Neural systems supporting navigation

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Much is known about how neural systems determine current spatial position and orientation in the environment. By contrast little is understood about how the brain represents future goal locations or computes the distance and direction to such goals. Recent electrophysiology, computational modelling and neuroimaging research have shed new light on how the spatial relationship to a goal may be determined and represented during navigation. This research suggests that the hippocampus may code the path to the goal while the entorhinal cortex represents the vector to the goal. It also reveals that the engagement of the hippocampus and entorhinal cortex varies across the different operational stages of navigation, such as during travel, route planning, and decision-making at waypoints.

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Introduction

The ability to navigate is a fundamental behaviour shared by most motile animals on our planet. In order to navigate an animal must determine the direction to travel in, how far to travel and subsequently keep track of its progress through the environment. The challenges of navigating vary depending on the environment. For example, navigating an open featureless terrain presents different challenges to traversing an urban street network. Similarly, recalling where a location is and how to get there is likely to be more challenging in a novel environment than a well-known one. When navigation requires travelling along familiar habitual routes evidence indicates that stimulus–response associations stored in the dorsal striatum allow an animal to determine in which direction to proceed and when they have travelled far enough to arrive at the goal [1–3]. However, when navigation relies on determining self-location in the environment and computing the spatial relationship to the goal, the hippocampus and connected structures of the medial temporal lobe (MTL), such as the entorhinal cortex, are needed for navigation [4–8]. MTL and striatum also operate as part of a wider brain network serving navigation. In summary, it is thought the parahippocampal cortex supports the recognition of specific views and the retrosplenial cortex converts between allocentric (environment-bound) representations in hippocampal–entorhinal regions to egocentric representations in posterior parietal cortex [9•,10,11]. In addition, the prefrontal cortex is thought to aid route planning, decision-making and switching between navigation strategies [12,13] and the cerebellum is required when navigation involves monitoring self-motion [14]. Here we focus on the role of the hippocampus and entorhinal cortex because of recent discoveries from functional magnetic resonance imaging (fMRI) and single unit recording studies and the development of new computational models.

Electrophysiological investigations have revealed several distinct neural representations of self-location (see Figure 1 and for review [15]). Briefly, place cells found in hippocampal regions CA3 and CA1 signal the animal's presence in particular regions of space; the cells' place fields [16] (Figure 1a). Place fields are broadly stable between visits to familiar locations but remap whenever a novel environment is encountered, quickly forming a new and distinct representation [17,18]. Grid cells, identified in entorhinal cortex, and subsequently in the pre-subiculum and para-subiculum, also signal self-location but do so with multiple receptive fields distributed in a striking hexagonal array [19,20] (Figure 1b). Head direction cells, found throughout the limbic system, provide a complementary representation, signalling facing direction; with each cell responding only when the animal's head is within a narrow range of orientations in the horizontal plane (e.g. [21], Figure 1c). Other similar cell types are also known, for example border cells which signal proximity to environmental boundaries [22] and conjunctive grid cells which respond to both position and facing direction [23]. It is likely that these spatial representations are a common feature of the mammalian brain, at the very least grid cells and place cells have been found in animals as diverse as bats, humans, and rodents [15].

Goal-related coding in spatial cells

Do these representations of self-location play a role in guiding navigation? The activity of spatial neurons co-varies with navigational performance, for example, accumulated

