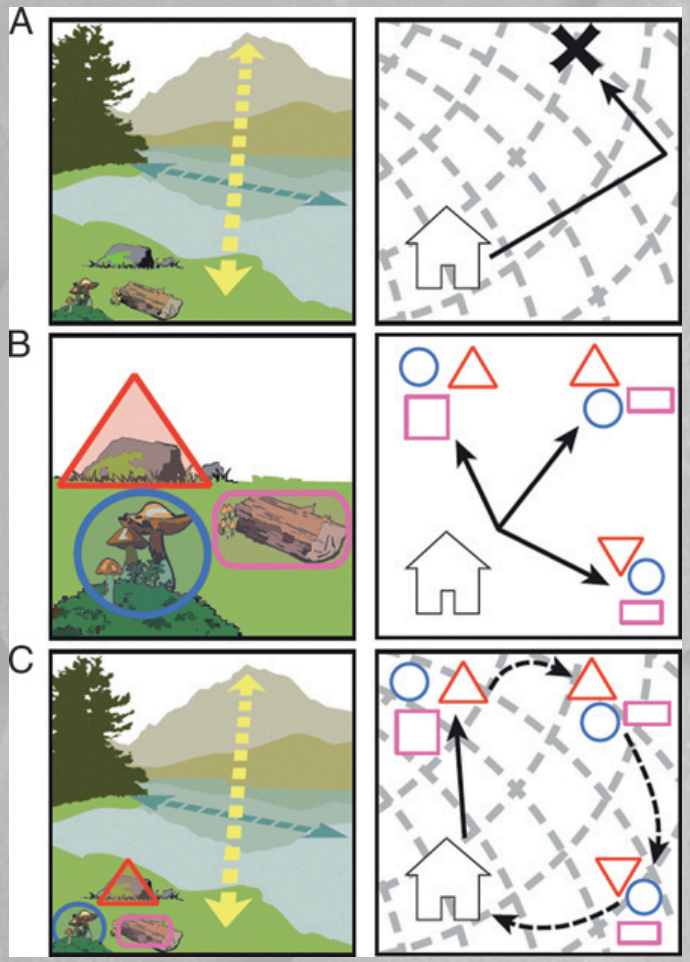
Geometric relationships and landmarks emerge to form an **odorant space.**




Wilson and Stevenson, 2006; Jacobs, 2003

# The affordance of advanced navigation strategies




**Parallel Map Theory**

By encoding the location of positional cues (i.e., Sketch Maps) on a bi-coordinate map (i.e., Bearing Maps), the navigator can compute **novel vectors between two known points**, that is, cognitively map.

Jacobs, 2003; Jacobs, 2013

# The evolution of a neural spatial processing system

All spatially tuned cells are found in phylogenetically old cortical areas.

Homethermy → explore → novel odorants → **evolved** olfactory system.

Brain size increased with olfactory size and home range.

By utilizing **additional environment information** (e.g. gradients of reflected photons), an organism would be able to increase their spatial resolution.

**However, these sources would need to be integrated in order for them to be informative**

Aboitz, 2015; Rowe and Shpher, 2015; Jacobs, 203; Moser, 2014; Keeton, 29174

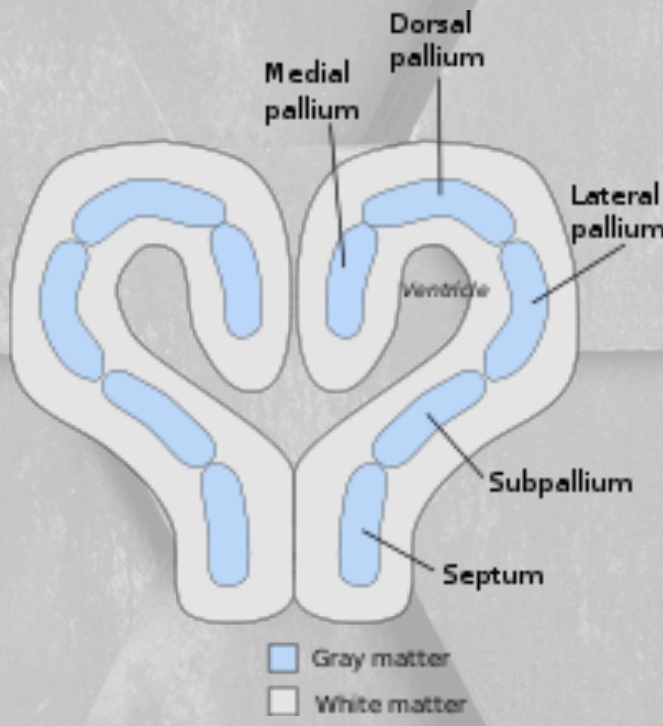
# Integrated spatial maps: introducing the hippocampus

The medial pallium, whose allocortex forms the **hippocampal formation, evolved alongside human navigation into novel terrain**.

After creating space itself, the next logical step would be to **associate** landmarks with outcomes.

The **binding** necessary for association could also be used to bind multiple senses.

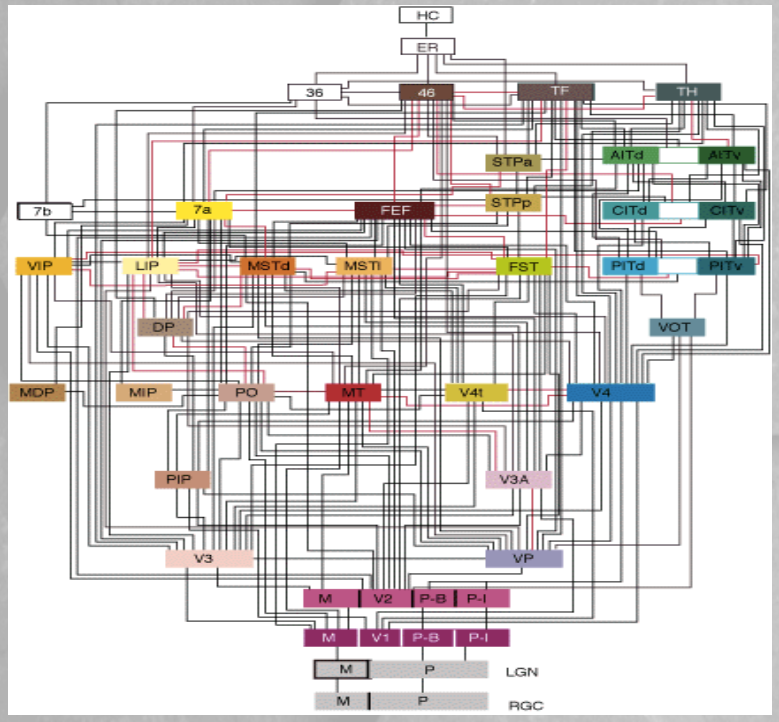
Orthogonal representations generated by the modular representation of space during mammalian evolution **laid the ground for storing independent representations.**




Eichenbaum, 1998; Zelenitsky, 2011; Jacobs, 2003; Netsky, 1981

# Integrated spatial maps: introducing the hippocampus

The hippocampus rests at the apex of all sensory processing in the brain, indicating its role in accommodating the multi-modal integration that enhanced early spatial processing.




Olfactory-hippocampal projections are conserved in all amniotes. The entorhinal cortex helped to funnel additional senses as they evolved.

Neurogenesis in this region could allow for unique neural populations that encode a unified percept.

Eichenbaum, 1998; Vanderwold, 2001; Felleman, 1991

# Part I Summary

**Movement** allows organisms to fulfill their ultimate objective: preserving their existence.

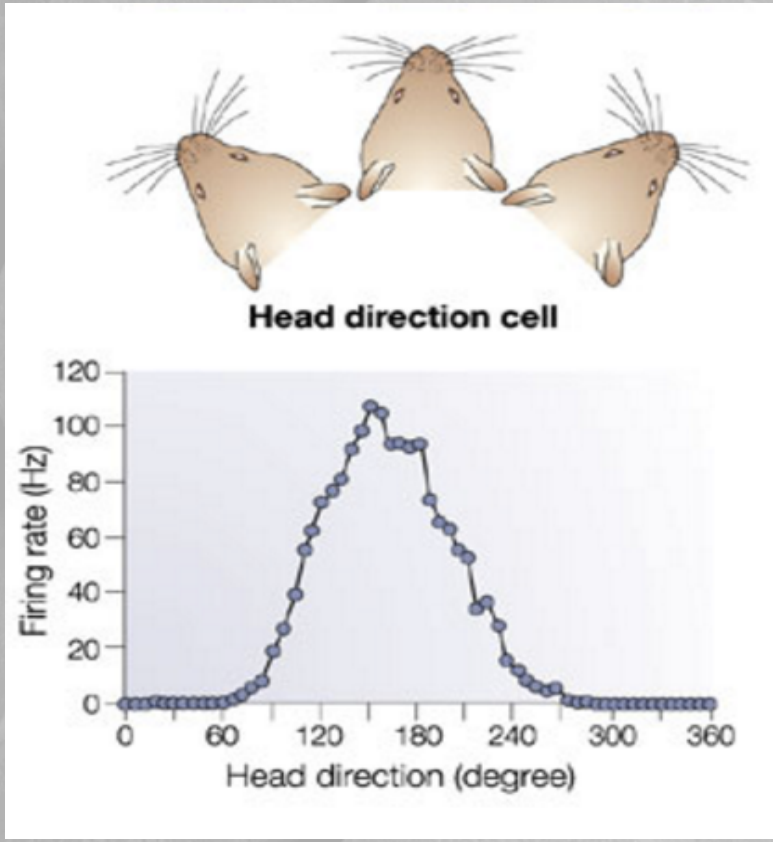
**Information** allows for organisms to make purposeful movements. Predicting the future efficiently yields a continuation of existence.

**Chemical gradients** afford an organism with that information and, thus, the ability to execute purposeful navigation and create a discretized representation of space.

The **hippocampus** seems to have evolved to integrate. It integrated olfactory information to form a cognitive map and then began to funnel in additional sensory information as it was made available. This construct allowed for the emergence of additional information (e.g. shortcuts).

# The building blocks of spatial processing

## Head Direction Cells




Compass Direction sensitive.

Thousands of them = 360° representation.

Tied to environmental landmarks, but retain their relative relationships.

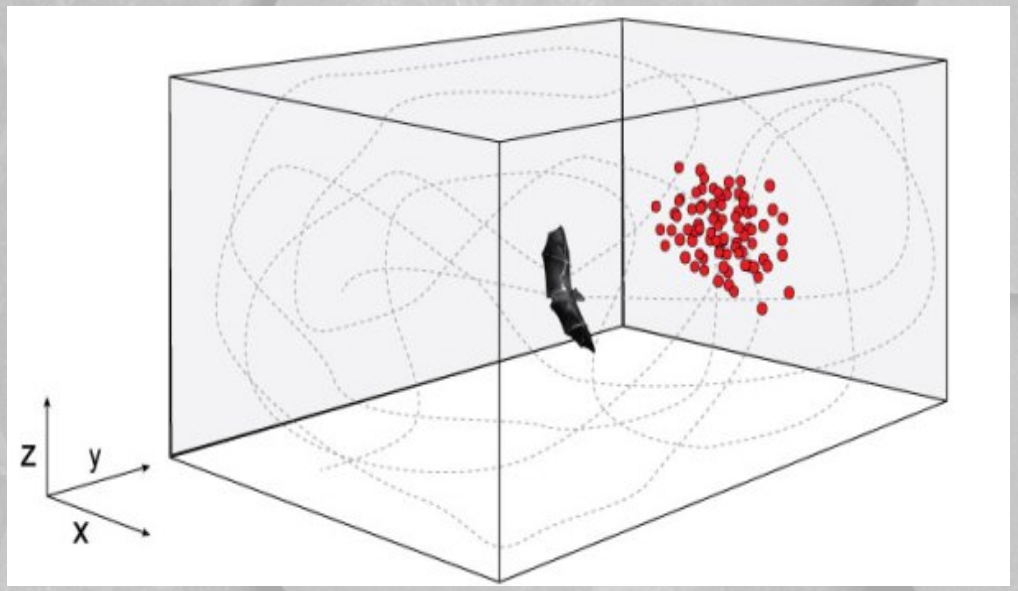
Triggered by inferred movement.

