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Cognitive Brain Research 14 (2002) 75–90

COGNITIVE BRAIN RESEARCH

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Review

Multisensory processing in the elaboration of place and head direction responses by limbic system neurons

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Abstract

This review explores the roles of several sensory modalities in the establishment and maintenance of discharges correlated with head position and orientation in neurons of the hippocampus and associated structures in the Papez circuit. Focus is placed on the integration of signals related to environmental cues and to displacement movements, both of external and internal origin. While the visual, vestibular and motor systems each exert influences, position and head direction signals are nevertheless maintained in the absence of any one of these respective inputs. Context-related changes in hippocampal discharge correlates are also highlighted. These characteristics provide these signals with robustness and flexibility, properties particularly suited for cognitive processes such as contextual processing, memory and planning. © 2002 Elsevier Science B.V. All rights reserved.

Theme: Other systems of the CNS

Topic: Limbic system and hypothalamus

Keywords: Papez circuit; Navigation; Orientation; Idiothetic; Place cell

1. Introduction

The hippocampal system receives inputs from multisensory and high order sensory and motor cortical areas and integrates them with inputs concerning emotion and motivation, including internal sensor signals concerning the degree to which the needs of the organism have been fulfilled. This information is then employed in association with other brain structures for comparing current events and context with previous experiences in order to implement appropriate behaviors, make decisions and form memories. While there is abundant evidence for spatial processing by the hippocampal system, this can be considered as but a single facet of a more general function, the treatment of contextual information. Hippocampal system efferents to cortical areas have been suggested to be involved in memory consolidation while outputs also go to other areas involved in autonomic function, expression of emotion and motivated goal-directed behaviors. The prefrontal cortex, believed to be involved in decision-making and executive functions, also receives hippocampal inputs in rats [13,25,43,105]. An emergent property of these processes is the reconstruction of a seamless internal representation of the composite of sensory signals that we experience as conscious awareness, which is perhaps the ultimate manifestation of multisensory integration.

An exhaustive review of all multisensory interactions occurring in the limbic system would be a lengthy exercise beyond the scope of the present review. Furthermore, this vantage point might not capture what many believe to be the fundamental elements of this system's role in cognitive brain functions. However in order to broaden the perspective of the issues discussed in other manuscripts in this Special Issue, exemplary evidence for multisensory integration are reviewed for two experimentally tractable types of neuronal responses found in the rat hippocampus and related structures. (For reviews considering evidence for an important role for the hippocampal system in memory storage, contextual learning, autonomic function, navigation, etc., see Refs. [2,14,29,30,49,51,58,61,65,72,77,101,109,117].) These neurophysiological data will demonstrate how diverse converging input signals are engaged in the elaboration of cue-invariant representations of the relation between the animal and its environment.

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PII: S0926-6410(02)00062-9

In these brain systems many synapses distant from the sensory epithelia, the approaches of classical sensory physiology are rarely applicable for analysing the events leading to activation of neurons. Such strategies have historically been based on a conceptual framework of hierarchically organized series of relays from sensory receptors to primary, then cascading to higher order cortical areas. In contrast, in limbic structures the convergence of inputs from a wide variety of brain regions and extensive reciprocal connections at many levels provide neurons with rather sophisticated discharge correlates, which are often considered in terms of *internal representations of the environment*. This anthropomorphic expression is unsatisfactory since it suggests that there is an internal observer, as well as a tangible representation, rather than a series of dynamic changes of patterns of cell activity. Rather, this may better be considered as a *mapping* in a mathematical sense, where each situation that is experienced would have a corresponding activity distribution in the brain of a given individual. (The term 'mapping' is used to avoid misinterpreting it in the sense of an internal map, which once again raises the problem of the poor homunculus who must decipher it.) In this way, these patterns of neuronal activation are sensitive to ongoing changes in the animal's relations and interactions with the environment, as well as the effects these have on the internal sensors and regulators of the physiological state of the individual. In effect the limbic neurons integrate inputs signalling external events with the internal emotion-related responses that they trigger. Unfortunately little is known about the influence of internal state on the spatial responses that will be discussed here, and this may well prove to be a fruitful line of investigation for future studies, in light of the considerable evidence for hippocampal involvement in autonomic function and in disorders such as stress, anxiety and depression (e.g. Ref. [29]).

We focus here on two types of limbic forebrain neuronal responses that are influenced by multisensory as well as internally generated motor-related information: *place* and *head direction* responses. These complementary types of information are coded by distinct, but interconnected groups of neurons. Since experimental lesions to these structures provoke impairments in certain types of orientation and navigation behaviors [57,102,106], they are considered to code spatial information concerning the environmental context that is employed for episodic memory (e.g. Refs. [36,83]). First we will provide a theoretical basis for describing these spatially correlated discharges, followed by a brief summary of their basic properties, then the main body of the paper will provide a more detailed, but not exhaustive, presentation of evidence of their multisensory aspects.

1.1. Reference frames

The problem of describing body displacements raises the vital, but sometimes confusing, issue of *reference frames*. The *egocentric* reference frame identifies the positions of external stimuli relative to the animal and its receptor organs. This is suitable while the animal remains stationary. However, once the animal moves, the egocentric orientations of stable objects in the environment vary heterogeneously as a result of perspective. These complex changes are taken into account by brain systems which employ *allocentric* reference frames—these are centered on environmental cues only, irrespective of the position of the perceiver's body and sensory organs. Most often this involves the configuration of, or relations between fixed landmarks in the environment. Special cases of allocentric reference frames may be centered on a single object, or even one in motion. For example, in order for a predator giving chase to pounce upon escaping prey, it fixes its gaze on the prey and the positions of stationary environmental cues are perceived as moving relative to this central object.

It is not known what algorithms are actually performed by neural circuits to direct displacement movements. Processes equivalent to triangulation could be employed to derive information on the spatial relations between multiple cues sensed by the animal. In order to explain the capacity of animals to return to the origin of a long trajectory, after the initial orienting cues are no longer available, the Mittelstaedt's [55] invoked 'path integration', a memory mechanism where successive displacement movements would provide proportional increments onto an internal representation of the distance and angle required for the return journey. The neurons described below could participate in such processes.

1.2. Sensory signals related to one's own movements

Motor activity provides an often underestimated and poorly understood source of information about the environment. Well-known examples include movements of sense organs (orienting towards a source of signals, active touch, sniffing). The brain must accurately signal body displacements in order to compensate for movements of the sensory apparatus. This is necessary to distinguish whether to attribute perceived movements to one's self or to targets in the environment. Furthermore, displacements produce parallax effects providing depth information and permitting reconstruction of the spatial relations among landmarks. Displacement information can be transmitted by optic field flow, vestibular, proprioceptive, motor command and efferent collateral systems, as well as combinations of these multi-'sensory' signals of movement.