Figure 1
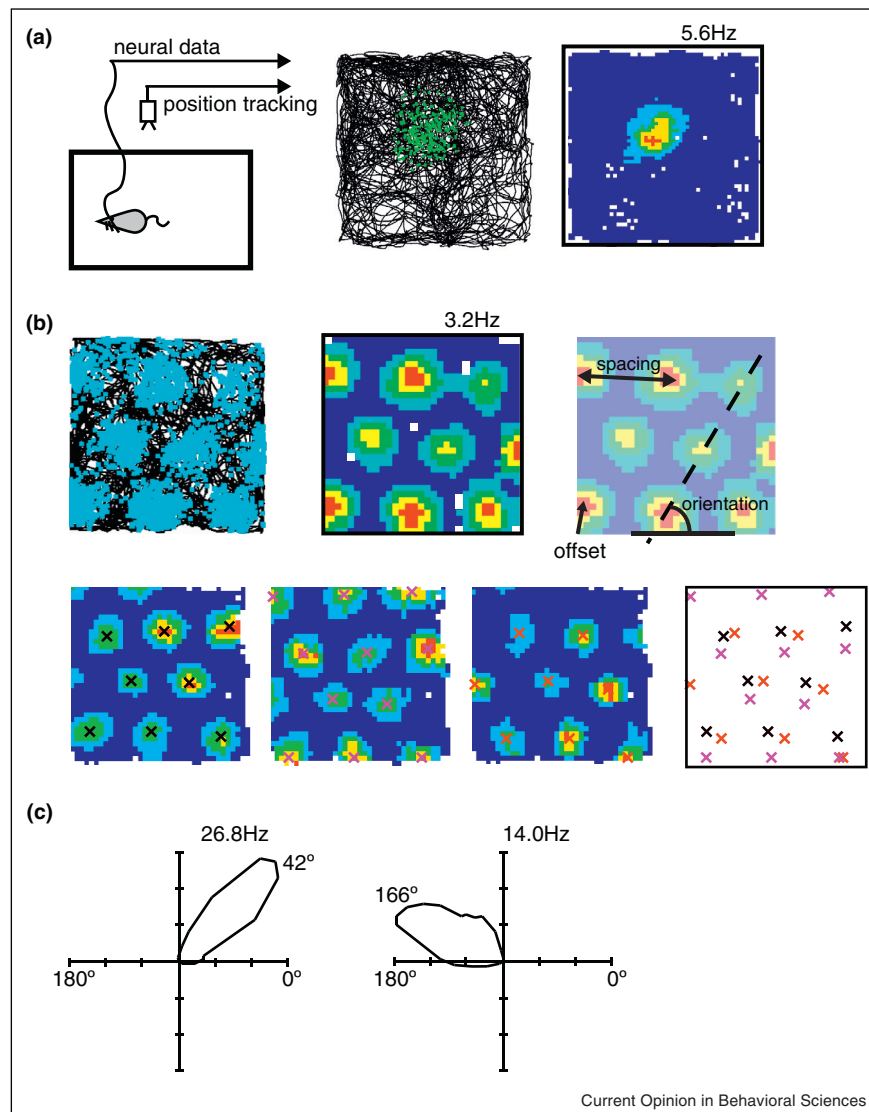
Single-unit recordings of neurons encoding aspects of self-location. **(a)** CA1 place cell recording made from a rat. Left-hand figure shows a typical experimental setup, the animal forages in a 1 m² open field environment, in concert its position is tracked by an overhead camera and action potentials are recorded from implanted electrodes. Centre, raw data: the black line indicates the animal's cumulative path over 20 min; superimposed green dots indicating the location at which this cell fired action potentials. Right, the same data processed to show firing rate (number of spikes divided by dwell time) per spatial bin. 'Hot' colours indicate high firing rates and 'cold' colours low firing rates, white bins are unvisited, peak firing rate is shown above the map. **(b)** Top row, raw data and corresponding rate map for a single medial entorhinal cortex (mEC) grid cell showing the multiple firing fields arranged in a hexagonal lattice. Bottom row, three co-recorded mEC grid cells, the centre of each field is indicated by a cross, colours corresponding to different cells. The firing pattern of each cell is effectively a translation of the other co-recorded cells as shown by the relative position of the crosses (right). **(c)** Two head direction cells recorded from mEC deep layers (V/VI). Firing rate is displayed as a function of head direction, the cell on the left has a peak firing rate of 26.8 Hz achieved when the animal was facing at an orientation of 42° (measured anti-clockwise from the horizontal axis of the environment).
Figure adapted from [15,59].

error in the head direction system predicts the bearing rats take when attempting to reach a goal [24,25] and similar results are known for place cells [26]. While this suggests that these cells form the basis of navigational computations it is not clear what form those computations take and where they are made. In particular, how spatial networks encode goal location and utilise this information to determine an appropriate route are still to be determined. However, the last decade has seen some progress with the former of these problems. For example, it is now known that place cell populations encode information in addition to the representation of self-location, such as presence of reward at a goal locations [27], or the recent and future turns to be made in a route [28,29]. There have been conflicting reports as to

whether rodent hippocampal place cells preferentially represent goal locations [12]. Navigation in environments composed of tracks (such as T-mazes or plus-mazes) has tended not to find goal-location related firing [30,31]. By contrast, in open-field environments, which make greater demands on self-localisation for navigation, elevated place cell activity proximate to goals has been reported [32•,33–35]. Similarly, the activity of hippocampal cells in pre-surgical epileptic patients navigating in a virtual town has been shown to be modulated by the current goal [36]. A recent important study in which rats learned new goal locations each day in an open arena, found that CA1, but not CA3, place cells, showed shifts in firing towards the newly learned goal locations [32•]. Cells in the prelimbic frontal cortex have also been reported to show activity clustered around goal locations in an open arena. However, no such clustering of activity near goal locations was observed when rats could rely on a visual marker of the goal, rather than their memory, to locate the goal [35,37].

Computational models of navigational guidance systems

Numerous computational models have sought to understand how navigation can be conducted on the basis of the known or predicted neural representations. Before the discovery of grid cells this work was primarily focused on place cells (e.g. [38–41]). However, because place cells exhibit a sparse spatial code of irregular fields it is not obvious that they encode the structure of large scale space; they do not provide a spatial metric [42]. In other words, based on the population activity of place cells at two positions in the environment it is does not appear that the relative proximity of those positions can be easily inferred.

Models addressed this issue in several ways; one possibility being that the relative proximity of place fields is learnt during a period of exploration. For example, Hebbian-like or spike time dependent plasticity will tend to strengthen connections between place cells with neighbouring fields because adjacent locations are visited more frequently and in closer temporal sequence than distant locations [40,41]. In this way the connectivity between place cells, normally identified with the CA3 recurrent connections, is updated to reflect the relative position of their fields in space and can be used to test or infer potential routes [41]. A weakness of this approach though is that the animal must thoroughly explore an unfamiliar environment before it can navigate effectively; specifically the network cannot identify routes that traverse unvisited sections of space. Thus, the system cannot exploit potential shortcuts when changes to the environment occur. Conversely, it does mean that the network learns about the relative accessibility of points in known space, allowing the shortest route to be selected and dead-ends avoided. Muller et al.'s [41] model of the CA3 place cell network as a resistive grid took advantage of this effect to determine the shortest viable route to a goal. An

alternative proposal is that navigation could be affected by moving to maximise the similarity between the place cell representation of the goal and current location. However, such an approach is only successful when travelling between points separated by less than the diameter of the largest place field. Beyond this distance the overlap between representations will be flat affording no gradient to follow. Although the size of the largest place fields is unclear, recordings made from the ventral hippocampus of rats suggests that fields might exceed 10 m in diameter [43]; though larger than a typical experimental room this is much smaller than the range of wild rats which can be hundreds of metres [44].