Found in Post Subiculum, Retrosplenial, Thalamus, LMN, DTN, Striatum, and Entorhinal cortex.

Taube, 1990; Sargolini, 2006; Taube, 2007

# The building blocks of spatial processing

## Place Cells




Originally seen in CA1, place cells fire when an animal is in a particular….**place.**

O'Keefe, 1971; Yartsev, 2013

# The building blocks of spatial processing

## Place Cells

A cell that constructs the notion of a place in an environment by integrating across several multisensory inputs and remains in the absence of even most of those inputs.

Some fire only when the animal is moving; Some fire only when the animal is sitting

Misplace cells fire when the animal doesn't find what it expected in a place.

Some fire to *meaning* or *reward*

Some have a place x goal interaction effect.

Even naïve observes can observe their robustness

O'Keefe, 1978; Best and Ranck, 1975; Burgess, 1996; Knierem, 2002

# The building blocks of spatial processing

## Place Cells

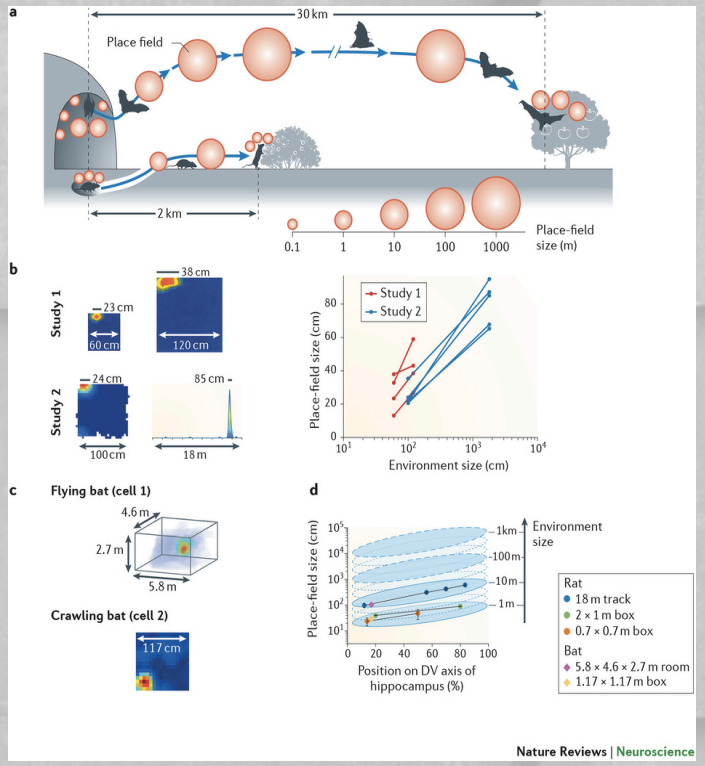
Found in CA1, CA3, DG, and the MEC

Perforant path provides sensory information and the septo-hippocampal afferents provide information about the animal's spatial displacements.

No retinotopy nor systematic relations.

**Place field size increases along the dorsoventral axis.**

Could reflect a varying gain of the motion signal.

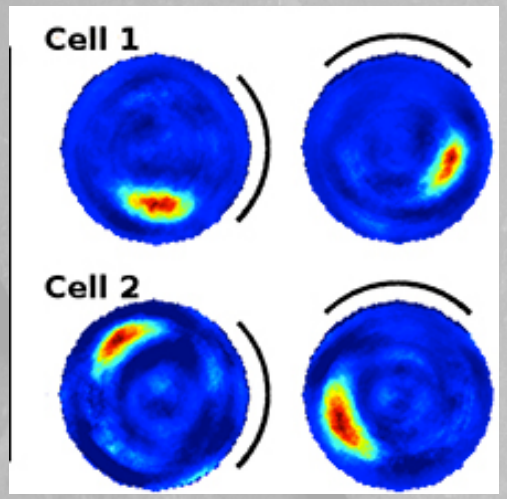


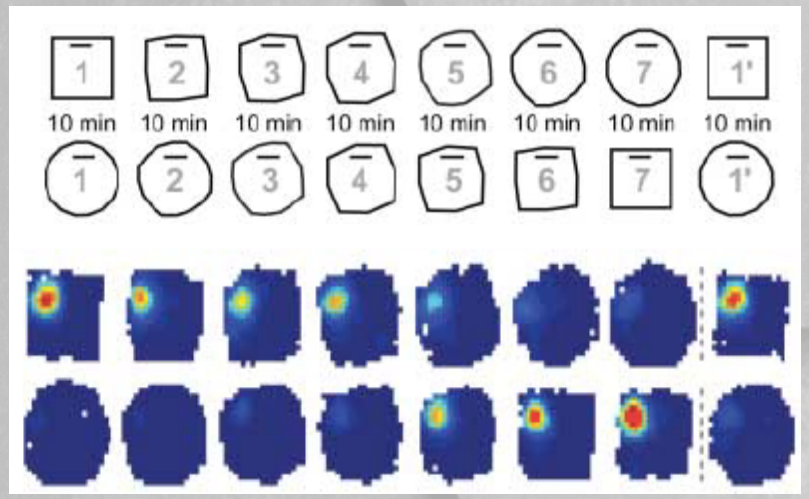

Best, 2001; Brun, 2008; Burgess, 1996; Arendt, 1994; McNaughton, 1996; Rolls, 2015; Mauerer, 2005

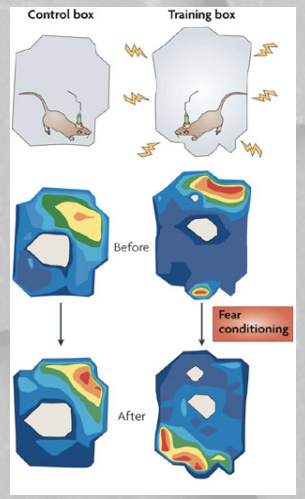
# The building blocks of spatial processing

## Place Cells

Rotate with environmental cues or “remap” if environment becomes too different.



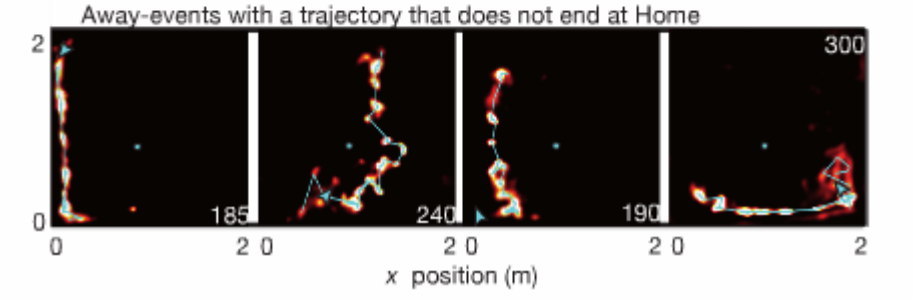



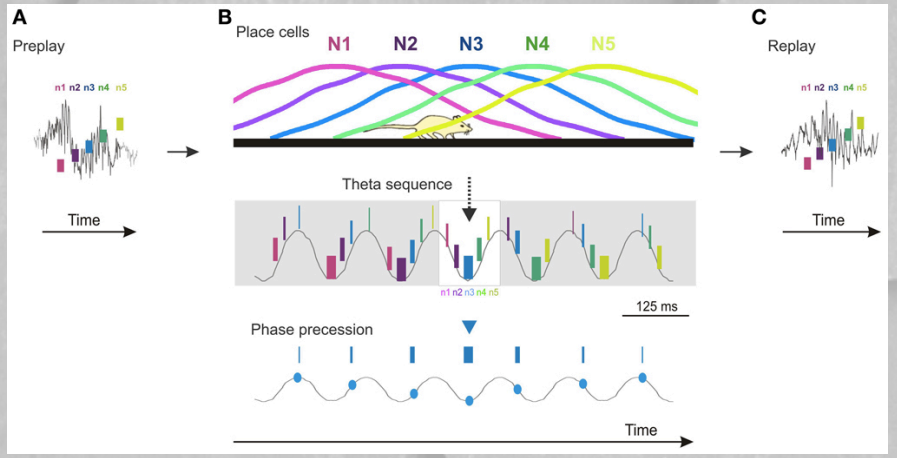




Muller and Kubie, 1987; Schonfeld, 2015; Moita, 2004; Leutgeb, 2005

# The building blocks of spatial processing

## Place Cells



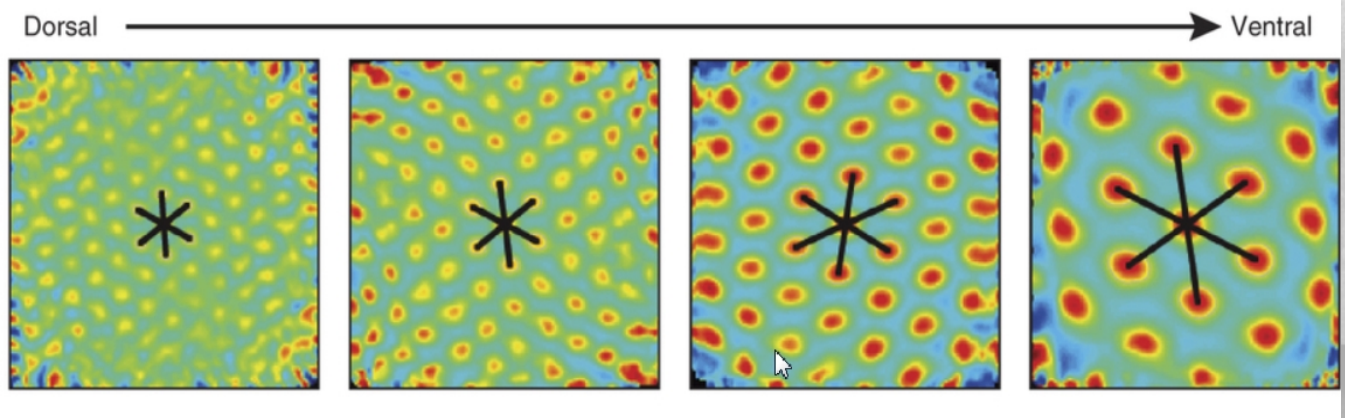

Place cell sequences can be reinforced by reward to form trajectory-finding-mechanisms
Place cell sequences are **replayed** during sleep and quiet wakefulness. The fidelity of this replay can predict error rate. Firing rate is highest during theta troughs.
Upcoming place cells show phase precession.

Carr, 2011; Gupta, 201; Pfeiffer and Foster, 2013; Robitsek, 2013; Girardeau, 2009

# The building blocks of spatial processing

## Grid Cells

Fire in tessellating patterns about an environment such that it would fire in one position in space and then in 6 equidistant peaks in 60-degree outshoots.




