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Origins of Landmark Encoding in the Brain

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Abstract

The ability to perceive one's position and directional heading relative to landmarks is critical for successful navigation within an environment. Recent studies have shown that the visual system dominantly controls the neural representations of directional heading and location when familiar visual cues are available, and several neural circuits, or streams, have been proposed as critical for visual information processing. Here, we summarize the evidence that implicates the dorsal presubiculum (also known as the postsubiculum) as a critical brain structure responsible for the direct transfer of visual landmark information to spatial signals within the limbic system.

Introduction

The ability to navigate is one of the fundamental cognitive functions necessary for survival. Whether it is finding your way to your car at the end of a workday or driving it home, you would be literally lost without this skill. Two fundamentally different forms of navigation are recognized by researchers - path integration and landmark navigation [1]. Path integration (often referred to as dead-reckoning) uses internally-derived sensory/motor information in a continuous manner in order to monitor and update one's orientation relative to some reference point. In contrast, landmark navigation (often referred to as piloting) is based on the spatial relationships between various stimuli in the environment and is an episodic process—for landmark navigation to be accurate, one only needs to refer to the landmarks occasionally. Under normal conditions, both forms of navigation operate simultaneously and complement one another. However, because errors accumulate over time during path integration, attention to landmarks is required to restore accuracy. Landmark navigation is a complex process, which can be broken down into a number of components, including orientation, computation of a planned trajectory or route, and execution of that plan (BOX 1). In addition to way-finding, landmarks are also useful for other spatial processes such as the retrieval of the correct spatial reference frame or for determining distances between two points. Given the importance of navigation in our everyday lives, it is important to identify the neural circuits involved in the detection and use of visual landmarks for navigation – particularly those related to the process of self-orientation, which is required before deriving a navigational plan to a goal. Although landmarks can consist of other types of sensory information besides visual, including auditory and tactile cues, we

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focus here on visual landmarks because they likely provide the most important reference for navigation compared to other sensory stimuli.

The past decade has seen a wealth of discoveries, both in humans and rodents, which have elucidated some of the underlying neural circuits involved in landmark navigation. In humans, functional magnetic resonance imaging (fMRI) studies have revealed that several brain regions, including the parahippocampal place area (PPA) and retrosplenial complex, become highly active when subjects view images of scenes or objects that can collectively be classified as landmarks (for a recent review, see [2]). In contrast, electrophysiological studies in rodents have identified another area that is crucial for processing landmark information – the postsubiculum (PoS; also known as the dorsal presubiculum). The PoS is one of the principal nuclei forming the subicular complex, and lies between the subiculum proper and parasubiculum. This area has been underappreciated in terms of its role in processing visual landmark information. Here, we argue that the PoS is an important area for processing landmarks, and discuss how it is situated in a key anatomical position to integrate landmark and path integration information (Glossary).

Physiological Studies – Neural Representations of Space

The neural signals that underlie the ability to process spatial information have been studied in several non-human species. Many of these studies have been conducted in rodents, due to the relative ease of performing electrophysiological recordings while animals freely explore the environment – an important consideration when studying the processes underlying orientation and navigation. In rats, neural representations of location, distance, and direction are encoded by place cells, grid cells, and head direction (HD) cells [3, 4]. Place cells, which have been recorded throughout the hippocampus, subicular complex, and entorhinal cortex (EC) [5, 6], show an increased firing rate when the rat enters a discrete location within an environment, and become virtually silent when the rat is at all other locations. Grid cells, which have been identified in the EC [7] and pre- and parasubiculum [8], fire at multiple locations in an environment, such that the locations form a repeating, grid-like pattern. HD cells, known to be located in several limbic system areas [4], and which are particularly abundant in the PoS [9] and anterior thalamus [10], show an increased firing rate when an animal's head is pointed in one direction within the yaw plane, and become silent when the head points in all other directions. Importantly, the HD signal provides a consistent representation of direction, regardless of the animal's location and on-going behavior. The HD signal appears to be generated from self-movement information within the reciprocal connections between the dorsal tegmental nuclei and the lateral mammillary nuclei [11]. From here, it is projected to more rostral structures via an ascending circuit that includes the lateral mammillary nuclei → anterodorsal thalamus → PoS connections [12, 13] (Fig. 2). The PoS, in turn, sends a major projection to the superficial layers of the EC [14], which then projects to the hippocampus, where directional information can be integrated with location information from place cells.

