Neural Mechanisms Underlying Self-Localization in Rodents

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Abstract

The ability to self-localize and navigate in both stable and changing environments is crucial for the survival of many species. Research conducted on the non-human mammalian hippocampus and surrounding brain structures has uncovered several classes of spatial related cells. These cells provide the rest of the brain with knowledge of the animal’s location and direction—knowledge that is subsequently used in spatial navigation. This thesis provides an overview of three types of cells underlying this ability in rodents. First, place cells located in the hippocampus encode the animal’s specific location in the environment. Second, head direction cells found throughout the Papez circuit convey the angular direction of the animal’s head. Last, grid cells in the medial entorhinal cortex generate a regular triangular grid spanning the entire explored setting. The focus of this review lies on the most salient features of these types of cells. It is also considered how the cells respond to manipulations of external and internal information, as well as how different lesions affect their activity.

Keywords: place cells, head direction cells, grid cells, self-location, spatial processing
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Introduction

Self-localization refers to the ability to determine one’s current position and orientation within the environment (Barry & Burgess, 2014). This function is crucial to position and navigate oneself, which is constantly used in everyday life. Yet, the cognitive functions that underlie this ability are frequently taken for granted, and one rarely spares a thought as to how it is possible to always have a sense of certainty of where one is situated in the current setting. Furthermore, self-location is the primary function of spatial navigation. The ability to know how to move from one point to another is one of the most fundamental functions that mammals depend on (Taube, 2007). It is crucial not only for knowing where the toilet seat is located in the bathroom in the dark, but also for surviving in the wilderness by trying to find the way home, a stash of food, or a way safe from predators. However, spatial navigation without information about location or direction has little or no chance of success (Taube, 2007).

In the scientific community, the research regarding self-localization has been quite extensive for the last 50 years. However, how the brain accounts for the sense of location and direction has been of interest for scientific research for more than a century. Even Charles Darwin speculated on the nature of the information that animals and man use to self-locate and navigate (Darwin, 1873). Therefore, the neural mechanisms underlying these functions are important to consider.

As a result of extensive research conducted on the rat, it is today widely acknowledged that self-localization relies to a large part on three different classes of cells: place cells, head direction cells, and grid cells (Hafting, Fyhn, Molden, Moser, & Moser, 2005; O’Keefe & Dostrovsky, 1971; Taube, Muller, & Ranck, 1990a). The field of research focusing on such a positioning system in the brain was also honored with the Nobel Prize in Physiology or Medicine in 2014 (Nobel Media AB, 2014). The prize was awarded one half to John O’Keefe and one half jointly to May-Britt Moser and Edvard I. Moser for their discoveries of place cells and grid cells in the rat, respectively. As Neil Burgess (2014) has noted, the 2014 Nobel Prize in Physiology or Medicine "recognizes both a
paradigm shift in the study of cognitive neuroscience, and some of the amazing insights that have followed from it concerning how the world is represented within the brain” (p. 1120).

The aim of this thesis is to present relevant neuroscientific research to provide a fairly comprehensive account of the spatial-related cells necessary for self-localization in rodents. To accomplish this aim, place cells, head direction cells, and grid cells will be presented individually. The primary focus will be to describe the most salient properties of the cells, how the cells’ firing can be manipulated by external and internal information, and how their activity can be disrupted. However, a review of the origin of the spatial signals requires the inclusion of theoretical models. Such models are outside the scope of this thesis, and will therefore not be included. Following the presentation of the cells, the discussion will mainly provide a general overview of the most central findings and briefly address the contribution of these spatial cells in goal-directed navigation (i.e. navigation and path planning to a known goal). Lastly, some future directions will be suggested.

**Place Cells in the Hippocampus**

The experiment which initially discovered place cells was performed by O’Keefe and Dostrovsky (1971). It was carried out to examine the hippocampal function in navigation after it had been observed that rats with hippocampal damage, in contrast to healthy rats, performed poorly at spatial tasks. In the pursuit of understanding hippocampal contribution in navigation, response properties were obtained from units located in the dorsal hippocampus (fields CA1 and CA4) and the dentate gyrus. The response patterns elicited by most units could be associated with a particular stimulus or behavior, or could not be associated with either due to inconsistent and unpredictable response patterns. A small part of the recorded units even showed no response at all. However, it was observed that specific units in the hippocampus have preferred spatial orientations, responding solely or maximally when the animal is located in a specific part of the testing area (O'Keefe & Dostrovsky, 1971). Since then, these units have been named place cells, and it has become widely acknowledged that they encode the location of the animal. It has further been argued that these
findings suggest that the hippocampus provides the rest of the brain with a context-based spatial reference map of the environment (O'Keefe & Dostrovsky, 1971). Specifically, it is thought that unit activity in such a map specifies the rat’s position in space in relation to environmental landmarks, and that the reference map would be lost following damage to the hippocampus (O'Keefe & Nadel, 1978).

**Place Fields**

The most frequently used testing apparatus is a cylindrical enclosure with high walls in which the rat is allowed to move freely. If a place unit fires when the rat is situated in a particular part of the testing platform, either by occupying it for some time or merely running past it, then that location is called the place field of that specific unit (Figure 1; O'Keefe, 1976). The highest firing rate of the place cells is reached when the rat arrives at the appropriate place field, and it slowly diminishes over time even when the rat remains in the same location. When the rat is not situated in a specific location, the place cells show almost no spontaneous firing (O'Keefe, 1976). Most units fire only in one place field, with the exception of a few units having two or even three fields in the same environment. No correlation has been found between units recorded next to each other in the CA1 pyramidal layer and the spatial relationship of their place fields; neighboring cells in cortex sometimes do have place fields alongside each other, but more often do not (O'Keefe, 1976).

*Figure 1.* Place fields recorded from four different place cells in the hippocampus. A, a roughly circular field. B, a large elliptical field in the center of the cylinder. C, an elliptical field that touches the cylinder wall. D, a crescentic field. From “Spatial firing patterns of hippocampal complex-spike cells in a fixed environment,” by R. U. Muller, J. L. Kubie, and J. B. Ranck Jr., 1987, *The Journal of Neuroscience, 7*, p. 1941.
Approximately 90% of all active hippocampal pyramidal cells can exhibit place fields, however only 15-50% of the cells do so in any given environment (Bush, Barry, & Burgess, 2014; Thompson & Best, 1989). The place fields of the cells which do participate in representing more than one environment show, however, no topographic relationship between the settings (O’Keefe & Conway, 1978). From knowing the location of a cell’s place field in one testing chamber, it is still impossible to predict the same cell’s place field location in a second chamber (Muller & Kubie, 1987). Additionally, it doesn’t matter if the place fields of two different cells are paired next to each other in one environment, they may not be close to each other in another setting, regardless of the two cells’ spatial relationship in cortex. The transformation of firing fields has also been shown not to be attributed to the geometric shape of the testing platform since two environments with the same shape (e.g. circular or square) then should have identical maps of place fields, which they have been shown not to have (Muller & Kubie, 1987).

These findings have led to the suggestion that the map produced by the hippocampus is not spatially isomorphic to the experienced surrounding (O’Keefe & Conway, 1978). How these maps are shaped is therefore still unknown, but it is thought that place fields remap between environments. Remapping refers to what happens when a novel environment is encountered; a new organization of place fields is established with no connection to the structure in the previous setting (Muller & Kubie, 1987). Furthermore, this new organization is initially less robust in a novel environment but establishes quickly with exploration (Wilson & McNaughton, 1993).

Environmental Control of Place Cell Firing

Both a maze configuration correlate (where cell activity represents the identification of a component of a maze) and an event correlate (where activity represents the registration of an event or that a certain time has passed since that event) have been ruled out as explanations to why the place units fire in their specific place fields (O’Keefe & Conway, 1978). In accordance with suggestions from previous studies, it has been determined that place cell firing indeed is location-
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specific rather than behavior-specific. However, it cannot be completely ruled out that place cells do not occasionally fire in association with certain behaviors or stimuli (for place cell firing in association with goals, see the Discussion section in this thesis; Muller, Kubie, & Ranck, 1987). Although it is still unknown what determines where each place cell fires, certain cues within an isolated environment have been observed to be able to control the place cells’ firing as long as the map has been established (O’Keefe & Conway, 1978).

