Developing cognitive maps

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Space and memory (and the brain, 20th-21st CE)

• Neural circuits supporting episodic memory and spatial processing are largely shared (hippocampus, anterior thalamus, mammillary bodies, retrosplenial and parahippocampal cortices).



Hippocampus

Memory: 'episodic'



Henry Molaison ('Patient H.M.') Scoville & Milner, 1957

The development of the neural map of space

Overall goal of our research is to understand the development of cognitive maps.

Two key themes:

1) Can development provide insights into the function of adult spatial memory and navigation circuits?

2) Which aspects of neural maps development are experience-dependent, and which are internally specified (e.g. genetic/molecular/spontaneous activity)?



Space [...] exists in the mind *a priori*, [...], it can contain, prior to all experience, principles which determine the relations of these objects' (*Immanuel Kant*, *Critique of Pure Reason*).

Developmental timeline of spatial responses in the rat



al 2018, Current Biology.

Talk outline

- How do neural representations of space and memory emerge during development?

(1) <u>Maturation of spatial signaling – self-organized processes vs. external inputs</u>

- The role of self-organised processes in directional and grid cell signalling
- Allocentric and egocentric signalling of environmental boundaries

(2) Development of neural correlates of memory

- Neural mechanisms for consolidation: the development of place cell replay
- The development of pattern separation for specific memories

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How is the Head Direction cell circuit assembled during development?

• Adult HD cells maintain fixed offsets between tunings following rotation or disorientation.

Co-recorded cells rotate together

Trial 1 Trial 2 Cell C Cell B Cell A Cell C Cell A Cell B 1. Self-organised

• This is thought to reflect network architecture (Skaggs et al 1995, Zhang, 1996).



- Hypotheses
- 1. <u>Self-organised</u> mechanism 2. <u>Spatially stable</u> Instructive Input
- How does connectivity arise during development? Does this process depend on the presence of stable landmarks or is it self-organised?

When can sensory inputs spatially stabilise HD cell firing?

Vision (distal sensory cues): from eye-opening (P14/15)

Boundaries (proximal sensory cues): from P13



Hui Min Tan

Bassett, Wills & Cacucci, Current Biology, 2018

Josh Bassett

Is attractor network connectivity in place at P12?

Is attractor connectivity already present at P12, in spite of spatial instability?



Temporal cross- correlogram A vs C Time-windowed (10 sec) spatial cross-

correlogram Connectivity 2. Spatially stable

Instructive Input

Learning



The spatial and temporal offsets between putative HD ٠ cells are fixed even at P12, before environmental anchoring. Network connectivity likely self-organised.

Early emergence of the grid cell attractor?





٠



Recent technological

(Moser lab).

visualisation of toroidal

topology of network activity

- Grid field shifts A>B for all cells. Y-Coord Shift X-Coord Shift λ/2 $|_{-\lambda/2}$
- Grid cells show fixed phase offsets, as soon as stable firing emerges.

Wills, Barry & Cacucci, 2012

advances have allowed direct



Gardner et al, 2022

This network structure may be present in the MEC from P10 ٠ onwards – Guardamagna et al, 2024, SfN Abstracts 190.07.

A drifting grid cell attractor may also be present in the mEC, before stable grid cell signalling.



Conclusions: Sensory and internal influences on developing attractors

 Functional signatures of the Head Direction (HD) cell and Grid cell continuous attractor networks are present <u>before</u> spatially stable HD and GC signaling can be recorded, and <u>before</u> young animals engage in spatial exploration. Network architecture likely achieved without external inputs/learning.

 HD can be anchored/stabilized through different sensory inputs at different ages (boundaries/early, visual cues/eye opening).

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Environment boundaries stabilise place fields in pre-weanling pups

• On average, place cells are immature at the onset of exploration and then mature slowly ...



• ... but some place fields are adultlike early in development:



• Before weaning (P21), place fields are more stable closer to the arena boundary. After weaning, equally stable throughout arena.



• Place cell accuracy (1/decoding error) is higher close to boundaries, only before weaning.



Grid Cells



Muessig, Hauser, Wills, Cacucci, 2014, Neuron

far from boundaries. Consistent with appearance of stable grid cells around weaning.

Boundary Vector Cells: place cell building blocks?

Boundary Vector Cell (BVC) model of place cell firing:



Hartley T, Burgess N, Lever C, Cacucci F, O'Keefe J. (2000). Hippocampus. 10(4):369-79.



CA3 CA2 CA1 DG SUB PrS PaS V-V1 CD CA1 DG PrS PaS

Per



٠

• Lever *et al* (2009) reported BVCs in the subiculum.

- Solstad *et al* (2008) reported 'Border Cells' in the mEC.
- Border cells can be thought of as <u>short-range</u> BVCs.



 Boundary responsive neurons can therefore be found <u>both</u> at the input and output ends of the hippocampal formation.

Subiculum BVCs develop slowly, whilst MEC BVCs mature early





Laurenz Muessig

Fabio Ribeiro Rodrigues



 Bjerknes et al (2015; Neuron) found mature Border Cells in mEC as early as tested (P17).



Late subiculum development consistent with maturation following tri-synaptic loop (**Donato** *et al*, **2017; Science**):

Muessig, et al, 2024, Nature Comms

Conclusions: Development of allocentric boundary responses



• Boundaries are a foundational input for the developing cognitive map. They enable stable neural maps before other inputs are available, e.g. for place cells, before weaning. Grid cells would stabilise place maps far from boundaries after weaning.