Given the PoS →EC →hippocampus pathway one could predict that the HD signal plays an important role in the functions of grid cells and place cells. Indeed, several models have implicated the HD cell signal as a necessary component for generating grid cell activity [15, 16], and recent experiments have provided preliminary evidence in support of this prediction (Clark, B.J. and Taube, J.S., Society for Neuroscience abstract 729.11. 2011). In contrast, generation of the place cell signal does not depend on the HD system for its generation, as damage to the anterior thalamus, PoS, or EC failed to eliminate location-specific firing in CA1 neurons, although EC lesions reduced the robustness of the place cell signal [17-19]. Nevertheless, HD, grid, and place cell signals are similarly influenced by the position of spatial cues, or landmarks, in the environment [7, 20-22]. It is therefore possible that these

signals share a common input that is responsible for maintaining their representation relative to the landmarks. As discussed below, we argue that the most likely candidate for this landmark input is the PoS.

Experimental assessment of landmark processing typically relies on the manipulation of landmarks as a tool to evaluate the degree to which place, grid, and HD cells shift their representation to correspond to the novel position of the landmark(s). Various visual cues have been used as landmarks, which can vary from two-dimensional pictures or surfaces taped to room walls, to three-dimensional objects placed proximally or distally to the arena, as well as the arena boundaries themselves [20, 23, 24]. Landmark control is often tested by placing a rat within a cylindrical arena that contains a salient 'cue card' affixed to the wall as the sole visual landmark. If this cue card is rotated between recording sessions while the animal is out of view and the animal is disoriented before being returned to the cylinder, all three spatial cell types show a similar shift of their spatial representation in correspondence to rotation of the cue card (Figs. 1, 3A) [7, 20-22]. The landmark control exerted by the cue card can be powerful and occurs even when the cue(s) is moved in the animal's presence and conflicts with the animal's internally-derived spatial information from idiothetic cues [25, 26]. All three spatial cell types respond to landmarks placed proximally or distally to the arena [22, 27, 28], however, when both types of cues are presented simultaneously, distal cues tend to exert greater control over HD cells than proximal cues [24, 28]. At present, very little is known about the neural processes involved in proximal vs. distal landmark control, although some researchers contend that proximal cues are processed in parietal cortex [29], while distal cues are processed in EC [30]. To understand the brain areas involved in landmark control, we will focus primarily on HD cells, but will mention the other spatial signals when data are available.

Landmark Control of Spatial Signals - Importance of the PoS

The visual information that is used for landmark control of spatial signals presumably originates in the visual cortex. Indeed, hippocampal place cells show a moderate landmark control impairment after visual cortical lesion in rodents [31] (Fig. 3E). Assuming HD cells and grid cells depend on similar visual signals, one could predict a similar effect of visual cortical damage on HD cell activity. If true, then one or more of the several pathways from visual cortex to the limbic system may transmit visual information to these spatial cells. These visual pathways include: 1) the dorsal visual stream through the parietal cortex that processes object localization in space, 2) the ventral visual stream through the inferior temporal lobe that processes object identification, and 3) the tecto-visual pathway that includes the superior colliculus (SC), pulvinar, and lateral dorsal thalamus (Fig. 2A).

Anatomically, one possible entry point of visual information to the limbic system is the PoS, indicated by its direct input from areas 17 and 18b and from retrosplenial cortex, which also receives visual input [14, 32]. In turn, the PoS projects to the EC, anterior thalamus, and mammillary nuclei (Fig. 2B) [14]. The importance of the PoS in processing landmark information is demonstrated by lesions of the PoS, which severely impaired landmark control of HD cells in both the anterodorsal thalamus [13] and lateral mammillary nuclei (Yoder, R.M. and Taube, J.S., Society for Neuroscience abstract 90.9. 2008) (Figure 3B). Similarly, the PoS is critical for the landmark control of place cells in the hippocampus, as lesions of the PoS, but not the anterodorsal thalamus, disrupted landmark control and reduced location specificity in hippocampal place cells (Fig. 3E,F) [18]. Behaviorally, PoS lesions impaired performance on spatial memory tasks, such as the water and radial arm mazes, where landmark cues are necessary for task completion [33].

In addition to visual input, the PoS receives a small projection from CA1 [14], which is strongly linked to the association and storage of spatial information, including spatial relations between landmarks [34]. However, lesions of the hippocampus in rats did not influence landmark control of HD cells, as rotation of a cue card led to similar shifts in the cells' preferred firing directions [35] (Fig. 3E). Furthermore, this study showed that HD cell responses to a novel environment and set of visual cues were consistent across days, despite the fact that hippocampal damage would likely have prevented the conscious recollection of prior experiences within the novel environment. Thus, visual stimuli are able to maintain control of the HD cell system in the absence of hippocampal inputs. Taken together, these findings strongly suggest that the PoS is critical for processing visual landmark information, and raises the question of how visual landmark information is conveyed to the PoS. Does it use the dorsal, ventral, or tectal visual streams – or some combination of these? While these separate visual pathways are widely recognized in humans and primates [36], it is not clear whether they are present in rodents. Some researchers have argued for this distinction [37], with the lateral occipital cortex 2 (Oc2L) involved in pattern recognition and the medial occipital cortex 2 (Oc2M) involved in spatially oriented actions. In contrast, other researchers distinguish separate pathways based on perception versus action [38]. Regardless, the dorsal/ventral stream dichotomy provides a convenient framework for examining the rodent data.