Visual cue control. In experiments conducted to test the possibility to manipulate firing fields using environmental landmarks, a rectangular white cue card placed on a darker wall of the testing chamber is the most frequently used visual cue. In response to the rotation of such a cue card—90° clockwise and then 90° counterclockwise back to its original position—the firing fields rotate with equal angles each time (Figure 2; Muller & Kubie, 1987). The white cue card has therefore been defined as a polarizing stimulus, since the control it possesses regards the angular coordinates of firing with respect to the laboratory frame.

Not all visual landmarks can, however, be used as polarizing stimuli for controlling place

![Figure 2](image)

*Figure 2. Effects on cue card rotation on place cell firing. Rate map A shows the firing field of a specific cell recorded with the cue card’s initial position on the wall at 3 o’clock. The location of the cue card is indicated by the black curved line to the right of the map of the cylindrical platform. A firing response from a single place cell can be seen at approximately 5 o’clock. Rate map B shows a virtually identical rotation of the place field in relation to the 90° counterclockwise rotation of the cue card. Last, when the cue card is rotated 90° clockwise back to its original position, the firing field rotates back with equal angle, as is shown in rate map C. From ”The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells,” by R. U. Muller and J. L. Kubie, 1987, The Journal of Neuroscience, 7, p. 1954.*
fields. Three-dimensional objects placed in the center of the recording platform are not able to control the angular position of firing fields (Cressant, Muller, & Poucet, 1997). Since the visual relationship of centrally placed objects changes in regard to the rat’s location, it has been suggested that such a cue configuration is too complex to be used as a spatial landmark. On the other hand, the relation of more distal cues placed in the peripheral regions of the recording apparatus do not change depending on the rat’s position. Therefore, distal cues exert better stimulus control than proximal, and they are preferentially used when both are present (Cressant et al., 1997). Moreover, when salient distal and proximal cues are rotated in opposite directions, place cells show an unpredictable behavior. Some place fields follow the distal cues, some follow the proximal cues, some fields split into two, and some fields remap (Yoganarasimha, Yu, & Knierim, 2006). It has therefore been concluded that place fields do not act as an internally coherent network.

Furthermore, cue control over hippocampal place fields is not necessarily an inherent property of the place cell system (Knierim, Kudrimoti, & McNaughton, 1995). The degree to which a cue exerts control over place fields strongly depends on the prior experience of the rat and the rat’s assessment of the cue’s stability. In particular, it appears that it is necessary for the rat to learn that a visual cue is a stable directional reference to allow for it to act as stimulus control. Alternatively, it may be that the cue has control by default, unless the rat learns that the cue is unstable (Knierim et al., 1995).

The effect on place fields by the removal of visual cues has been shown to depend on the rat’s previous experience. The majority of place cells are unaffected by visual cue removal by darkening the chamber if the rat has had the opportunity to experience the recording apparatus during a preceding light period (Quirk, Muller, & Kubie, 1990). If the place fields are given a chance to remap and again placed in the same—but initially dark—recording chamber without any non-visual cues, the same place cells show altered firing patterns. Most of the place cells whose firing patterns are altered in initial darkness usually remain in the changed pattern even when the lights are turned
on, and do not return to the pattern recorded in the initial light segment in the preceding experiment (Quirk et al., 1990). Only small portions of place cells exhibit different firing behavior. Some place cells are always consistent in their firing, and appear to be unaffected by darkness regardless of preceding light segments. Other place units show altered firing patterns in all dark segments independent of preceding light, suggesting the necessity for constant visual stimuli for these cells (Quirk et al., 1990).

These findings suggest that place cell activity can be maintained but not established without access to prominent visual (or non-visual) stimuli (Quirk et al., 1990). Nevertheless, the finding that the majority of firing patterns are not changed by darkness after initial light is supported by the finding that if place fields are initialized by visual cues, then the elimination of the cues neither abolishes nor alters the place field firing (Martin & O'Keefe, 1998).

**Non-visual cue control.** The discovery that only a few recorded cells are completely dependent on constant visual stimuli (see Quirk et al., 1990) suggests that non-visual stimuli also can control place cell firing. Support for polymodal cue control has been received from rats made blind by surgical removal of the eyes before eye opening (Save, Cressant, Thinus-Blanc, & Poucet, 1998). The deprivation of all visual experience causes no disruption of place cell activity if the rats have access to prominent non-visual stimuli. The place cells of blind rats are fully functional and virtually indistinguishable from those of sighted rats, except from a lower rate of place cell firing. Even without vision, blind rats can cautiously find objects (acting as somatosensory cues) placed in the peripheral recording platform through exploratory behavior. Rotation manipulations have shown that blind rats successfully can anchor place fields to the objects by the use of touch (Save et al., 1998), suggesting that even blind rats can create functional place maps to determine their location in space. It is possible that sighted rats also can anchor their place fields to three-dimensional objects using touch in darkness by light extinction. However, experiments testing place map formation in darkness (e.g. Quirk et al., 1990) have not tested the influence of somatosensory cues, and no
In the light of these results, it has been proposed that although place cells can be anchored by visual stimuli when such are accessible, they also receive input from non-visual modalities (Save et al., 1998). More specifically, it has been shown that olfactory information successfully can be used to compensate for the lack of visual information in an initially dark recording chamber (Save, Nerad, & Poucet, 2000; Zhang & Manahan-Vaughan, 2013), allowing for both blind and sighted rats to create place maps of the environment.

**Idiothetic Control of Place Cell Firing**

Idiothetic cues are self-motion cues and can derive from internal sources (e.g., vestibular discharge or motor system signals) or external sources (e.g., optic flow cues), as consequences of the animal’s movements (Knierim, Kudrimoti, & McNaughton, 1998). Each type of cue will be fully explained in their respective subsection.

When the rat is left without any stimuli by the combined extinction of visual and olfactory cues, the place fields shift unpredictably or the place cells cease their firing altogether (Save et al., 2000). In other words, when the animal has not experienced the environment in light before darkness, and has no non-visual cues to anchor place fields to, the rat is unable to rely solely on idiothetic information to support place field stability. However, if the animal knows its starting position (i.e., has had some experience of the environment in light or access to stable non-visual cues) idiothetic cues may be used to estimate its current position and direction in the absence of environmental stimuli (Taube & Burton, 1995). This contribution of idiothetic information in maintaining place field stability is supported by the finding that the majority of place fields remain unaltered in darkness after the place field map has been established (Quirk et al., 1990). The use of idiothetic information to successfully navigate in the absence of external landmarks is more commonly known as path integration (Mittelstaedt & Mittelstaedt, 1980).

**Vestibular information.** The vestibular system is located in the inner ear and provides the
hippocampal place cells with information about self-produced movement, such as ongoing head
movement and sense of balance (Angelaki & Cullen, 2008). In addition to available external
landmark cues, hippocampal place cells continually monitor vestibular input to maintain a current
representation of the environment (Stackman, Clark, & Taube, 2002). However, when there no
longer are external cues available to anchor place fields to, such as in darkness, vestibular
information has been shown to be sufficient to maintain stable place fields. The only requirement is
that the rat has had some previous experience of the environment with available visual or non-visual
cues (Sharp, Blair, Etkin, & Tzanetos, 1995).

Motor programming system information. The motor programming system provides the
place cells with information about the rat’s planned and ongoing movement. (The latter is referred
to as motor efference copies, and will be briefly discussed in the head direction cell section.) By
restraining the rat, thus making it immobile, place cells become virtually silent even when the rat is
within the place field of the recorded cell. The place cell activity is regained when the rat is released
from the restraint, even if the rat stays immobile (Foster, Castro, & McNaughton, 1989). It has
therefore been suggested that there is an influence of information from the motor programming
systems on hippocampal place cells. Although active motion may not be essential for the firing of
hippocampal place cells (Stackman et al., 2002), it is a possibility that they require the rat to be
prepared to move and navigate in the environment to fire in their place fields (Foster et al., 1989).