Worthy of further attention is the so-called vestibular system, which provides a notable multisensory exception to classical concepts of the organization of primary sensory systems. Even at the level of the second synapse from the vestibular sensory epithelium there is already convergence with inputs from the optokinetic system and also proprioceptive and (at least from the oculomotor system) motor efferent collateral inputs [6,31]. A common property of these systems is sensitivity to the movement of the head in space. The rich variety of these inputs confers enhanced responsivity to a wide range of dynamic movements under light and dark conditions. However the internal mechanisms of these systems are susceptible to faulty processing which can give rise to illusory perceptions of orientation and movement. The effective stimulus for the vestibular end-organs is acceleration due to gravity as well as to inertial forces from rotational and linear movements. These forces also excite many somatosensory submodalities including proprioceptive, kinesthetic and visceral systems. The vestibular end-organs are sensitive to acceleration, but not to constant velocity movements, and the velocity signals carried by vestibular primary sensory neurons arise from (mathematical) integration of accelerations. For this to be applied to update the position and orientation responses discussed below, yet another integration must take place. This gives rise to inevitable errors which can accumulate over time, becoming unacceptably inaccurate after 10–20 s. Golden hamsters passively displaced in darkness following an outward journey from the nest accurately take into account relatively brief rotations, but not longer duration linear displacements in their return trajectories [17]. This indicates that for this type of spatial orientation problem (which Matthews et al. [48] have shown requires an intact hippocampus) vestibular signals concerning rotations are employed, but those for translations are ignored. The brainstem vestibular nuclei also receive optic field flow information transmitted from the specialized *accessory optic* system which, in contrast, is primarily sensitive to low velocities. In effect, movements of the animal, or of the visual field, trigger a retinal slip velocity signal which can induce vection—the well-known illusion of self-movement elicited by an adjacent train starting to leave the station. This will be further discussed below as a possible cue for updating of orientation and position representations.

1.3. A few technical considerations

Many of the results presented below come from chronic recordings in awake, freely moving animals. While this technique provides insight into fundamental processes without interference by anesthesia and restraint, this limits recordings to extracellular action potentials and EEG activity. The electrodes optimal for these recordings might select non-representative subpopulations of cells with particular geometric properties, such as large diameter. After the rat has recovered from surgical implantation of an advanceable group of electrodes, a cable containing lamps is attached to the head stage. As the animal moves about, cell activity is recorded and head position and orientation are tracked automatically with a video system. The rats are often pre-trained to perform simple foraging and exploration tasks, and in some experiments even to solve mazes and other problems. This technique provides the opportunity to observe brain activity under somewhat more ‘natural’ conditions, without interference from the anesthetics required for acute recordings. To take a specific example, the hippocampal electroencephalogram (EEG) shows rhythmic slow wave activity in the *theta* band (4–12 Hz), which occurs primarily as the unrestrained animal walks, sniffs and performs other ‘automatic’ behaviors. This corresponds to rhythmic waves of alternating hyperpolarizing and depolarizing membrane potentials of the hippocampal principal neurons induced by excitatory and inhibitory septal inputs. Many hippocampal neurons discharge in synchrony with this rhythmic activity, for example, pyramidal cells show phase precession, gradually changing their preferred phase over several theta cycles [70]. Anesthetics alter this kind of synchronizing activity which has been proposed to be vital for ensembles of neurons to coordinate their activity as well as for multisensory integration. Even immobilizing restraint in awake animals sharply alters the properties of these neurons and synchronous rhythmic activity. However recordings in freely moving animals introduce the risk that behavior is difficult to monitor completely, and that animals will adopt undesired behaviors. This creates a challenge for conclusive identification of cell responses.

It is important to note that the word ‘responses’ is employed here in a different manner than the classical usage for sensory physiology. A more suitable expression is ‘discharge correlates’, but for convenience, ‘responses’ will also be used interchangeably. A wide variety of sensory and motor events can be associated with discharges of these neurons and, as will be described below, the current behavioral state is an important factor for this. For example, a single hippocampal neuron can show different discharge correlates when the rat (or monkey) is confronted with a different behavioral context [120]. Furthermore, while the spatial coding of place and head direction neurons is influenced by sensory and motor information, this can rarely be studied as cell responses time-locked to punctual stimuli as sensory neurophysiologists are accustomed. This is due in part to the need to sample cell activity as the rat is in many positions (or head orientations) in order to determine selective firing properties, and also to the fact that the cells no longer respond in the same manner when the animal is restrained.

2. Hippocampal place responses

Pyramidal neurons of hippocampal subregions CA3 and CA1 discharge selectively when the rat (or mouse) occupies a small region (the ‘firing field’) as it forages or explores in the experimental environment [50,64,86]. O’Keefe [69] (p. 425) has defined a ‘place cell’ as ‘[. . .] a cell which constructs the notion of a place in an environment by connecting together several multisensory inputs each of which can be perceived when the animal is in a particular place in the environment' (data supporting this are presented below). In simultaneous recordings of several single neurons, each cell has a distinct firing field and the ensemble of the fields can span the environment [16,35,64,121]. Since the discovery of these hippocampal responses by O'Keefe and Dostrovsky in 1971 [68], many experiments have investigated the types of cues informing these hippocampal location-selective responses.

