Evidence for grid cells in a human memory network

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Presented by:

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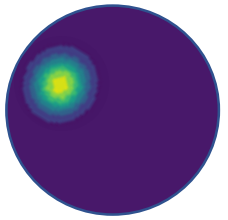
structure

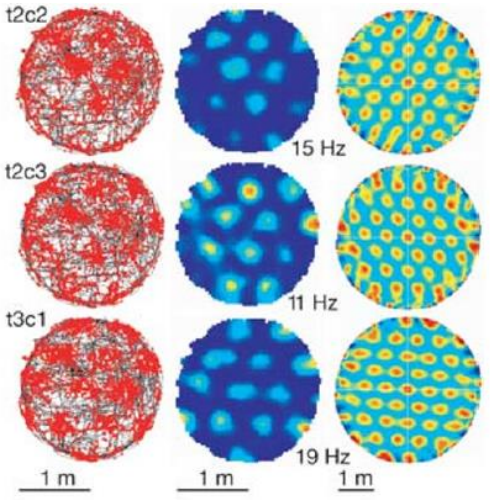
- What are grid cells and why are they so cool? (part 1)
- Measuring grid **cells** in **fMRI**?
- Grid code in fMRI
- fMRI adaptation (or: repetition suppression)
- What are grid cells and why are they so cool? (part 2)
- Limitations and future thoughts
- Discussion & questions

Feel free to interrupt me at any time with questions!

What are grid cells and why are they so cool (part 1)?

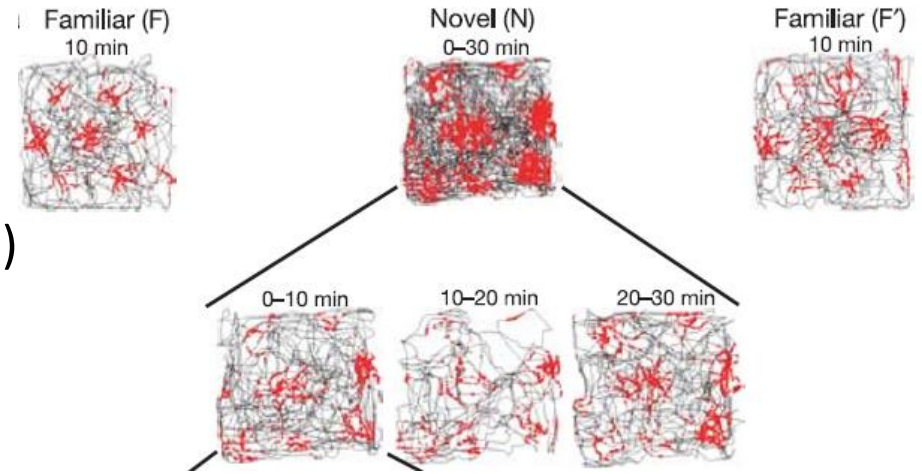
- Place cells
  - Where am I? Fire at a particular location in space
- Head direction cells
  - Where am I going/looking? Fires when the animal gazes to a particular location
- Grid cells
  - Integration of place & direction
  - Representation of the entire map





Grid cells offer context independent position map

- Place cells are context dependent (**remapping** in new environments)
- Grid cells **preserve structure** in novel environments (albeit **rotate**)



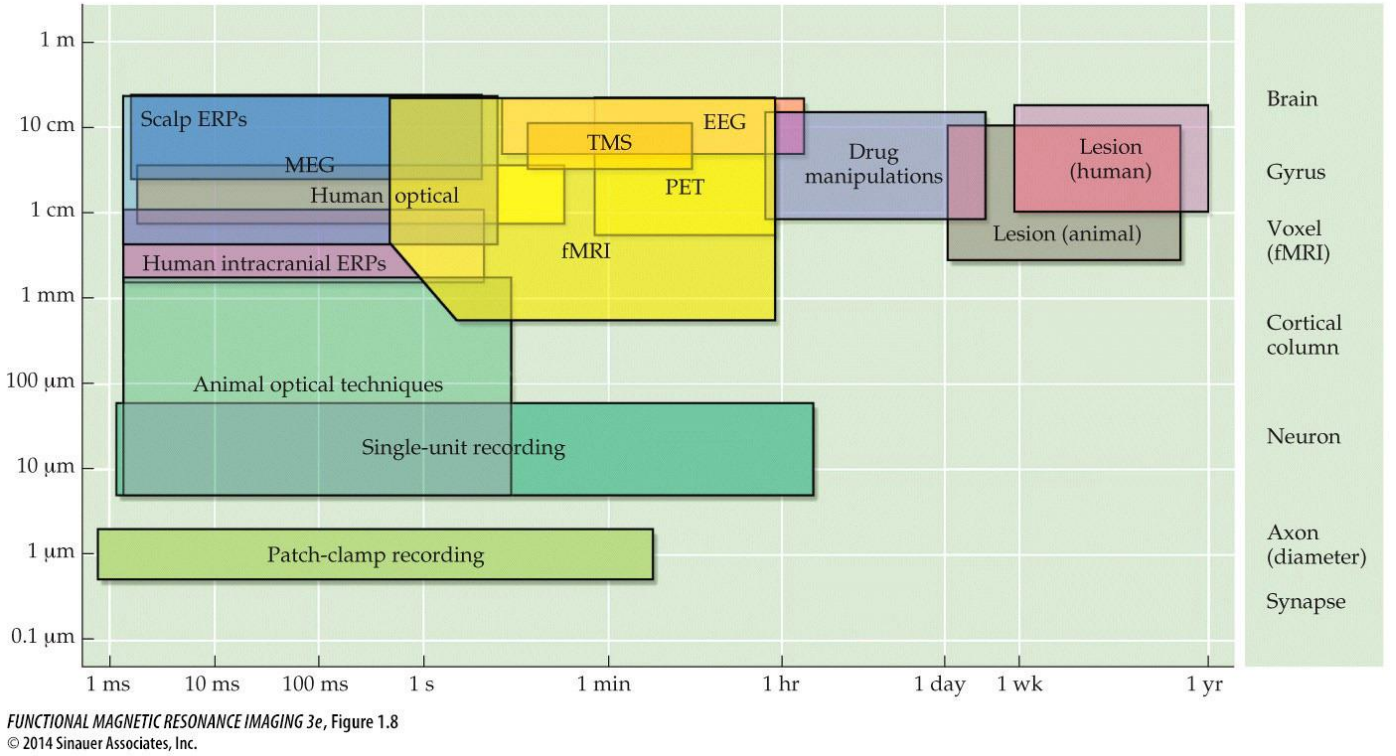
Hafting, T., Fyhn, M., Molden, S., Moser, M. B., & Moser, E. I. (2005). Microstructure of a spatial map in the entorhinal cortex.

Measuring grid **cells** in **fMRI**?

fMRI is **non invasive recording** imaging methods allows us to measure activity in subcortical areas.

