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The Integrative Level of the Hierarchical Spatial Orientation System in Animals

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This review of the literature analyzes knowledge of the higher, integrative level of the physiological system by which animals orient themselves in space. Studies of the patterns of operation of the system at this level are relevant as impairments may underlie degradation of the ability to orient in space (spatial agnosia), an important sign of a number of brain diseases, particularly Alzheimer's disease. Studies over recent decades have identified the main functional components of the system integrating information on an animal's spatial position. The significance of these findings is reflected in a number of prestigious awards and honors, including the 2014 Nobel Prize in Physiology and Medicine.

Keywords: place cells, grid cells, boundary cells, head orientation cells, hippocampal formation.

The physiological system by which animals orient themselves in space can be seen as a pyramid of hierarchically organized levels. The base of the pyramid consists of nerve receptors. Subsequent levels consist of relay nuclei and the sensory zone of the cerebral cortex. Information relating to the topographic relationships of stimuli from receptors persists at these levels. For example, information from muscle and tendon receptors projects to the somatosensory zone of the cortex as a "body map" (the so-called "sensory homunculus"). Information on the spatial relationships between elements in the surroundings passes from the sensory zone to the associative areas of the cortex and then to the higher levels of the pyramid – the deep areas of the temporal cortex, the entorhinal cortex, and the hippocampal formation. Information arriving from different sensory systems is integrated at this level, losing modal specificity.

Studies of the patterns of the operation of the hierarchical system by which animals orient themselves in space at the higher, integrative level are relevant as impairments to these patterns may underlie degradation of spatial orientation ability (spatial agnosia) – an important feature of brain diseases in humans – Alzheimer's disease [16, 22, 54], Parkinson's disease [36, 64], and others. For example, modeling of Alzheimer's disease in experimental animals identifies impairments to the functions of one of the elements involved in integrating information on the animal's position in space (place cells), correlating with the severity of elements of the pathology modeled, i.e., memory deficit and the number of amyloid plaques in the brain [11, 69].

The main components integrating information on an animal's spatial position were discovered in recent decades. The importance of these discoveries is reflected in various prestigious awards and honors, including the 2014 Nobel Prize In Physiology and Medicine [44]. In particular, the brains of humans and many animal species show several functional systems of nerve cells whose activity depends on the animal's position in space – "space cells." The activity of place cells, boundary cells, and grid cells depends on the animal's position, while the activity of head orientation cells depends on how the head is oriented.

Place cells are special neurons whose action potential frequency increases sharply (from tenths to tens of spikes/second) every time the animal finds itself in a particular spatial zone (place fields) [47]. The activity of place cells is an integral expression of the information arriving in the brain in the framework of the individual sensory systems and does not depend on the animal's behavior or the orientation

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and trajectory of its body [42]. These place cells differ from neurons in the secondary sensory and associative cortex, whose activity also depends on the animal's position but is linked to information of defined sensory modalities.

Place cells account for the majority of pyramidal neurons in the dorsal hippocampus, as well as many of the neurons in the dentate gyrus and entorhinal cortex [24, 33]. The mutual locations of place cells in the hippocampus do not correspond to the relationships between their zones in space [38], so individual parts of the hippocampus can reflect the position of the animal in any place in space, though with less accuracy than the hippocampus as a whole. Place cells located in the ventral hippocampus have smaller zones (about 5 cm in rats), while those in the dorsal hippocampus have larger zones (about 1 m in rats) [29, 31].

Place cells display activity the first time the animal finds itself in the corresponding zone, though stable functioning takes some time to develop [24].

The activity zones of adjacent place cells partly overlap and, taken together, form a single area which can be illustrated as a map. Place cell maps are "bound" to spatial orientation markers – keys consisting of features in the environment surrounding the animal, i.e., objects and their parts. These keys are usually several in number, though they have different levels of significance. Disappearance or changes in the position of low-significance keys does not affect the place cell map. When such changes affecting important keys, the zone map is renewed: place cells are "tuned" to the new zones with binding to the new orientation markers (remapping) [5, 43, 46]. Remapping is seen not only in response to changes in the geometrical characteristics of the place, but also in response to changes in the odors or colors of surrounding objects [68].