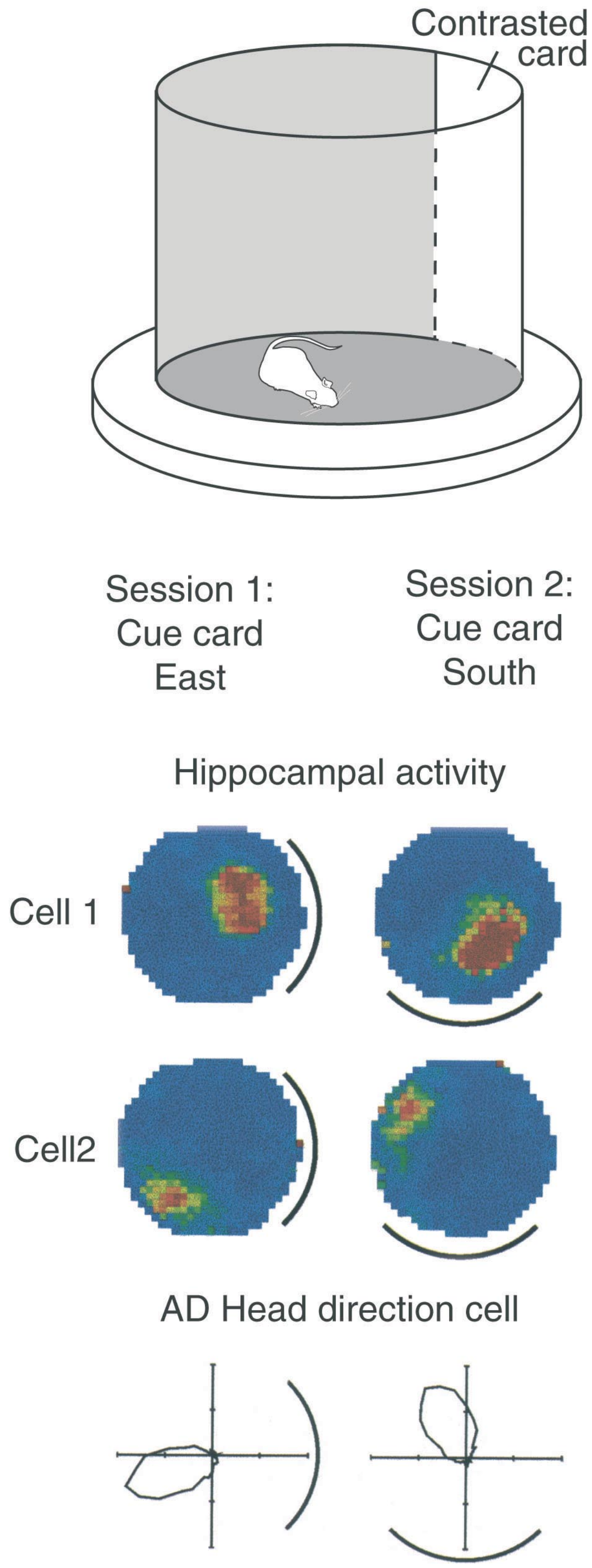

Fig. 1. Simultaneous recording of hippocampal place and AD head direction cell responses before and after cue card rotation (data of Knierim et al. [38]). Above, the experimental apparatus consisted of a 76 cm diameter cylindrical enclosure containing a white ('cue') card on the wall [60]. Middle, responses of two hippocampal neurons recorded simultaneously. The plots represent overhead views of the enclosure, and the colors correspond to the average firing rate of the neuron as the rat occupied the respective locations. These are calculated by counting the number of action potentials discharged at each location, dividing by the occupancy time then smoothing. The color scale indicates the firing rate with the maximum (9 impulses/s for cell 1, and 12 impulses/s for cell 2) in red graded to the minimum (0 impulses/s) in blue. The firing fields maintained the same distance and angle relative to the cue card before and after it was rotated. Below, the polar plots indicate the discharge rate of a head direction cell as the rat oriented its head in the respective directions. Data for each head direction is pooled over visits to places throughout the 76 cm diameter cylindrical enclosure as the rat foraged for food pellets. The total number of action potentials is divided by the total time the rat's head was oriented in the respective directions. The position of the cue card is indicated by the arc outside the circle. Rotation of the position of the card on the wall by 90° induced the same rotation of the preferred direction. The scale maximum is 12 impulses/s in the left panel and 10 impulses/s to the right. (Adapted from Knierim et al. [38] with permission.)

2.1. *Influence of visual stimuli*

In some of the earliest investigations of hippocampal place responses, the rat was placed on an elevated maze with several arms radiating from a central platform (the *radial arm maze*). This was placed in the center of a neutral room containing an array of highly salient, movable cues. Cell activity was recorded, then the rat was removed from the maze. To test which cues controlled the position-selective responses, successive manipulations either rotated the maze by a fixed angle, or shifted the array of cues in the room, rotating them about the stationary maze. In either case, when the rat was returned, the firing fields of the neurons remained in the same position relative to the array of cues in the room, but the positions of the respective maze arms were not taken into account [64,74]. This indicates that the visual signals concerning cues in the room exert a greater influence than cues on the maze itself such as odors or textural irregularities of the maze surface. However the visual cues were also particularly salient in these experiments since the maze arms were intentionally designed to be indistinguishable. These results are important because they establish that distal, allocentrically-referred cues *can* control hippocampal place selectivity. Evidence presented below will show that the hippocampus has access to many other types of information as well.

In a still popular protocol introduced by Muller et al. in 1987 [60], a partially food-deprived rat forages for food pellets randomly distributed in a cylindrical enclosure (76 cm in diameter and height). The principal landmark cue is a highly contrasted poster board (referred to as a 'cue card') subtending a 100° angle along the wall. Evidence for visual cue control of the location-selective discharges comes from experiments where the position of the cue card is rotated along the enclosure wall (while the rat is secluded elsewhere). When the rat is returned to the enclosure, the firing fields of the recorded neurons maintain the same distance and angle with respect to the wall-mounted visual cue but have shifted relative to the experimental room and stationary cylinder floor (see top part of Fig. 1). Incidentally this also demonstrates that the position-selective activity of these neurons is not controlled by geo-magnetic fields, consistent with results from earlier experiments [67].

But which properties of these visual stimuli are critical for their powerful influence over the position-selective responses of hippocampal neurons? In Muller et al.'s [60] experiments, the highly contrasted left and right edges of the card and the visual angle subtended between them appear to be the most obvious landmark features. These could be employed for localization via algorithms like triangulation. Shapiro et al. [92] observed a higher incidence of firing fields along those three walls that held cue cards in their square enclosure. In these experiments, removal of individual cards changed the discharge characteristics of those neurons with nearby firing fields. Fenton et al. [19] recorded hippocampal place responses in rats placed in a cylindrical enclosure with two cue cards on the wall. In experimental manipulations, positions (and hence, relative distance) of the cards were changed. In general the firing fields most influenced by this were those nearest the respective cards. One hypothesis is that cue saliency might be critical in determining which cues control position-selective discharges [122]. However Markus et al. as well as Lipa et al. compared response properties in cue-rich and cue-poor environments and found no significant differences in the incidence of cells with firing fields [45,46] (in general only 30–50% of hippocampal neurons discharge in any given environment [107]), or in other measures of position responses such as reliability, specificity, selectivity or directionality. However Markus et al. [46] found significantly fewer cells had firing fields in recordings in complete darkness (only about 20%) and there was significant degradation in the various measures. The Lipa and the Markus experiments were performed on an albino strain, and it would be interesting to compare this with results from pigmented rats (which have better vision), and also with the incidence of place responses in blind rats (cf. Ref. [89]). The issue of landmark cue selection will be taken up again below in the discussion of head direction cells.

2.2. Geometry

In addition, the *walls* of the enclosure define the space where the rat may move and there is evidence that this geometrical constraint can be a powerful reference cue [10,32] whether perceived with or without vision. O'Keefe and Burgess [66] found that displacing the walls of a rectangular enclosure generally had the greatest effect on the firing fields along the axis of the displacement. Similarly Gothard et al. [28] studied rats shuttling between the ends of an extensible linear track. When one of the ends was moved closer, fields formerly adjacent to the end shifted along the track, irrespective of distal cues in the room. Kubie and Ranck [42] recorded the same hippocampal neurons in rats exposed to environments with different geometry and described dramatic changes in spatial responses including unpredictable shifts in the positions of firing fields and cessation in firing. This was confirmed by Muller et al. [59] who found that hippocampal cells had completely unrelated position responses when rats were transferred between square and cylindrical enclosures equipped with the same type of cue card. This *resetting* of the hippocampal cell responses demonstrates context sensitivity and is believed to originate within the hippocampus [117] since it is not found in areas feeding directly into the hippocampus. It would be interesting to determine whether these resets are triggered when the hippocampal circuitry detects a mismatch between expectation and actual experience, a function attributed to the hippocampus (see ref. 113, p. 572).

2.3. Proximal versus distal stimuli

One possible interpretation of the results of O'Keefe and Burgess [66] and Gothard et al. [28] is that in these situations, distinctive proximal (rather than distal) cues had a greater impact on the place responses. The borders of the environment were near to the animals. The highly contrasted cue card employed in many studies is also touched by the animals, so non-visual attributes of this cue could also be of critical importance. In experiments where proximal and distal cues are displaced independently in order to present conflicting spatial referents, hippocampal cells can typically show a variety of responses: their firing fields may stay fixed relative to the distal cues, or the proximal cues, or the room, while other cells may simply stop discharging [28,71,99,119]. In a recent study where rats alternated between two tasks requiring the use of platform cues or room cues, we found that the hippocampal place responses were selective only for the more distal room cues [108]. In these experiments the rats were required to seek rewards at four open boxes equally spaced along the border of a 1.8 m diameter circular open field. The baited reward sites were either indicated by a lit object cue within (a proximal cue), or by the configuration of cues in the room reference frame (distal cues) [108]. While the proximal light cues were salient, and were attended to by the rats permitting them to achieve high performance levels, perhaps their instability did not permit the hippocampal neurons to anchor to them—they were not contextual cues. Cressant et al. [11] placed a group of objects within the experimental cylinder and compared the responses of hippocampal place cells before and after rotating the objects along the walls of the cylinder, always maintaining their positions constant relative to one another. The firing fields rotated by the same angle as the objects when the latter were positioned adjacent to the wall of the enclosure. However when the group of objects was placed near the center of the enclosure, then rotated, the firing fields did not follow. While the authors accounted for this by proposing that the centrally-placed objects are ignored because they are less reliable at the center, an alternative explanation is discussed below on the basis of comparable experiments with head direction cells.