Optic flow cues. Optic flow refers to retinal image-shifts, i.e. the motion of light, objects,
surfaces, and edges in a visual scene projected onto the retina, induced by movement (Krapp &
Hengstenberg, 1996). Optic flow cues are also known as visual motion cues. They should, however,
not be confused with stationary visual cues. The former refers to the motion of a visual stimulus and
the latter to the visual stimulus itself. For example, whereas a stationary visual cue could be a dot of
light projected onto a surface, the motion of said dot of light would be the visual motion cue. Few
experiments have been conducted on the control of place cell firing by optic flow cues, and the
findings suggesting such control is less straightforward than that of vestibular control (Sharp et al., 1995). Overall data patterns suggest that visual motion information reaches the hippocampal circuitry. When tested in combination with vestibular inputs, the indication of an influence of visual motion cues on place cell control is present, although subtle (Sharp et al., 1995).

Long-Term Stability of Place Cell Activity

A significant portion of experiments have shown that place cells show altered firing patterns in response to manipulations of external and internal information. These findings suggest that place cells in the hippocampus are capable of plasticity. In this context, plasticity refers to experience dependent changes of neuronal responses, from one stable functional state to another (Thompson & Best, 1990). It is a crucial feature to accommodate for novel environments and alterations in the current setting. However, stability of neuronal activity may be just as important. There are few experiments which have tested the basic principle of long-term stability of neuronal activity in hippocampal place units, in contrast to, say, the sensorimotor systems. When examining place field activity over long periods of time in an environment with fixed spatial cues, it has been shown that the location of the place fields of all units are stable over all time periods tested, for intervals up to 153 days (Thompson & Best, 1990). It has therefore been concluded that field locations do not move over time in a fixed environment but remain stable, and that the hippocampus is a site of both plasticity and of long-term stability of neuronal responses.

Lesions Affecting Hippocampal Place Cell Activity

According to a neural framework developed by Burgess and O’Keefe (1996) to explain the firing of place cells and the mechanisms underlying spatial navigation in rats, the hippocampus plays a central role in the processing of spatial information. It is therefore expected that damage to the hippocampus severely impairs the rat’s ability to solve spatial tasks. However, it is not only damage to the hippocampus that disrupts place cell firing, lesions to the vestibular system and the head direction network may also impair the hippocampal place signal.
Lesions to the hippocampus. In the classic Morris water maze experiment, the rat is placed in a circular pool of water and tasked with escaping the water by finding a platform hidden beneath the water surface (Morris, Garrud, Rawlins, & O’Keefe, 1982). Hippocampal-lesioned rats show a severe impairment on this navigation task; not only do they not improve at the same rate as normal rats at escaping the water, they also take longer and more circuitous routes searching for the hidden platform than do healthy rats (Morris et al., 1982). Additionally, impaired rats cannot find the hidden platform even if it is located at a location previously occupied by a visual platform, which the rat could locate regardless of hippocampal damage. It has therefore been implied that hippocampal-lesioned rats do far worse in learning where the hidden platform is located than do healthy rats, and are never able to learn to swim directly towards it from a distance (Morris et al., 1982).

Additionally, the impaired performance in the Morris water maze has been shown to strongly depend on the specific type of damage to the hippocampus. Out of several different types of bilateral and unilateral hippocampus and dentate gyrus lesions (electrolytic lesions, kainic acid-induced CA3-CA4 lesions, and colchicine-induced dentate gyrus lesions), all types of damage greatly impair rats in finding the hidden platform, with the exception of unilateral CA3-lesions (Sutherland, Whishaw, & Kolb, 1983). Rats with unilateral CA3 hippocampal damage perform as well as controls at the task. However, it cannot be assumed that an intact hippocampus in one hemisphere is sufficient for spatial processing, since unilateral damage to the dentate gyrus produces severe deficits in solving the Morris water task (Sutherland et al., 1983).

Hippocampal lesions do not only impair the rat’s performance in spatial tasks. When hippocampal-lesioned rats are allowed to freely explore an open platform containing a number of three-dimensional objects, they show deficient habituation (Save, Buhot, Foreman, & Thinus-Blanc, 1992). Removal of the objects induces re-exploration in healthy rats, suggesting that the rat reacts to the mismatch between the current environment and the representation of the previous environment.
created during the initial exploration. The act of renewed exploration as a reaction to a changed environment is a strong sign that animals can construct a cognitive spatial map. In contrast to healthy rats, hippocampal-lesioned rats do not re-explore the location where an object has been removed. This is again suggesting that the hippocampal formation plays a crucial role in the processing of spatial information, and possibly also in the construction of associative spatial representations of the environment (Save et al., 1992).

In conclusion, lesions to the hippocampal formation impair the ability to encode information about the animal’s environment, and spatial representations that potentially could form the basis of a cognitive map are lost (McGregor, Hayward, Pearce, & Good, 2004). The cognitive map theory of hippocampal function, which argues for such a map, will be briefly discussed in the end of the place cell section.

**Lesions to the vestibular system.** Even though place cells are located mainly in the hippocampus, lesions in other parts of the rat brain can severely impair place cell activity. Although not tested specifically in relation to place cell firing, it has been shown that complete vestibular lesions partly disrupt navigational behavior (Stackman & Herbert, 2002). When visual landmarks are present, vestibular-lesioned rats perform as well as controls in spatial learning tasks. They are, however, markedly impaired when the navigation solely depends on idiothetic cues. This suggests that vestibular-lesioned rats are critically dependent on landmark cues, and that vestibular information is important for updating internal representations of the environment that support spatial behavior (Stackman & Herbert, 2002). Since such environmental representations are assumed to partly consist of place cell activity (O’Keefe & Dostrovsky, 1971), it is also fair to assume that place cell activity is impaired by vestibular lesions.

Experiments conducted specifically to test vestibular lesions and place cell activity have shown that, in accordance with the previous assumption, location-specific place cell firing indeed is disrupted by vestibular lesions (Stackman et al., 2002). It has also been observed that vestibular
inactivation disrupts place cell activity even in the presence of a visual cue card (Stackman et al., 2002), which contradicts previous results. These differing results can possibly be explained by the fact that the first mentioned experiment tested navigational behavior (Stackman & Herbert, 2002), and not place cell activity per se. It is therefore possible that other factors come into play to support the use of visual landmarks in navigation.

**Lesions to the head direction network.** It is noteworthy that lesions to the head direction cell network, which will be discussed thoroughly in a later section, also influence place cell activity. Following lesions to the anterior thalamic nuclei (ATN) or postsubiculum (PoS) in the rat—both containing head direction cells—hippocampal place cells continue to exhibit location-specific activity. However, the place cell signal is significantly decreased and the cells are more directionally sensitive than pre-lesion (Calton et al., 2003).

Additionally, place fields in PoS-lesioned rats cannot be controlled by visual landmarks in rotation conditions, and shift unpredictable between sessions (Calton et al., 2003). This finding indicates therefore that the PoS is important for allowing visual landmarks to control place cell firing. ATN-lesioned rats also allow for less landmark control than controls, but this impairment is only mild in comparison to that of PoS-lesioned rats (Calton et al., 2003).

Together, these findings suggest that the head direction system is not required for the maintenance of hippocampal place fields, but lesions to brain regions in the rat that encode head direction information can decrease the place signal, and that the PoS is required for visual landmarks to control place fields (Calton et al., 2003).

**The Cognitive Map Theory**

As presented in the previous sections, place cells located in the hippocampus convey the current position of the rat in an environment, depending on external and internal stimuli to control the place fields. This feature of the place cells is one of the vital elements of the cognitive map theory of hippocampal function, first outlined by O’Keefe and Nadel (1978). According to this
theory, each individual place cell represent a specific part of an environment. Together, place cells constitute a neural system which forms a spatial map of each setting. The theory is supported by both unit recording and lesion studies, which together converge to indicate a central role for the mammalian hippocampus in map-based navigation. The cognitive map theory is not, however, within the scope of this thesis. It will therefore not be discussed further, but see O’Keefe and Nadel (1978) for more information.

**Head Direction Cells in the Papez Circuit**

In addition to hippocampal place cells, a second population of cells to contribute to self-localization are head direction cells, which were discovered in rats 25 years ago. In the first extensive study conducted on these units, single-cell recordings were performed in the deep layers of the postsubiculum (PoS) of the freely moving rat (Taube et al., 1990a). The experiment was carried out with the animal positioned in a cylindrical chamber with a single white cue card on the wall, a setting identical to the one used in experiments of place cells (see Muller et al., 1987). In contrast to place cells, the found population of head direction cells did not show location-specific firing. Instead, the PoS cells exhibited precise directional firing; with low background activity (usually <1 spike/sec), they fired maximally when the head of the rat was directed in a single specific angle in the horizontal plane (Figure 3; Taube et al., 1990a). This feature is today acknowledged as the most salient characteristic of head direction cells. Further, it is known not to be connected to either spatial view or gaze movement, confirming that the cells convey direction-specific information (Robertson, Rolls, Georges-François, & Panzeri, 1999).