Found in MEC and scale as one moves along the dorsal-ventral axis.

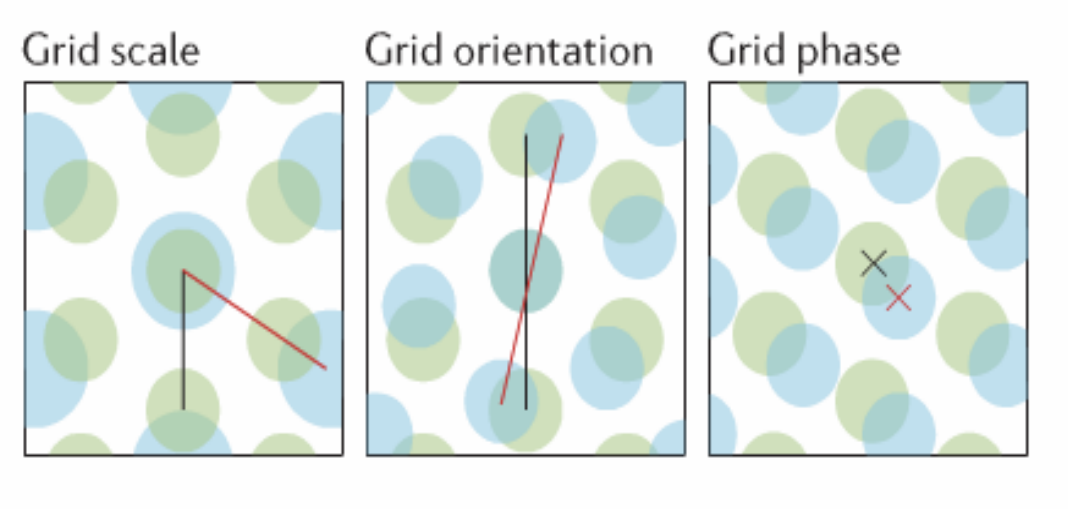
Hafting, 2005; Buzsaki, 2013; Stensola, 2012

# The building blocks of spatial processing

## Grid Cells

Grid cells cluster into modules that share scale, orientation, and asymmetry, but not phase.

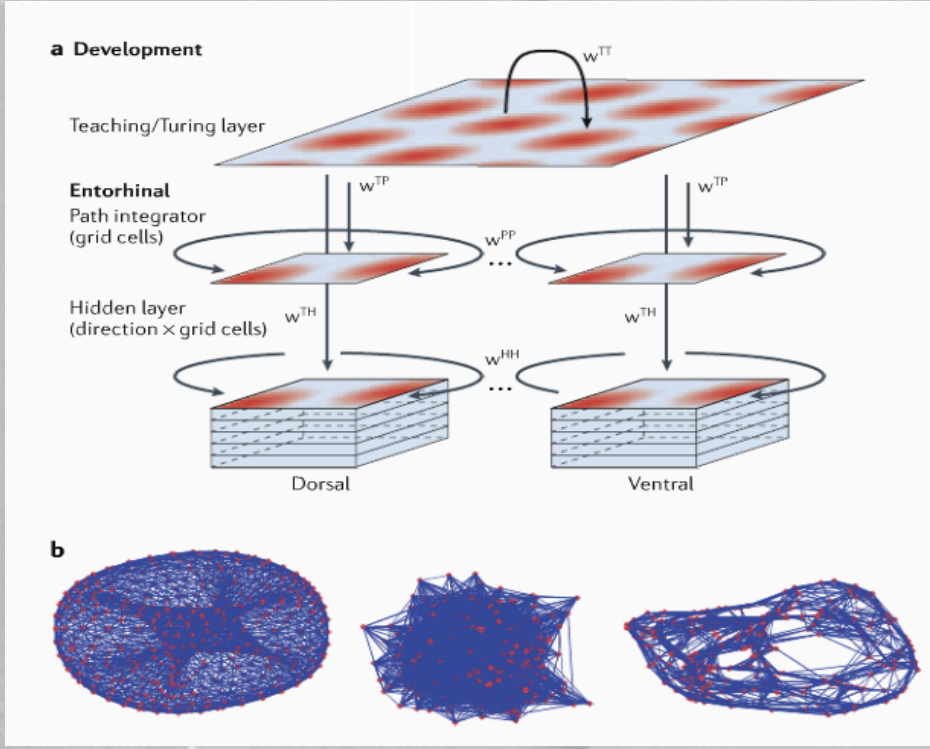
The modules scale up on average by a factor of 1.42 (√2)




Hafting, 2005; Buzsaki, 2013, Stensola, 2012

# The building blocks of spatial processing

## Grid Cells




McNaughton, 2006

# The building blocks of spatial processing

## Grid Cells

Don’t need visual input.

Visual cue rotation does rotate the grids.

Maintain spacing and relative offsets with their neighbors.

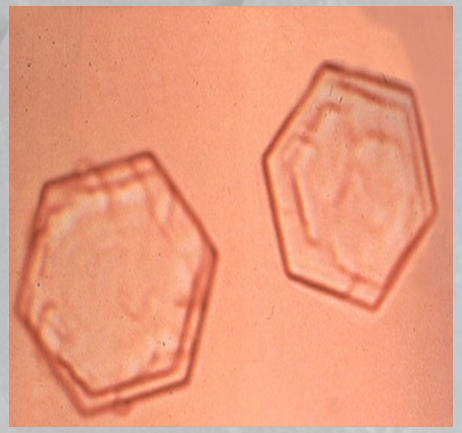
Speed cells may provide grid cells with information about changes in position.

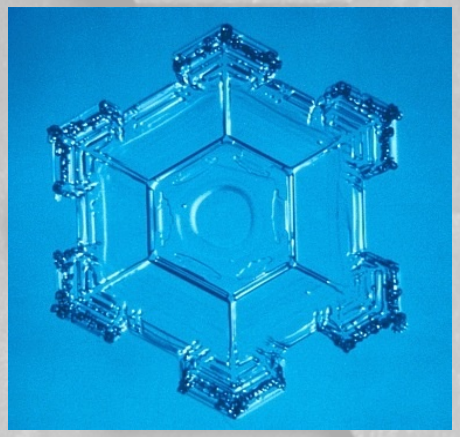
There also exist grid x direction cells.

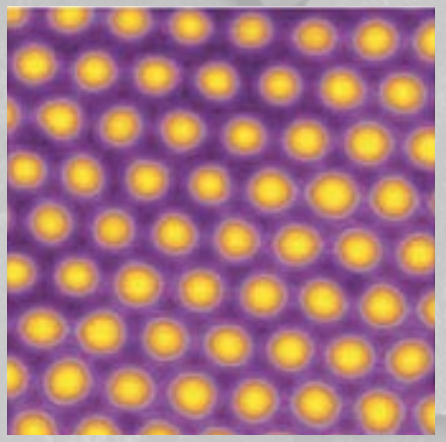
Hafting, 2005; Kropff, 2015; Sargolini, 2006

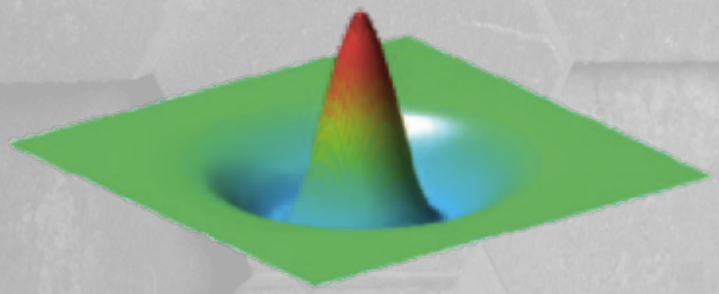
# Why Grids?

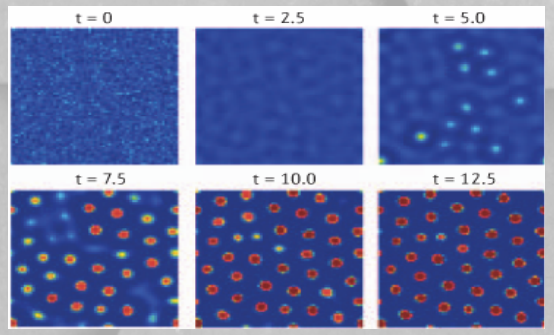
**The Honeycomb Conjecture** | **Mexican-Hat-Connectivity**







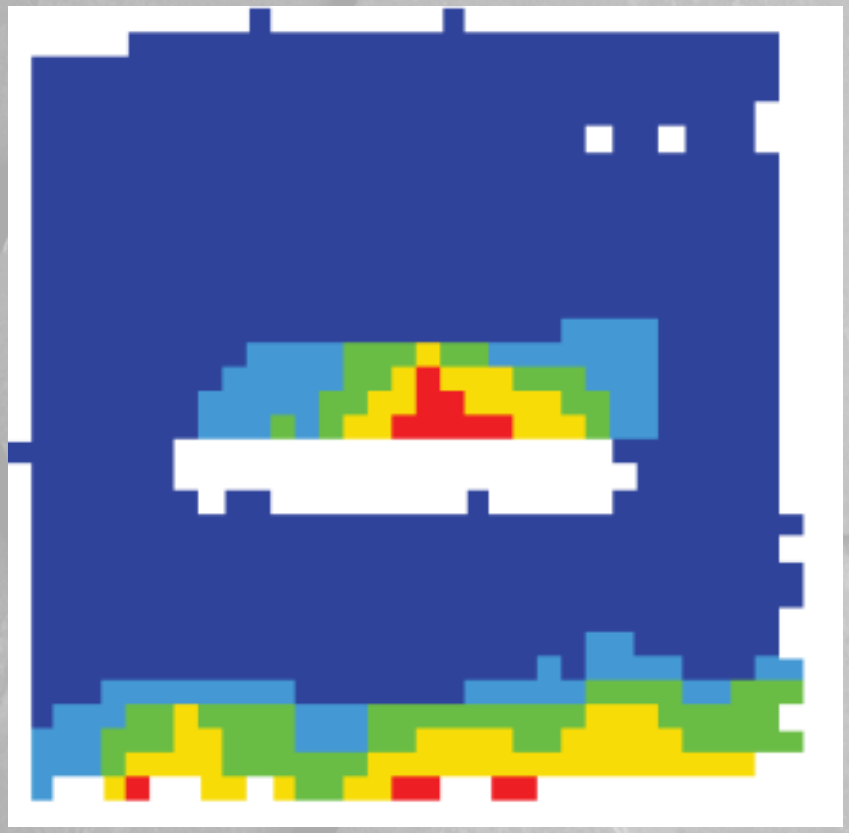





Varro, 36BC; Kelvin, 1887; Hales, 1999; McNaughton, 2006;

# The building blocks of spatial processing

## Border Cells



Fire along, and a slight bit away from, functional “borders” of an environment.