A series of experiments by Eichenbaum and co-workers [92,99,122] have employed a four arm ('plus') maze with several highly contrasted insets (such as sandpaper and meshes) which provided distinctive visual, textural and olfactory stimuli in the respective arms. The maze was placed in a cue-controlled room and surrounded by a neutral curtain, or, in other experiments, an array of several salient objects. After place-correlated hippocampal activity was recorded as the rats moved about in the maze, they were removed, and each maze arm inset was displaced to the adjacent arm. In those experiments where there were objects in the room, these were also shifted by 90°, but in the opposite direction. Both types of manipulations revealed neurons with place fields that shifted by the same angle as the maze insets, while others showed responses anchored to room cues. This also suggests that proximal cues such as textural and olfactory stimuli may also be taken into account to establish position-selective responses in hippocampal neurons, although this remains to be confirmed since the insets provided distinctive visual cues as well.

2.4. Multimodal cue control

O'Keefe and Conway [67] trained rats to perform a spatial orienting task in an elevated plus maze. Salient multisensory cues were positioned in the room behind each of the goal sites at the ends of the arms. These included a light bulb, a fan, a buzzer and a large white card. As above, experimental shifts in the position of these landmark cues in the room provoked coherent shifts in the firing fields of the neurons. Although the buzzer and fan can also be considered as visible cues, these data suggest that auditory and somatosensory cues could contribute to updating hippocampal place responses. Furthermore, when, in successive manipulations, these investigators [67] removed any two of these cues the firing fields persisted in maintaining their orientation and distance relative to the remaining cues. This was interpreted as evidence that the hippocampal neurons code a representation of the environment independent of any particular cue. These data, as well as studies of spatial impairments of hippocampal lesioned rats, suggest that position-selective responses in the hippocampus depend upon the configurations of multimodal environmental cues. The fact that subsets of the original array of cues can be used to apparently reconstruct the complete representation demonstrates a fundamental process that the hippocampus implements for cognitive functions—this is referred to as *pattern completion* [53,85].

Although the importance of visual cues for place responses is well established, place-correlated firing also remains even after the room lights are turned off [78]. One explanation for this holds that an internal representation of the position of the rat is updated by path integration of self-movement information, including vestibular, proprioceptive, motor command, efferent collateral signals. The rat might also touch or smell landmark locations (including walls) to reset internal representations of current position and orientation. Such an explanation invokes a representation of the layout of the environment and comparison of this with incoming information to provide an updated representation.

2.5. Influences of non-visual cues

Perhaps the most conclusive evidence for place responses being updated by non-visual cues comes from recordings of hippocampal location-selective responses in blinded rats [89]. Poucet et al. trained the animals to forage in the cylindrical enclosure with three-dimensional objects along the walls as described above. At the beginning of the session, the cell did not fire the first time the rat entered the previously determined firing field. First the rat had to contact one or more of the objects or the wall, and only then did the cell discharge on subsequent entries in the firing field. The rats likely identified the objects on the basis of somatomotor information concerning the paws, vibrissae and muzzle, and possibly olfactory cues. But once the animal left these sites the system would have been required to update the representation of subsequent spatial positions on the basis of changes in body orientation as well as distances covered by the rat during its active movements (and perhaps geometric information from contact against the wall). This would invoke a mechanism like path integration as described above.

Hill and Best [33] recorded hippocampal neurons of rats first deafened by chronic neomycin treatment, then masked to obscure vision for the recording experiments. Place responses were observed as the rats performed on a six arm radial maze. Rats were then removed from the maze, which was rotated about the central supporting axis by 60 or 120°. Four of 15 neurons maintained their firing field in the same location relative to the room, while seven had fields that shifted with the maze (and the remaining four shifted to an intermediate location). The authors suggested that the four neurons that persisted in maintaining their field locations could have been informed by path integration of the passive trajectories of the rat when it was removed from and replaced in the maze. Those neurons with position selective discharges that followed the maze may have relied upon olfactory or textural cues.

Recent experiments indicate that olfactory cues may also be used in updating hippocampal positional responses in the absence of other orienting cues. Save et al. [90] recorded hippocampal neurons in male rats left for prolonged periods in a featureless cylindrical enclosure in light and dark conditions. In series where the floor was cleaned (after a first session where an orienting cue was present), the firing fields recorded in subsequent sessions were unstable in both light and dark conditions. However if the floor was not cleaned, the majority of firing fields remained stable. This indicates that markers left by the rat were necessary for updating of position responses, and the path integration information alone was not sufficient. The latter is consistent with the notion that errors rapidly accumulate in path integration.

2.6. Displacement related information

Physiological, anatomical and pharmacological evidence for vestibular inputs to the hippocampus has been reviewed by Smith [94]. As mentioned above, the ‘vestibular system’ is actually multisensory since even at the level of the brainstem vestibular nuclei, there is a convergence of signals from proprioceptive and optokinetic systems as well as the vestibular end-organs. Experiments attempting to isolate vestibular contributions are difficult to design since the required acceleration stimuli also evoke somatosensory and visceral responses, as well as postural reflexes. For this reason, we refer to these stimuli as ‘inertial cues’, not vestibular cues. In freely moving rats subjected to passive rotations in the dark, we have shown that firing field positions are updated by the use of inertial cues [119]. After the experimental apparatus was rotated in darkness (while the rat remained within), these cells still maintained their position responses relative to their original absolute position in space, taking into account the rotations. However, in this same experiment, position responses of other hippocampal neurons were preferentially influenced by visual cues presented after the rotations in the dark, and the firing fields of yet other neurons remained anchored to the floor. While in the former case the responses were likely to have been updated with vestibular or visual information, in the latter case they are rather more likely to be related to somatomotor or to olfactory inputs indicating the position of the rat relative to the floor.

The experiments described above in freely moving animals do not permit us to distinguish the respective roles of sensory and motor signals associated with active displacements. In order to test for vestibular updating of place responses, in the absence of motor signals, experiments have been carried out in rats and in monkeys [73] passively displaced on mobile robots. We [24] trained rats to be restrained while displaced passively on a mobile robot in a cue controlled room (Fig. 2). In order to engage the attention of the rat, it was partially water deprived and provided with a drop of water each time the robot arrived at one of the corners of the room, which also contained a salient visual cue. The hippocampal neuronal discharges maintained position-selectivity, even during displacements in complete darkness. This provides evidence that inertial cues related to displacements are sufficient to update hippocampal position representations in a familiar environment. Other neurons showed responses during specific types of movements, and in certain cases this was also location-selective.