As noted, head direction cells were first discovered in postsubiculum (PoS; Taube et al., 1990a), but have since then been identified in several other brain regions both within and outside the Papez circuit. The Papez circuit consists of a loop of connections combining different brain regions, running from the thalamus through the cingulate gyrus, entorhinal cortex, hippocampus, septal area, hypothalamus, mammillary bodies, and returning to the thalamus (Beaumont, Kenealy,
& Rogers, 1996). Since the information regarding head direction cells presented in this section applies to all cell populations regardless of their location in the rat brain, they will here be treated as a collective group of cells, unless other is stated. See a later subsection for additional brain regions and differences between cells in relation to where they are recorded.

**Preferred Directions**

Any given cell has a "preferred direction", and the activity of the cell reaches a maximum each time the head turns either clockwise or counterclockwise to point in, or passing through, the preferred direction. The increase and decline of firing rate to and from the peak appears linear with the head rotations leading to and from the preferred direction, and the function of firing rate and head direction is therefore treated like triangles (Taube et al., 1990a).

The preferred direction of a given cell remains the same regardless of the rat’s location on the testing platform, and lines drawn to represent the preferred direction at different head angles indicate that all the vectors are parallel and do not converge toward a single point. Additionally, the preferred directions are evenly distributed over a 360° angle, showing no trend for clustering of
preferred directions around a particular head direction (Stackman & Taube, 1998).

In contrast to hippocampal place cells, the firing of head direction cells is not affected by the animal’s location, nor the direction of the trunk (Taube, 1995). For example, the animal’s head can be pointing in the preferred direction and the body in another, and the head direction cells still discharge maximally. Also, they stay silent if the body is pointing in the cells’ preferred direction while the head is not (Taube, 1995). The firing is also independent of ongoing behavior; the directional activity stays constant and unaffected by eating, grooming, sniffing, rearing, walking or running (Stackman & Taube, 1998; Taube, 1995; Taube et al., 1990a). There is, however, a trend for higher firing rates when the animal moves rapidly than when it is motionless (Taube, 1995; Taube et al., 1990a).

While the rat’s head is oriented in the preferred direction of a given cell, neither head pitch (up or down rotation) up to 90° vertically, head roll (rotation along the anterior-posterior axis), nor rearing of the rat, significantly alters the firing of that cell (Stackman & Taube, 1998). Moreover, when the rat is subjected to a vertical plane in addition to a horizontal, as is also seen in the animal’s natural habitat where it is required to integrate movements in both horizontal and vertical planes, the discharge properties of the head direction cells are sustained (Stackman, Tullman, & Taube, 2000). This means that head direction cells are capable of maintaining the firing patterns outside the horizontal plane as long as the head orientation corresponds to the preferred direction of the cells. This maintaining of firing is also independent of whether the rat climbs up (+90°) or down (-90°) the vertical plane. It can therefore be concluded that when the rat is locomoting the vertical plane, the head direction cells treat the current plane of locomotion according to the horizontal reference frame (Stackman et al., 2000).

**Additional Brain Regions Containing Head Direction Cells**

Aside from the original discovery of head direction cells in the PoS (Taube et al., 1990a), direction sensitive cells have also been identified in other brain regions within the classical Papez
circuit. These areas include the anterior thalamic nuclei (ATN; Taube, 1995), lateral mammaillary nuclei (LMN; Stackman & Taube, 1998), and medial entorhinal cortex (mEC; Sargolini et al., 2006). They have also been found in areas outside the Papez circuitry, such as in the lateral dorsal thalamus (LDN; Mizumori & Williams, 1993), dorsal striatum (Wiener, 1993; Mizumori, Ragozzino, & Cooper, 2000), retrosplenial cortex (Cho & Sharp, 2001), and the dorsal tegmental nuclei of Gudden (DTN; Sharp, Tinkelman, & Cho, 2001), among others. None of these regions contain exclusively head direction cells. The ATN probably possess the greatest share of head direction cells, with ~60% of their cells found to discharge in relation to head direction (Taube, 1995). It is followed by ~30% in the LDN (Mizumori & Williams, 1993), and ~25% both in the PoS (Taube et al., 1990a) and in the LMN (Stackman & Taube, 1998).

Even though the most fundamental head direction cell features, such as the function of head direction and firing rate, are shared across all cell groups, certain features differ depending on in which brain region the cells are located. The perhaps most significant difference is that head direction cells recorded from different brain areas may exhibit dissimilar temporal relationships. Head direction cells recorded in the ATN shift their mean firing direction as a function of angular head velocity (which is a function of head direction and head-turning speed); the mean firing direction of ATN cells is shifted to the left during clockwise turns of the rat's head, and shifted to the right during counterclockwise turns (Blair & Sharp, 1995). Additionally, the ATN cell firing peak is optimized when it is adjusted to the animal’s future directional heading by +23.2 msec (Taube & Muller, 1998). The amount of time the peak firing rate of head direction cells leads or lags the animal’s immediate head direction is called the anticipatory time interval (ATI). Moreover, the ATI has been recorded to be +25.05 msec for head direction cells in the retrosplenial cortex (Cho & Sharp, 2001) and +95.8 msec for LMN cells (Stackman & Taube, 1998). In contrast, PoS head direction cells do not exhibit such a shift in mean firing direction in relation to angular head velocity (Blair & Sharp, 1995), and show a negative time shift of -6.2 msec (Taube & Muller,
1998). These findings indicate that while PoS head direction cells encode the rat’s current heading or its heading in the very recent past, ATN, LMN, and retrosplenial cells lead head direction and predict the future direction of the rat (Cho & Sharp, 2001; Blair & Sharp, 1995; Stackman & Taube, 1998; Taube & Muller, 1998).

There are, however, always exceptions. Not every ATN head direction cell anticipates the future directional heading of the rat, and a few of the PoS head direction cells exhibit such an anticipatory feature (Taube & Muller, 1998). It has been concluded that a certain brain region does not have a specific lead or lag time that applies for all head direction cells in that area. Head direction cells located in a particular brain area should therefore not be treated uniformly in terms of their lead or lag times (Taube & Muller, 1998).

Environmental Control of Head Direction Cell Firing

Visual cue control. The firing properties of head direction cells in relation to environmental cues are much alike those of hippocampal place cells. Since cue card rotation previously has been shown to influence place cell firing (Muller & Kubie, 1987), the same design has been used to test the effects on the preferred firing directions of head direction cells (Taube, Muller, & Ranck, 1990b). By rotating a white cue card—90° clockwise and 90° counterclockwise back to the original position—the preferred directions of cells recorded in PoS (Taube et al., 1990b), ATN (Taube, 1995) and LMN (Stackman & Taube, 1998) do follow the rotations with equal angle (Figure 4). Although the preferred directions shift in relation to the cue card, peak firing rate and directional firing rate do not change, which suggests that a single visual cue can exert control over head direction cell firing (Taube et al., 1990b). Such control is considered stable after eight minutes, but varying lower degrees of stability can be achieved earlier (Goodridge, Dudchenko, Worboys, Golob, & Taube, 1998). It should be noted, however, that the cells are not triggered by the visual cue in a simple sensory-like manner. The preferred directions would then be expected to converge toward a single cue rather than to be parallel, as they have been shown to be (Stackman & Taube, 1998).
Furthermore, preferred directions preferentially anchor to cues close to the visual background rather than foreground cues (Zugaro, Berthoz, & Wiener, 2001), as has been previously observed in hippocampal pyramidal cells (Cressant et al., 1997). It is hypothesized that if the configuration of cues is too complex in the sense that the view of the cues is dramatically altered when the rat moves around the testing chamber, the cues are then too unreliable to be used as spatial landmarks. In that case, more distal cues are used to anchor the preferred directions of the head direction cells if such are available (Cressant et al., 1997; Zugaro, Berthoz, & Wiener, 2001). However, when distal landmarks are rotated in the opposite direction of proximal landmarks, the entire ensemble of head direction cells are strongly bound to the distal cues, not allowing for the proximal cues to exert any control over head direction cell firing (Yoganarasimha et al., 2006). Such a mismatch rotation (where the two different types of cues are rotated in opposite directions) between distal and proximal landmarks show that, in contrast to place cells, the head direction units never split.