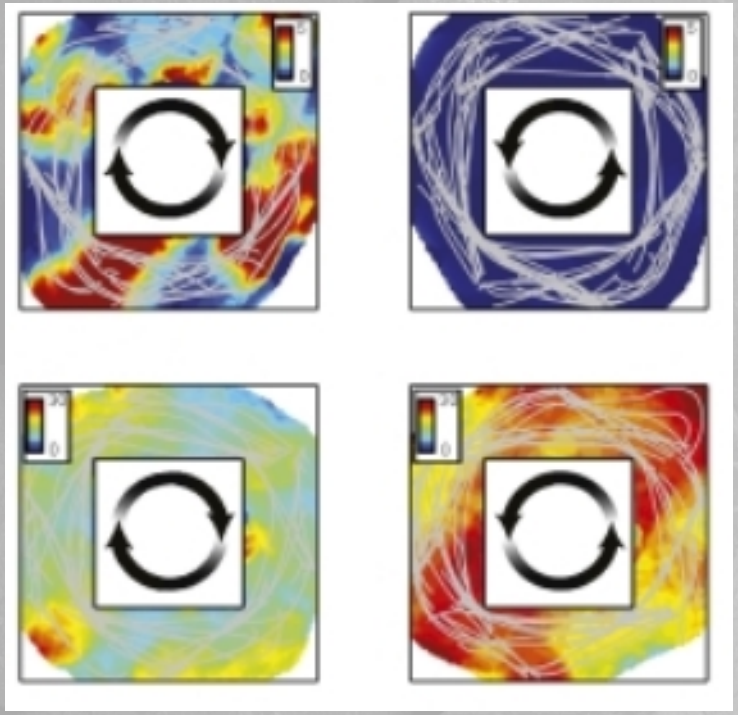
Different cells code for different faces of the environment and rotate in accordance with the environment.

Found in the MEC and parasubiculum.

Solstad, 2008; Lever, 2009

# The building blocks of spatial processing

## Path Cells



Cells in the entorhinal cortex show firing activity that is indicative of whether the patient is taking a clockwise of counterclockwise path around a virtual square road.

Persist across the whole environment.

Could help determine *which* map is used.

Jacobs, 2010; Markus, 1995; Frank, 2000

# Computing with the building blocks

## Grid Cells and Place Cells

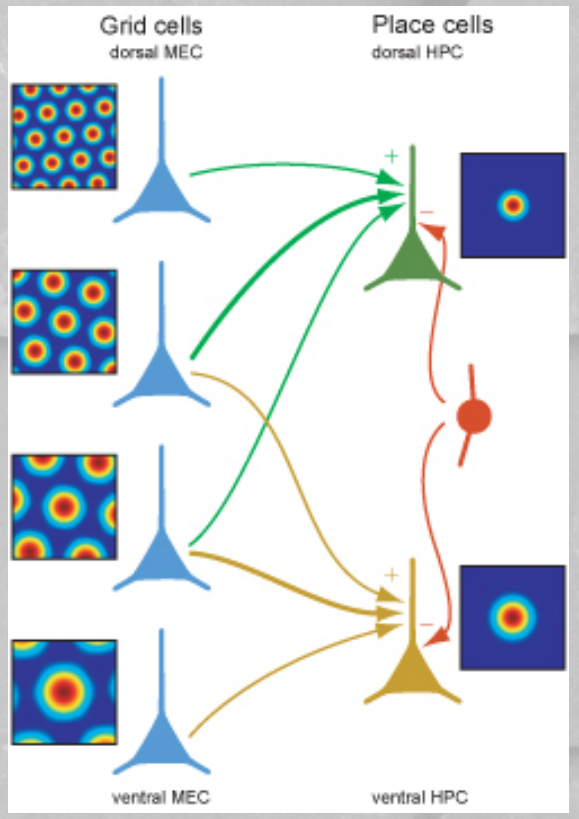
**Do Grid Cells create place cells? Seems promising...**

1) Grid Cells make up most of the mEC

2) Less mEC input make place fields less spatial.

3) Place fields decrease in size and are less stable after EC lesions and abolish phase precession.

4) Global remapping of place cell firing is accompanied by shifts in spatial phase and/or orientation of grid cell modules relative to the environment.




Bush, 2014; Barry, 2012; Brun, 2008; Langston, 2010; Brandon, 2014

# Computing with the building blocks

## Grid Cells and Place Cells

**However...**

1) Place cells develop and stabilize before grid cells and remain after lesioning MEC.

2) Place cells fire in the same location, even if a valley is introduced that creates greater traversions. Thus, place cells must be operating in **allocentric** representational space.

3) Inactivating the medial septal area disrupts grid cells, but not place cells.

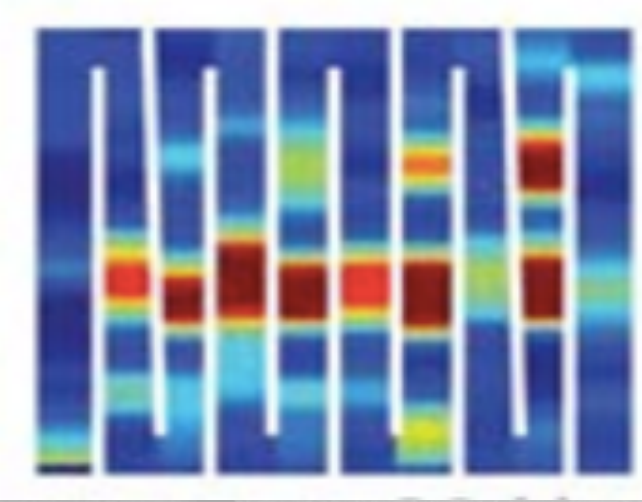
4) mEC firing is after hippocampal principle cell activity during theta-associated behavior.

5) When the hippocampus is inactivated, grid cell patterns are lost and function as HD cells.

Langston, 2010; Brandon, 2011; Moser, 2013 SfN poster; Moser, 2014; Brandon, 2014; Bonnevie, 2013

# Computing with the building blocks

## Grid Cells and Place Cells



Grid cells seems to be acting as **path integrators** and providing a **metric** of the environment.

The whole grid system is "reset" after turns in a hairpin maze, insinuating idiothetic reliance.

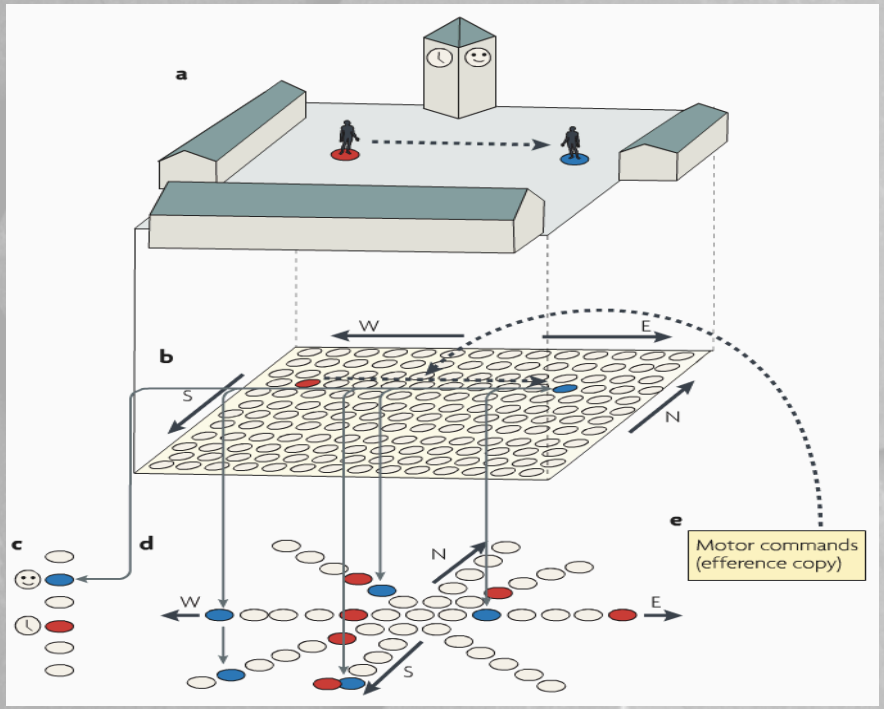
Grid cells *could* be stabilizing place fields, like how the cerebellum refines motor movements.

Taken together, grid cells and place cells provide a **coordinate** system and a **placement** system.

Derdikman, 2009; Moser, 2008

# Computing with the building blocks

## Place Cells and Border Cells




Boundary cells provide a piloting system and may environmentally modulate place cells since place field positions can be predicted by their relation to previous boundaries.

Taking grid cells, but not boundary cells, offline does not affect place cell firing. The opposite is not true.

Burgess and O'Keefe, 2011; Barry, 2006; Bird, 2008

# Theta Encoding

"If you want to find the secrets of the universe, think in terms of energy, frequency and vibration."
– Nikola Tesla

Neurons on the descending phase, trough and ascending phase of the theta waves represent the sequences of the past, current and future positions of the animal's journey.

Travel distances between landmarks during navigation can be expressed in the temporal domain by a time-compressed format in the theta waves.

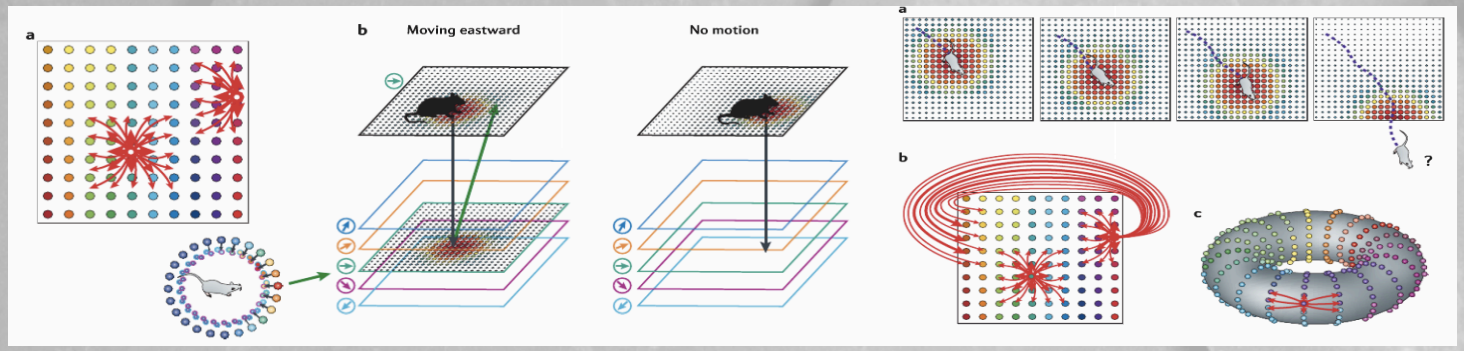
If locations are regarded as analogous to individual items in a memory buffer, the theta-nested assembly organization limits the number of items that can be stored within a single theta cycle.

Buzsaki, 2011; Skaggs, 1996; Buzsaki, 2013; Dragoi, 2006; Tort, 2009

# Purposeful Navigation

## Path Integration

Path integration sums the vectors of distance and direction travelled from a start point to estimate current position. Grid cells, with direct access to direction and speed cells as well as vestibular feedback, seem to permit this considering they even fire in the dark and have predictable patterns.




Gerbils can return home after foraging in the dark.