2.7. Related work in the monkey

The latter work was based on the protocol that O’Mara et al. [73] employed for recording hippocampal neurons in seated macaques passively displaced on a mobile robot. They observed neurons activated by whole body motion, with selective responses for particular directions of rotations or translations. Vestibular inputs were suspected to play a significant role since in certain cases the responses persisted when the movements were replicated in total darkness. In other cases neurons were selective for a particular type of movement, but only when the animal had a particular view of the experimental environment, similar to the neurons described above for rats [24]. Furthermore Rolls et al. [84] found what they termed ‘view neurons’ with responses selective for where the monkey was looking in the environment, but not for the position of the monkey within the environment. This could support context processing in memory since covering this part of the room with a curtain did not affect the responses. In contrast, Ono et al. [75] found position selective responses in hippocampal neurons in macaques in a small enclosure displaced passively. In these experiments the animals moved a lever triggering the movements. These responses persisted when the experiments were repeated with the enclosure rotated by 90° and the animal viewed the room from a different angle [62]. Thus these responses were not related to a particular view that the animal perceived at these positions, but to the position itself. Feigenbaum and Rolls [18] required monkeys to perform visual discrimination tasks using stimuli presented on a video monitor. They observed neurons selective for the position of the stimulus either relative to the monitor screen, or to the absolute position in the room, or a combination of the two.

2.8. Motor related signals

The precise role of motor command signals or motor efferent collaterals in updating hippocampal representa-

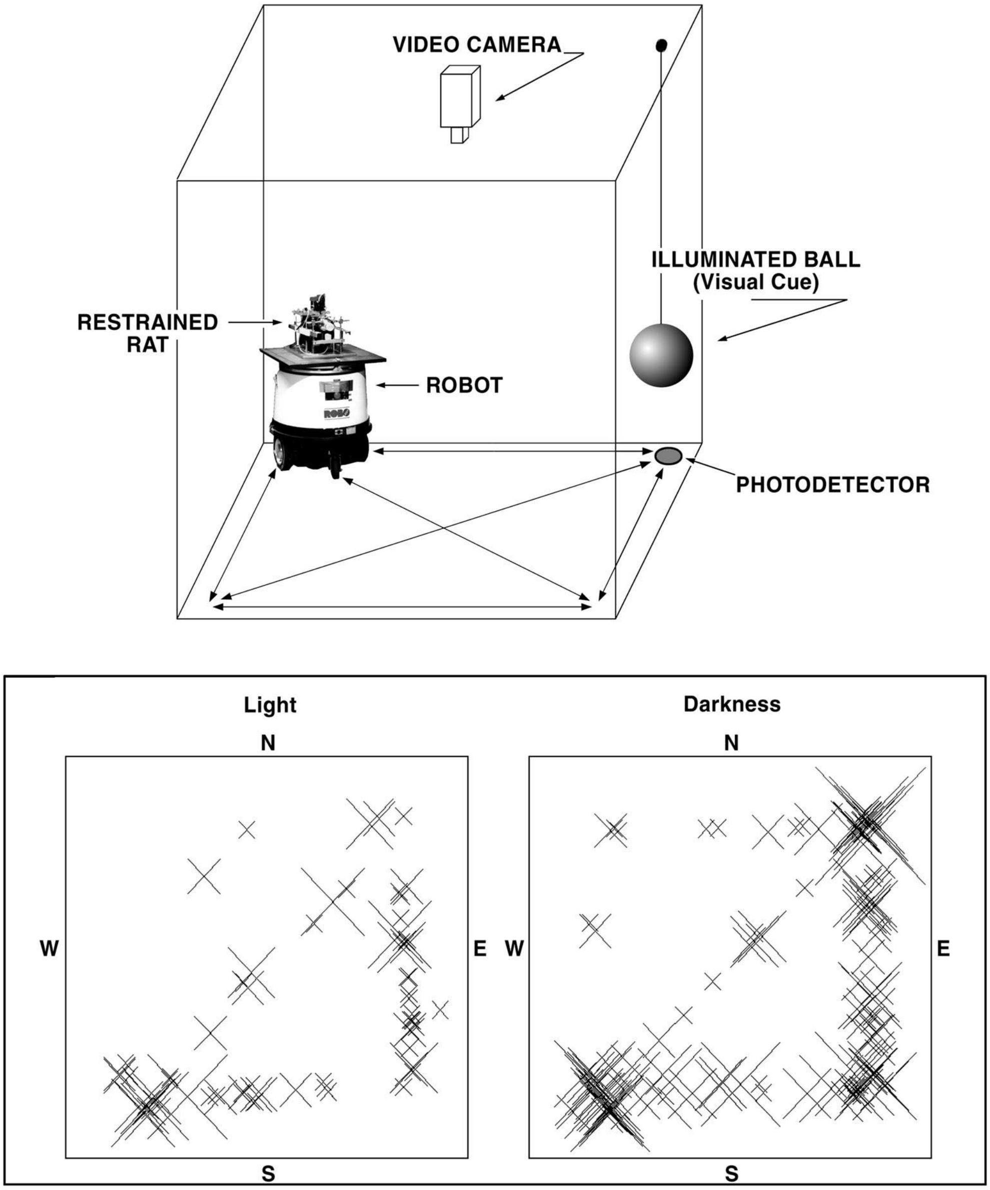

Fig. 2. Position-selective hippocampal responses in the absence of visual and locomotor cues. (A) The rat was trained to remain immobile while restrained and transported on a mobile robot. The robot moved along the walls of the curtained enclosure forwards and backwards, and also crossed the center diagonally. (B) In these overhead schematic views of the enclosure, the spatial distribution of discharges of the neuron are indicated by Xs with the size proportional to the number of action potentials in the sample. In the dark, all room lights were extinguished and a thick felt cloth placed over the apparatus holding the rat. In dark conditions, the neuron maintained the same position-selective discharges as in the light. (Adapted from Gavrilov et al. [24] with permission.)

tions has never been tested directly. However it must be pointed out that in our experiments on rats passively displaced on a mobile robot where such motor signals were suppressed, the cells fired as the rats occupied areas much broader than typical firing fields recorded in freely moving rats [24]. In earlier experiments, Foster et al. [20] first examined positional firing in hippocampal neurons of freely moving rats, then tightly restrained the animals and recorded again when they were placed in the previously determined firing fields. The cells fired at dramatically lower rates than before. However if the animals were only loosely restrained, the activity level in the firing field was indistinguishable from the freely moving condition. This shows that the inability to move leads to changes in the responses in this system, but that motor signals related to active displacements are not necessary for place responses.

2.9. Displacements and hippocampal theta EEG

Hippocampal rhythmic slow activity in the theta frequency range (4–12 Hz), which is observed as the animal makes active displacements, is also triggered by the onset of passive translations and rotations [22,23]. This observation was replicated in light conditions and total darkness, indicating that self-movement cues are sufficient to trigger resynchronization of hippocampal activity. Fourier analyses showed that higher velocity rotations (300 deg/s) elicited greater power amplitudes at theta frequencies than did lower velocity rotations (100 deg/s). However the decelerations at the end of these movements, which provided an equally powerful vestibular stimulus, failed to trigger this theta rhythmic slow activity. Optokinetic stimulation (with a planetarium-like projector) also elicited theta frequency rhythmic slow activity. This activity is thus associated with several types of sensory stimuli related to displacement movements, and could have a functional role in synchronizing hippocampal neurons to organize the orderly activation of a succession of neurons corresponding to overlapping and adjacent firing fields.