However….
Problem 1: temporal resolution
One image of “BOLD” activity every 2.6 seconds (today: 1.5s)

Problem 2: spatial resolution (still)
Ca. 600,000 **(-ish)** neurons in each **cortical** voxel (today 180,000)
(they say “thousands” in the paper)



FUNCTIONAL MAGNETIC RESONANCE IMAGING 3e, Figure 1.8

Figure: Huettel, S. A., Song, A. W., & McCarthy, G. (2004). *Functional magnetic resonance imaging*
Voxel calculation roughly from: https://www.cfn.upenn.edu/aguirre/wiki/doku.php?id=public:neurons_in_a_voxel

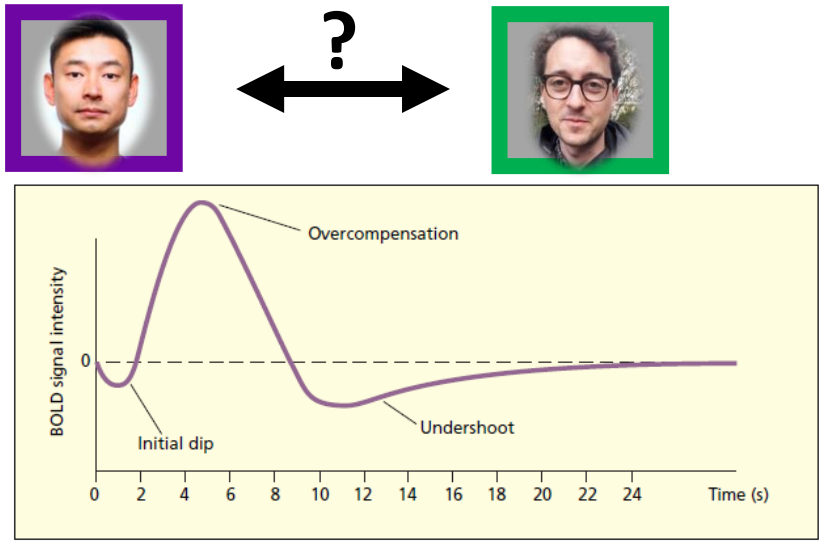
Intro to fMRI in 1 slide: from cells to BOLD

Problem 1: temporal resolution

- "Event" causes neurons to fire & use oxygen
- Deoxygenated Hemoglobin has a magnetic moment measurable in fMRI
- **BOLD** („Blood Oxygen Level Dependent") **is slow!** (ca. 20-30 seconds).
- In fMRI (Mass univariate analysis), for each voxel we fit:

$$activity \sim \beta_1 A + \cdots + \varepsilon$$

Which voxels started this activity when the picture appeared?

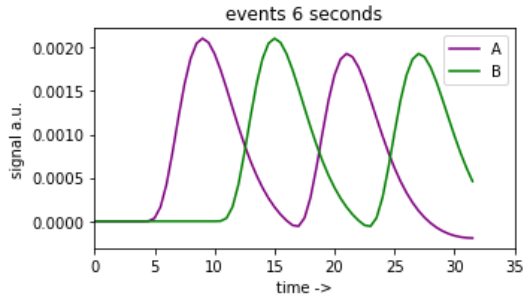


Ward, J. (2015). *The student's guide to cognitive neuroscience*.

$$activity \sim \beta_1 A + \beta_2 B \ \ldots + \varepsilon$$

any shared variance between β_1 and β_2 goes to neither(!)
bad design can only work against you.

Temporal correlation (collinearity) is controlled with random spacing between events ("jittering") and smart designs, allowing for faster events.



*40 trials...

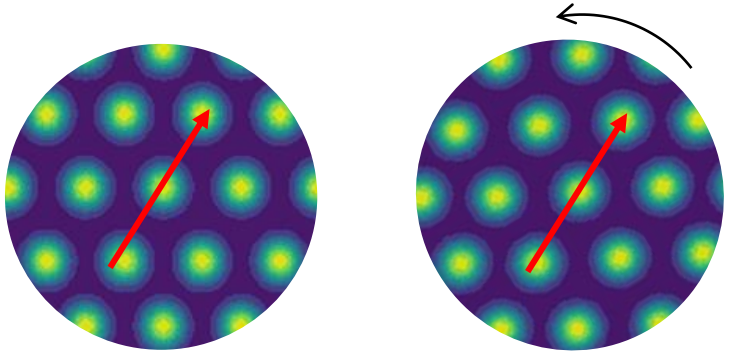
Take home: Events can be closer together in time, as long as the temporal autocorrelation is controlled

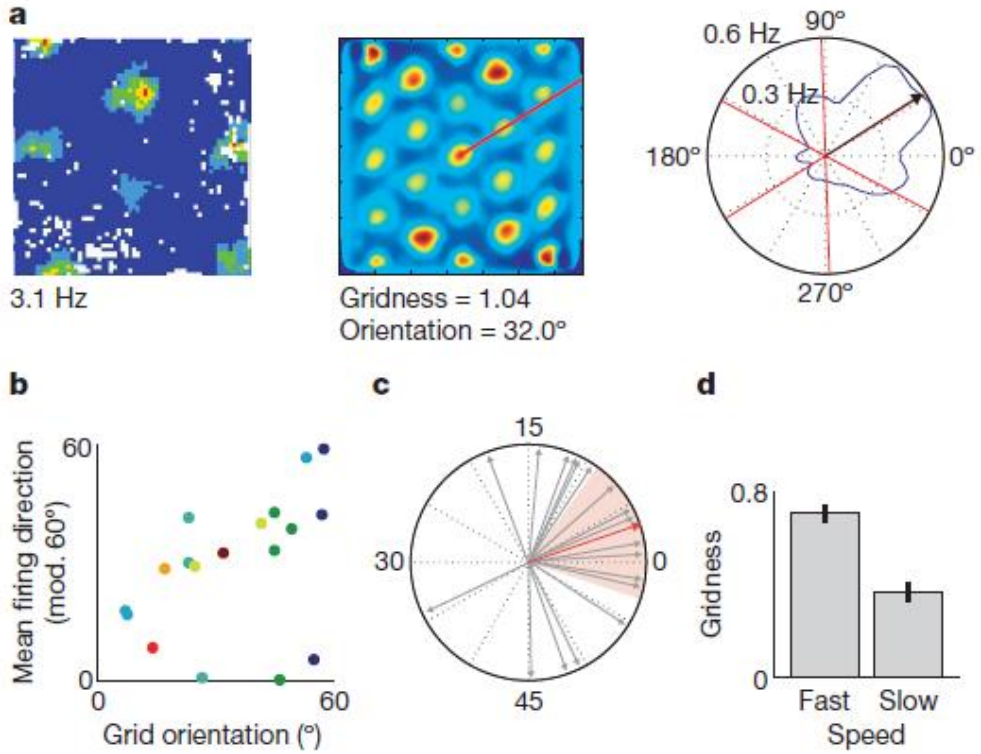
How do we measure grid cell activity in fMRI?

Problem 2: spatial resolution (still)

~600,000 neurons in each **cortical** voxel (today 180,000)

Each cell has a specific “Grid orientation” (tilt angle of the field)





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Barry, C., Hayman, R., Burgess, N. & Jeffery, K. J. (2007).