Instead, they act as a network where all preferred directions rotate together by the same amount.

*Figure 4.* The firing of two head direction cells recorded in the PoS in response to cue card rotation. The solid line represents the cells’ initial preferred direction. With the cue card rotated, 90° clockwise for cell A and 180° for cell B, the preferred firing direction of the cells rotates approximately the equal degree in response, represented by the dash-dot lines. Last, with the cue card returned to its initial position, the preferred firing directions follow by reverting back to their original degrees, seen as dash-dot-dot lines. From “Head-direction cells recorded from the postsubiculum in freely moving rats. II. Effects of environmental manipulations,” by J. S. Taube, R. U. Muller, and J. B. Ranck Jr., 1990b, *The Journal of Neuroscience, 10*, p. 438.
with fixed angles apart from one another (Yoganarasimha et al., 2006).

After a cue card has gained control over head direction cell firing, visual cue removal leads only to an unpredictable shift of preferred directions, while both peak firing rate and firing range stay unaffected. Importantly, the head direction cells do not cease their firing as a response to cue card removal (Taube et al., 1990b), suggesting that such a prominent visual cue is not necessary to constantly maintain head direction cell activity. Similar firing responses can be observed when the rat is stripped of all visual experiences. By depriving the rat of visual stimuli by blindfolding, it has been observed that neither PoS nor ATN head direction cell firing is abolished in darkness after initial light; all cells continue their direction-specific firing with only an incalculable shift in preferred direction angles (Goodridge et al., 1998). When the rat is placed in an initially dark testing platform with no previous visual experience of the environment and without access to non-visual cues, the directional specificity and preference of head direction cells recorded in the LDN are disrupted and the cells fire as if the rat moves in several directions simultaneously (Mizumori & Williams, 1993). When the platform is then lighted, the head direction cells reorient rapidly (80 ± 10 msec for a 90° reorientation) to the preferred directions anchored by the visual cues in the previous experiment (Zugaro, Arleo, Berthoz, & Wiener, 2003). Only after a light period does the directional specificity of the cells endure in darkness, but the directional firing is maintained only for about 2-3 minutes. After this period it systematically rotates in either the clockwise or counterclockwise direction (Mizumori & Williams, 1993). The fact that directional firing can be maintained in the absence of visual cues for a short period of time once it has been established in light supports the hypothesis that visual input integrates with other types of information to uphold direction-specific activity (Mizumori & Williams, 1993).

**Non-visual cue control.** Some non-visual landmark cues can exert stimulus control over the firing of head direction cells. Rotations of olfactory cues do exert a small but nevertheless significant degree of stimulus control of head direction cell firing. Such control is, however,
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considerably less than the control exerted by visual cue cards (Goodridge et al., 1998). Furthermore, auditory cues have not been found to exert complete stimulus control on its own (Goodridge et al., 1998; but see Rossier, Haeberli, & Schenk, 2000, for stimulus control by auditory cues when associated with visual cues). There have as of yet been no extensive experiments conducted on tactile cues for stimulus control over head direction cell firing, and experiments testing the influence of three-dimensional objects to establish preferred directions in neither blind rats nor in sighted rats placed in dark environments has been found.

**Idiothetic Control of Head Direction Cell Firing**

As noted in previous sections, idiothetic cues refer to self-motion information deriving from the animal’s movements (e.g., vestibular signals, motor system signals, or visual motion cues; Knierim et al., 1998). With knowledge only of the starting position, the rat can use these internal cues to estimate its current position and direction by maintaining the stability of its directional heading independently of external landmarks (Taube & Burton, 1995). As mentioned, this ability is also known as path integration (Mittelstaedt & Mittelstaedt, 1980).

**Vestibular information.** Idiothetic cues such as the rat’s ongoing head movement is relayed by the vestibular system (Blair & Sharp, 1996), which detects the head position and head motion in space (Stackman & Taube, 1997). In light conditions, visual cues do not have sole control of head direction cell firing; information from external landmarks have an interactive influence together with idiothetic cues. However, in the event of cue card removal and darkening of the recording chamber, the use of idiothetic information can explain the maintenance of head direction cell activity (Blair & Sharp, 1996). Additionally, it has been shown that when the rat moves from a familiar environment in which it has established preferred directions, to a novel unfamiliar environment with no landmark cues, preferred direction and direction selectivity are maintained (Taube & Burton, 1995). This suggests that internal cues including information regarding the angular head movements of the rat can sustain the preferred firing directions of head direction cells.
when familiar external cues are not available.

**Motor efference copies.** A motor efference copy is an internal copy of a movement-producing signal conveyed by the motor system (Jeannerod, 2003), telling the rat how it is moving. Denial of volitional motor behavior by tightly restraining the rat’s movements leads to the ceasing of ATN head direction cell firing (Taube, 1995), but not PoS cell firing (Taube et al., 1990b), even when that rat is passively rotated through the preferred firing direction. In contrast to place cells, the peak rate of directional firing decreases even when the rat is unrestrained but passive (Zugaro, Tabuchi, Fouquier, Berthoz, & Wiener, 2001). In addition, there is a small but significant correlation between head direction firing rate and the velocity of the rat when it moves across the recording platform (Taube et al., 1990a; Taube, 1995). Together, these findings indicate that motor efference copies exert a state-dependent modulation of ATN head direction cell firing (Zugaro, Tabuchi, et al., 2001). This means that ATN head direction cells require some type of motor signal for activation (Taube, 1995), which is consistent with the notion that head direction information is critical during active self-produced movement and less so during motionless activities (Zugaro, Tabuchi, et al., 2001). Note that the cell activity is not influenced by specific behaviors, such as eating or grooming (Stackman & Taube, 1998; Taube, 1995; Taube et al., 1990a), only self-produced movement in general.

**Optic flow cues.** As noted, optic flow (i.e., visual motion) refers to the movement-induced changes of images of the visual scene projected onto the retina (Krapp & Hengstenberg, 1996). Experiments have shown that visual motion cues can influence the preferred direction of head direction cells (Blair & Sharp, 1996). The influence on ATN head direction cells by optic flow is weak when it is in conflict with internal signals (Arleo et al., 2013), but it has been hypothesized that the influence on preferred directions by optic flow cues is greater when they are corroborated by vestibular cues (Blair & Sharp, 1996).
Conflict between External Landmark Cues and Idiothetic Cues

Previously mentioned experiments have shown that both external and internal cues exert strong influence on the preferred direction of head direction cells. However, none of them discuss the collaboration or conflict between the two kinds of cues. In studies where visual cues has been tested (Taube et al., 1990b; Taube, 1995), the influence of internal cues was minimized by removing the rat from the recording chamber between test and control sessions. Furthermore, experiments testing idiothetic cues (Blair & Sharp, 1996) were conducted in the absence of polarizing visual cues.

When stable and prominent visual cues come in conflict with idiothetic cues in a small mismatch rotation condition (45°; in which the two different types of cues are rotated in opposite directions), the spatial information acquired from visual landmarks usually supersede the information from idiothetic cues (Knierim et al., 1998). Another experiment has shown that if the spatial information from visual and vestibular sources mismatch in a cue card rotation condition, the angles of rotation of preferred directions are smaller than that of the cue card. This suggests that even under conditions in which information derived from visual landmarks usually dominate, idiothetic cues still exert some control over head direction cell preferred firing directions (Zugaro, Tabuchi, & Wiener, 2000). Nevertheless, if the mismatch is larger (180°) between visual and idiothetic cues, idiothetic input usually predominates over the visual landmarks (Knierim et al., 1998), possibly because the visual cues are deemed too unstable.

Lesions Affecting Head Direction Cell Activity

Since head direction cells are present in several distinct but interconnected brain regions, understanding how the head direction signal is generated is complicated. It follows therefore that damage to different parts of the head direction circuitry affects different head direction populations in a variety of ways.