By contrast to place cells, the spatial activity of grid cells is inherently regular, spanning the available space with repetitive firing patterns [19] that may provide a spatial metric (though see [45]). In the medial entorhinal cortex medial entorhinal cortex (mEC) grid cells are known to exist in functional modules, the cells in each module having grid-like firing patterns that are effectively translations of one another; sharing the same orientation and scale but having different offsets relative to the environment [19,46–48] (Figure 1b). Modules are distributed along the dorso-ventral axis of the mEC with those at more ventral locations tending to be of larger scale such that the size of the peaks in the grid firing pattern and the distance between them is increased [19,23,47]. Analysis of the grid code suggests that it provides an extremely efficient representation of self-location; modules of different scales behaving similarly to the registers in a residue number system such that capacity of the network greatly exceeds the scale of the largest grid [49,50]. Because of these properties grid cells are currently thought to be a core component of the neural system responsible for path integration; their repetitive firing fields being a cumulative representation of self-motion cues (e.g. [51,52]). It is interesting then to note that navigation is not dissimilar to the inverse of path integration: the former requires the calculation of the vector between two allocentric locations, while the latter uses recent motion, expressed as a vector, to update an allocentric representation of self-location. As such it seems possible that the neural architecture that supports path integration might also play a role in navigation.

Indeed, several authors have recently proposed models of navigation in which grid cells are seen as the central component of a network able to determine the allocentric vector between an animal's current location and a remembered goal [53–55]. However, the mechanisms employed by the models differ markedly, ranging from an iterative search for the appropriate vector [53] to a complex representation of all possible vectors projected into to the cyclic grid space [54]. As such, at the neural level, it is still too early to predict how the activity of individual grid cells might be modulated during navigation. However, at

the population level accessible to fMRI, it seems plausible that metabolic activity in the entorhinal cortex should correlate with allocentric spatial parameters. Indeed it is already known that the coherence of the directional signal associated with grid cells correlates with navigational performance [56]. Furthermore, in light of the limitations imposed on place cell models of navigation by the irregular distribution of place fields, it seems more likely that activity in the hippocampus will reflect route based variables.

Neural representations of the distance to the goal

A number of recent fMRI studies have examined whether brain activity is correlated with the distance between landmarks or to goals during navigation. During navigation a number of spatial parameters represent the navigator's relationship to the goal (Figure 2a) and these parameters change over the different key events and epochs that characterise navigation (Figure 2b). Humans have been shown to be reasonably good at estimating

Figure 2

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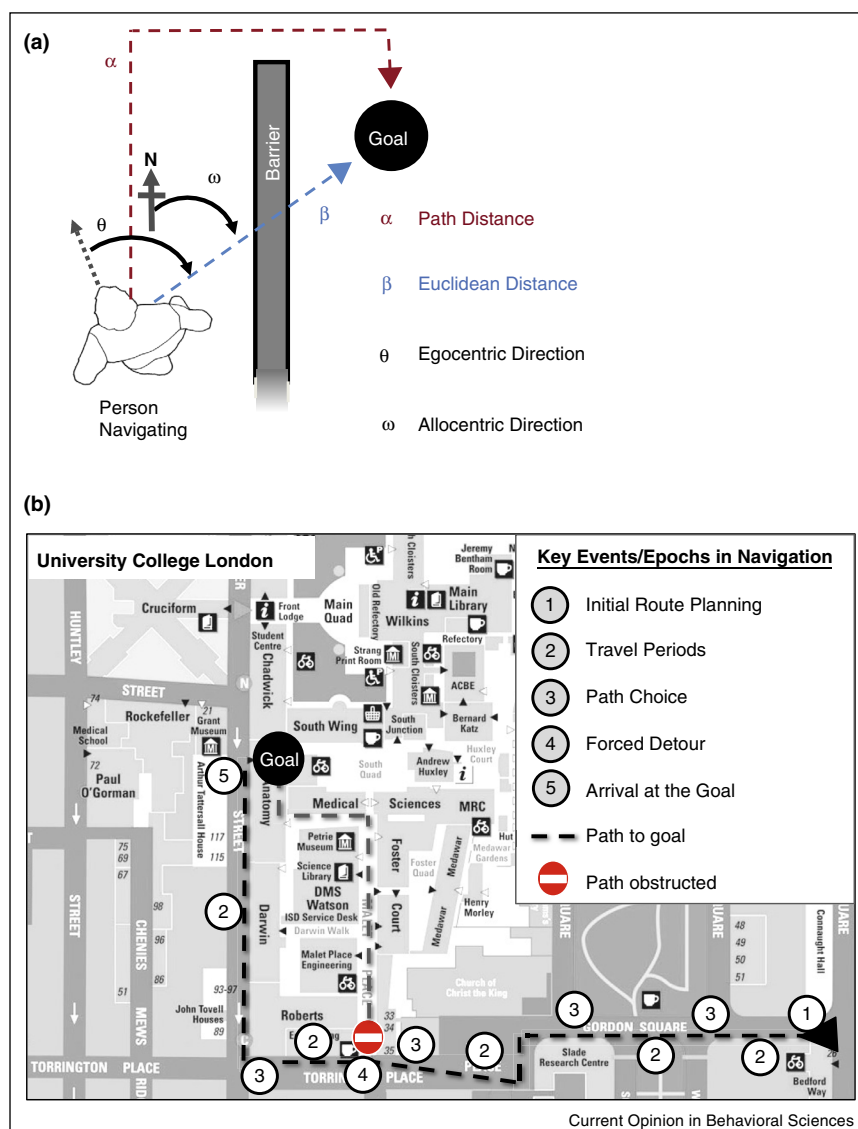
Spatial goal parameters and key events/epochs in navigation. **(a)** Four different spatial relationships are depicted between a person navigating and their goal. Path distance refers to the distance along the path to their goal (also referred to as the 'city-block distance' or 'geodesic distance'). The Euclidean distance is the distance along the shortest straight line connecting current position and the goal. Egocentric direction is the angle between person's current facing direction and the direction along the Euclidean. The allocentric direction is angle between a fixed reference direction in the environment (e.g. North) and the Euclidean. **(b)** A map of part of University College London, with route between the first author's office (black triangle) and the second author's office (goal) shown. Five key events/epochs are shown along the journey. A forced detour is illustrated where a change in the path is required.