Place cells are taken to constitute the structural-functional basis of cognitive maps [48], as theorized in the mid-20th century by psychologist Edward Tolman [63]. Every cognitive map in a given animal is based on the activity of its specific ensemble of place cells. Different ensembles are active at different times and in different surroundings. Some authors believe that cognitive maps based on the activity of place cell ensembles are related not only to the animal's orientation in space, but also provide a general material basis for superimposing new experiences on old and forming interactions between them (memory traces) [41, 48].

Support for the involvement of place cells in learning and memory processes is provided by a phenomenon termed hippocampal reactivation (replay) and hippocampal preactivation (preplay). Hippocampal reactivation occurs when an animal in the resting state or asleep develops bursts of activity in place cells in the same sequence as occurred during active waking prior to the resting state [20, 34, 66]. Hippocampal preactivation is the phenomenon of sequential activation of place cells without movement activity, as though outlining the trajectory of movement to a target [17, 18].

Place cell activity is closely linked with the hippocampal θ rhythm. The hippocampal θ rhythm consists of slow, sinusoidal changes in the bioelectrical activity of the hippocampus and dentate fascia recorded as subcorticograms [25, 65]. This rhythm is seen during REM sleep or during active interaction with the surrounding environment of locomotor or manipulatory character, linked with mobilization of the attention function. The frequency of the hippocampal θ rhythm in rats is 6–10 Hz, while in rabbits, dogs, and cats it is 3–7 Hz. The existence of rhythmic activity in the hippocampus in the range 4–8 Hz in humans is dubious. However, data have been reported showing that the human hippocampus displays rhythmic activity at a frequency of 1–4 Hz, which is analogous to the hippocampal θ rhythm in rodents, as its amplitude is linked with cognitive activity [26]. This activity is also termed the hippocampal θ rhythm, though its frequency is rather lower than that of the traditional human EEG θ range. The "driver" of the hippocampal θ rhythm has not been identified precisely. Candidates are the septal nuclei – which send cholinergic and GABAergic projections though the fornix and induces synchronous activity in hippocampal neurons, i.e., neurons in the structures generating the θ rhythm [1–3, 15].

The link between place cells and the hippocampal θ rhythm is apparent as precession: as the animal moves through the zone of a given cell, the discharges of this cell fall at ever earlier phases of the hippocampal θ-rhythm wave [10, 48]. When the animal transfers to the next zone, the activity of the cell corresponding to this new zone arises at the late phase of the hippocampal θ-rhythm wave and the activity of the place cell corresponding to the zone from which the animal departed arrives at the early phase.

Boundary cells[1] are specialized neurons whose activity increases when the animal's movement brings its head to a particular distance from an object delimiting its position on a particular side independently of how the head itself is oriented. Two types of objects are defined; rising (walls) and dropping (gaps) [58].

The existence of boundary cells was predicted by Nobel Laureate John O'Keefe and colleagues on the basis of observations of how the place cell map changes when the configuration of the space changes [45]. They observed that when the box containing the experimental rat was lengthened, the activity zones of some place cells remained close to the boundaries of the space, while the zones of others changed their positions such that the ratio of the distances to the boundaries was preserved. The authors suggested that cells whose activity zones remained close to the boundary were activated as a result of summation of the spikes from hypothetical cells (boundary vector cells) with the properties described above. These cells – boundary cells – were later found in the medial entorhinal cortex [53, 55], the subiculum [7, 35], and the presubiculum and the parasubiculum [8].

Apart from boundary cells, the rat subiculum contains cells with the opposite function: they are active when the

[1] Synonyms: boundary vector cells, boundary cells, border cells.

animal does not approach to within a particular distance of a boundary [58].

Grid cells are neurons whose discharge frequency increases sharply every time the animal's head is within defined zones of a given location, these forming the nodes of an imaginary two-dimensional mosaic network of triangles, termed a grid [21, 23]. Thus, in contrast to place cells, each grid cell corresponds to multiple zones. Grid cells are stellate cells in the medial part of the entorhinal cortex, presubiculum, and parasubiculum [8]. Like place cells, grid cells have been found not only in rats, but also in other mammals, including humans [27].