Dorsal Visual Stream and Landmark Control

The dorsal visual stream includes the projection from visual cortex → posterior parietal cortex, which then projects indirectly to PoS via the retrosplenial cortex (Fig. 2). Before discussing the involvement of visual stream structures in landmark control, it is important to note that damage to visual cortex impaired landmark control in only about two-thirds of place cells [31]. However, rats in this study were not disoriented between sessions, and path integration mechanisms could have maintained directional orientation across sessions. This reliance on non-visual cues can be seen in the angular shift plot, where most place cells had consistent preferred firing locations across sessions rather than a random shift, regardless of the position of the visual cue (Fig. 3E).

Damage to the parietal cortex, which effectively disrupts the dorsal visual stream at an early point, failed to impair landmark control of HD cells in anterodorsal thalamus [39] and only mildly affected landmark control of hippocampal place cells [40] (Fig. 3C). Behaviorally, water maze performance based on distal landmarks, but not proximal cues, was spared following parietal lesions [29], suggesting distal and proximal cues may be processed differently. The distinction between proximal and distal cues is critical for our understanding of the landmark control of HD and place cell signals, given that both signals are strongly controlled by the position of distal cues [23, 28].

The visual cortex also projects directly to retrosplenial cortex (areas 29 and 30 in humans) [41, 42], which along with the posterior cingulate region and areas 23 and 31, is sometimes termed the retrosplenial complex [2]. In rodents, however, there is no directly comparable region to areas 23 and 31, and the entire region that includes areas 29 and 30 is referred to as the retrosplenial cortex [43]. Several studies suggest that the rodent retrosplenial cortex may contribute critical visual landmark information to spatial signals. First, retrosplenial damage moderately impaired landmark control of anterodorsal thalamic HD cells [44] (Fig. 3C). Second, selective lesions of the retrosplenial cortex produced a modest navigation impairment in spatial memory tasks [45, 46]. Interestingly, some retrosplenial regions appear to have greater influence on spatial processing than others. For example, spatial deficits occurred when lesions include a subregion of area 29 - specifically area 29b, but not 29a [47]. Area 29b receives direct input from the visual association cortex (area 18b) [42],

and this connection may be relevant to the important role that the retrosplenial cortex plays in landmark navigation.

In sum, the evidence indicates that the first component of the dorsal visual stream, the parietal cortex, does not contribute to the landmark control of HD cells, whereas the retrosplenial cortex appears to play a more important role. With respect to the HD cell system, it is important to note that the landmark control impairments induced by retrosplenial lesions are less severe than those induced by PoS lesions. This point can readily be seen in Figure 3, where the data points for PoS-lesioned animals appear to be more randomly distributed compared to retrosplenial-lesioned animals, which are more clustered around under-rotated values. Regardless, the important roles that the PoS and retrosplenial cortex play in landmark control, along with the strong reciprocal connectivity between these structures, suggest that critical information related to visual landmarks reaches the rodent limbic system through these structures.

Ventral Visual Stream and Landmark Control

An alternative pathway between the visual cortex and PoS is the ventral visual stream, which includes projections from visual cortical areas to various structures in the inferior temporal lobe (Fig. 2). Of special interest in terms of the ventral visual stream is the parahippocampal cortex, which in monkeys is reciprocally connected with widespread cortical areas involved with processing primary sensory information, as well as with the frontal, cingulate, and retrosplenial areas [48]. The rat homolog of the parahippocampal cortex is the postrhinal cortex, which also receives input from visual areas and projects to EC, retrosplenial cortex, and subiculum [49, 50]. Lesions of the postrhinal cortex did not disrupt location-specific firing in CA1 place cells [51], but unfortunately, this study did not evaluate whether landmark control was intact following the lesions. Behaviorally, lesions of the postrhinal cortex have not produced consistent results, with some studies reporting landmark-based navigation impairments on radial-arm, water, and T-mazes [52], and others reporting no spatial deficits on these tasks [53, 54]. Future studies are therefore warranted to reveal the contribution(s) of postrhinal cortex to landmark processing.