Lesions to the anterior thalamic nuclei or postsubiculum. Experiments have uncovered
that complete lesions of the anterior thalamic nuclei (ATN) abolish head direction cell firing in the postsubiculum (PoS), indicating that the ATN is necessary for intact direction-specific activity in the PoS (Goodridge & Taube, 1997). In contrast, a substantial portion of the head direction population in the ATN remains intact after PoS lesions. This dissociation implies that the PoS receives the head direction signal from the ATN, and that the ATN therefore does not require the PoS to maintain stable head direction firing (Goodridge & Taube, 1997). ATN head direction cells do, however, exhibit significant differences after a PoS lesion. First, the ATN head direction cells’ firing range are larger than in rats with the PoS intact. Second, the anticipatory time interval (ATI) is increased to almost twice the time (41 msec rather than 23 msec), suggesting that ATN head direction cells predict the future direction to a greater extent post-lesion than pre-lesion. The third and perhaps most major difference is that the preferred firing directions of the ATN head direction cells after a PoS lesion cannot be controlled by external landmarks, but rather shifts incalculably after cue card rotations (Goodridge & Taube, 1997). These results have led to the suggestion that the PoS is important in allowing visual landmarks to exert control over ATN head direction cells (Goodridge & Taube, 1997). This feature of the PoS has been mentioned regarding hippocampal place cell activity as well (see Calton et al., 2003).

**Lesions to the lateral mammillary nuclei or dorsal tegmental nucleus.** Bilateral lesions to the LMN completely abolishes the directional firing properties of head direction cells in the ATN, and they have as of yet not been seen to recover in any animal (Bassett, Tullman, & Taube, 2007; Blair, Cho, & Sharp, 1998). The ATN cells do not fall completely silent, but they lose their directional firing and fire spontaneously as the rats move around the recording chamber (Blair et al., 1998). Additionally, the destruction of the mammillary bodies and/or the ascending mammillo-thalamic track has been reported to cause the complete destruction of head direction cell activity in the PoS (Sharp & Koester, 2008). The distribution and robustness of the direction cells in the ATN has also been observed to be reduced after a lesion to the DTN (Bassett et al., 2007). Together, these
findings indicate that the ATN and PoS receive the head direction signal from the LMN, and that the DTN-LMN circuit is overall important for the generation of the head direction signal (Bassett et al., 2007).

**Lesions to the vestibular system.** Not only lesions to the head direction circuit disrupt head direction activity. Complete lesions to the vestibular apparatus also result in a total loss of the head direction cell firing in the ATN (Stackman & Taube, 1997). Interestingly, the directional firing of ATN head direction cells is lost as a function of vestibular lesions regardless of present landmarks previously shown to exert control over preferred directions of ATN head direction cells. In the case of ATN cells, it is therefore assumed that vestibular information is not only necessary for maintaining stable preferred directions in conditions when path integration is needed, but is also crucial for the generation of the head direction cell activity in the ATN (Stackman & Taube, 1997). Furthermore, since lesions to the vestibular system abolish the ATN directional firing (Stackman & Taube, 1997) and lesions to the ATN disrupt head direction cell firing in the PoS (Goodridge & Taube, 1997), it can be suggested that PoS cell activity may also be disrupted as a result of vestibular lesions via the ATN. However, this has not yet been confirmed.

**Grid Cells in the Entorhinal Cortex**

The search for the origin of the place cell signal took a new turn when it was found that place fields in the CA1 persist even after the disruption of all intrahippocampal input, with only the CA1-entorhinal circuit intact (Brun et al., 2002). This finding raised the possibility that CA1 receives spatial information through direct connections from the entorhinal cortex, and the search for spatial maps shifted to that specific brain region. Research that followed uncovered a third type of spatial correlate that may play a part in self-location and navigation—the grid cell. These cells are present in the medial entorhinal cortex (mEC), and they fire when the rat moves freely in the environment (Hafting et al., 2005).
Similar to hippocampal place cells, grid cells convey the rat's location in space. However, whereas place cells have only one distinct firing field for each cell, single grid cells have multiple discrete sites in the environment in which they fire when the rat passes through (Hafting et al., 2005). These locations, with distinct inhibitory surroundings, are also known as the grid fields of a certain grid cell. In every isolated mEC grid cell, the multiple firing fields form a repeating triangular grid-like pattern covering the entire environment explored by the rat, with the points of activity resembling the layout of a Chinese checkerboard (Figure 5; Hafting et al., 2005).

The grid cells in the mEC appear to be clustered into functional modules; neighboring cells share a common orientation and spacing (Stensola et al., 2012). However, they typically differ in their firing locations (i.e., their phases; Hafting et al., 2005), so that any local ensemble of grid cells cover all possible positions of the rat in the environment at any time (Fiete, Burak, & Brookings, 2008). Independent modules separated by larger distances along the mEC have, on the other hand, different spacing and size of individual grid fields (Figure 5). Recordings obtained from the dorsal three-quarters of the rat mEC have shown that cells in the dorsal tip of the dorsal mEC exhibit the
smallest measured grid field scale with 30 cm between the phases. The largest scale of 3 meters has been recorded in the ventral tip of the dorsal three-quarters of the mEC (Brun et al., 2008).

It is not yet clear if the grid cell map extends to the mEC’s most ventral part (Brun et al., 2008). However, by generalizing the trend of increasing field size of grid cells down to the ventral mEC, it is possible that the largest grid field size could be up to 10 meters (Fiete et al., 2008). Interestingly, the size and spacing of the grid fields have been shown not to be smaller in the mouse than in the rat, in spite of the mouse’s smaller body size, suggesting that grid fields do not scale up proportionally with body size (Fyhn, Hafting, Witter, Moser, & Moser, 2008).

When introduced to a novel environment, some exposure is needed for the stabilization of the grid (Hafting et al., 2005), and during the familiarization with it, grid cell firing patterns undergo marked changes (Barry, Ginzberg, O'Keefe, & Burgess, 2012). Initially, the scale of the grid fields expand and become irregular. During further exploration, they progressively return to the more regular and significantly smaller spatial scale seen in familiar environments (Barry et al., 2012). Even though the fields initially show reduced stability, grid spacing, grid orientation and spatial phase distribution are still preserved across environments (Fyhn, Hafting, Treves, Moser, & Moser, 2007). Additionally, if two grid cells have closely located firing locations in one environment, they fire at similar locations also in another environment. These findings indicate that the grid map in the mEC realigns with environmental changes without losing its intrinsic spatial phase structure (Fyhn et al., 2007). This realignment suggests that the grid cells provide an universal map that is used across all environments, in contrast to hippocampal place cells which remap and create novel representations for every new environment.

**Environmental Control of Grid Cell Firing**

Due to the fact that grid cells were discovered only a decade ago, research done on allothetic (external) and idiothetic (internal) cue control of grid cell firing is scarce. Additionally, there is still disagreement in how these cues generate the grid map—separately, together, or at all. However, the
finding that grid phases remain stable across successive trials in the same setting is the first clue to that allothetic cues can exert a significant influence over grid cell firing. Indeed, cue card rotation experiments (90°), have shown that the grid rotates together with the cue card without any change in grid scaling or field size. These findings suggest that it is possible for a single cue card to serve as stimulus control, and that phase and orientation may be influenced by external landmarks (Hafting et al., 2005).

Additionally, the removal of visual cues by darkness has no significant effect on the grid’s spacing or firing rate. This finding indicates that the grid-like firing structure is not dependent on external information, and that it therefore plays a part in path integration (Hafting et al., 2005). However, when placed in an initially dark environment, the vertices are weakly dispersed or displaced. Such a decrease in spatial correlation is consistent with the notion that environmental cues may be responsible for aligning the grid to the external reference frame, but not for maintaining the grids (Hafting et al., 2005). Since it has been shown that stationary non-visual cues contribute only minimally to the grid cell firing patterns in darkness (Hafting et al., 2005), the maintenance of a stable grid map in darkness points to the integration of self-motion information. Such information is hypothesized to play an important part in the grid structure (see a later subsection for theories of grid map function), but has as of yet not been explicitly tested.

**Boundary Control of Grid Cell Firing**

Additional environmental control can be attributed to the boundaries of the setting. As noted, the grid map scale is significantly expanded in a novel environment in contrast to familiar surroundings and progressively decreases in scale during exploration (Barry et al., 2012). However, when the rat has familiarized itself with the environment and the borders of the setting change, the grid map is affected in a variety of ways.