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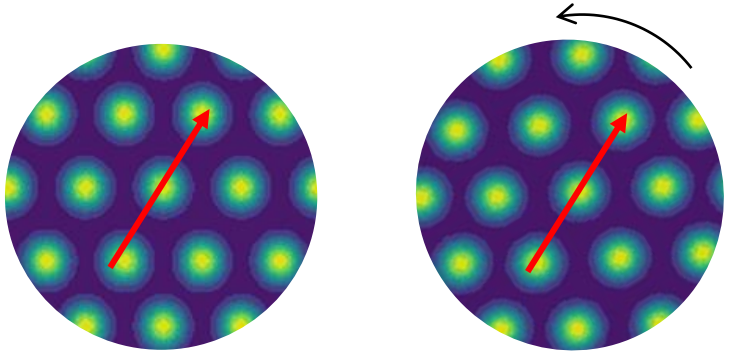
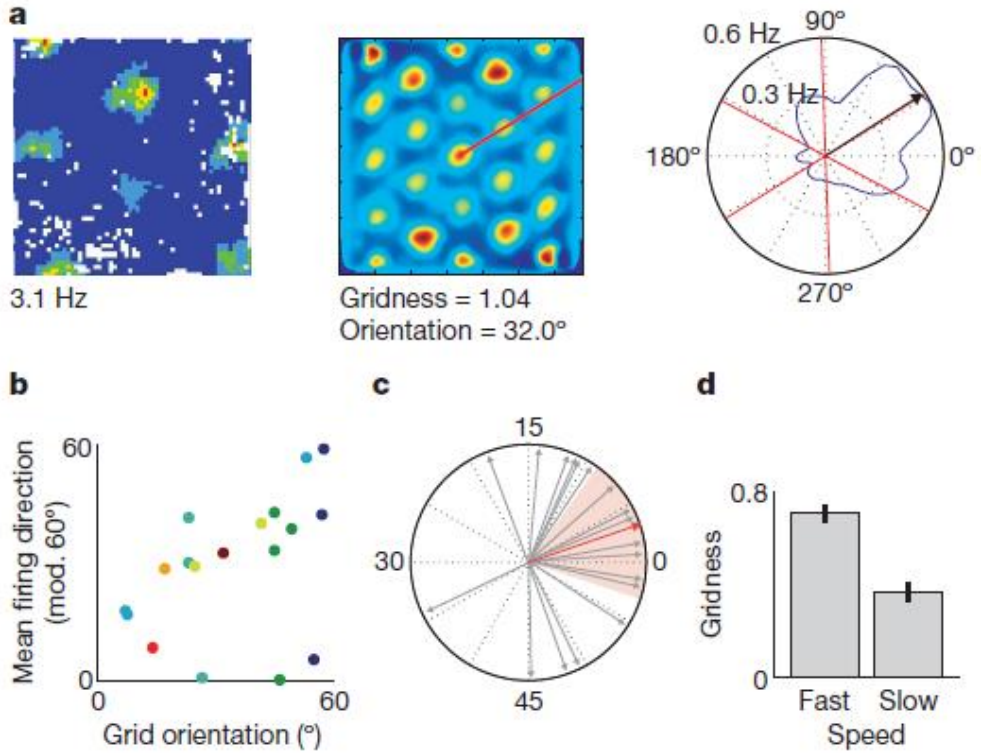


Grid cells orientation is similar across the entire Entorhinal cortex.

“Conjunctive” directional grid cells are modulated by running speed **and** share orientation with other grid cells.

Assumption (supported by animal work, Fig. 1):
Grid-orientation remains constant across multiple grid cells ->
we can treat a voxel as if all its grid cells have the same orientation.

(Note: orientation varies between subjects)



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Aligned vs misaligned navigation & speed modulation

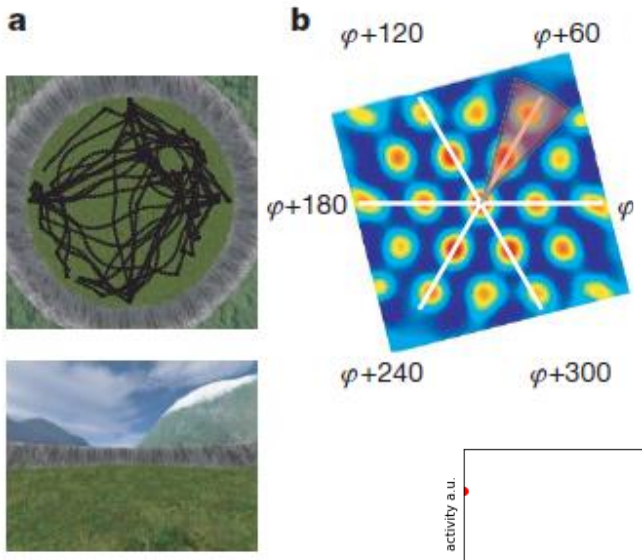
Virtual reality memory game in the scanner

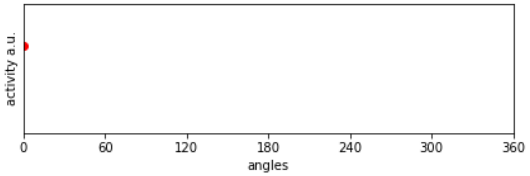
Design: three regressors, separated by the participant's speed of movement (three equal tertiles for high, medium and slow speed).

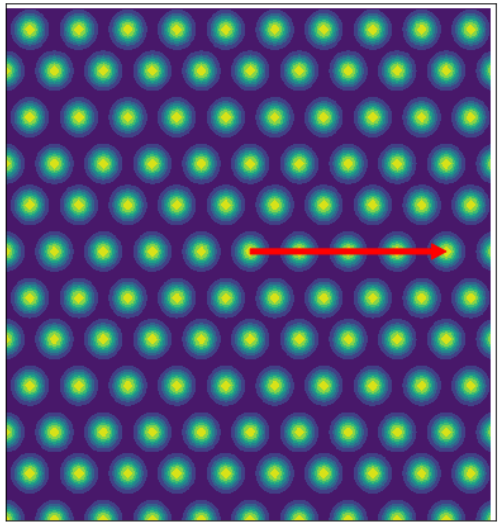
No report of collinearity, however – any shared variance goes to neither of the regressors, i.e. this can only work against them.