Another ventral stream structure that could convey landmark information to the hippocampus is the perirhinal cortex, which receives input from ventral temporal association areas and also projects to the EC, subiculum, and CA1 [55]. Although no studies have evaluated perirhinal involvement in landmark control of spatial signals, lesions of perirhinal cortex impaired the tendency of hippocampal place cells to reliably represent the same location across a delay period [56]. Further, consistent with a previous demonstration of perirhinal cortical involvement in object recognition [57], perirhinal cortex lesions reduced the amount of time rats spent exploring novel objects, but failed to disrupt their navigational ability in a water maze task [58]. Thus, perirhinal cortex may be involved in memory for objects or landmarks, even though perirhinal lesions generally do not impair performance on spatial tasks where landmark information is needed.

Assuming that postrhinal cortex is involved in the landmark control of limbic spatial signals, then several connections may be responsible for this influence. The most likely route is the continuation of information flow through the inferior temporal lobe that ultimately reaches the EC [55]. Indeed, EC lesions have been found to impair landmark control in some CA1 place cells, but interestingly, impairments only occurred in about half of the sessions [19] (Fig. 3D). This result is surprising because if postrhinal cortex plays an important role in landmark processing, then EC lesions should have disrupted landmark control more severely. In addition, EC lesions would have been expected to disrupt information flow from the PoS to the hippocampus, since 1) the EC is one of the major outputs of the PoS and 2) PoS lesions disrupt landmark control of hippocampal place cells (see above, Fig. 3B). It is

possible, however, that EC lesions in this study did not always include the dorsal portions of the medial EC region, which receives a stronger input from PoS relative to the lateral EC [59]. In any event, EC lesions had a greater effect on hippocampal place cells than on HD cells in the anterodorsal thalamus, which showed normal landmark control following lesions of the caudal EC [60] (Fig. 3D). These findings cast doubt on the importance of the postrhinal cortex and ventral visual stream in the landmark control of HD cells, although these connections could have a greater influence on place cells and grid cells.

Tectal Visual Stream and Landmark Control

In addition to the cortical streams, tectal pathways may also influence spatial signals within the hippocampal formation. The SC and pretectal areas receive retinal input and project to the laterodorsal thalamic nucleus, which is reciprocally connected to PoS and EC [61, 62]. Additionally, the laterodorsal thalamus contains cells that are directionally selective in light and for a brief period in darkness [63], suggesting the laterodorsal thalamus may be an important part of the visual landmark processing circuit. This observation has led some of the earlier computational models to propose that visual information enters the HD cell circuit through the laterodorsal thalamus [64]; however, damage to the laterodorsal thalamus does not impair landmark control of HD cells in anterodorsal thalamus [65] (Fig. 3B). Nonetheless, it remains possible that these tectal inputs complement the signals arising from the cortical streams, with neither pathway being responsible for all components of the visual landmark control of spatial signals. Indeed, laterodorsal thalamus inactivation disrupted the location-specific activity of place cells, suggesting a role for tectal pathways in some aspects of spatial processing [66].

Environmental Geometry and Landmark Control

Numerous behavioral studies suggest that environmental geometry can act as a salient landmark, contributing to the landmark control of spatial signals and orientation of animals (see [67] for a review). Although it does not appear that environmental geometry is favored over non-geometric landmarks [68], there is considerable physiological evidence in rodents showing that geometric cues have a significant influence on place cells [69], grid cells [27], and HD cells [70, 71]. For example, when the arena was changed from a square to a rectangle, hippocampal place cells frequently expanded their place fields to represent a larger area, or “split” their place fields along the axis of the environment to represent two locations [69]. This observation led to the suggestion that place cell activity is formed by the summation of cells encoding the distance to environmental boundaries and the directional heading of the animal [72]. Recent work has identified border cells, also known as boundary-vector cells, which appear to represent this type of information – namely the location of boundaries. These cells have been identified in several limbic areas, including the medial EC [73, 74], subiculum [75], parasubiculum, and PoS [8]. Like other limbic spatial signals, border cells can be controlled by visual landmarks [74]. Thus, given the close connectivity between the brain regions containing border cells, it is possible that the PoS mediates the association of border cell activity with visual landmarks.

Summary of Rodent Data

Given the absence of evidence for major involvement of the dorsal, ventral, and tectal visual streams in the landmark control of spatial signals within the limbic system, we propose that the most likely route for landmark information to reach the limbic system is via the direct projections from visual cortex to PoS, although the retrosplenial cortex also appears to play some role. In turn, PoS projections to the EC and other subcortical areas where HD cells are found, are the likely pathways by which landmark control is conveyed to hippocampal place cells and throughout the HD cell circuit. Thus, at least in rodents, the PoS appears to be a

critical node where visual landmark information is transferred to brain structures that participate in spatial cognition.