parameters such as Euclidean distance, path distance, and direction to distant locations, at least in large complex buildings [57]. Two studies have reported increased activity in the mid to anterior hippocampus at the start of navigation when route planning was required [8,58]. Such activity may relate to the initial demands of planning the route to the goal, however it was not clear whether this activity was related to the distance to the goal. The first fMRI study to examine spatial goal coding found that activity in the entorhinal cortex of London taxi drivers was significantly positively correlated with the Euclidean distance to the goal during the navigation of a virtual simulation of London, UK [9•] (Figure 3a). This result is consistent with the entorhinal cortex coding an allocentric vector to the goal [53–55,59]. Several recent studies have adopted a similar approach (Figure 3b–d). These studies vary substantially in terms of the types of environments (e.g. a city region versus terrain devoid of landmarks), the amount of prior learning (e.g. 4 years versus 10 s), and the task required (navigate to a remembered goal versus choosing the path to a visible goal). Despite these differences all studies have consistently reported a significant relationship between hippocampal activity and goal proximity. However, less consistent have been the sign of the correlations (see Figure 3b–d), with some studies reporting a positive correlation [52] and others a negative correlation [53,54].

A recent study by Howard *et al.* [55] provides some insight into these apparently conflicting results, and the respective roles the hippocampus and entorhinal cortex during the different stages of navigation (shown in Figure 2b). Howard *et al.* had subjects learn, via a map and a walking tour, a previously unfamiliar real-world environment and on the following day navigate to goals in a virtual simulation of the environment (Figure 3e). Routes navigated were designed such that they separated the Euclidean distance from the path distance to the goal and permitted brain activity during the various stages of navigation to be examined (Figure 2b). While posterior hippocampal activity was correlated with the path distance at several stages of navigation, entorhinal activity was correlated with the change in the Euclidean distance to goal when initially planning the route. Thus, consistent with some computational perspectives, the entorhinal cortex might provide information for a goal vector and the hippocampus processes the path to the goal [53–55,59].

Howard *et al.* also found that the relationship between hippocampal activity and the distance to the goal differed depending on the operational stage of navigation. At path-choice points hippocampal activity was negatively correlated with the distance (and with orientation) to the goal (i.e. increasing with goal proximity), while during travel periods it was positively correlated with the distance to the goal (Figure 3e). When the task demands in other studies reporting activity correlated with distance

(Figure 3a–d) are considered a similar pattern emerges. In tasks involving either purely path decisions [53] or multiple decisions in quick succession about the direction to travel [54], a negative correlation between activity and distance was observed (Figure 3c,d). Whilst, in studies involving updating locations viewed [51], or mainly updating self-location during travel [50], activity was positively correlated with the distance to the goal (Figure 3a,b). One possibility is that updating the distance to a goal is more demanding when far from the goal, leading to a positive correlation. This would be consistent with studies linking hippocampal activity to spatial updating demands [64–66]. Activity increasing with proximity to the goal at path choice points may relate to reports of hippocampal place cell activity clustered near goals [32•,33–35], which would lead to a negative correlation between distance and activity. More research will be required to determine how task demands relate to distance coding in the hippocampus and entorhinal cortex.

A potential pitfall with studies using correlations between parametric parameters and brain activity is that uncontrolled properties of the stimuli might be responsible for mediating the effects. By including a control condition Howard *et al.* revealed that simply being led to the goal was not sufficient to elicit a significant correlation between activity and the distance. Thus, representing information related to the distance to the goal in the hippocampus and entorhinal cortex appears to require active goal-directed navigation. An important line of future enquiry will be to determine whether the correlations between MTL activity and distance are related to other factors involved in goal-directed navigation.

Three important factors that may co-vary with the distance to the goal are: firstly memory demands, secondly the time required to travel to the goal and finally reward associated with reaching the goal. Recalling the route to far away goal locations would arguably make greater demands on retrieval of the environment than recalling the route to close by locations. Thus, it may be that retrieval demands might underlie the positive correlations observed between hippocampal activity and the distance to the goal. It has been argued that the hippocampal role in navigation is purely to retrieve stored knowledge of the environment, not to make the path calculations [67]. Independently manipulating the distance from the number of turns and junctions along a route would help determine whether the hippocampus processes information related directly to the distance or process information related to the number of fragments of the environment that constitute the route. Hippocampal cells have recently been found to code for the time elapsed during navigation [68] and to modulate their activity depending on future rewards [69], thus it is possible that the time required to reach the goal or expected reward might underlie the correlations between