**Environment expansion.** If the familiarized setting expands by removing the rat from the enclosure and placing it in an identical but larger box, and both the large and small environments
are familiar to the animal, the number of activity nodes increases while the density remains constant (Hafting et al., 2005). It has therefore been suggested that the grid map may potentially be of infinite size (Hafting et al., 2005). On the other hand, if the rat is situated in a small enclosure during a wall removal manipulation revealing a larger box, the grid map is significantly altered (Savelli, Yoganarasimha, & Knierim, 2008). Even though the rat is present for the wall removal and should be able to use idiothetic cues and the unaltered distal cues of the laboratory to keep the firing fields stable, wall removal alters most spatial firing fields. This finding demonstrates that external boundaries have some control over grid cell firing, and overrides self-motion cues even under conditions where the rat knows where it is situated during wall removal (Savelli et al., 2008).

**Environment deformation.** Additionally, grid cells in rats familiar with either a large square or a vertical rectangular enclosure show a change in firing patterns in response to environmental deformation (Barry, Hayman, Burgess, & Jeffery, 2007). When the environment is deformed along both dimensions, the grid map shows both horizontal and vertical changes in the firing pattern simultaneously. Following deformation along only one dimension, grids do not only rescale in that dimension, they also show a reaction in the opposite dimension (Figure 6; Barry et al., 2007).

![Figure 6](image.png)

*Figure 6. Grid cell pattern alteration from two cells in the mEC in response to environmental deformation. Action potentials (green or red dots) overlapping the animal’s path (black) reveal the triangular tesselating characteristic of grid cells, and how these maps are deformed along the deformation of the environment. Trials 1 and 5 were recorded in the initial familiar setting (red outline) in either a large square (A) or a vertical triangle (B). From "Experience-dependent rescaling of entorhinal grids," by C. Barry, R. Hayman, N. Burgess, and K. J. Jeffery, 2007, *Nature Neuroscience, 10*, p. 682.*
The asymmetry of the grid cell pattern appears to be highly dependent on which environment the rat is familiar with. For example, in rats familiar with the square enclosure, the grid map is altered when the environment is deformed into a rectangular setting. However, rats familiar with the rectangular setting show such an alteration not in the rectangular, but in the square box. That is, in both cases, the asymmetry is significantly greater in the unfamiliar than in the familiar configuration (Barry et al., 2007). Additionally, grid asymmetry induced by deformation of a familiar environment disappears if the rat is introduced to a new environment in the shape of the deformed setting. It has therefore been suggested that grids become associated with environmental boundaries in a familiar environment, and that grid structure asymmetry in response to altered environments reflects the experience (i.e., familiarity) of the environment rather than the shape of the current setting (Barry et al., 2007).

**Border cells.** These findings may be explained by another class of cells present in the entorhinal cortex: the border cells. These cells make up approximately 10% of the active entorhinal cell population. They fire exclusively along one or several walls of the enclosure, irrespective of border length, continuity with other borders, or environment size (Solstad, Boccara, Kropff, Moser, & Moser, 2008). By defining the boundaries of the environment, it is possible that border cells bind the grid cell firing to the borders of the setting to keep the internally generated grid map adjusted with respect to the external world (Savelli et al., 2008).

Although border cells are believed to play a part in the formation of the grid map, they are not directly involved in the function of self-localization to the same degree as place, head direction, and grid cells. For that reason, they will not be further discussed in this thesis.

**Co-Localization with Head Direction Cells**

In addition to border cells, grid cells have been found to co-localize with a substantial number of cells in the deeper layers of the mEC (i.e., III, V, and VI) which have been identified as head direction cells. The general properties of the head direction cells recorded in the mEC are similar to
those recorded in other brain areas mentioned previously. However, certain cell populations in the mEC show overlapping features from both head direction cells and grid cells; some grid cells are directionally tuned and some head direction cells have grid correlates (Sargolini et al., 2006). Conjunctive grid × head direction cells, pure grid cells, and pure head direction cells all show a positive relation of speed and firing rate, which indicates that a substantial portion of the network also conveys information about the speed with which the animal is moving (Sargolini et al., 2006). These findings have led to the suggestion that as the animal moves across the environment, conjunctive cells are likely to play a crucial role in the process of updating the position vector through the integration of position, direction, and speed signals in the mEC.

Lesions Affecting Grid Cell Activity

Inactivation of the hippocampus. Not much is known about the mechanisms by which grid cells interact with place cells, although it is commonly thought that the formation of place cells relies to some degree on grid cells (Fyhn, Molden, Witter, Moser, & Moser, 2004; Zhang et al., 2013). Fairly recent research has, however, shown that the grid structure is dependent on hippocampal back-projections (Bonnevie et al., 2013). During the inactivation of the hippocampus by muscimol infusion (selective agonist for GABA receptors), the spatial periodicity of the entorhinal grid steadily dissolves and the locations of the firing fields progressively become more scattered (Bonnevie et al., 2013). The disruption of the grid pattern co-occurs with a directional sensitivity emerging in formerly non-directional grid cells, as well as reduced firing rates. From these findings, it has been suggested that the hippocampus might contribute to the formation of the grid map, since cells in the mEC do not express normal grid patterns when no active hippocampal back-projections are available (Bonnevie et al., 2013).

Lesions to the head direction network. Very recent research has shown that inactivation or lesioning of the ATN significantly disrupts grid cell firing in addition to head direction cell firing (Winter, Clark, & Taube, 2015). ATN inactivation by lidocaine (an anaesthetic which blocks the
voltage-gated Na+ channels in the neuronal cell membrane [Strichartz, Zhou, Sinnott, & Khodorova, 2002]) abolishes grid like firing patterns, and large lesions significantly reduce the number of grid cells (Winter et al., 2015). These findings suggest that the head direction signal is projected to the entorhinal cortex and that this signal is involved in the generation and function of grid cell activity.

**Function of the Grid Map**

The scientific community is united regarding the function of place and head direction cells; place cells convey the location of the animal and head direction cells encode the direction of the animal’s head. The function of grid cells has, however, been problematic to reach agreement on. In a way, grid cells convey information about the rat’s location in an environment similar to place cells, and the fact that a cell’s grid field has the same spacing even across environments indicates an environment-independent function for the grid map. However, the purpose of grid cells has not yet been fully resolved in the relatively short time since their discovery, but there are of course theories.

**Grid cells as precursors for place cell firing.** After the discovery of grid cells, it was initially hypothesized that grid cell responses were the precursors for place fields in the hippocampus (Bush et al., 2014), placing grid cells higher up in the hierarchy of processes than place cells. Computational models explaining this grids-to-places transformation are outside the scope of this thesis, but see Rolls, Stringer, and Elliot (2006), and Solstad, Moser, and Einevoll (2006), for examples.

Without involving computational models, theories of a grids-to-places transformation are supported by the fact that hippocampal place cells receive excitatory projections from grid cells in the mEC (along with other spatial and non-spatial cells such as border and head direction cells; Zhang et al., 2013). The finding that CA1 place cell responses are not disrupted by the removal of input from CA3 (Brun et al., 2002) provides additional support, suggesting that entorhinal input is sufficient for place cell firing to be established and maintained.
Challenging this theory is the finding that place fields and grid fields differ in the time required to stabilize in a novel environment. Both are less robust and increased in size in a novel environment than in a familiar setting, but while place fields become stable rapidly (Wilson & McNaughton, 1993), grid fields may not become stable for hours or even days (Barry et al., 2012). This finding suggests that the input from grid cells change continuously long after place cell responses have been stabilized, and that grid cell responses therefore cannot solely give rise to place cell firing.

**The grid map as an intrinsic metric for path integration.** The evidence against a grids-to-places transformation indicates that even in the absence of stable input from the mEC grid cells, place fields can be both established and maintained. Instead, a more recent theory suggests two different but equally important roles for place and grid cells. This view argues that place cells combine multimodal sensory information to define stable landmarks cues, and that the role of grid cells is to provide a spatial metric for path integration, independent of context (Bush et al., 2014). In this view, grid cells are not placed higher up in a hierarchy of processes than place cells. Rather, they provide complementary information that is combined in the hippocampal map to support the coding of space (Bush et al., 2014). To put this in context, it is argued that grid cells provide an absolute metric that encodes distance information which adds to the orientation signal from head direction cells and the spatial representation signal conveyed by place cells (Poucet et al., 2014).