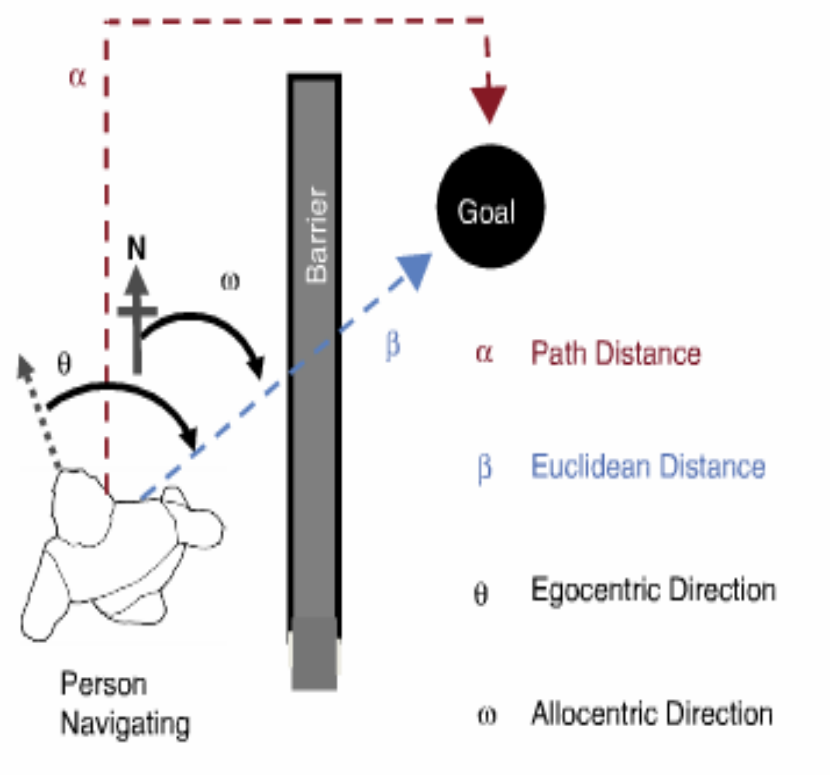
Without grid cells, animals fail to path integrate.

CA1 place cells rely on grid-cell firing in the absence of visual input.

McNaughton, 2006; Gothard, 2011; Tsodyks, 1999

# Purposeful Navigation

## Directed Navigation




Directed navigation requires the calculation of the vector between two allocentric locations.

The PHC extracts allocentric spatial information from salient visual landmarks. The hippocampus can bind these features and compute maps.

Dorsolateral Enthorhinal can take in external sensory information and the Ventromedial can take in information about self-position and motion.

By combining egocentric and allocentric information, we can purposefully navigate.

Ekstrom, 2003; Spiers, 2015; Lisman, 2007

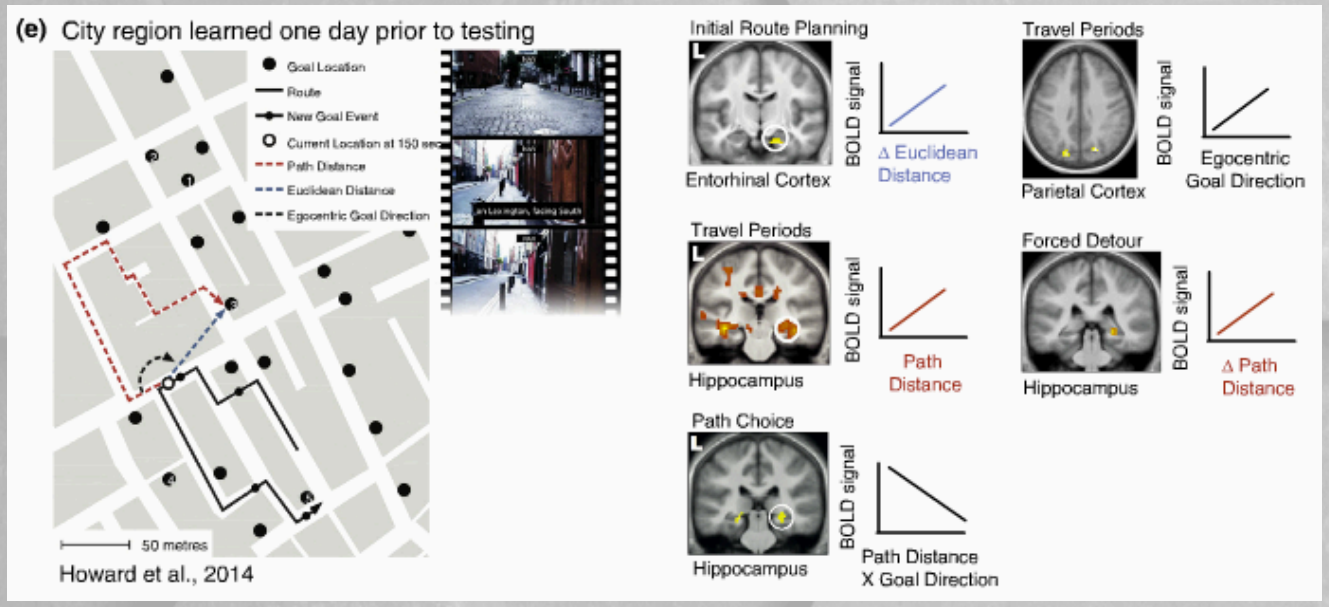
# Purposeful Navigation

## Directed Navigation

Mid to anterior hippocampus increases activity at the start of navigation when route planning was required. Posterior hippocampal activity is correlated with path distance.

At path “choice points”, hippocampal activity is negatively correlated with the distance to the goal .

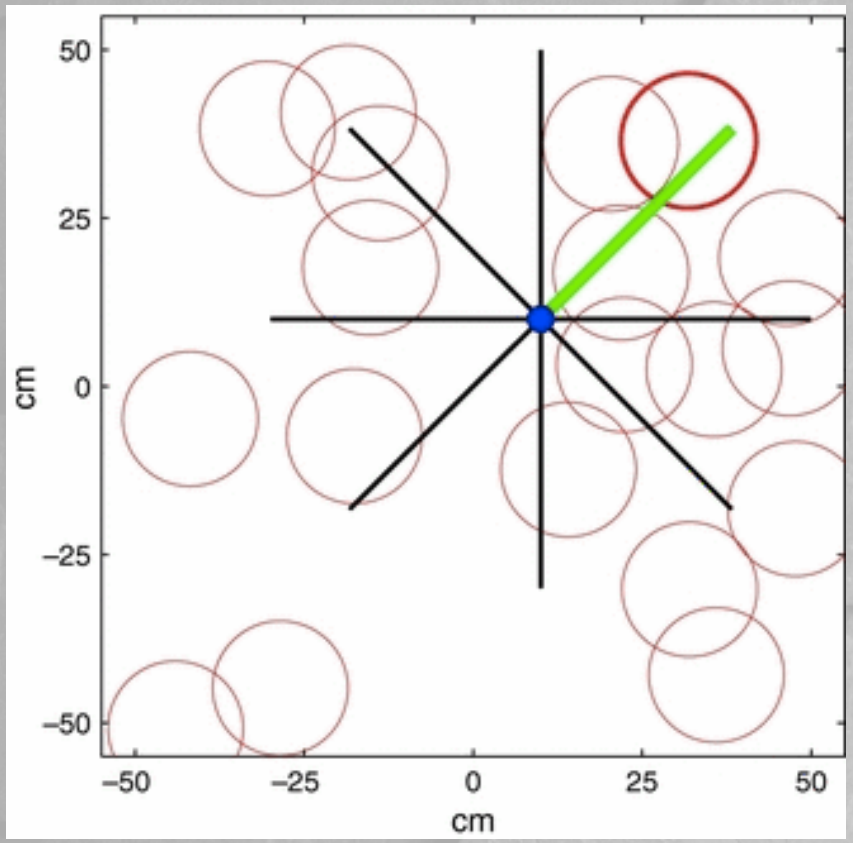
During “travel”, hippocampal activity was positively correlated with distance to the goal.




Howard, 2014; Spiers, 2015

# Purposeful Navigation

## Directed Navigation




Linear look-ahead probes allow for a sampling of potential trajectories while an animal is stationary.

Potential routes can be inferred through head direction and grid cell spiking and simulated place cells through a phase interference model.

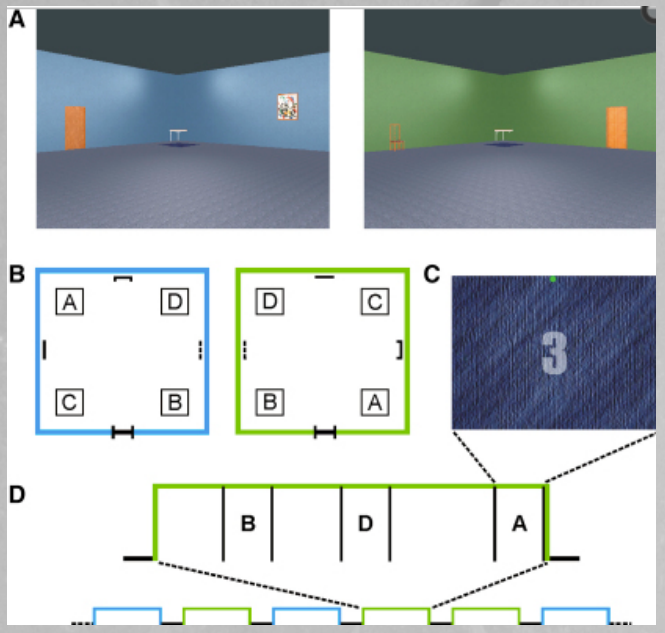
Routes that lead to activation of PFC cells with highest reward are typically chosen.

This also helps to create place-goal cells.

Multiple landmarks? Hippocampus. One? Caudate. Novel vectors.

Hasselmo, 2008; Burgess, 2007; Erdem, 2012; Ekstrom, 2003; Spiers, 2015; Wegman, 2014

# Spatial Representation




Highly abstracted representations of space are expressed across tens of thousands of coordinate neurons in the human hippocampus in a structured manner.

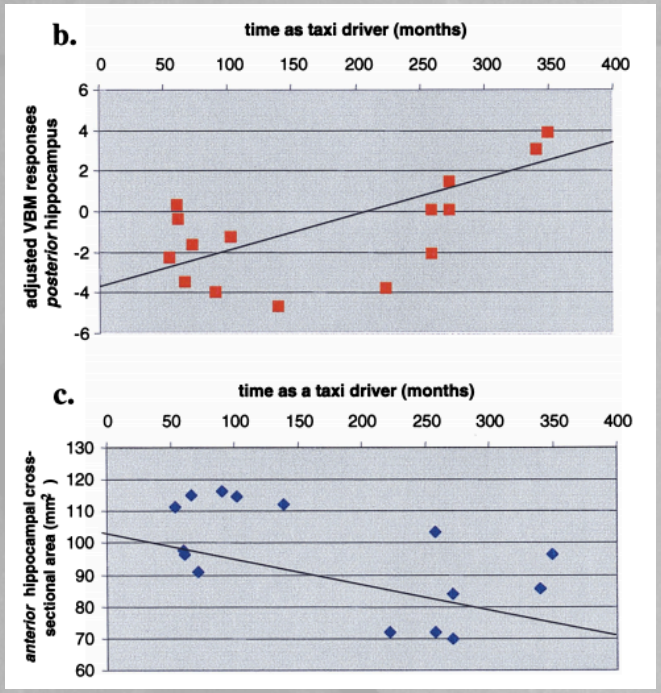
Furthermore, the posterior hippocampus has been shown to be concerned with spatial details, such as the precise position of individual landmarks.

Object location recruits hippocampus, but not object color associations.

Hassabis, 2009; Poppenck, 2013; Piekema, 2006

# Spatial Memory

**The human hippocampus is certainly involved in spatial memory.**




CA1 activity is positively correlated with performance when subjects learn a spatial environment independent of starting point and direction.