Figure 3

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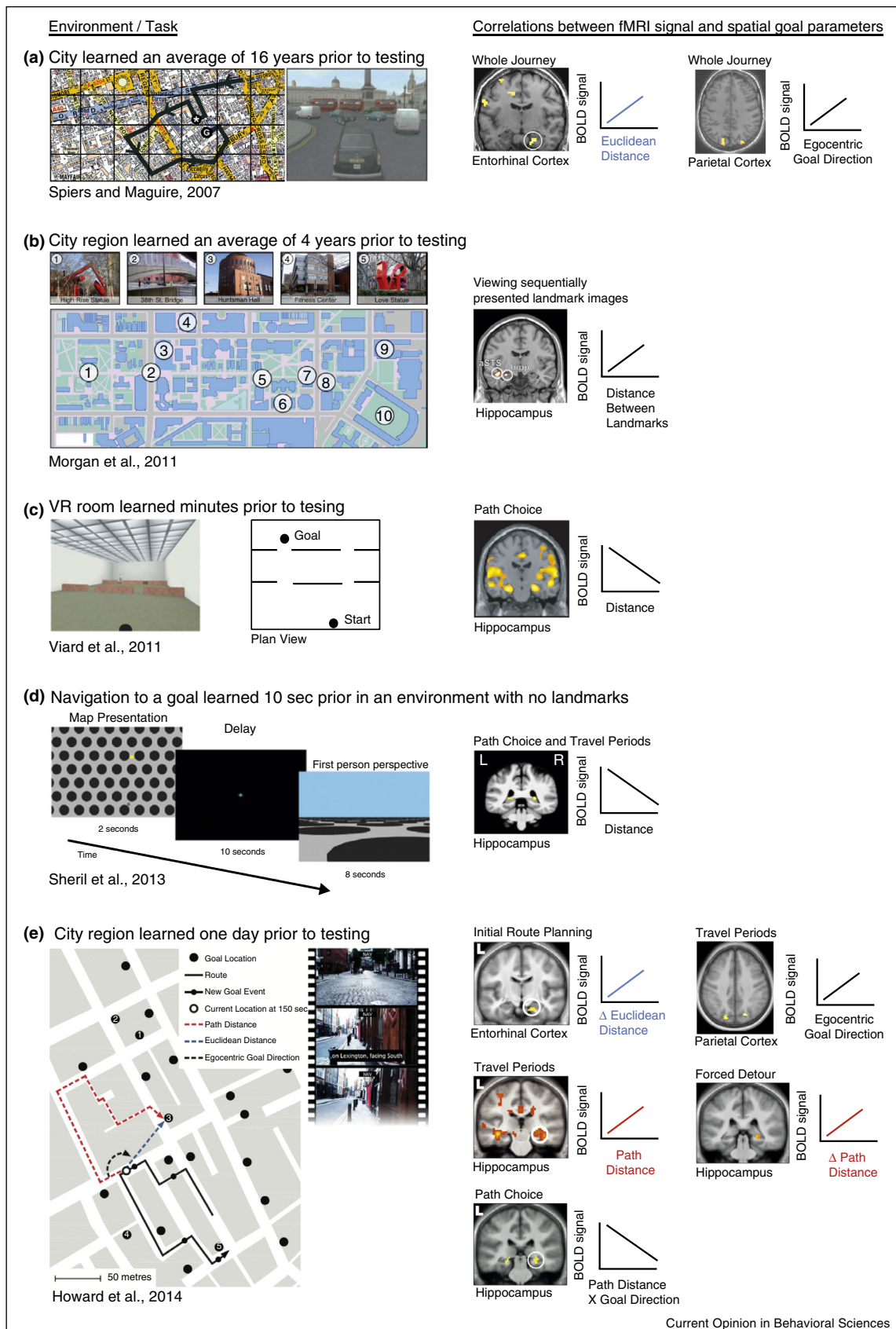
hippocampal activity and distance. Future neuroimaging studies which vary reward, time and distance, will be helpful in teasing apart these possibilities, as will research directly testing whether neuronal firing patterns are correlated with spatial goal parameters.

An important recent single unit recording study explored how hippocampal place cell activity related to the trajectory to the future goal during navigation epochs. Pfeiffer and Foster [70•] recorded CA1 place cells while rats foraged for rewards in an open field environment. After foraging for, and finding, a reward in the arena rats returned to a rewarded 'home' location that was stable within a day, but changed day to day. Pfeiffer and Foster found that before travelling to the goal, during ensemble population spiking events in CA1, the brief activation of place cells coding locations between the rat and its future goal occurred. The activation was not a faithful 'read-out' of the exact future path, but appeared to encompass a range of possible trajectory positions falling between the rat and its future goal. Although not quantified in the study, it appears that the longer the distance the greater the number of cells activated in the populations spiking events. This would potentially provide an explanation for why hippocampal activity may be greater when the navigator is far from their goal [61•]. However, such a mechanism cannot explain why activity increases with proximity to the goal when choosing the path (Figure 3). Thus it is likely that multiple mechanisms operate in the hippocampus to code information about spatial goals.

Neural representations of the direction to the goal

While emerging data implicates the entorhinal region in coding the Euclidean distance along a vector to the goal [50,55], it is not yet clear whether entorhinal grid cells, or conjunctive grid cells underlie this phenomenon. Models predict that the allocentric direction to the goal (Figure 2a) is initially computed in medial temporal lobe structures and subsequently converted to the egocentric direction to guide body movement through space [53,71]. Consistent with this two fMRI studies have reported activity patterns in posterior parietal cortex associated with the egocentric direction to the goal during travel

periods ([50,55]; Figure 3a,e). Evidence for allocentric goal direction coding has yet to be reported, and thus its existence is currently only a theoretical prediction.