Hypotheses:

1. Each voxel (with similar orientated grid cells) will fire strongest when running direction is at **60 degrees to its orientation**







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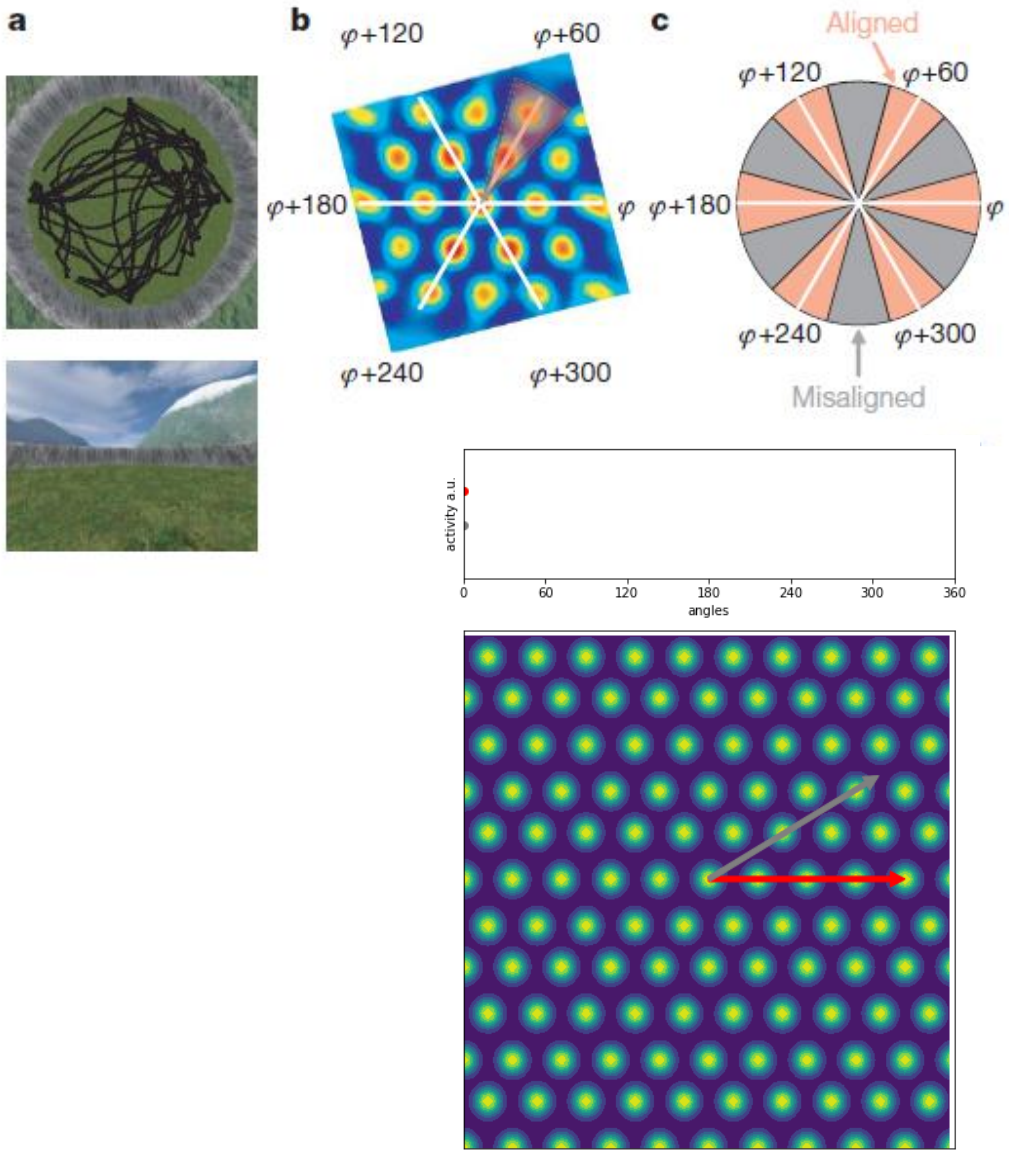
2. Maximum firing difference at **aligned compared to mis-aligned**



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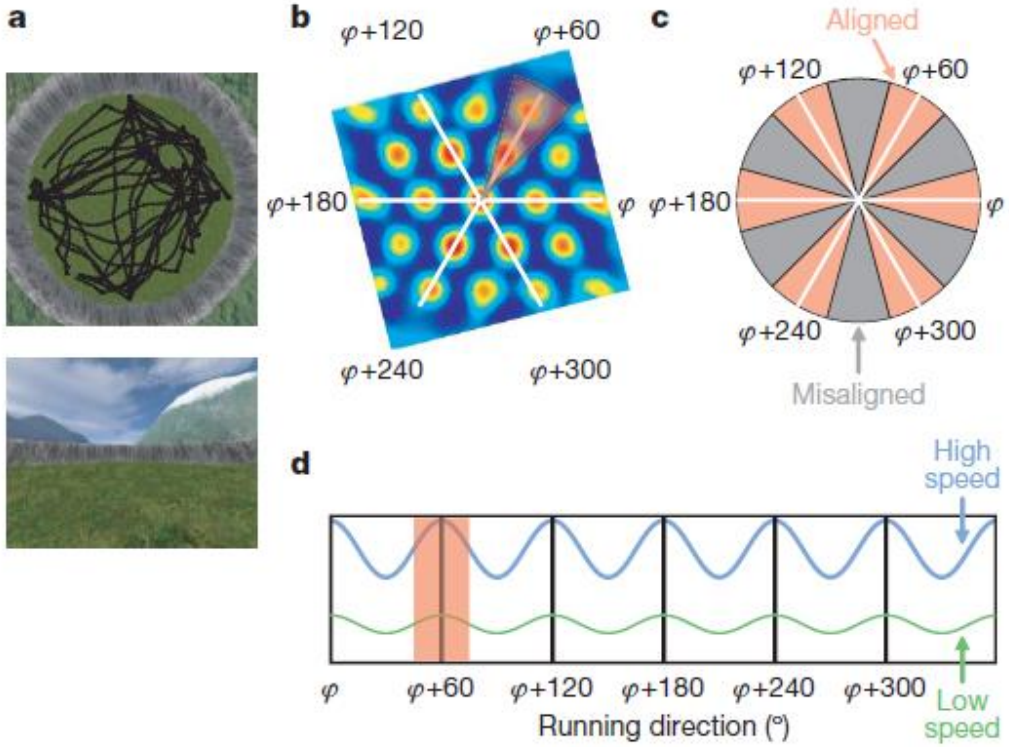
3. **Faster running** increase signal strength (crossing more fields).



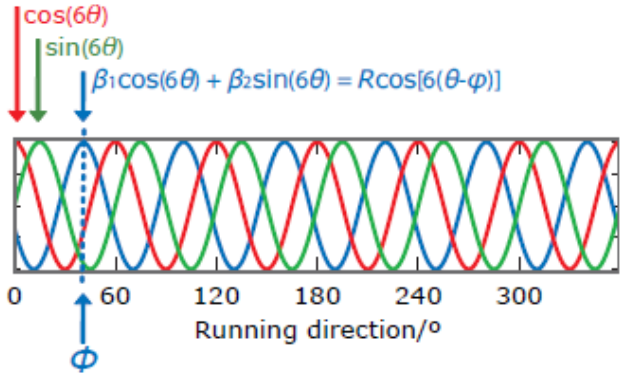
Q: How does the directional modulation change following the running speed?