Thinking of local spatial details from past life events, such as wedding seating arrangements, evokes more pHPC activation than thinking of the general location of those events, which evokes aHPC activation

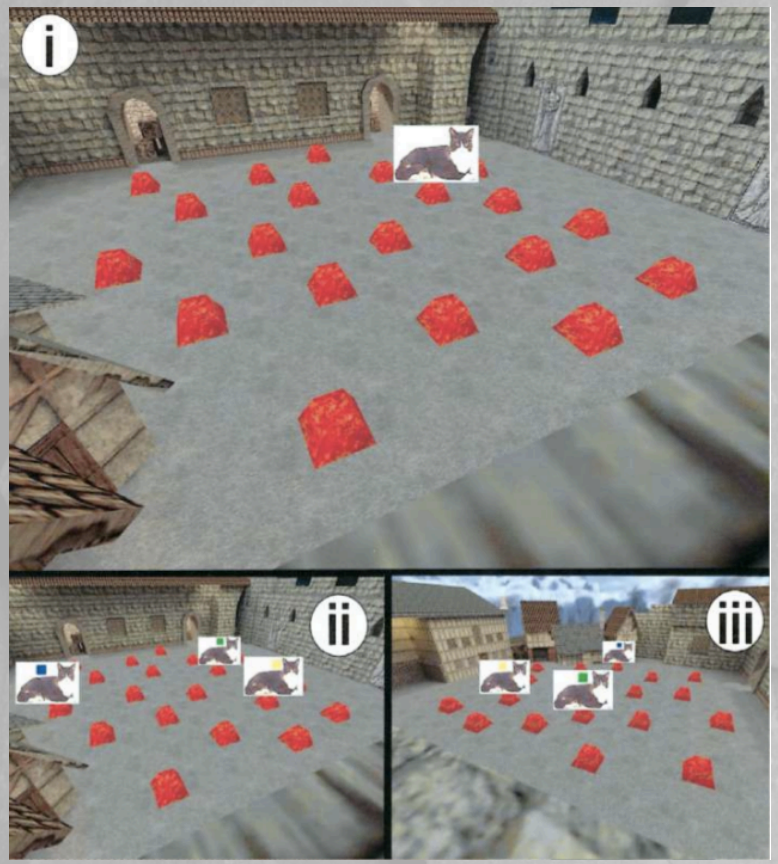
Posterior hippocampus also shows activation for memory concerned with both shorter spatial and temporal distances.

Without a hippocampus, memory for objects can be recognized, but not *where* they were learned.

Nadel, 2013; Nielson, 2015; Suthana, 2009; Maguire, 2000; Olson, 2006; Lavanex, 2006; Spiers, 2001

# Spatial Memory

**The hippocampus seems to be particularly involved in allocentric representations**




Shown view of objects.
Test from either same or different view.

Shifted views require an allocentric representation.

Hipp subject could not perform the shifted views.

According to cognitive map theory, damage to the hipp should cause deficit in memory for location defined relative to the environment as opposed to locations defined by their sensory characteristics or by their location relative to the body.

King, 2002; Spiers, 2001

# Memory Functions

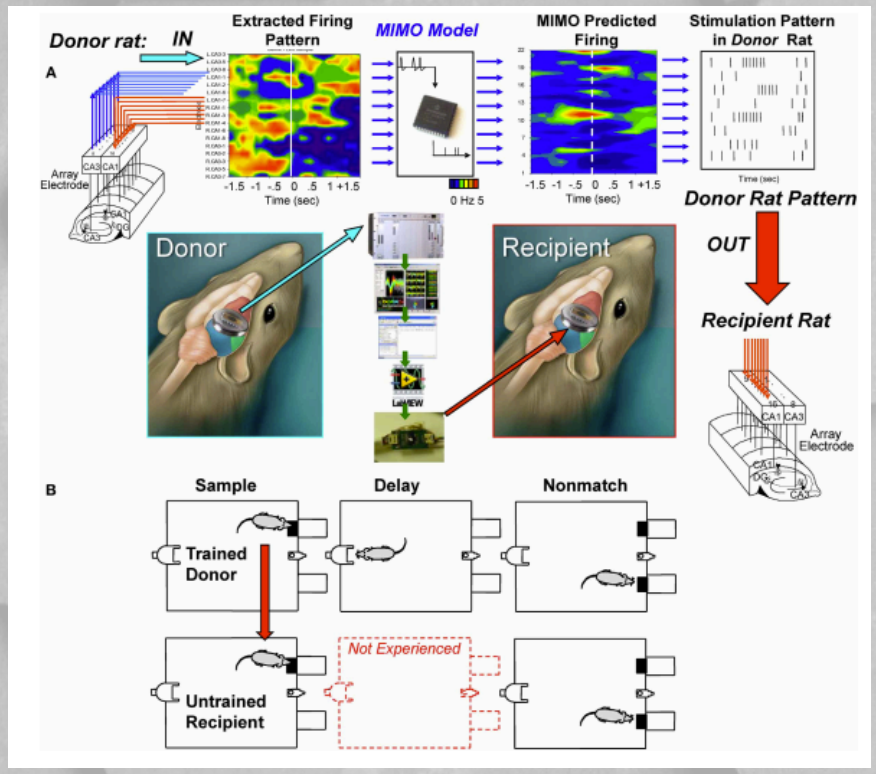
**There is no doubt that the hippocampus and surrounding MTL is necessary for particular aspect of non-spatial mnemonic function.**

Patterns within MTL are predictive of whether stimuli will be remembered.

MTL supports memory by encoding overlapping representations.Later recognition ispredicted by greater pattern distinctiveness.

See Rissman, 2012 for more.

The hippocampal code for memory is so robust that it can even be transferred across animals.




Shibata, 2011; Ranganath, 2012; Xue, 2010; LacRocque, 2013; Deadwyler, 2013

# Memory Functions

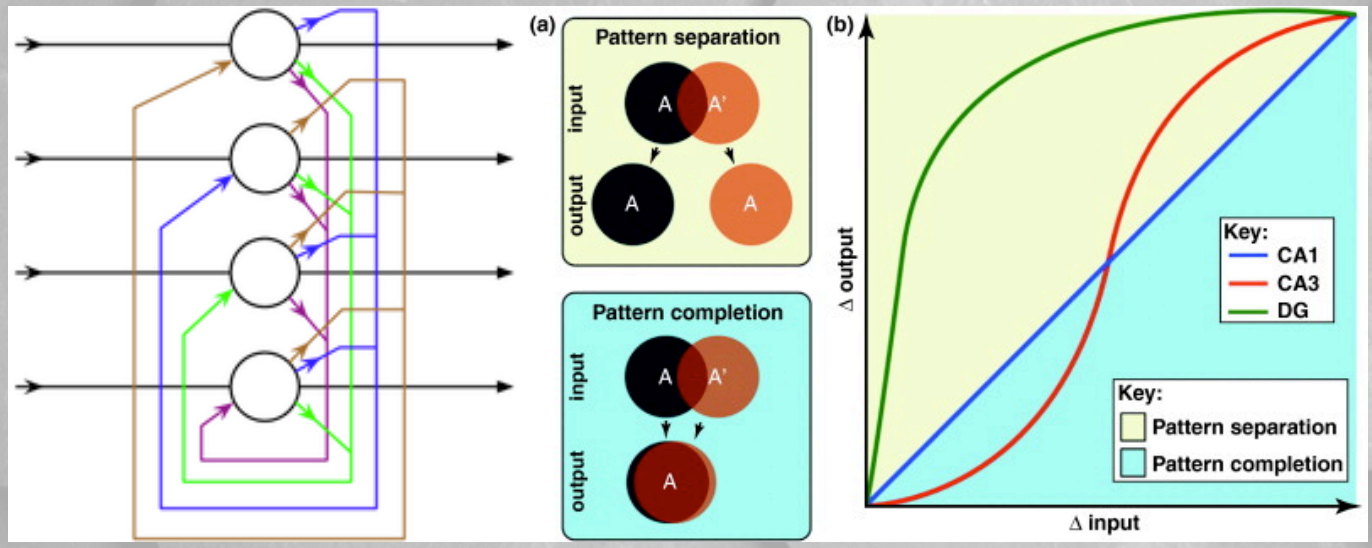
Your memories could start by place cells activating each other via these dense interconnections and then reactivating boundary cells to create the spatial structure of the scene around your viewpoint. And grid cells could move this viewpoint through that space. Head direction cells could define the viewing direction from which you want to generate an image for your visual imagery, so you can imagine what happened when you were at a wedding, for example.

- Burgess, 2014

# Memory Functions

## Pattern Completion and Separation

Attractor dynamics, as seen with Hopfields and afforded to circuitries like CA3's recurrent collaterals serve as a mechanism for the low interference storage of arbitrary input patterns to the hippocampus.



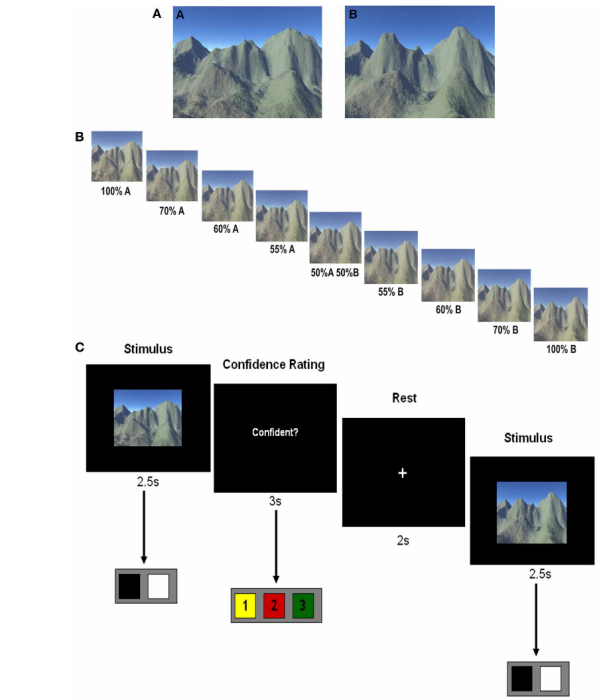

Since place cells maintain their location specificity after removing many of the landmarks, pattern completion is at play. Remapping is reminiscent of pattern separation.

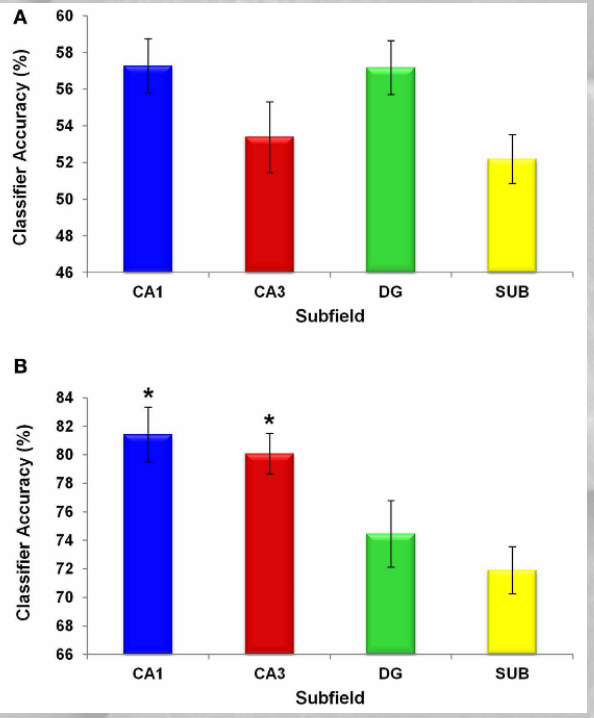
Yassa and Stark, 2011; Bird, 2016; Leutgeb, 2005; Moita, 2004

# Memory Functions

## Pattern Completion and Separation

By presenting perceptually ambiguous stimuli and forcing subjects to classify them, we can observe pattern completion mechanisms.