Conclusion

Recent computational models, fMRI, electrophysiological studies have begun to shed light on how the brain may encode the spatial relationship to the goal during navigation. Current evidence implicates the entorhinal cortex in coding the distance along a vector to the goal, the hippocampus representing the path to the goal and posterior parietal cortex coding the egocentric direction to the goal. How hippocampal activity relates to the distance to the goal, appears to depend upon the operational stage of navigation, whether the navigator is travelling, choosing the path, or planning the route. Future research integrating rodent electrophysiology and neuroimaging data to test model predictions will be important to advance our understanding of the neural systems supporting navigational guidance.

Conflict of Interest

Nothing declared

References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest
•• of outstanding interest

1. Packard MG, McGaugh JL: **Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning**. *Neurobiol Learn Mem* 1996, **65**:65-72.

2. Berke JD, Breck JT, Eichenbaum H: **Striatal versus hippocampal representations during win-stay maze performance**. *J Neurophysiol* 2009, **101**:1575-1587.

3. Van der Meer M, Kurth-Nelson Z, Redish AD: **Information processing in decision-making systems**. *Neuroscientist* 2012, **18**:342-359.

4. Scoville WB, Milner B: **Loss of recent memory after bilateral hippocampal lesions**. *J Neurol Neurosurg Psychiatry* 1959, **20**:11-21.

(Figure 3 Legend) fMRI studies reporting brain activity correlated with spatial goal parameters. On the left are shown examples of the stimuli and environments used in the studies. On the right are shown statistical parametric maps (SPMs) overlaid on structural images showing regions with activity correlated the spatial parameters. Next to each SPM is a schematic illustration of whether the correlation was positive or negative and the event/epoch (see Figure 2b) examined listed above the SPM. **(a)** A map with one of the seven routes driven in the simulation of London (UK) and image from with the simulation at Trafalgar Square (figure adapted from [9•]). **(b)** Five examples from the larger set of landmarks sequentially shown to subjects during scanning, below is a map of the University of Pennsylvania campus with landmark locations marked (figure adapted from [60•]). **(c)** Left: example of a stimulus viewed during testing, middle: a plan view of the room, not shown to subjects. Subjects had to choose the shortest route to the goal from a range of different starting points along the back wall of the room (figure adapted from [62]). **(d)** Subjects view a plan view of a map indicating their current location and goal location in a VR world composed of tessellating obstructive black cylinders on a grey plane. After a 10 s delay with fixation subjects navigated to where they thought the goal was located (figure adapted from [63•]). **(e)** A map with one of the 10 routes navigated in the Soho region of London (UK) (figure adapted from [61•]). The path distance and Euclidean distance to the goal are shown illustrated at a time point 150 s into the route. The filmstrip show a short segment of the footage used to simulate the environment. In the illustrative plots Δ = the change in the parameter. Large changes in the parameters occurred when a new goal was presented and initial route planning was need or when a forced detour occurred.

5. Morris RGM, Garrud P, Rawlins JNP, O'Keefe J: **Place navigation impaired in rats with hippocampal lesions**. *Nature* 1982, **297**:681-683.

6. Spiers HJ, Burgess N, Maguire EA, Baxendale SA, Hartley T, Thompson PJ, O'Keefe J: **Unilateral temporal lobectomy patients show lateralized topographical and episodic memory deficits in a virtual town**. *Brain* 2001, **124**:2476-2489.

7. Hartley T, Maguire EA, Spiers HJ, Burgess N: **The well-worn route and the path less traveled: distinct neural bases of route following and wayfinding in humans**. *Neuron* 2003, **37**:877-888.

8. Spiers HJ, Maguire EA: **Thoughts, behaviour, and brain dynamics during navigation in the real world**. *Neuroimage* 2006, **31**:1826-1840.

9. Spiers HJ, Maguire EA: **A navigational guidance system in the**
• **human brain**. *Hippocampus* 2007, **17**:618-626.
First study to examine the distance and direction to the goal during navigation with fMRI.

10. Vann SD, Aggleton JP, Maguire EA: **What does the retrosplenial cortex do?** *Nat Rev Neurosci* 2009, **10**:792-802.

11. Epstein RA: **Parahippocampal and retrosplenial contributions to human spatial navigation**. *Trends Cogn Sci* 2008, **12**:388-396.

12. Poucet B, Lenck-Santini PP, Hok V, Save E, Banquet JP, Gaussier P, Muller RU: **Spatial navigation and hippocampal place cell firing: the problem of goal encoding**. *Rev Neurosci* 2004, **15**:89-107.

13. Spiers HJ: **Keeping the goal in mind: prefrontal contributions to spatial navigation**. *Neuropsychologia* 2008, **46**:2106-2108.

14. Rochefort C, Arabo A, Andre M, Poucet B, Save E, Rondi-Reig L: **Cerebellum shapes hippocampal spatial code**. *Science* 2011, **334**:385-389.

15. Barry C, Burgess N: **Neural mechanisms of self-location**. *Curr Biol* 2014, **24**:R330-R339.

16. O'Keefe J, Dostrovsky J: **The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat**. *Brain Res* 1971, **34**:171-175.

17. Muller RU, Kubie JL, Ranck JB Jr: **Spatial firing patterns of hippocampal complex-spike cells in a fixed environment**. *J Neurosci* 1987, **7**:1935-1950.