Landmark Processing in Humans

Significant insight into the neural systems involved in landmark processing in humans has come from clinical reports of patients suffering from topographic disorientation - a condition in which a patient is unable to find his or her way through an environment, even if the environment was familiar before clinical onset. The first reported case of topographic disorientation dates to 1876, when Hughlings-Jackson described way-finding difficulties in a patient with a glioma in the right temporal lobe [76]. Since then, clinicians have identified several forms of topographic disorientation, each being traced to a specific cortical or limbic region [77, 78]. One category of topographic disorientation that occurs after lingual gyrus damage is often referred to as landmark agnosia, which impairs the ability to recognize both familiar and novel landmarks [79]. In contrast, anterograde disorientation, which can result from damage to the parahippocampal gyrus, impairs the recognition of novel landmarks, but preserves the ability to recognize previously familiar ones [80]. Patients with damage to either the lingual or parahippocampal regions have a preserved sense of orientation; that is, they can reportedly describe the spatial relationships between locations and can determine their directional orientation by referring to small details within the environment [80]. Further, these patients can path integrate over short distances [81]. Despite their preserved sense of orientation, these patients quickly get lost – possibly because of their recognition deficits [80].

The importance of these areas in processing landmark information is also indicated by anatomical studies in non-human primates. The parahippocampal cortical region includes temporal lobe areas TF and TH, which receive input from areas V4 (visual area 4), TEO, and TE; area TF also receives input from the retrosplenial cortex, which receives input from the posterior parietal cortex [48]. Thus, the parahippocampal cortex receives input from both the ventral and dorsal visual streams, and projects back to these same areas – V4 and parietal cortex – as well as to CA1 [82] and subiculum [83]. Because the hippocampus is important for navigation [84], parahippocampal input may be critical for this function. However, parahippocampal input to the hippocampus proper is indirect, via the EC, which would presumably contain spatially relevant signals. Indeed, recent fMRI studies suggest the presence of grid cells in the EC that may function similarly to those of rats [85]. Furthermore, single-unit recordings in the EC have reported cells which are responsive to the direction of turn (clockwise vs. counterclockwise) in a virtual navigation task [86].

In the parahippocampal gyrus, one particular area, the PPA, showed increased neural activity when subjects viewed visual stimuli associated with spatial layout, such as landscapes, or objects that provide navigationally relevant information [87-90]. In contrast, the PPA showed less activity when subjects were viewing non-scene objects, and not at all when subjects were viewing faces [87]. The PPA also showed increased activity when subjects were presented with objects located at decision points during virtual navigation, regardless of whether or not the object was explicitly remembered [88], or when subjects were required to retrieve context-specific cues for navigation within a familiar environment [91]. Additionally, PPA appears to discriminate between landmarks, regardless of their spatial layout within a larger scene [2, 92], and may contribute to the decision of whether or not to rely on a particular landmark for navigation. Further, PPA activation was recently found to be insensitive to mirror image reversals – meaning that the orientation/spatial features of a scene were not the critical elements that caused PPA activation [93]. Another study noted the spatial mnemonic features of the PPA by showing increased activity when the subject recalled the spatial layouts of scenes [94]. It is important to note, however, that

the PPA has also been shown to represent categories of objects, whether or not these categories include spatially relevant objects [95]. Thus, the PPA appears to be a critical structure for encoding and classifying objects that are navigationally relevant, and distinguishes between viewpoints within the overall environment by encoding snapshots of observer-centered scenes, although some studies have challenged this view, contending that the PPA is more involved with processing specific spatial qualities of the visual stimuli (e.g., the expansiveness of the scene), rather than scene recognition [96, 97].

Another category of topographic disorientation occurs when patients lose their sense of direction; that is, they are unable to determine which direction to proceed to reach a goal [98-101]. This condition is frequently called heading disorientation and is associated with injury to the retrosplenial complex. In contrast to patients with damage to the posterior parahippocampal region, heading disorientation does not typically involve impairments in landmark or visual scene recognition; however, patients are unable to use landmarks for directional information or orientation [77]. Consistent with this clinical observation, fMRI studies report that the retrosplenial complex shows strong activation when subjects both navigated and recalled spatial information in a virtual environment [102, 103]. In addition to its role in determining directional heading, clinical studies have also found that patients with retrosplenial damage cannot learn the spatial layout of unfamiliar environments, or draw maps of familiar territory such as homes or neighborhoods [98, 100]. Thus, it is possible that the retrosplenial complex utilizes the spatial relationships and routes between landmarks to encode the spatial structure of the environment [104].