2.10. Context-dependent switching of response modality

Although place cell activity is observed in rats while foraging or performing other tasks requiring orientation and displacement movements, when animals are required to perform other types of tasks, hippocampal neurons can show a wide variety of discharge correlates which are relevant to each situation. For example, we trained rats to learn two different odor discriminations [120]. Odor pairs were presented simultaneously from two ports and the rats were required to make nose-poke responses to the port presenting the odor associated with rewards. Individual hippocampal neurons were selectively active during the respective stages of the task, including trial initiation, odor sampling, displacements, etc. Certain neurons fired during odor sampling only when a particular odor configuration was presented. These neurons with responses specific to particular episodes in the olfactory task were also recorded when the rat performed a spatial water search task in the same enclosure. In this situation, *these same neurons* showed position responses, often at parts of the enclosure distant from the odor ports. Thus individual hippocampal neurons can switch between different types of responses, employing information from different sensory modalities. These dramatic context-related changes in discharge correlates appear to correspond to the changes in place responses of single cells when rats are transferred between two environments with different geometry as described above. Another aspect of context-dependence is that neurons with nearby firing fields in one environment can show a wide separation between the fields in another environment [42]. Furthermore comparisons of different electrode placements show no evidence for anatomical grouping of representations of particular parts of the environment. This indicates that there is no obvious topographic organization of the representation of firing fields in the hippocampus, more similar to the organization found in the olfactory system, than in primary visual, auditory or somatosensory cortices.

2.11. Multimodal sensory correlated discharges and their context dependence

Sensory stimuli presented to restrained rats [54] and rabbits [114] elicit discharge activity lasting for extended periods, on the time scale of seconds. In freely moving rats performing a spatial orientation task, we [40] observed similar activity following visual stimulation (room lights turned off or on) as well as passive rotations applied to the animal. This occurred independently of the position of the rat or of ongoing behavior. In experimental recordings from animals performing operant conditioning tasks, hippocampal neurons discharge following the cue tone [1,21,34,91]. However it is possible that the discharges in these experiments were associated with behaviors related to anticipation of the unconditioned stimulus—thus such putative sensory discharge correlates might also be related to motor preparation. It may be more prudent to refer to these as ‘sensory-triggered’ activity rather than as ‘responses’ [41]. In the nictitating membrane response classical conditioning paradigm, hippocampal neurons initially discharge only to the airpuff (unconditioned stimulus) to the eye. However, cells will also fire following a cue tone (conditioned stimulus), but only as the animal learns that this predicts the airpuff [49]. Sakurai [88] innovated an experimental design which distinguished sensory and motor components of task-related cell activity. The rats were required to perform two different tone discrimination tasks respectively requiring working memory or reference memory. Certain hippocampal neurons discharged selectively during presentation of a given tone in one task but not when the same tone was presented in the other task. This is similar to the results described above where cell responses changed when the rats switched between two tasks, suggesting that these auditory responses are also context-sensitive. In rats trained to discriminate sequences of tones, Foster et al. [21] showed hippocampal neurons discharging selectively for certain sequences of go and no-go trials. This is yet another type of context-dependency that has been replicated in odor discrimination tasks [15,76].

Vinogradova et al. [114] recorded hippocampal neurons in restrained awake rabbits and observed that 68% of the 203 neurons showed responses to sensory stimuli of one or more modalities: visual (light flashes, turning room lights on or off), auditory (clicks, tones) and somatosensory (stroking the fur). Some neurons responded with increases in discharge rate, while others showed inhibition of spontaneous tonic activity. In restrained awake rats, Delacour and Houcine [12] also found hippocampal neurons responsive to somatosensory (vibrissal) stimulation. Some neurons actually anticipated the stimuli which were presented regularly at 20-s intervals. Some anatomical and pharmacological data relevant to such hippocampal sensory responses are reviewed by Korshunov et al. [40].

Other studies in behaving monkeys have shown hippocampal discharges selective for the presentation of visual stimuli related to the task, or of interest to the animals [7,8,80,82,112,115]. Ono's group has shown monkey hippocampal discharges selective for viewing objects such as food, with responses sometimes lasting over 10 s [63,75,97,98]. While some neurons respond non-differentially to many objects, others are selective for particular categories related to reward value, aversiveness, or novelty. Spatial selectivity for auditory cues has also been found in monkeys: the hippocampal neurons discharge preferentially when the tone originates at a particular position [75,97]. In some neurons this position is relative to the monkey (egocentric), while in others the preferred sound source is in a position relative to allocentric cues in the room.

3. Multisensory processing in head direction cells

In rats, mice and macaques, head-direction (HD) cells are a likely substrate of an internal representation of the momentary orientation of the head in the horizontal plane [37,79,81]. They discharge selectively when the head of the animal is oriented in a specific 'preferred' direction, independently of position or ongoing behavior. Thus as the animal moves about a complex environment, such a cell will discharge preferentially when the head is oriented, for example, toward the north-east, regardless of where the animal is, and what appears in its visual field. However there is no evidence that these neurons are influenced by geo-magnetic fields. These cells have been found in many different areas of the rat brain, such as the postsubiculum (PoS) [104], the anterodorsal thalamic nucleus (AD) [100], the dorsal striatum [116], the lateral dorsal thalamic nucleus [56], the lateral mammillary nucleus [3,96], certain areas of parietal and retrosplenial cerebral cortices [9] and also have recently been reported in the lateral dorsal tegmental nucleus of Güddens [1a,93] and the hippocampus [44]. Some of these areas compose an ascending series of nuclei known as the 'Papez circuit', projecting to the hippocampus. This could provide a pathway for head orientation information to enter the hippocampus.

3.1. Influences of visual cues

HD cells have been shown to be strongly influenced by the position of a cue card on the wall of the cylinder in experiments similar to those described above for hippocampal neurons [100,103]. In simultaneous recordings in rats foraging for food in cylindrical enclosures, both types of cells respond similarly to rotation of a contrasted card along the wall [38] (see Fig. 1). Recent and ongoing research efforts are focused on discerning the mechanisms by which these neurons select among multisensory cues to anchor and update the head direction signals. The strong influence of visual cues on the preferred direction of AD and PoS HD cells [27,100,103] was demonstrated in conditions where the influences of inertial cues and substratal cues (such as tactile and olfactory cues on the floor) were minimized: between the control and test sessions, the rats were removed from the recording cylinder and disoriented, and paper on the floor was changed to remove potential cues. Goodridge et al. [26] were only able to show evidence for minor influences by olfactory and tactile cues, but none for auditory cues.

3.2. Identifying effective visual cues

In order to better understand what type of visual stimuli are most effective at controlling preferred directions in anterodorsal thalamic neurons, we [123] adapted the experimental design of Cressant et al. [11] where three objects were placed in the cylindrical enclosure with the rat (Fig. 3). The objects were placed adjacent to the wall in an equilateral triangle configuration and neurons were recorded as the rats explored and foraged. The rat was then removed and disoriented in total darkness. The objects were shifted along the cylinder wall by 120° and after the rat was returned, the preferred directions rotated by the same angle. Then this experiment was repeated in the absence of the cylindrical enclosure. In this case, *the objects no longer had any control over the preferred directions* even though they were in the exact same position and configuration as in the previous condition. Thus the objects influenced the preferred directions of the HD cells only when the objects were close to the visual background, the cylindrical enclosure. However a more distal background (the curtains in the room) dominated control of the preferred directions in the absence of the cylinder. Behavioral analyses indicated that the objects remained salient after the cylinder was removed, since the rats continued to make contact with the objects.