18. Bostock E, Muller RU, Kubie JL: **Experience-dependent modifications of hippocampal place cell firing**. *Hippocampus* 1991, **1**:193-206.

19. Hafting T, Fyhn M, Molden S, Moser M-B, Moser EI: **Microstructure of a spatial map in the entorhinal cortex**. *Nature* 2005, **436**:801-806.

20. Boccara CN, Sargolini F, Thoresen VH, Solstad T, Witter MP, Moser EI, Moser M-B: **Grid cells in pre- and parasubiculum**. *Nat Neurosci* 2010, **13**:987-994.

21. Taube JS, Muller RU, Ranck JB: **Head-direction cells recorded from the postsubiculum in freely moving rats. II. Effects of environmental manipulations**. *J Neurosci* 1990, **10**:436-447.

22. Solstad T, Boccara CN, Kropff E, Moser M-BB, Moser EI: **Representation of geometric borders in the entorhinal cortex**. *Science* 2008, **322**:1865-1868.

23. Sargolini F, Fyhn M, Hafting T, McNaughton BL, Witter MP, Moser M, Moser EI: **Conjunctive representation of position, direction, and velocity in entorhinal cortex**. *Science* 2006, **312**:758-762.

24. Valerio S, Taube JS: **Path integration: how the head direction signal maintains and corrects spatial orientation**. *Nat Neurosci* 2012, **15**:1445-1453.

25. Van der Meer MAA, Richmond Z, Braga RM, Wood ER, Dudchenko PA: **Evidence for the use of an internal sense of direction in homing**. *Behav Neurosci* 2010, **124**:164-169.

26. O'Keefe J, Speakman A: **Single unit activity in the rat hippocampus during a spatial memory task**. *Exp Brain Res* 1987, **68**:1-27.

27. Komorowski RW, Manns JR, Eichenbaum H: **Robust conjunctive item-place coding by hippocampal neurons parallels learing what happens where**. *J Neurosci* 2009, **29**:9918-9929.

28. Ainge JA, Tamosiunaite M, Woergoetter F, Dudchenko PA: **Hippocampal CA1 place cells encode intended destination on a maze with multiple choice points**. *J Neurosci* 2007, **27**:9769-9779.

29. Wood ER, Dudchenko PA, Robitsek RJ, Eichenbaum H: **Hippocampal neurons encode information about different types of memory episodes occurring in the same location**. *Neuron* 2000, **27**:623-633.

30. O'Keefe J, Conway DH: **Hippocampal place units in the freely moving rat: why they fire where they fire**. *Exp Brain Res* 1978, **31**:573-590.

31. Van der Meer MAA, Johnson A, Schmitzer-Torbert NC, Redish AD: **Triple dissociation of information processing in dorsal striatum, ventral striatum, and hippocampus on a learned spatial decision task**. *Neuron* 2010, **67**:25-32.

32. Dupret D, O'Neill J, Pleydell-Bouverie B, Csicsvari J: **The**
• **reorganization and reactivation of hippocampal maps predict spatial memory performance**. *Nat Neurosci* 2010, **13**:995-1002.
Provides evidence for CA1, but not CA3 re-mapping in relation to goal-locations during updating goal locations.

33. Fyhn M, Molden S, Witter MP, Moser EI, Moser M: **Spatial representation in the entorhinal cortex**. *Science* 2004, **305**:1258-1264.

34. Hollup SA, Molden S, Donnett JG, Moser MB, Moser EI: **Accumulation of hippocampal place fields at the goal location in an annular watermaze task**. *J Neurosci* 2001, **21**:1635-1644.

35. Hok V, Lenck-Santini P-P, Roux S, Save E, Muller RU, Poucet B: **Goal-related activity in hippocampal place cells**. *J Neurosci* 2007, **27**:472-482.

36. Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, Fried I, Dale J, Kandil F, Nishida S: **Cellular networks underlying human spatial navigation**. *Nature* 2003, **425**:184-188.

37. Burton BG, Hok V, Save E, Poucet B: **Lesion of the ventral and intermediate hippocampus abolishes anticipatory activity in the medial prefrontal cortex of the rat**. *Behav Brain Res* 2009, **199**:222-234.

38. Burgess N, O'Keefe J: **Neuronal computations underlying the firing of place cells and their role in navigation**. *Hippocampus* 1996, **6**:749-762.

39. Burgess N, Jackson A, Hartley T, O'Keefe J: **Predictions derived from modelling the hippocampal role in navigation**. *Biol Cybern* 2000, **83**:301-312.

40. Foster DJ, Morris RG, Dayan P: **A model of hippocampally dependent navigation, using the temporal difference learning rule**. *Hippocampus* 2000, **10**:1-16.

41. Muller RU, Stead M, Pach J: **The hippocampus as a cognitive graph**. *J Gen Physiol* 1996, **107**:663-694.

42. O'Keefe J, Nadel L: *The Hippocampus as a Cognitive Map*. Oxford: Oxford University Press; 1978, .

43. Kjelstrup KB, Soldstad T, Brun VH, Hafting T, Leutgeb S, Witter MP, Moser EI, Moser M-B, Solstad T: **Finite scale of spatial representation in the hippocampus**. *Science* 2008, **321**:140-143.

44. Russell JC, Towns DR, Anderson SH, Clout MN: **Intercepting the first rat ashore**. *Nature* 2005, **437**:1107.

45. Derdikman D, Whitlock JR, Tsao A, Fyhn M, Hafting T, Moser M-B, Moser EI: **Fragmentation of grid cell maps in a multicompartment environment**. *Nat Neurosci* 2009, **12**:1325-1332.