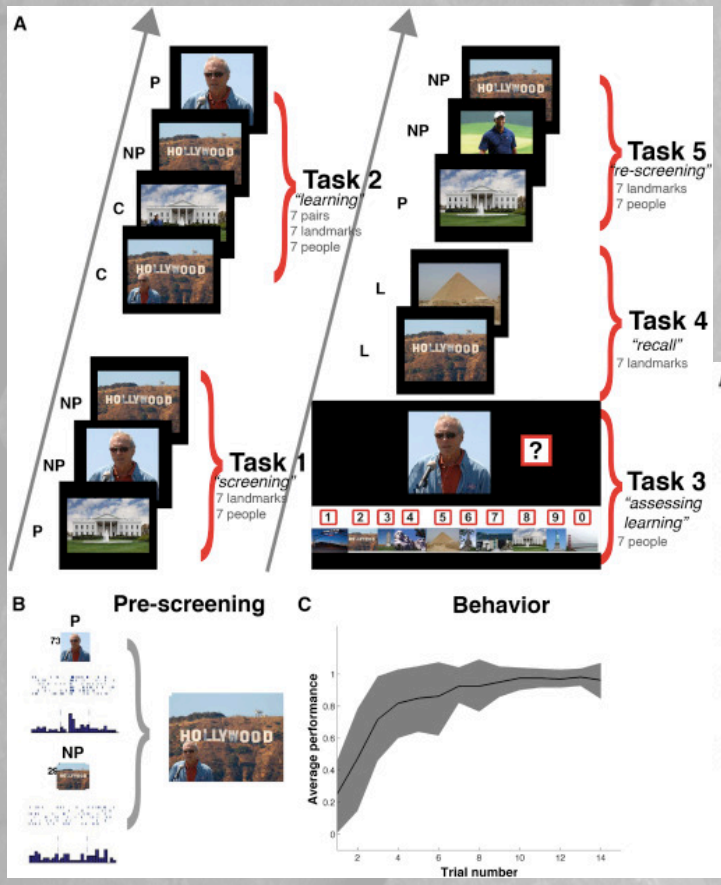

**100% A | B**

**50% A ^ B**

Bonnici, 2012

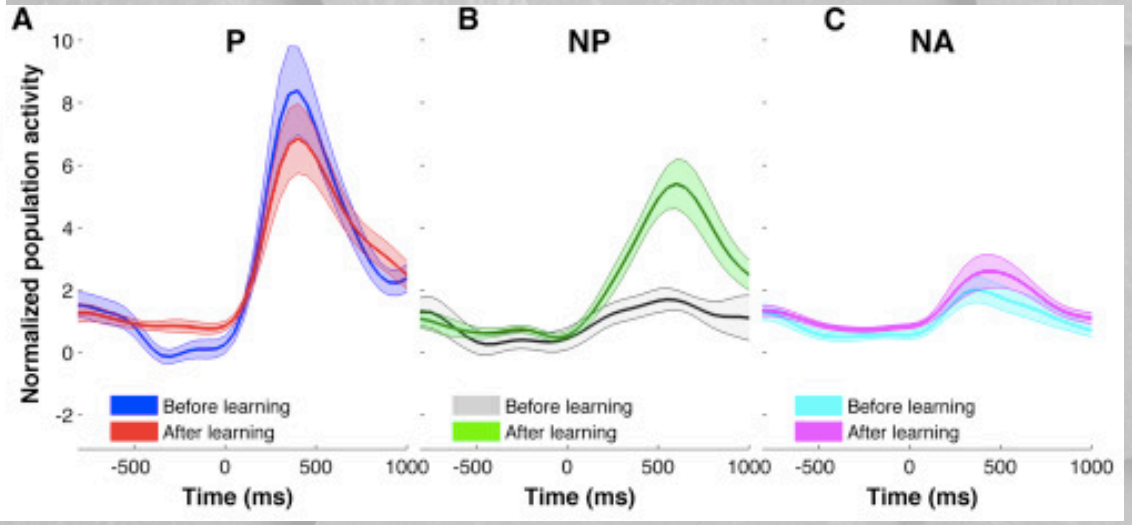
# Memory Functions

## Associations




Much in the same way as they integrate perceptual modalities and space with landmarks, hippocampal neurons can make associations across a variety of stimuli.

Firing patterns change as a function of item pairings.

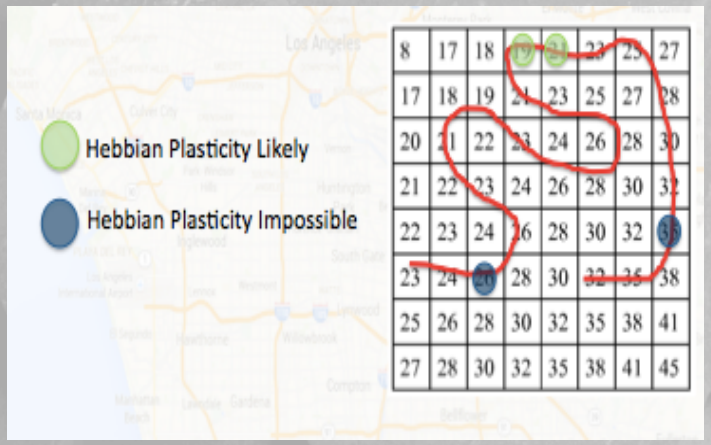



Ison, 2015; Eichenbaum, 1999; Davachi and Wagner, 2002

# Memory Functions

## Episodic Memory

At their core, hippocampal memories (i.e. memories for episodes that have an inseparable spatiotemporal component) are characterized by events that are tied together in sequences




It's easy to see how this same cell assembly principle can be applied to time instead of space, such that temporally adjacent occurrences are most likely to be **bound** into a single "episode" as opposed to a "path".

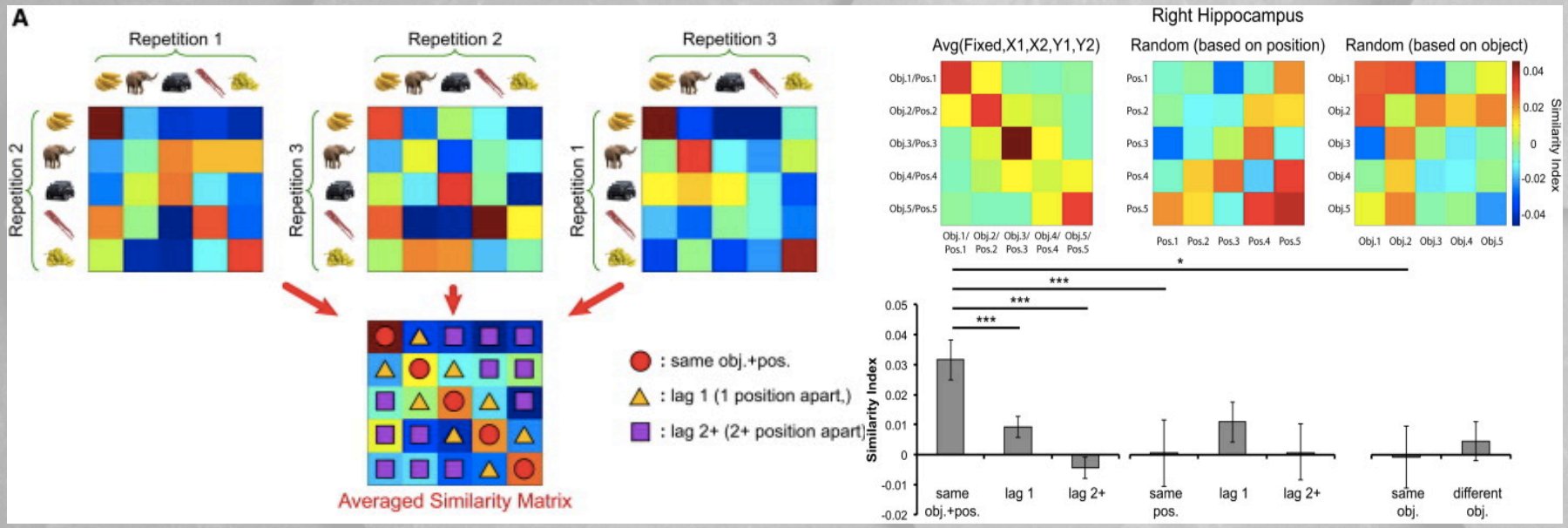
Kids with hippocampal lesions are perfectly fine at learning facts, but have trouble with episodes

Tulving and Markowitsch, 1998; Vargha-Khadem, 1997

# Memory Functions

## Episodic Memory

Hippocampal activity patterns encode information about specific sequences, despite the fact that all of the sequences comprised of the same objects.