Numerous grid cells operate simultaneously in the brain, these differing from each other in terms of their grid parameters: cell size, cell asymmetry, angle of rotation of the grid, and the phase of displacement of the grid relative to external orientation markers.

Grid cells function as a small number of independent spatially localized modules of interconnected cells with cells of identical size, angles, and rotations, and identical relationship to θ-rhythm phase but different displacement phases [57]. Thus, no topographic pattern in relation to grid displacement phase for different cells is seen: the displacement phases of grid cells located at large distance from each other differ only slightly, while those located close together differ strongly (this type of organization is described in the literature as a "salt and pepper mix"). In contrast to displacement phase, grid cell sizes of different cells follow a topographical pattern: functional modules of cells with smaller cell sizes and smaller zones are located in the dorsal part of the medial entorhinal cortex, while larger ones are located in the ventral entorhinal cortex. In rats, the cell sizes of different grid cells vary from 25 cm to several meters [9, 57].

As the number of functional modules of grid cells is small, the multitude of grid cells shows marked discreteness in those parameters which are identical in cells within modules: cell size, rotation angle, and relationship to θ-rhythm phase; in other words, the values of these parameters form a small number of groups [57].

Grid cells display their properties as soon as the animal starts to explore a new environment [6]. This leads to "tuning" of one or several modules of grid cells. In tuning, the grid parameters of a given module change concordantly to take up new values (rescaling) and the activity of the grid cells becomes "bound" to various spatial orientation markers which may be features in the surrounding apparatus or its boundaries [40]. Grid cells are resistant to the removal or displacement of individual orientation markers, such as the disappearance of visual orientation markers when the light in the experimental apparatus is switched off [23]. The researchers felt that significant spontaneous rebinding of grid cells could occur in the absence of changes in the surrounding context. However, the frequency and sequence of rebinding is now known. It has been suggested that rebinding might occur at particular time intervals (imposed, for example, by the θ rhythm of the entorhinal cortex) or as a result of accumulation of errors in determining the animal's position [39].

Head orientation cells[2] are specialized neurons whose activity increases when the animal's head is positioned at a particular angle in relation to external orientation markers [49, 61]. The discharge frequency of activated head orientation cells is 5–120 spikes/sec with irregular interspike intervals. Cell activity is independent of the rotation of the head around the frontal and sagittal axes up to 90° from the horizontal plane [59].

A set of these cells operates like a compass, whose input signal is the whole set of sensory systems rather than just a magnetic field. At any point in time, one of the cells in the set shows maximal activity corresponding to the orientation of the animal's head. Similar sets are seen in the postsubiculum [61], the entorhinal cortex (along with grid cells) [52], the retrosplenial cortex [56], the thalamus [60], and the mammillary bodies [24]. These cells have been seen in humans in the subicular complex and entorhinal cortex [12].

The reliable operation of the set of head orientation cells has been demonstrated in terms of the reverse task – determination (reconstruction) of the animal's head orientation using data obtained from simultaneous recording of the activity of a multitude of head orientation cells [28].

The set of head orientation cells is able to alter its binding to orientation markers (primarily visual) when they move significantly, disappear, or when the animal's position changes. However, the angular relationship between the orientation axes of individual cells always remain unaltered [62].

Interaction of space cells of the different functional types. One of the most likely hypotheses for the functioning of the cell types listed here is that cells of each type operate together to form a system with the properties of a continuous attractor.[3] This hypothesis has been actively discussed in relation to functional systems of visual cortex cells [30], head orientation cells [14], grid cells [40], and place cells [50]. These functional systems tend to a state of elevated activity of some neurons on the background of low activity of others, which for them is an attractor. The attractor in these systems is continuous, as different cells in the system can display elevated activity in different situations.

Within an individual system, cells are functionally connected to each other on the "each with every other" principle (directly or via other cells). Each individual cell excites itself and functionally close cells and inhibits more distant cells. The influence of each cell on other cells in the system de-

[2] Translator's note: Footnote addresses difficulty in translating the English-language term "head direction cell" into Russian, as the word which has entered the language implies movement rather than static position.