In our view, a likely explanation for the difference in influence exerted by the objects in the two experiments is their relative distance to the background. Such a criterion would be of functional utility since stimuli which are furthest in the background remain more stable as the animal moves about. Such stability would confer upon them greater reliability as landmarks. Relative depth in the visual field could be transmitted from other areas in the central nervous system capable of discriminating on the basis of various stimulus attributes including occlusion (objects blocked by others are more distant), parallax (during active displacements more distant objects appear to move less), texture, contrast, shadows, vergence, etc. For example, the optokinetic system is particularly sensitive to optic field flow at velocities on the same order of magnitude as those observed during active displacements. The ensemble of the most distant objects, or visual contrasts, in

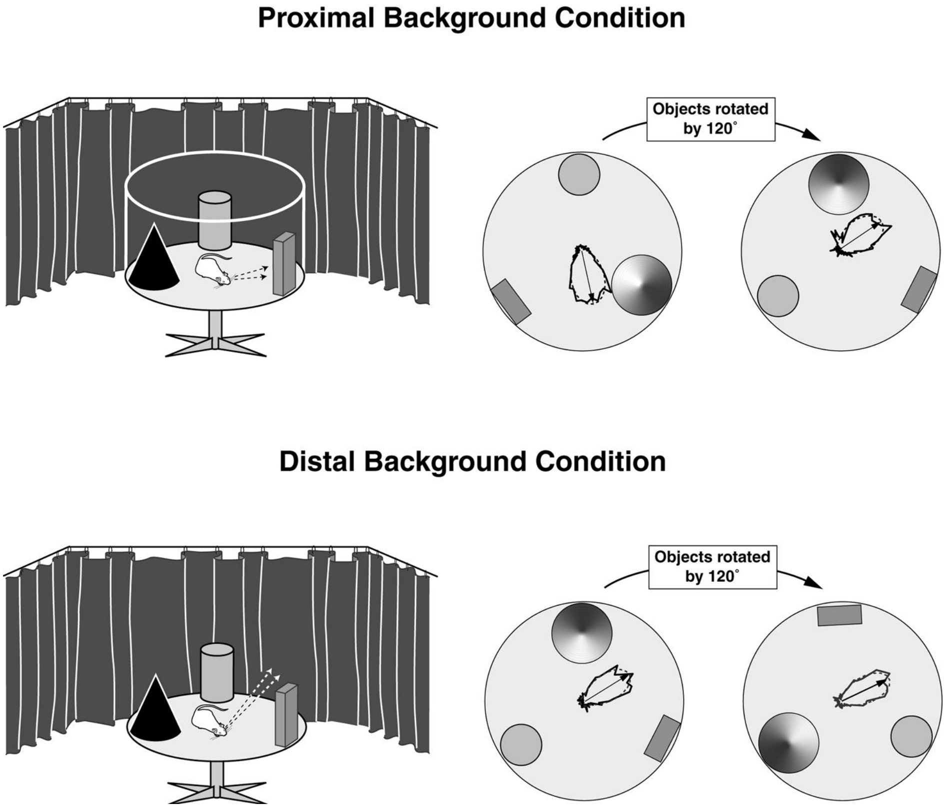

Fig. 3. Left panels, the experimental set-up. The elevated platform was surrounded by black curtains hanging along the four walls. A cone, a cylinder and a building brick placed on the platform served as orienting cues. In the *proximal background* condition, a black cylindrical enclosure was placed on the platform, restricting view and movements of the rats. In the *distal background* condition, the enclosure was absent. Thus the surrounding black curtains were a more distal backdrop for the three-dimensional objects. Right panels, directional response curves of a typical HD cell recorded while the objects were at their initial positions (Middle panels), and after they were rotated by 120° (Right panels), while the rat had been secluded in darkness. The directional response curves (*continuous curves*) are plotted along with their Gaussian-like fits (*dashed curves*). Above, in the presence of the enclosure, the preferred direction of this neuron shifted by 112°. Below, when the enclosure was absent, the preferred direction of the cell remained virtually unchanged after the objects were rotated by 120°. (Adapted from Ref. 123 with permission.)

the environment might be expected to provide an effective stimulus to this system during displacements. It remains to be determined precisely what stimulus attributes of background cues are most effective at driving head direction cells, and whether these correspond to signals from the optokinetic, or other optic flow detection systems. Such a mechanism is consistent with the control of hippocampal place responses by peripherally placed objects as presented above [11]. This is also consistent with the notion that the head direction signal feeds into the hippocampus and that hippocampal firing fields and HD cell preferred directions are updated in a coherent manner [38].

3.3. Self-movement cues

Indirect evidence that self-movement signals are influential in updating the preferred directions of HD cells is provided by experiments showing that directional selectivity persists in total darkness [5,9,39,56]. While the rat is in close proximity with landmark cues, non-visual modalities such as touch and smell might help to determine position and orientation. However, it is most likely that movement information is used to update the directional signals when the rat is oriented away from these cues. Further evidence for this is provided by the observation that directional responses are abolished after lesions of the vestibular apparatus, even when visual cues remain available [95].

Blair and Sharp [5] investigated the relative importance of dynamic visual cues and inertial cues for directional responses in neurons of AD thalamus. The visual cues consisted of a series of four vertical black and white stripes covering the inner wall of a cylindrical enclosure. This ensured that the visual pattern remained in the same orientation after the wall was rotated by an angle of 90°. Since the four cue cards were symmetrically placed, they did not polarize the environment like the cue card in other studies, and they could not have served as distinguishable landmark cues. As rats performed a foraging task, the floor or enclosure wall were rotated independently or simultaneously. When the wall and the floor were rotated together (thus provoking no optic field flow), in most cases the preferred directions remained anchored relative to the room. Since the rat was rotated passively at easily perceptible velocities, and there was no optic field flow, only the inertial cues could be responsible for the stability of the preferred directions relative to the room frame of reference. However the preferred directions shifted when rats were rotated in darkness at accelerations below vestibular threshold [5]. Moreover, when only the wall was rotated by multiples of 90° (in the light), there were no shifts in the preferred directions (note that this provided no inertial stimulation, simply brief movement in the visual field—and after the rotations, the environment appeared unchanged). This indicates that cues concerning actual body movements dominated over visual cues indicating that the body had moved. This contrasts with other results observed in environments where the single cue card provided a visual landmark cue [100,103], and this took priority over inertial stimuli. This distinction explains why the results of Blair and Sharp [5] are compatible with the observations of Taube et al. [100,103].