Comparison of Rodent and Human Data

One important distinction between the rodent and human studies is that all the experiments with rodents involved active movement, which contrasts with the supine position of humans performing a virtual reality task. Virtual navigation does not activate the same sensory systems that are activated during real-world navigation, including vestibular, proprioceptive, and motor efference copy systems, which are known to play an important role in spatial orientation [105, 106]. Nonetheless, the brain structures that perform the high-level, cognitive landmark processing may be similar. For this reason, comparisons between the rodent and human data are warranted. However, a caveat worth mentioning here is that the blood-oxygen-level dependence (BOLD) signal measured in fMRI studies may be more representative of active afferent inputs (i.e., local field potentials) rather than the firing of neurons located in the recorded brain area [107].

Despite the increased BOLD signal in the PPA when landmark-like objects are viewed [87], and the PPA's prominent projection to the EC, the lack of landmark control deficits following EC lesions in rats questions the importance of the PPA/postrhinal cortex for landmark processing. Instead of a critical component in landmark perception, it is possible that the human PPA is involved in the use of contextual information from memory to retrieve spatial layouts relevant to a navigation task [91]. Similarly in rodents, the contextual information processing [53, 108] and spatial memory deficits [51] following postrhinal lesions could be interpreted as deficits in perceiving spatial context. Consistent with this interpretation, the postrhinal cortex is important for encoding the spatial features of environments that influences future navigation within the same environment [109]. Thus, the PPA/postrhinal cortex may be more important for the retrieval and/or encoding of spatial context than for processing landmark information *per se*, and further suggests that the postrhinal and entorhinal cortical areas play broad roles in spatial and mnemonic processing in support of episodic memory [110, 111].

Another difference between the rodent and human studies is the role of the retrosplenial cortex in processing landmarks. Whereas the human data clearly indicate that the retrosplenial cortex has an important contribution to processing landmarks, lesions of the rodent retrosplenial cortex only led to mild impairments in landmark control over HD cells (Fig. 3C). This point is particularly important, given the severe landmark-based navigation deficits produced by limbic system damage [43]. It is possible that this discrepancy may involve the rather broad definition of the retrosplenial complex in human studies, which also includes the posterior cingulate region. Indeed, it has been noted recently that the posterior occipital and anterior calcarine regions are sometimes misidentified as the retrosplenial cortex [43]. Alternatively, it is possible that instead of a strict role in landmark processing, the retrosplenial region may be more involved in switching between different spatial reference frames [43, 112]. This view is supported by data from rats demonstrating that retrosplenial lesion-induced deficits were greater when task demands were altered – for instance, when intra-maze and extra-maze cues were placed in conflict [113], or when switching from tests in light to darkness [44, 114]. In both cases, the animal would be required to switch from relying on visual information (based on an allocentric representations) to a path integration strategy (based on idiothetic representations) to maintain orientation. Consistent with these rodent data, clinical reports suggest that patients with retrosplenial dysfunction often have difficulties switching between allocentric and egocentric representations [2, 115]. For example, patients are often unable to use maps to determine their orientation within an environment, and have difficulties placing objects on a map after changes to their orientation. Computational models of retrosplenial function have been developed with spatial strategy switching in mind, but because of its strong anatomical connectivity with the parietal cortex and the limbic system, it is often modeled to guide changes between egocentric and allocentric reference frames [112].

A recent review postulated that the dorsal parietal visual stream gives rise to three different streams of visual information [116]. One anatomically complex stream, which was postulated to play an important role in navigation, projected to the posterior cingulate and retrosplenial cortices and to several areas within the medial temporal lobe. This view argues that information processing within the caudal inferior parietal lobule (cIPL) is a crucial first step in processing this visual information. Yet, as discussed above, lesions of the posterior parietal area in rodents did not interfere with landmark control in HD cells - and we attributed this result to the fact that landmark visual information was conveyed directly to the PoS via projections from visual areas 17 and 18b [32]. Thus, at least for rodents, the parietal cortex does not appear to play a critical role in landmark processing for HD cells. Furthermore, we argue that such findings cast doubt on the extent to which the dorsal visual stream plays a major role in processing landmark information. This raises the issue of whether there are similar direct projections from the visual cortex to presubiculum/PoS in humans.

Concluding remarks

Taken together, recent studies have revealed many details of the brain circuits that underlie the dominant influence of visual landmarks on spatial processing. In rodents, the PoS appears to function as a node that transmits landmark information from the visual cortex (and to a lesser extent, retrosplenial cortex) to several structures that contain HD and place cells. In humans, the PPA and retrosplenial areas appear to be heavily involved in landmark processing, but whether the PoS (or a homologous structure) is also the critical node for landmark control of spatial signals in humans has not been conclusively demonstrated. Beyond the systems level approach to understanding which brain areas process landmarks, it will also be important for future experiments to explore how landmark information at the cellular level mechanistically resets neuronal activity (BOX 2). The possibility of combining

intracellular recording techniques with behavioral approaches that utilize virtual navigation [117] promises to lead to a better understanding of how landmarks are encoded at the mechanistic and systems levels, and could potentially bridge the gap in knowledge between virtual and real-world navigation.