46. Barry C, Hayman R, Burgess N, Jeffery KJ: **Experience-dependent rescaling of entorhinal grids**. *Nat Neurosci* 2007, **10**:682-684.

47. Stensola H, Stensola T, Solstad T, Frøland K, Moser M-B, Moser EI: **The entorhinal grid map is discretized**. *Nature* 2012, **492**:72-78.

48. Yoon K, Buice MA, Barry C, Hayman R, Burgess N, Fiete IR: **Specific evidence of low-dimensional continuous attractor dynamics in grid cells**. *Nat Neurosci* 2013, **16**:1077-1084.

49. Fiete IR, Burak Y, Brookings T: **What grid cells convey about rat location**. *J Neurosci* 2008, **28**:6858-6871.

50. Towse BW, Barry C, Bush D, Burgess N: **Optimal configurations of spatial scale for grid cell firing under noise and uncertainty**. *Philos Trans R Soc Lond B Biol Sci* 2014, **369**.

51. Burgess N, Barry C, O'Keefe J: **An oscillatory interference model of grid cell firing**. *Hippocampus* 2007, **17**:801-812.

52. McNaughton BL, Battaglia FP, Jensen O, Moser EI, Moser MB: **Path integration and the neural basis of the "cognitive map"**. *Nat Rev Neurosci* 2006, **7**:663-678.

53. Erdem UM, Hasselmo M: **A goal-directed spatial navigation model using forward trajectory planning based on grid cells**. *Eur J Neurosci* 2012, **35**:916-931.

54. Kubie JL, Fenton AA: **Linear look-ahead in conjunctive cells: an entorhinal mechanism for vector-based navigation**. *Front Neural Circuits* 2012 http://dx.doi.org/10.3389/fncir.2012.00020.

55. Barry C, Bush D, Burgess N: **How to use grid cells for high-precision large-scale vector navigation**. *SfN Abstr* 2014, **848**.

56. Doeller CF, Barry C, Burgess N: **Evidence for grid cells in a human memory network**. *Nature* 2010, **463**:657-661.

57. Thorndyke PW, Hayes-Roth B: **Differences in spatial knowledge acquired from maps and navigation**. *Cogn Psychol* 1982, **14**:560-589.

58. Xu J, Evensmoen HR, Lehn H, Pintzka CWS, Håberg AK: **Persistent posterior and transient anterior medial temporal lobe activity during navigation**. *Neuroimage* 2010, **52**:1654-1666.

59. Barry C, Bush D: **From A to Z: a potential role for grid cells in spatial navigation**. *Neural Syst Circuits* 2012, **2**:6.

60. Morgan LK, Macevoy SP, Aguirre GK, Epstein RA: **Distances**
• **between real-world locations are represented in the human hippocampus**. *J Neurosci* 2011, **31**:1238-1245.
Provided key evidence from a non-navigation task that simply viewing landmarks can activate distance representations.

61. Howard LR, Javadi AH, Yu Y, Mill RD, Morrison LC, Knight R,
• Loftus MM, Staskute L, Spiers HJ: **The hippocampus and entorhinal cortex encode the path and Euclidean distances to goals during navigation**. *Curr Biol* 2014, **24**:1331-1340.
Provides a break down of the different stages of navigation and the correlations with distance and egocentric direction to the goal at these different time periods.

62. Viard A, Doeller CF, Hartley T, Bird CM, Burgess N: **Anterior hippocampus and goal-directed spatial decision making**. *J Neurosci* 2011, **31**:4613-4621.

63. Sherrill KR, Erdem UM, Ross RS, Brown TI, Hasselmo ME,
• Stern CE: **Hippocampus and retrosplenial cortex combine path integration signals for successful navigation**. *J Neurosci* 2013, **33**:19304-19313.
Reports evidence that the hippocampus is correlated with the distance to the goal during navigation of a landmark-free environment.

64. Howard LR, Kumaran D, Ólafsdóttir HF, Spiers HJ: **Double dissociation between hippocampal and parahippocampal responses to object-background context and scene novelty**. *J Neurosci* 2011, **31**:5253-5261.

65. Wolbers T, Wiener JM, Mallot HA, Büchel C: **Differential recruitment of the hippocampus, medial prefrontal cortex, and the human motion complex during path integration in humans**. *J Neurosci* 2007, **27**:9408-9416.

66. Kumaran D, Maguire EA: **Which computational mechanisms operate in the hippocampus during novelty detection?** *Hippocampus* 2007, **748**:735-748.

67. Eichenbaum H, Cohen NJ: **Can we reconcile the declarative memory and spatial navigation views on hippocampal function?** *Neuron* 2014, **83**:764-770.

68. Kraus BJ, Robinson RJ, White JA, Eichenbaum H, Hasselmo ME: **Hippocampal "time cells": time versus path integration**. *Neuron* 2013, **78**:1090-1101.

69. Lee H, Ghim J-W, Kim H, Lee D, Jung M: **Hippocampal neural correlates for values of experienced events**. *J Neurosci* 2012, **32**:15053-15065.

70. Pfeiffer BE, Foster DJ: **Hippocampal place-cell sequences**
• **depict future paths to remembered goals**. *Nature* 2013, **497**:74-81.
Indicates that place cells encoding locations along potential paths to a goal are 'pre-activated' before navigation.

71. Byrne P, Becker S, Burgess N: **Remembering the past and imagining the future: a neural model of spatial memory and imagery**. *Psychol Rev* 2007, **114**:340-375.