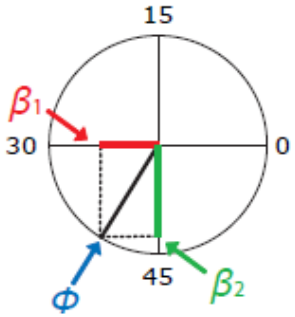
Q: why "grid patterns of neighboring cells are offset" makes it hard to detect grid cells with fMRI, so we look at running direction and speed?

BREAK and Questions

Formal tests of grid-like code

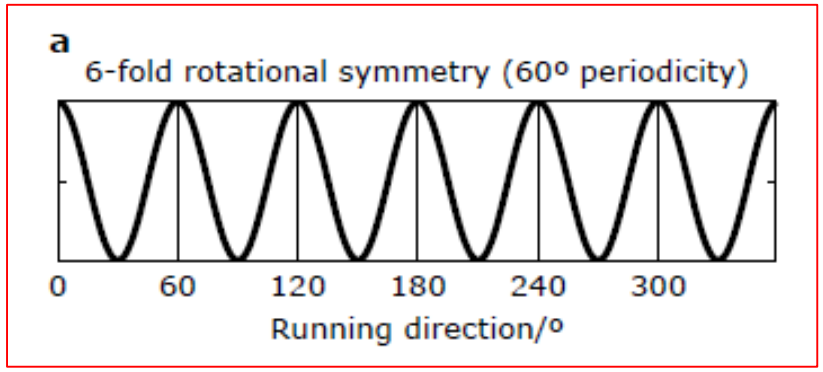
Grid orientation is indeed clustered (at least for fast runs)

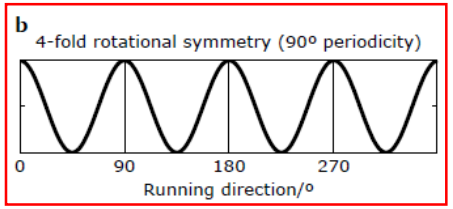


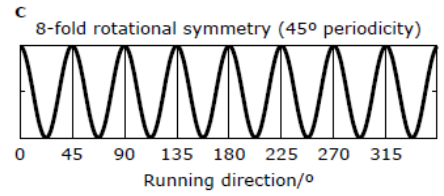


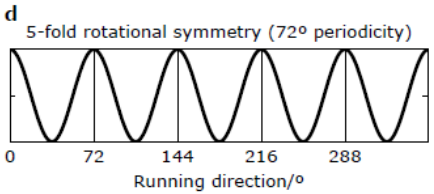
Q: why is the movement direction not encoded with e.g. four- or eight-fold or other symmetry?
"Unlike triangles and squares, hexagons do not divide into smaller versions of themselves, meaning they are very efficient for making sturdy walled containers with minimal material."

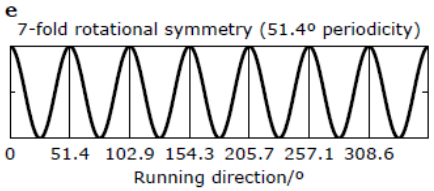
Signal is periodical specifically at 60 degrees (6-fold)











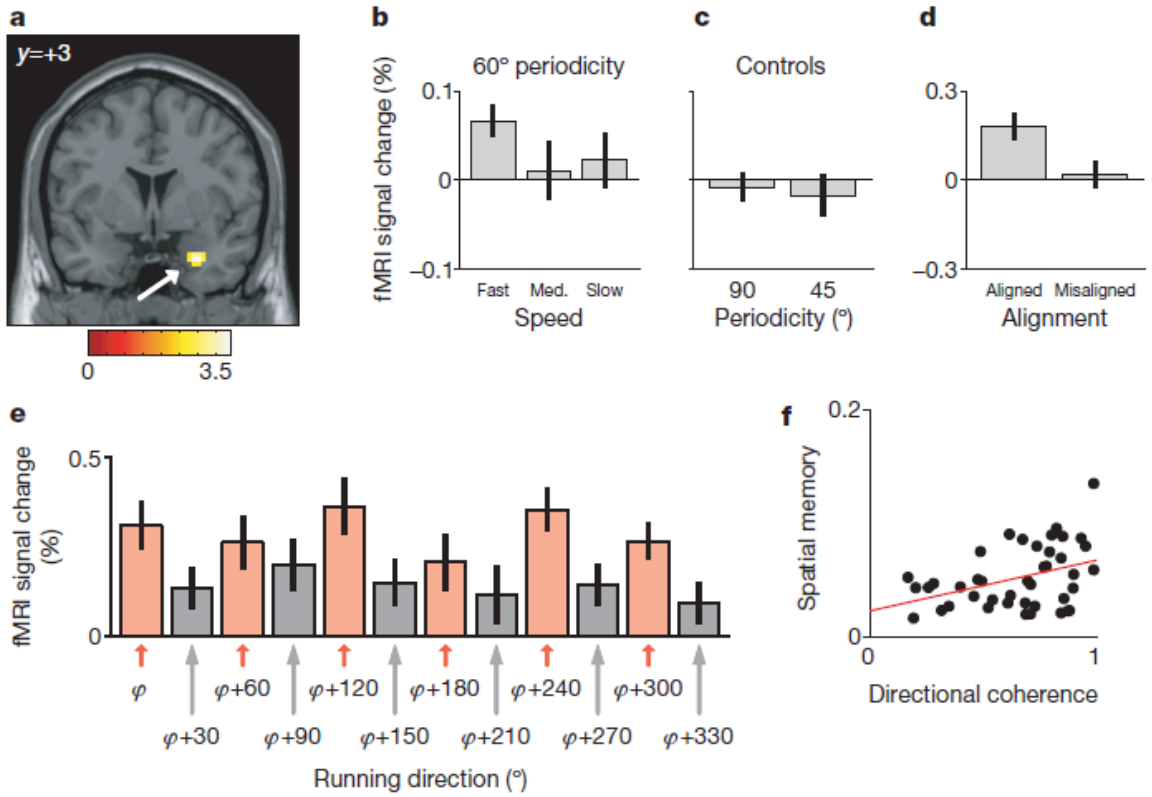
6 fold symmetry grid code in Entorhinal cortex

Region Of Interest (ROI) analyses:

Split data to 2 halves:

- 1st half: what is the orientation?
- 2nd half: given orientation, where do we see combined grid signal?