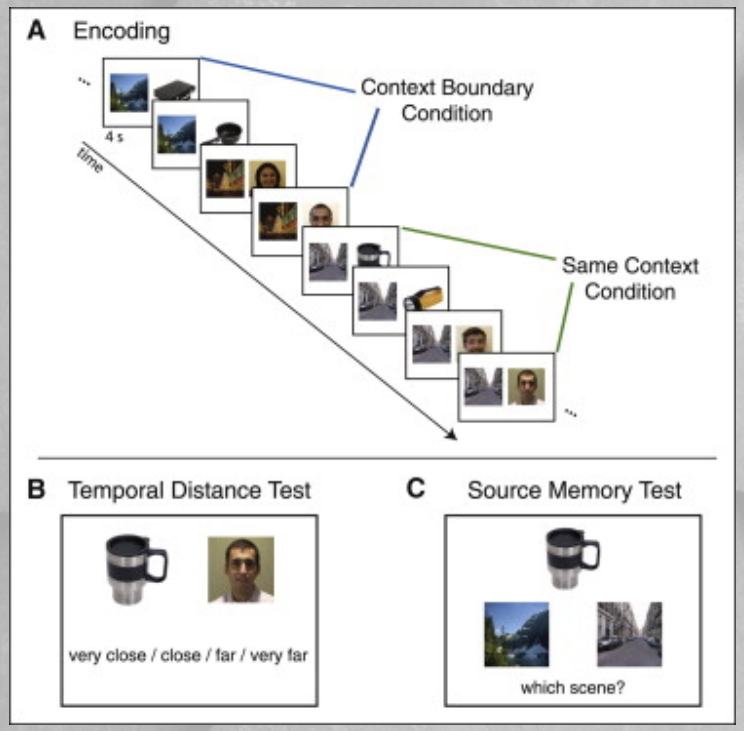


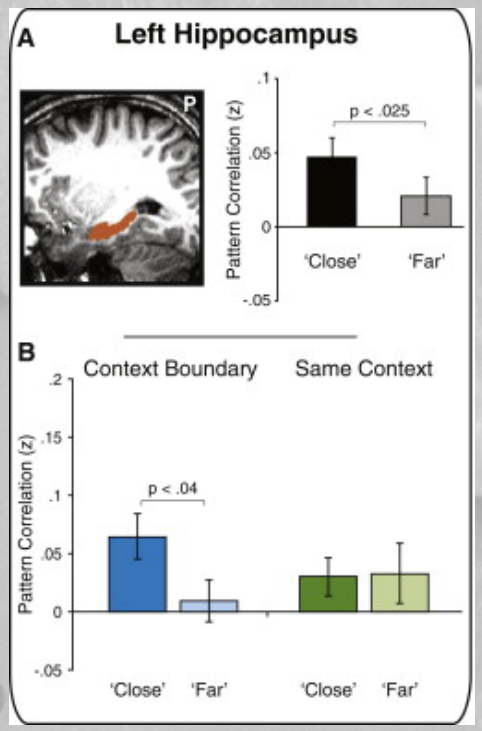

Hsieh, 2014

# Memory Functions

## Episodic Memory

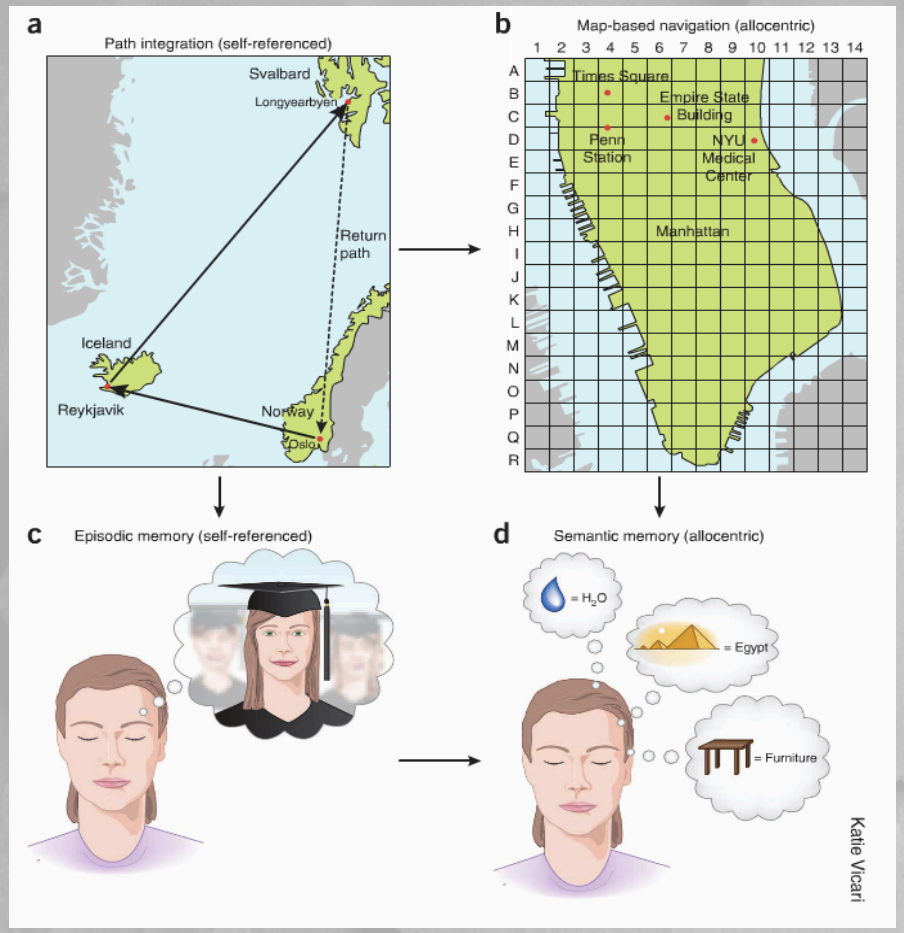
Differentiation in hippocampal voxel patterns between two events is related to successful discrimination of the temporal order of events in memories




Ezzyat and Davachi 2014; Davachi and Dubrow, 2015

# A cognitive map

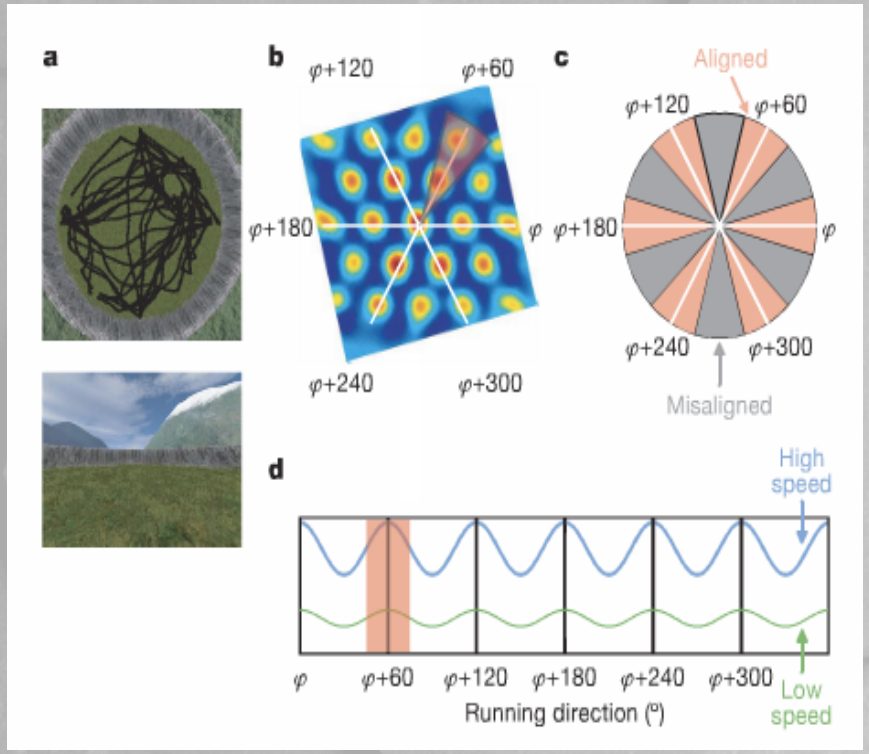


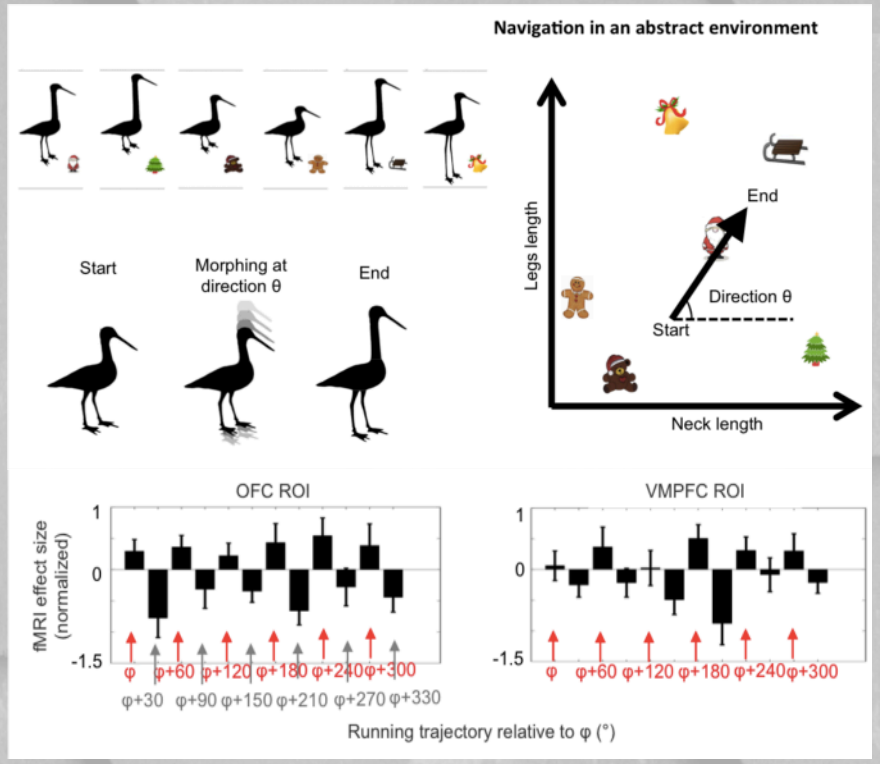

The neuronal mechanisms that evolved to define the spatial relationship among landmarks can serve to embody associations among objects, events, and other types of information.

Buzsaki and Moser, 2013

# Enhancement

Aligning with grids enhances memory.



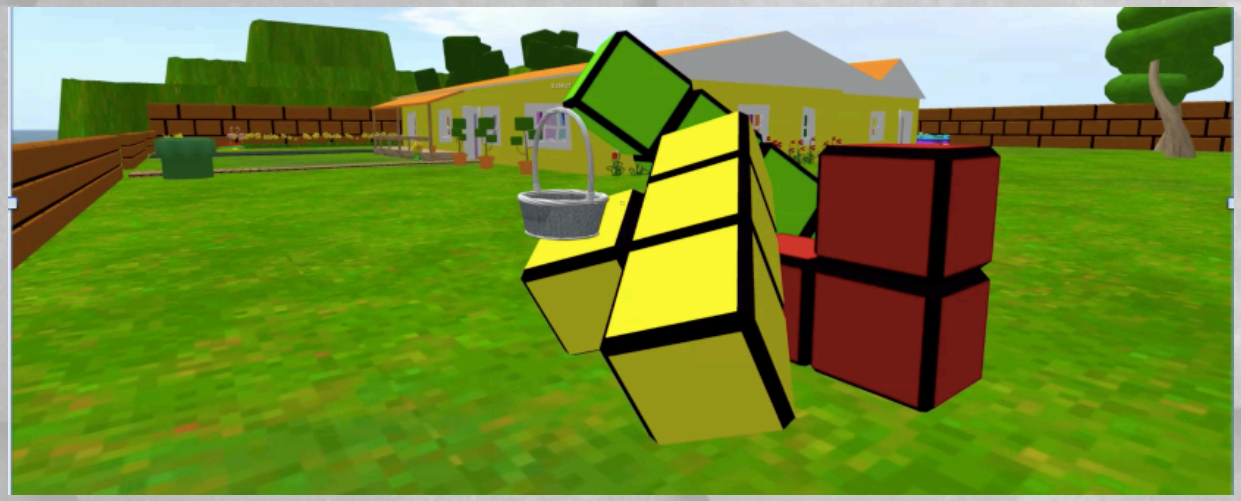

Young adults at genetic risk for AD (APOE-e4 carriers) exhibit reduced grid-cell–like representations and altered navigational behavior in a virtual arena

Doeller, 2011; Constaniceua, 2015; Kunz, 2015

# Enhancement

**Scenes are the primary currency of the hippocampus**

Hippocampal place cells show enhanced activity during recognition of objects that had been previously encountered in the cells' place fields.



By placing items within a spatial environment, like in the Method of Loci, our neural systems are able to tap into their ancestral roots and most optimally encode the to-be-remembered stimuli.

Maguire, 2013; Miller, 2013; Epp, 2008

# Summary & Conclusions

ChemoTaxis → Organizing Principles → Space → Computation → Integration → Memory

An event happens, a person experiences it, memory traces are laid down representing the event, the past vanishes and is replaced by the present. The memory traces of the event continue to exist in the present, they are retrieved, and the person remembers the event. It took biological evolution a long time to build a time machine in the brain, and it has managed to do it only once, but the consequences have been enormous: By virtue of their mental control over time, human beings now wield powers on earth that in many ways rival or even exceed those of nature itself. It is difficult to imagine a marvel of nature greater than that.

- Tulving

# Woah.