[3] "Attractor" is synergetics term referring to one or several states in a complex system, which tends to transfer between them. Attractors may be discrete (a state to which the system trends constantly) or continuous (a state which my change). For more detail see [51].

creases with distance from it. The signal from the sensory or associative cortex corresponding to the animal's position in space excites only one or a few cells in the system. As a result, the system forms a zone of increased neuronal activity which persists even when the signal inducing it disappears. When the animal's position changes, the signal entering the circuit acts on another cell such that the zone of elevated neuronal activity changes its position in the system. A system functioning in this way allows the continuity of space to be reflected in the brain by a limited number of cells.

Moser et al. suggested that a grid cell system functioning in this way acts as follows: grid cells with close displacement phases are connected together via excitatory connections, while those with different phases are connected by inhibitory connections [40]. Formation of a zone of increased neuronal activity is suggested to occur as a result of spikes from head orientation cells and speed cells. The authors emphasized that the hypothesis requires some correction in relation to grid cells, as there are no excitatory connections between cells in the medial entorhinal cortex, where grid cells are located, as it contains only inhibitory connections. However, such a system would have the properties of a continuous attractor, where there is a different rule for influences on neighboring elements, promoting the spontaneous formation of the stable triangular (hexagonal) excitation patterns characteristic of grid cells. The possibility that the triangular pattern of grid cells can form spontaneously has also been demonstrated by mathematical simulation [4].

Hypotheses for the interaction between functional types of space cells. Views on the interaction between the cell types described here currently involve a great many hypotheses based on known morphofunctional connections between brain structures and the results of some experiments in which these connections are interrupted in animals.

The end element of the integration of information on the animal's spatial position is taken to be the place cell system in the hippocampus. Other space cell systems (head orientation cells, boundary cells, and grid cells) are known to have axonal projections to the hippocampus. This provides grounds for suggesting that the formation of place cell maps in the hippocampus occurs as a result of the summation of information (on the animal's location, head orientation, and speed of movement) arriving in the hippocampus from these cells and from speed cells (data on the existence of these latter have recently appeared in the literature [32]).

The widely held view is that calculation of the animal's ongoing position, as reflected in the activity of place cells, occurs by two means: as a result of calculation of the path followed by the animal and in relation to features in the surrounding environment [19]. Each of these means is performed by a separate system, though both converge on the place cell system.

The first means of determining position – calculation of the path (distance covered and turn angles) – is carried out by grid cells on the basis of integrating information arriving from the statokinetic and proprioceptive analyzers [40]. Grid cells, whose bodies are located in the entorhinal cortex, have direct axonal projections to place cells in the hippocampus [67]. This led to the suggestion that summation of spikes arriving from grid cells with close phases but differing in terms of cell size and grid rotation angle is important for the excitation of place cells [37, 40]. The results of the operation of the path integration system are compared with the results of the second system (external orientation markers) and errors in location lead to correction of the tuning of the path integration system (grid cell parameters) [19].

The second means of determining position – in relation to the features of the surrounding environment – operates on the basis of information arriving from the sensory systems (mainly the visual) detecting external stimuli and extracting orientation markers and boundaries. At a higher level of analysis, information on orientation markers is used for "tuning" or adjusting the state of the head orientation system, while information from boundaries is used for tuning the boundary cell system. Information from these two systems then "tunes" and adjusts the activity of place cells. About 25% of place cells operate within this means of determining position. This is evidenced by the results of experiments in which mice were able to see changes in visual orientation markers (keys) in conditions of virtual reality without information arriving from proprioceptors and the statokinetic analyzers (remained immobile) [13].

Conclusions

Discoveries in recent decades have demonstrated the existence of a higher hierarchical level in the spatial orientation system in animals.

Current data on the patterns of operation of systems at this level are mainly phenomenological in nature. In particular, the relationship between the spike frequency of individual brain neurons and the position of the animal in a given spatial context has been firmly established, and is known to result from integration of information arriving via sensory channels of different modalities. Several such types of relationship have been found. The brain structures in mammals containing neurons with different types of relationship have been identified. The influences of changes in the animal's environment on the activity of these neurons been studied.

The mechanism integrating information on the animal's spatial position has as yet received little study, and views are mainly hypothetical and speculative in nature. However, further investigation of these mechanisms is very relevant, as impairments to them constitute a significant part of the pathogenesis of a number of brain diseases accompanied by derangements to spatial orientation, particularly Alzheimer's disease.

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