Critique against this theory of grid map function is based on the finding that the grid map becomes asymmetrical as a result of environmental deformation (see Barry et al., 2007), which implies that grid cell field spacing is—to some extent—modifiable by experience. It has therefore been argued that since the spacing and even arrangement of grid fields are elastic, the grid cannot act as an absolute metric (Poucet et al., 2014).

**A role for grid cells only in the dark.** In a different view on grid cell function, it is suggested that the hippocampal map serves as a converging point of two parallel streams of spatial
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information; one derived from stable environmental landmark cues and the other derived from internal self-motion information (Poucet et al., 2014). The main idea of this view is that it ascribes the grid cells a role only in a dark environment. It argues that the self-motion information that grid cells receive is suppressed in a light environment (with available visual landmarks) to the extent that the grid cell firing pattern can be controlled by excitatory inputs from the hippocampus (Poucet et al., 2014). That is, in a light environment, the grid cell activity is controlled by visual stimuli relayed through the hippocampus so that the grid map is matched with place cell activity (even though self-motion cues are essential for generating the grid map). On the other hand, when it is dark and the animal has no access to external landmarks, it is argued that self-localization and navigation depends on grid cell input to the hippocampus, controlled by self-motion signals (Poucet et al., 2014).

In conclusion, if information from landmark cues is inaccessible, self-motion information conveyed by the grid cells in the mEC is used to prevent the animal from completely losing the ability to self-locate (Poucet et al., 2014).

Discussion

The last decade has witnessed a rapid growth of research regarding how the environment is represented within the brain. The ability to self-locate has been shown to be divided into various spatial representations sensitive to location, direction, or a conjunction of both. 44 years of research have uncovered that specific networks of cells throughout the cortex—each containing place cells, head direction cells, or grid cells—are responsible for these representations.

The main findings include the spatial properties of these three cell types. Place cells convey the location of the animal (O’Keefe & Dostrovsky, 1971), head direction cells encode the present or future angular direction of the animal’s head (Taube et al., 1990a), and grid cells produce a tessellating grid covering the entire explored environment (although it is not entirely established how or why; Hafting et al., 2005). All cell types have also been shown to respond to manipulations
of both the external environment (visual and non-visual cues; Goodridge et al., 1998; Muller & Kubie, 1987; Quirk et al., 1990; Save et al., 1998; Taube, 1995; Taube et al., 1990b) and internal self-motion information (vestibular information, motor system information, and optic flow cues; Arleo et al., 2013; Foster et al., 1989; Sharp et al., 1995; Stackman et al., 2002; Taube & Burton, 1995; Zugaro, Tabuchi, et al., 2001). Additionally, several different brain lesions have been shown to disrupt each cell type’s normal function (Bassett et al., 2007; Bonnevie et al., 2013; Calton et al., 2003; Goodridge & Taube, 1997; Morris et al., 1982; Save et al., 1992; Stackman & Herbert, 2002; Stackman & Taube, 1997; Sutherland et al., 1983; Winter et al., 2015).

These findings together show that the rodent brain truly possesses a positioning system, a finding which has had great impact on the neuroscientific community and its research. These discoveries have been awarded in themselves, by receiving the 2014 Nobel Prize in Physiology or Medicine (Nobel Media AB, 2014). The importance of this research is further apparent when considering the profound implications they have had on the understanding of the neuronal mechanisms behind spatial navigation, learning, and memory.

Although the majority of the experiments presented in this thesis have been conducted on rats, the navigational system consisting of place cells, head direction cells, and grid cells is not exclusive to rodents. For example, both grid cells and place cells have been found in the bat brain (Ulanovsky & Moss, 2007; Yartsev, Witter, & Ulanovsky, 2011), and head direction cells have been observed in macaques (Robertson et al., 1999) and fruit flies (Seelig & Jayaraman, 2015). Recent research has also begun to uncover these cells in the human brain (Baumann & Mattingley, 2010; Chadwick, Jolly, Amos, Hassabis, & Spiers, 2015; Doeller, Barry, & Burgess, 2010; Ekstrom et al., 2003; Jacobs et al., 2013). This research indicates that the system for self-localization (and ultimately spatial navigation) is similar across species. However, although several cell features and lesion effects are similar in both rats and humans, such as that lesions to the hippocampus impair spatial memory (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Morris et al., 1982), it cannot be
assumed that all results concerning place cells, head direction cells, and grid cells recorded in rats are directly translatable to humans.

Another important question for further discussion is if and how certain representations of self-location contribute to navigation. It has not yet been solved how spatial systems encode the location of a goal and apply this information to determine a suitable route. Nevertheless, research conducted over the last decade has shown that certain spatial cells exhibit extended goal-related coding used to guide navigation. For example, in addition to the representation of self-location, a number of place cells in rats also demonstrate a conjunctive item \( \times \) place coding (Komorowski, Manns, & Eichenbaum, 2009). These cells show a response to specific stimuli in locations where the stimuli are significant, such as rewards at goal locations. Place fields have also been reported to be over-represented in proximity to unmarked locations with behavioral significance (Hollup, Molden, Donnett, Moser, & Moser, 2001; O'Keefe & Conway, 1978). It has therefore been suggested that location-specific and goal-specific firing are two different place cell firing modes, and that the latter reflects the animal’s belief that it is accurately situated at the goal location (Hok et al., 2007). Moreover, it has been observed that place cells encode both the current and intended destination of the rat, which is indicated by differences in firing rate at the start of maze trials and before the final chosen destination (Ainge, Tamosiunaite, Woergoetter, & Dudchenko, 2007). The difference in firing rate is thought to reflect the encoding of a specific path and the selection between several alternative routes and turns to reach an intended goal, as well as the capacity to envision future events.

Recent research has also identified head direction cells as an important part in goal-based navigation. It has been shown that populations of head direction cells within the human entorhinal/subicular region can support—in addition to head direction—a neural representation of goal direction (Chadwick et al., 2015). The temporal dynamics of these populations have not yet been determined. Nevertheless, a first explanation of this function suggests that initially, these head
direction populations are involved in encoding the present or future facing direction and switch to representing goal direction when navigational planning is being initialized. A second explanation of these results argues for constant oscillations between head and goal direction in these entorhinal/subicular cell populations (Chadwick et al., 2015). Regardless, these findings provide the first signs of a network for goal direction representations within the mammalian brain.

Furthermore, grid cells are also hypothesized to have a role in navigation, beyond their possible contribution to path integration. Although it is still too early to discuss if and how the activity of individual grid cells might possibly influence spatial navigation, experiments have shown that the coherence of the directional signal conveyed by grid cells correlates with the rat's performance in navigational tasks (Doeller et al., 2010). While this finding is only a small first step, it still provides an indication that spatial behavior might partly be guided by grid-like representations.

All findings considered, it is indubitable that place cells, head direction cells, and grid cells do contribute to spatial navigation in addition to self-localization in mammals. However, further research is required to fully understand this contribution.

Conclusion

Everyday life requires knowledge of where one is located and in which direction one is oriented. Without this knowledge, one would be lost and unable to successfully move from one point to another. Although the importance of this ability has been stressed in the scientific community, and extraordinary progress has been made in uncovering the neural mechanisms underlying it, a complete understanding of the responsible systems is still far off. Place cells in the hippocampus and head direction cells throughout the Papez circuit have been experimented with in rats for decades. Even if much is left to discover—such as the origins of the signals—the scientific community has reached an united understanding of their properties and functions. A better understanding of grid cells, however, calls for further research. Not only were these cells discovered
only 10 years ago, but the cells’ properties and functions have also been shown to be far more complex than that of place and head direction cells. Furthermore, future research has additional important questions to answer. Until now, the majority of experiments conducted on place, head direction, and grid cells has been done on rats. Research has begun to uncover these cells also in the human brain, but more extensive experimentation has to be done to fully understand these networks and if and how they differ from those in non-human mammals. Future research will also need to focus on how the information from these spatial cells are integrated to constitute the ability to self-locate, and on how these networks contribute to spatial navigation and memory.
References