Knierim et al. [39] showed that when the floor and wall of the cylindrical enclosure containing the rat were rotated by a small angle (45°), the preferred directions of AD HD cells followed the single cue card on the wall. However after rapid rotations by a larger angle (135° or 180°), the preferred directions shifted only half of the time. The respective influence of visual and substratal (odor and texture) cues could not be distinguished here, because both wall and floor-related stimuli could have triggered the shifts. Furthermore, albino rats were used in this study, and their visual impairments could account for the reduced influence of visual cues. We [125] have examined the influence of visual, inertial and substratal cues upon the HD cell system in pigmented rats by rotating the wall of the cylindrical enclosure, or the floor, or both, in the presence of the rat. The results showed that visual cues had a strong but incomplete influence upon the updating of the preferred directions of the HD cells. Specifically, although the preferred directions tended to reorient following the cue card when it was rotated (even by large angles), the angles that they rotated were consistently 10% less than that of the cue card. This was interpreted as being due to the influence of inertial cues. In this experiment the influence of the cue card remained strong despite the fact that this provided a conflict. During active head movements the rats could well experience the same sensation of optic field flow elicited by the cue card—but this would also be accompanied by corresponding vestibular, motor and somatosensory signals related to active rotations. Relevant to this are the experiments of Rotenberg and Muller [87] where hippocampal place responses were recorded in rats as the cue card was displaced by 45° or by 180°. In most cases the firing fields followed the cue card for the smaller rotation but not the larger one.

One possible explanation of the difference between our results showing virtually all head direction cells remained anchored to the cue card after 180° rotations, and those of Knierim et al. [39] and Rotenberg and Muller [87], could be related to the exact nature of the sensory stimuli that are provided. Knierim et al. [39] rotated cues at 90–180°/s, while Rotenberg and Muller [87] removed the card from the wall, then re-attached it—thus providing a rapid displacement, especially for the 180° cue rotations. In contrast, we rotated the enclosure walls (with the attached card) much more slowly, at about 10°/s. This is consistent with the hypothesis that the preferred directions followed the cues only in those experiments where they are displaced sufficiently slowly. This would result from the slower cue displacements preferentially engaging the optokinetic system, and possibly inducing vection.

In summary, these results indicate that HD cells are influenced by a combination of environmental and internal cues related to displacements. However, visual and inertial cues have unequal influences on HD signals. This is consistent with the hypothesis that displacements provide cues that continuously update these internal representations of head direction, but that this is periodically corrected by realigning with familiar visual cues [52,56].

3.4. *Distinguishing the influences of motor command signals and efferent collateral discharges from sensory signals*

Several different brain systems such as optokinetic, vestibular, visceral somatosensory and proprioceptive can provide self-motion cues regardless of whether movements are active or passive. However locomotor command signals and motor efferent collateral information are absent in the case of passive displacements. How these respective signals are integrated in the HD system is not well understood.

When rats are tightly restrained, then rotated into the (previously determined) preferred direction, the directional responses are suppressed in most, if not all AD neurons, despite the continued presence of visual and inertial cues [38,100]. In contrast, HD neurons of the postsubiculum, which is reciprocally connected to the AD [110,111], only show decreases in firing rate by 30% during tight restraint ([103]; seven out of nine cells tested). The degree of reduction in PoS HD cell discharges is proportional to the intensity of the restraint (E.J. Markus, personal communication; cf. Ref. [47]). Chen et al. [9] recorded head direction neurons of retrosplenial cortical areas in rats first permitted to move freely, then passively rotated by 120–200° at velocities in the range 180–300°/s at regular intervals. To do this, the rats were placed on a small elevated platform bordered along the sides by barriers 2 cm high. These restricted the movements, but not the view, of the animals. The majority of the neurons that showed significant direction selectivity during active displacements had little or no directional firing during the passive rotations. It is unclear whether the reduced firing rates of head direction cells in these experiments is due to the absence of signals related to active movement initiation or other factors related to restraint.

Discharge rates of HD cells in the anterodorsal nucleus of the thalamus (AD) are reportedly higher during faster head turns [4,95,100]. However, because these results were obtained in freely behaving animals, it is not known whether this effect is mediated by sensory signals (such as vestibular or optokinetic) or motor-related signals (such as motor efferent copy or corollary discharge). There is discordance among these results [101]; this may be related to the fact that these experimental protocols were not explicitly designed to address this issue.

In order to test the specific influence of respective sensory signals of self-movement on the discharge rates of AD HD cells in the absence of active locomotor signals, we made recordings in immobile unrestrained rats as they were passively rotated in clockwise/counterclockwise oscillations at two different velocities [124]. This protocol was used because tight restraint suppresses the discharges of AD HD cells, as discussed above [100]. For this the animals were trained to remain stationary with the muzzle above a spout that periodically delivered droplets of water in the center of the recording cylinder. In order to sample a sufficient number of cell responses to generate directional response curves, the floor of the cylinder was rotated in clockwise/counterclockwise oscillations while the rat remained in place at the center. No enclosing cylinder was present, and the rats could view the experimental room. The results showed that the peak firing rates of the AD HD cells are increased by 36% on average during faster passive rotations. This indicates that the sensory signals of self-movement (such as vestibular and optokinetic signals) modulate the discharge rates of AD HD cells in the absence of active locomotor signals.

To further understand the influence of self-initiated motion cues on directional responses in AD cells, the passive rotatory oscillations protocol was used to compare recordings made during both active displacements and passive rotations [123b]. Directional responses were compared between active displacements and passive rotations in unrestrained animals. The preferred directions of the neurons did not change markedly between these conditions indicating that the visual cues, as well as certain self-motion cues present in both conditions, were sufficient to establish and maintain this critical component of the directional signal. However the peak firing rate decreased by 27% on average during passive rotations. This was attributed to those self-motion cues that were different in the passive and active conditions. Possible candidates include the command signals for movement initiation, motor set (e.g. signals disinhibiting the subsequent activation of specific motor pathways), signals from efferent collaterals and corollary discharges of pre-motor and motor pathways proper, and the interaction of the latter with proprioceptive signals triggered by mechanical interactions with the substrate (this is required since there could be slippage against the substrate due to poor traction). Since the magnitude of the directional response increased when the rat made active movements, these results suggest that the premotor and motor efferent collaterals (or corollary discharge) exert a state-dependent modulation of the AD head direction signal. However, while motor commands and motor set were different in the passive and active conditions, they were still required in both cases. Remaining immobile in our passive condition also required the rats to exert forces to maintain postural equilibrium, resist rotational forces and inhibit movements of the head away from the water reservoir.

4. Perspectives

This review has presented examples of convergence of several different types of sensory signals in the generation of discharges correlated with spatial position and orientation of the head. Within these and other limbic areas, convergence of inputs from high order sensory as well as multisensory areas leads to the generation of signals with rather sophisticated behavioral correlates. However a distinctive element here is also the integration with internally generated signals such as motor and autonomic activity. Furthermore, cell activity modulation is correlated with changes in behavioral state (vigilance, restraint, freezing, locomotion, sleep, etc . . .) and in corresponding identified states of synchronization of brain activity, as measured, for example, in local and large-scale EEG rhythmicity. Understanding the integration and regulation of these signals remains a challenge for future research.

Acknowledgements

Thanks to Professors Shane O'Mara and Alain Berthoz for helpful discussions and to Dr. L. Rondi-Reig for comments on the manuscript. Work described from this laboratory has been supported by the French Centre National d'Etudes Spatiales, Cogniseine, Human Frontiers Scientific Programme, EC ESPRIT and TMR programs. M.Z. was supported by a grant from the Fondation pour la Recherche Médicale.

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