- Higher signal for aligned vs misaligned
- Specific for 6-fold symmetry
- Better memory performance for participants that had stronger clustering



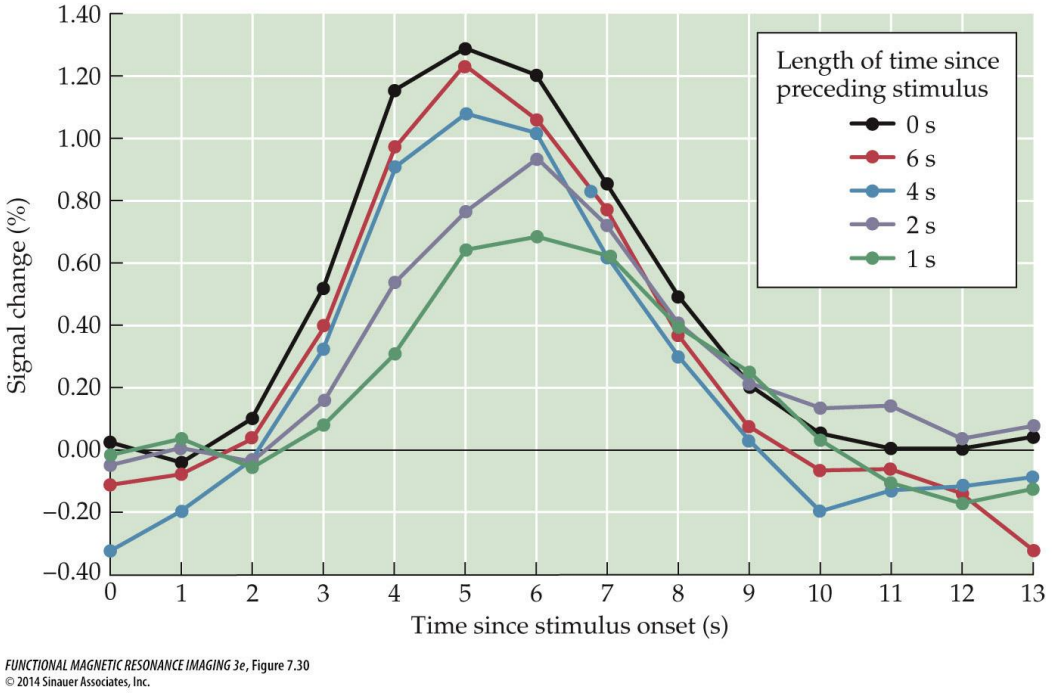
Q: Why only right hemisphere? No idea!

fMRI adaptation (or: repetition suppression)

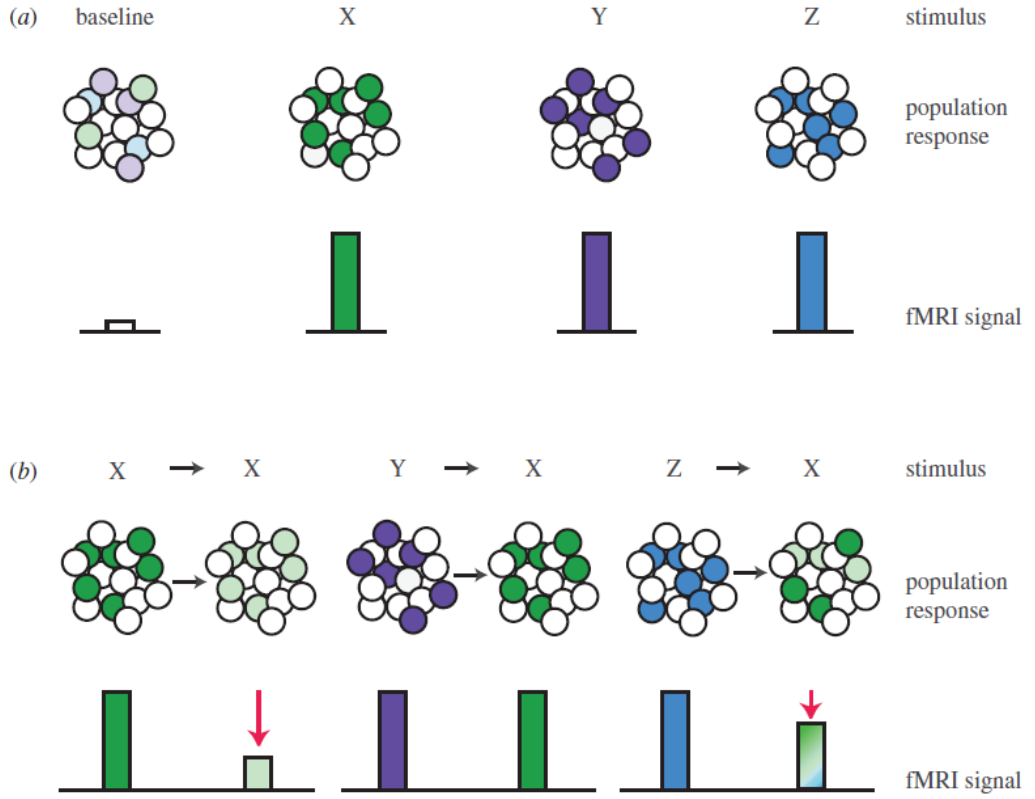
When an event repeats, there is a suppression of activation.

- This suppression is sensitive to the time since last presentation (left)
- In fMRI, this suppression is also sensitive to partial overlap (right)

Q: why log[time] regressor reflect the "adaptation"?
Log is usually done to normalize.
Evidence that perceived time works in log-scaling.
Couldn't find in the paper a reference as to why they logged.

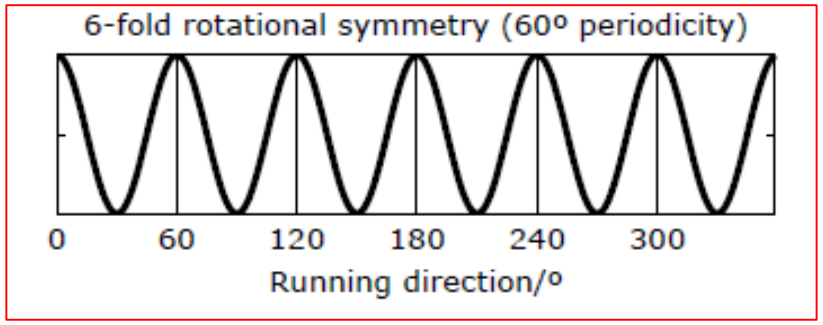


FUNCTIONAL MAGNETIC RESONANCE IMAGING 3e, Figure 7.30
© 2014 Sinauer Associates, Inc.



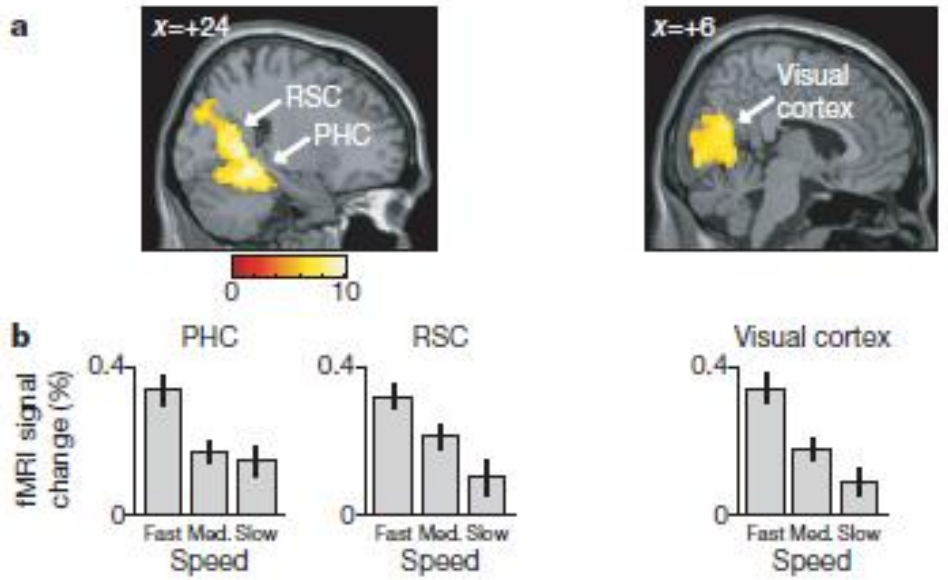
Left: Huettel, S. A., Song, A. W., & McCarthy, G. (2004). *Functional magnetic resonance imaging*
Right: Barron, H. C., Garvert, M. M., & Behrens, T. E. (2016). Repetition suppression: a means to index neural representations using BOLD