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GLOSSARY

Allocentric	Spatial reference frame is the world.
Dorsal/Ventral Visual Streams	The dorsal stream, which extends from the occipital lobe through the parietal lobe, is involved in the perception of object location. In contrast, the ventral stream, which extends from the occipital lobe through the temporal lobe, is involved in object recognition. Because of their functions, the dorsal and ventral streams have been termed the *Where* and *What* pathways, respectively.
Egocentric	Spatial reference frame is the organism.
Idiothetic	Self-movement information generated by the organism as it moves through the environment; includes vestibular, proprioceptive, and motor efference copy information.
Landmark control	The influence of visual landmarks on neural representations of space; for example, if a landmark, such as a cue card is rotated by 90°, perfect landmark control is demonstrated by a similar shift of the preferred firing direction of a HD cell, or the place field of a place cell.
Orientation	Perception of one's location and directional heading within an environment.
Path integration	The process by which organisms update their location and directional heading as they move through their environment using internally available self-movement information, such as idiothetic cues.
Virtual navigation	Imagined movement or movement perceived within a video display that does not involve actual body movements or changes in body position. Because the head and body do not move, virtual navigation does not stimulate the vestibular apparatus or motor/proprioceptive systems.
Yaw	rotation in the horizontal plane about an axis vertical to Earth.

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BOX 1

Processing Visual Landmark Information

Processing visual landmark information begins with retinal to primary visual cortex (area 17) via the lateral geniculate nucleus and processed further in secondary visual areas. From here, visual information is thought to be processed via two distinct streams: dorsal pathways through the parietal cortex for processing spatial aspects and ventral pathways in the inferior temporal lobe for processing object recognition [36]. Within the dorsal pathway, visual information is transformed from a retinotopic, egocentric reference frame to an allocentric (world-centered) reference frame. Various types of spatial information can be derived from the dorsal stream [119], including: 1) the distance between the viewer and object, as judged by both the size of the object's visual image on the retina and motion parallax, 2) movement of the viewer through the environment is provided by optic flow of visual stimuli across the retina, 3) the distance between objects based on binocular depth cues, 4) up-down orientation of the visual scene can be derived by viewing objects with known intrinsic polarity (e.g., a table with a top and four legs), 5) geometric properties of the environment, and 6) the two-dimensional (or 3D) spatial relationships amongst different objects and landmarks, (e.g., including large-scale objects such as mountains). Our perceived spatial orientation is derived largely from these last two categories.

For an object or scene to serve as a landmark, it must first be visually detected and identified, and then determined whether they are useful as landmarks. This process presumably occurs in the ventral visual stream [2]. Obviously, not all objects serve as useful landmarks; for example, movable objects, such as a hammer or book, would not be useful for deriving spatial information about one's orientation because of their spatial instability. Similarly, you are unlikely to use animate objects for landmarks because they, too, often move around. Further, landmarks are often selected based on their uniqueness relative to their surroundings [120], and can be learned rapidly and gain control of the animal's behavior [121, 122]. The classification of objects (or scenes) as landmarks is an important process and requires considerable cognitive capacity in terms of categorization. The brain appears to contain specialized modules that process particular categories that are highly relevant to the organism, such as faces, tools, animate vs. inanimate [123, 124]. Although it is not clear how many different types of categories are processed, having a system that identifies landmarks would certainly be valuable for accurate navigation.

Box 2

Outstanding Questions

- What is the contribution of the postrhinal cortex to the landmark control of HD cell activity in rodents?
- What is the effect on landmark control in HD and place cells after severing the direct pathway from visual cortex to PoS in rodents?
- Does the postrhinal cortex provide unique contributions to spatial signals in familiar vs. novel contexts?
- Does a human homolog of the rodent PoS serve as a critical node where landmark information is provided to cognitive representations of location and direction?
- Do humans have HD cells with characteristics similar to those of rodents?
- Does virtual navigation using visual landmarks activate the same higher-level brain structures as real navigation?
- What is the precise role of the retrosplenial cortex in landmark processing? Is it involved in translating information between different spatial reference frames (landmark-based to egocentric and *vice versa*) or does it have a broadly defined role in linking our sense of orientation with environmental landmarks?
- How do landmarks reset the orientation system at the neuronal level? A number of mechanistic models have been proposed to help address this question [125-127], including the hypothesis of the existence of visual feature detectors that respond when a particular feature is located at a specific angle with respect to the animal's head axis. While cells with some aspects of the properties have been described in the parietal cortex and SC [128, 129], more work is required to determine if these cells are indeed involved in landmark recognition, and to determine exactly how they mechanistically reset the system.