• Unlike entorhinal BVCs, adult-like, stable, Subiculum BVCs develop late. This is consistent with late emerging use of boundaries as a *spatial* cues (e.g. Bullens et al, 2010).



Bullens, et al, 2010, Dev. Sci

Egocentric inputs to allocentric spatial system



Egocentric tuning

 Egocentric Boundary Cells modulated by (allocentric) HD signal have been described in postrhinal cortex in adult rats (LaChance et al, 2019). In humans, neurons which encode locations in egocentric coordinates have been reported in the PHC (Kunz et al 2021).



• Postrhinal cortex is placed at the crossroads between the "what" and "where" visual pathways.

Detection of egocentric boundary tuning

• Detect egocentric boundary tuning by, 1) converting directions from allocentric to egocentric, then 2) constructing rate map in 'vector-to-wall' coordinates.



 If Spatial Information of vector map is > threshold based on shuffled data, cell is classified 'Egocentric Boundary Cell' (EBC).

Development of egocentric boundary responses





Lomi, et al, in progress! EBCs are present post-weaning, but the proportion is reduced compared to adults.



• Pup EBCs have poorer egocentric tuning: lower spatial information, larger field size and lower cross-trial stability.



Spatial distribution of egocentric receptive fields



EBC Distance tunings

- Adults show three distinct groups of distance tunings. Similar to EBCs in dorso-medial striatum (Hinman et al, 2019, Nat Comms).
- Pups lacking **short-** and long-range EBCs.

Egocentric distance tunings are late-developing



<u>Allocentric HD component of EBC signalling is present from earliest recordings:</u> ٠



ALLOCENTRIC

Conclusions: egocentric coding of boundaries

Preliminary evidence supports slow maturation of egocentric boundary responses in postrhinal cortex.
Unexpectedly, egocentric responses tuned close to walls are the last to emerge – suggests that EBCs are not simple sensory responses (see also Joeri et al, 2020, eLife).

• This could explain late emergence of spatial memory in rodents (as the allocentric to egocentric transformation is unavailable until late during development, e.g. Bicanski and Burgess, 2018, 2020)

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Mechanisms for hippocampal consolidation: Theta versus LIA states



Adapted from Buzsaki, 2015.

 Two prominent hippocampal "states": Theta during exploration/locomotion; Sharp-wave ripples during rest/consummatory behaviours.





- Place cell firing sequences seen in exploration are 'replayed' at compressed timescales during SWRs (sleep/pauses to locomotion).
- Replay could link together sequences of temporally or spatially separated events.

Aim - investigate developmental emergence of:

 Fine-time scale spike sequences, in theta and SWRs.

Gradual emergence of trajectory replay





Muessig et al, 2019, Current Biology

Decoded probability

210

- Early 'replay' events represent only single positions on the track.
- Gradual emergence of sequences which replay trajectories.



Trajectory replay and theta sequences develop together



Theta sequences emerge gradually P17-32



 Theta sequence score strongly correlated with subsequent replay (correcting for age).



Muessig et al, 2019, Current Biology

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The development of Pattern Separation

- Human children impaired in forming <u>specific</u> memories of events associated with a time and place ('Infantile generalization').
- 4-year olds impaired forming item-item associations, for similar contexts.



Ngo et al, 2019, J Exp Psych Gen

CA1 Place cells '**remap**' between different environments: possible neural code for pattern separation.



Remapping between <u>very</u> <u>different</u> contexts present from P16 onwards:



Muessig, Hauser, Wills & Cacucci, 2016, Cerebral Cortex.

Aims:

- What is hippocampal response to small context changes (more stringent test of pattern separation)?
- Test responses in putative pattern separation circuit, Dentate Gyrus.

Hippocampal circuits for pattern separation and completion

<u>Dentate gyrus</u> may create pattern separation through 'expansion coding'.





CA1

GCL

- Most DG Granule cells are born post-natally, and remain physiologically immature (over-excitable) for weeks.
- Possible mechanism for infantile generalization?



Dentate local circuit includes <u>Mossy Cells</u>, excitatory interneurons between Granule Cells and CA3



• Record Dentate Granule Cell, Mossy Cells, CA3

500 µm

4 3 2 1

 Separate Granule and Mossy using method of Senzai *et al.* 2017: PCA on 1) Waveform shape, 2) Spike bursting, 3) Mean Rate, 4) N Cells co-recorded.

Pattern separation in developing DG

- Test pattern separation with:
 - 1) **similar** context ('**SIM**'; new floor only)
 - 2) very different context (DIFF; all cues change)









Base vs BaseBase vs SimBase vs Diff

Isabella Varsavsky

 \rightarrow No significant pattern separation at any age





Base Sim Diff

P22-30

Base Sim Diff

P16-20

 \rightarrow Pattern separation postweaning only

Conclusions: development of neural mechanisms for memory

- Early hippocampal 'replay' is stationary: it consists only of reactivation of place cells in one location.
- Replay of spatial trajectories emerges late (gradually, post-weaning).
- Theta sequences co-develop with trajectory replay.
- Results consistent with recent adult study, in which mEC was inactivated. This abolishes theta sequences and trajectory replay, while preserving reactivation. (Liu, Todorova, Tang, Oliva & Fernandez-Ruiz, 2023, *Science*).
- Dentate gyrus pattern separation first emerges at around weaning age. Unexpectedly, this appears first in Mossy Cells.
- Raises questions: are mossy cells primary site of pattern separation (not granule cells), early in development?

Thanks to ..

Current lab members

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Collaborators

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Mums and pups



<u>Alumni</u>

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<u>Funders</u>



Thanks for listening!