Whole brain repetition suppression

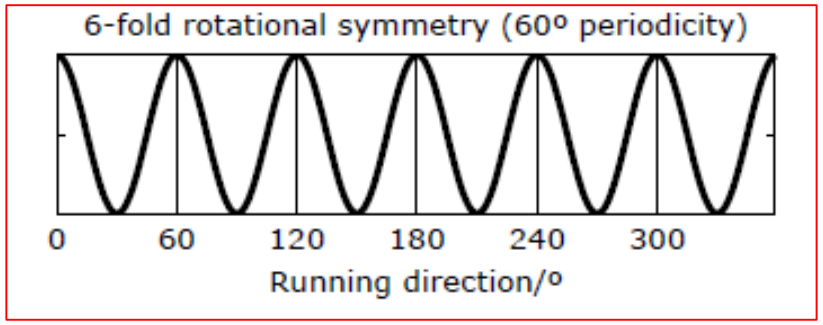


If the BOLD is 6-fold modulated,

a-b. Repetition of same angular trajectory should result in a decrease of activity



Whole brain repetition suppression



If the BOLD is 6-fold modulated,

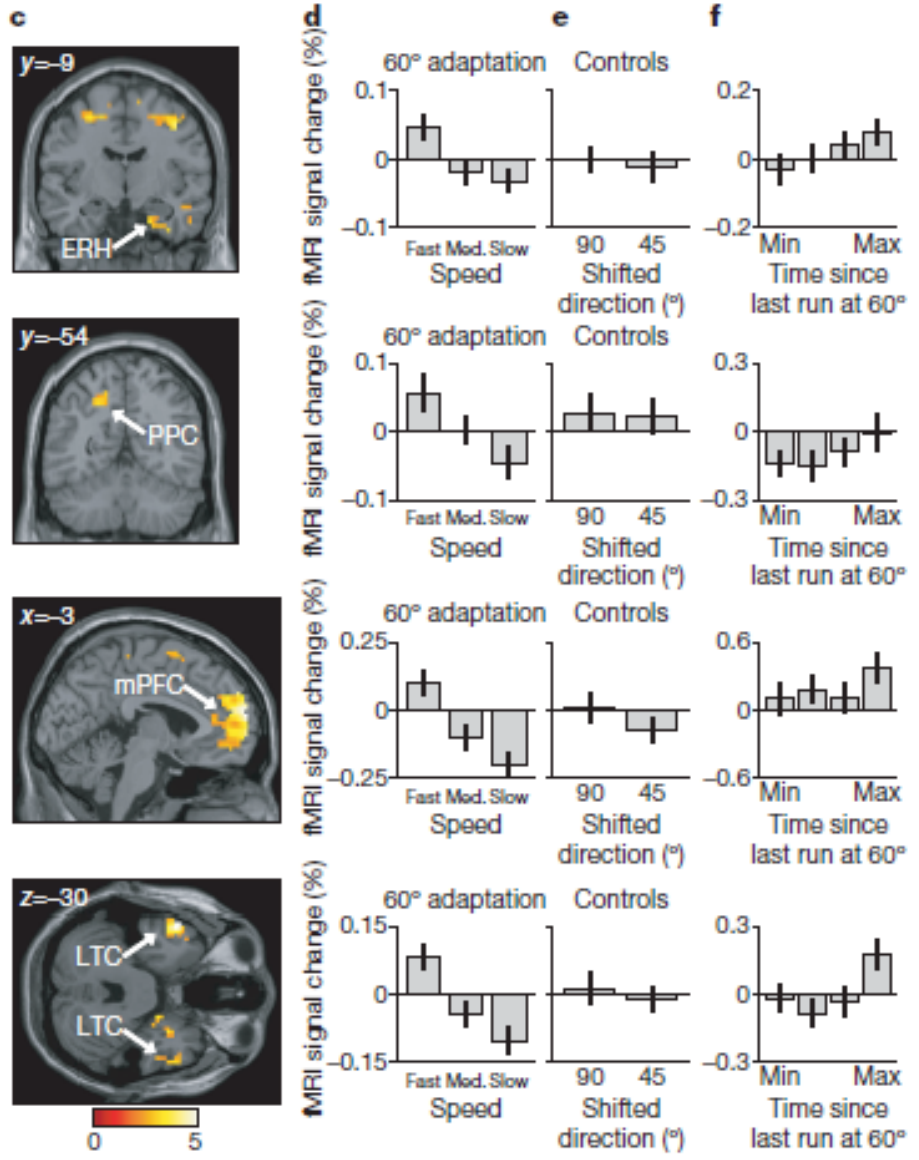
a-b. Repetition of same angular trajectory should result in a decrease of activity

c-f. and specifically when binning angles as their distance to 60 degrees.

Modulation of 60 degrees symmetry found in multiple regions raises fascinating questions, so far overlooked by animal work

(replicated in other human studies, animal studies on their way)

Q: How should we understand negative adaptations in med- and slow-moving speed?
Great Question! Any thoughts?



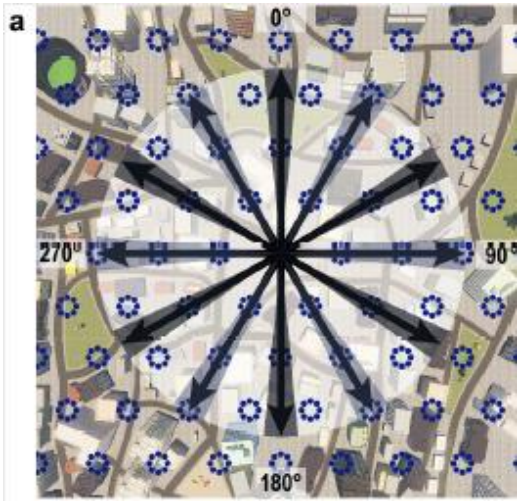
What are grid cells and why are they so cool (part 2)?