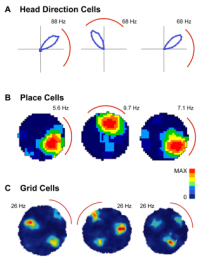

Figure 1.

Landmark control of spatial signals. Each panel displays the response of a different spatial cell type in rats to a 90° rotation of the salient visual landmark cue – a white sheet of cardboard attached along the inside wall of the enclosure (represented by a red arc in each panel). (A) The directional tuning curve of an anterior thalamic head direction (HD) cell, (B) the place field of a hippocampal place cell, and (C) the firing pattern of an entorhinal cortical grid cell show angular shifts of the spatial signal that approximate the amount of cue card rotation. Panel **A** is based on polar coordinates from [10]; **B** and **C** are based on data in [18] and [118], respectively. Data shown in plots B and C have been smoothed to improve presentation. Peak firing rates are indicated for each plot.

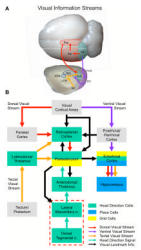

Figure 2.

Hypothesized landmark processing circuit and the visual stream pathways in rodents. **A)** Lateral and para-sagittal views of the rat brain showing the three major visual processing streams: dorsal (red arrows), ventral (purple arrows) and tectal (orange arrows). **B)** The head direction (HD) cell signal originates within the reciprocal connections between the dorsal tegmental nucleus and lateral mammillary nuclei (dashed red lines), and is generated from vestibular, proprioceptive, and motor information arriving from several subcortical areas. From the LMN, the HD signal projects rostrally to the anterodorsal thalamus, which projects to the postsubiculum (PoS). Current evidence suggests that landmark information from visual cortical areas could be conveyed to the HD cell circuit via several distinct routes, including the dorsal (red), ventral (purple), and tectal (orange) visual streams. Black arrows depict the major visual cortical projections. Abbreviations: ADN: anterodorsal thalamus, EC: entorhinal cortex, Hpc: hippocampus, LDN: lateral dorsal thalamus; LMN, lateral mammillary nuclei; Par: parietal cortex, PoR: postrhinal cortex, PoS: postsubiculum, Rsp: retrosplenial cortex, SC: superior colliculus, Vis: visual cortex.

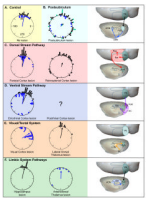

Figure 3.

Head direction (HD) cell and place cell responses to 90° cue rotation following lesions of various brain structures in rats. All HD cells are shown with dots outside the circle and were recorded from the anterodorsal thalamic nucleus (black dots) or the lateral mammillary nuclei (green dots). All place cells are shown with blue dots inside the circle. For all plots, each point represents the shift (in 6° bins) of a single cell's preferred firing direction or place field that occurred following a 90° rotation of the cue card, with positive shifts corresponding to the same direction of cue card rotation, regardless of whether the cue rotation was clockwise (CW) or counter-clockwise (CCW). For simultaneously recorded cells, the average shift of these cells is depicted; in some cases, these averaged values fell between 6° bins. Arrows in each plot represent the mean vector length of the overall data. For each panel, the right column shows the brain pathways and corresponding areas that were lesioned. Abbreviations and the color scheme used for different visual streams are the same as in Figure 2. **A**) In control animals, the shifts in the preferred firing directions and place fields were similar to the amount of cue card rotation [13, 18]. The mean vectors for the place and HD cell data overlap; thus, only the mean place cell vector is visible. **B**) Postsubiculum lesions severely impaired the landmark control of anterodorsal thalamus [13] and mammillary Yoder, R.M. and Taube, J.S., Society for Neuroscience abstract 90.9. 2008] HD cells, as well as hippocampal place cells [18]. **C**) Within the dorsal visual stream pathway, parietal cortex lesions had no effect on HD [39] and place [40] cells, whereas retrosplenial cortex lesions moderately impaired the landmark control of HD cells [44]. **D**) In the ventral stream pathway, EC lesions had no effect on the landmark control of anterodorsal thalamus HD cells [60] and only a mild impairment on hippocampal place cells [19]. **E**) Lesion of visual cortex had a moderate impact on landmark control of place cells [31], whereas a lesion within the tectal stream pathway (within the lateral dorsal thalamus) had little effect on HD cells [65]. **F**) Within the limbic system, hippocampal lesions had little effect on HD cells in anterodorsal thalamus [35], and anterodorsal thalamus lesions had little effect on place cells in the hippocampus [18]. Hippocampal place cell data from visual cortex, parietal cortex, and EC lesions are based on data published in [31], [40] and [19], respectively, and provided by Bruno Poucet.