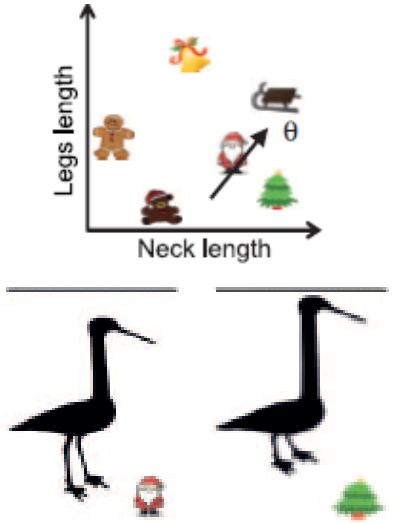
Grid modulation also found in…

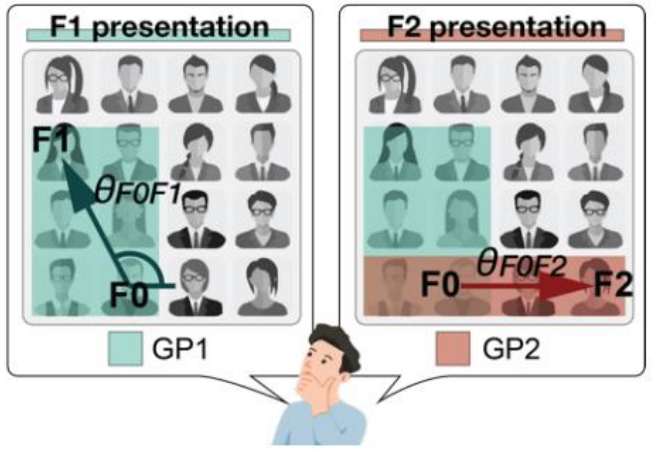
- Mental simulation in physical space
- Imagination of birds morphing their size
- Choosing business partners in a 2D social-hierarchy map (popularity & competence)

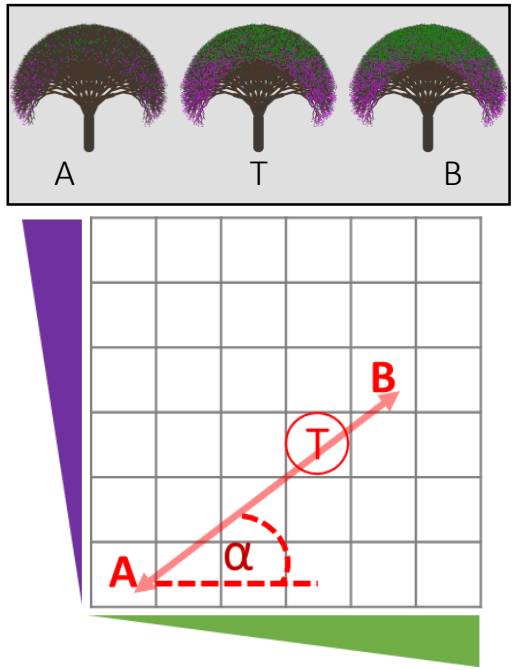
Q: how could grid cells look like in a social map?

Q: "tricking" grid cells? (e.g. teleportation). Didn't work in spatial.









Grid modulation involved in integrations of (at least) 2 dimensions of a cognitive map

Doeller, Barry, & Burgess. 2010
Bellmund, Deuker, Schröder & Doeller. 2016
Constantinescu, O'Reilly, & Behrens. 2016
Park, Miller & Boorman. 2021
Moneta, Wu, Doeller & Schuck. In prep.

Discussion & unanswered questions

- The virtual experiment takes place in a 3D environment. Is there a similar mean grid cell representation in three-dimensional space? Or is there maybe only in aquatic or flying animals?

YES! see: Grid cells in bats! Yartsev, Witter & Ulanovsky (2011).

- Provided the evidence that suggests a network of brain regions is complementary to the entorhinal cortex in showing grid-like activity, could further fMRI studies based on different requirement tasks reveal how the interaction of these brain regions guide behaviour? –

YES! A start can be seen in Value-dependent grid cell only in mPFC: Bongioanni, Folloni, Verhagen, Sallet, Klein-Flügge & Rushworth (2021).

- If not visual features (the study says the random variation of grid orientations between subjects rules this out), what might align the orientation of grid cells? Is the orientation consistent in individuals over trials? If so, how long do these orientations persists?

How long? At least 3 weeks in humans. Not sure the equivalent in rodents.
What aligns? Likely some cues in the environment, or first exposures, afaik it is still not clear to predict but super cool if someone will manage to do so!

- Was the grid-like map only created because the subjects were performing a spatial memory task, or would their activity in enthorinal cortex still be modulated by alignment to their grids if they were simply exploring the environment freely? How long since exposure to the environment does it take for such a map to form? Would a goal-directed task induce a faster generation (learning) of the map?

Great question!
It is believed that it is a bit more of a context-free representation that is recruited for a task.
In my work I give them 20 min of exposure before they start the task, I havn't looked at block-dependent strength but I should!

- What are other potential factors other than the three factors proposed in the paper that could help us provide evidence for grid cells' existence in humans using fMRI signal?

My first thought: Non spatial tasks (although grid was found In mice in sound frequency domain), as well as remapping and prediction of orientation would be great!

- The paper talks about the relation of grid cells and (spatial) memory. Do we know more about this relation today?

From unofficial chats all I know is that it is still unclear. E.G. I heard that there are no evidence for example on better memory for items "on a field" or "aligned" or bias to run "aligned" in a field.

Discussion & unanswered questions

- What can be the implied consequences and limitations of using virtual reality environments in fMRI measurements? What can be expected to be different compared to accessing rats that were being stimulated and interacting with a real environment?
- I had essentially the same question as Paula, especially when they are making assertions about head movement and running speed/direction. What other mechanisms might be important for grid cells besides visual input and simulation that are being neglected in a virtual scenario?

Good questions. Thoughts?

- According to the methods, the study was conducted on young men (forty-two male participants aged 18-31). Is there any reason to assume the results would be similar on females? Are there studies that tackle this? If not, would it be on the table?

Good one! Probably attempted to avoid balancing groups.
AFAIK usually done when there is no reason to think on gender differences, or to avoid control over hormonal status of females.
(unless there is an animal related reasoning). Personally I showed in pilots no gender effect in behavior and then ignored that factor all together.

- The paper mentions potential methodological limitations in regard to the definition of entorhinal cortex ROIs and the homology of human versus rodent subdivisions and states that future high-resolution imaging could solve this issue. In your opinion, how cautious do we need to be with interpreting the results of this paper and have newer papers/methods supported or contradicted the here presented data?

In my opinion, its not a real limitation on the results as much as on how much can one relate specific subdivisions of EC to rats/monkeys. Specifically, the Entorhinal anterior-posterior axis has gradually different spacing of grid-fields which they are limited to see. Also see the many conceptual replications of the results which I believe make the results better.

- The authors observe that the coherence of potential mean grid orientations of respective participants (in their right EC) is strongly correlated with spatial memory performance -- better coherence => better spatial memory performance; Could one expect to find some kind of criticality here with respect to coherence of grid cell representations, in its effects on spatial memory? (the methods used here could possibly make measuring this doable)

not sure what the question is, isn't this what they found?