

Univerzita Karlova v Praze
2. lékařská fakulta

Studijní program: Biomedicína
Studijní obor: Neurovědy



RNDr. Jan Svoboda

**Prostorové chování potkana v nestacionárních
prostředích: úloha posteriorní parietální kůry**

**Spatial behavior of the rat in non-stationary
environments: role of the posterior parietal cortex**

Disertační práce

Školitelé: RNDr. Aleš Stuchlík, PhD.; MUDr. Jan Bureš, DrSc., prof. emer.

Praha, 2011

Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracoval samostatně a že jsem řádně uvedl a citoval všechny použité prameny a literaturu. Současně prohlašuji, že práce nebyla využita k získání jiného nebo stejného titulu. Souhlasím s trvalým uložením elektronické verze mé práce v databázi systému meziuniverzitního projektu Theses.cz za účelem soustavné kontroly podobnosti kvalifikačních prací.

V Praze, 7.3. 2011

Podpis

List of abbreviations

AAPA	Active allothetic place avoidance
AF	Arena frame
CA	Cornu Ammonis
HD	Head direction
MEC	Medial entorhinal cortex
mPFC	Medial prefrontal cortex
PPC	Posterior parietal cortex
RF	Room frame
RSC	Retrosplenial cortex
TTX	Tetrodotoxin

Acknowledgements:

I would like to express my gratitude to both my supervisors, MUDr. Jan Bureš, DrSc., and RNDr. Aleš Stuchlík, PhD for their enthusiastic leadership. I also thank to Vanessa Doulames and Radek Pelc for a language check of the manuscript, to colleagues in Department of Neurophysiology of Memory for their help and stimulating discussions, as well as my family and friends for their long-term support; in brief, to all who provided me cues on my tortuous idiothesis finally pointing to a goal.

Preface

Better understanding of cognitive functions and their underlying neural substrate requires appropriate behavioral testing paradigms. For a laboratory rat, a model organism in studies of spatial cognition, plethora of tests have been employed. They usually examine spatial capabilities in stationary environments. However, this approach largely neglects a common feature of our daily lives – dynamic elements that may be relevant for navigation (such as conspecifics, predators or moving parts of the environment). Examining spatial abilities of the rat in such non-stationary environments represented a challenge when I and my colleagues joined the team of dr. Bureš who provided us with the possibility to attend a newly established branch of behavioral research which he conceptualized as navigation in dissociated environments.

Four articles published in journals with the impact factor are inserted into the body of the thesis. The work has been done in collaboration with my colleagues Mgr. Petr Telenský and MUDr. Karel Blahna. I therefore find it important to declare the specific contributions of the authors.

First article provides a methodological background for avoidance of a single, moving stimulus: **Telensky P, Svoboda J, Pastalkova E, Blahna K, Bures J, Stuchlik A., 2009. Enemy avoidance task: a novel behavioral paradigm for assessing spatial avoidance of a moving subject. J Neurosci Meth 180 (1), 29-33.** Contribution of authors: Petr Telenský and Jan Svoboda – writing the article, analyzing data, performing the experiments; Eva Pašťálková – initiation of the pilot experiments and development of the maze apparatus; Karel Blahna – analyzing data; Jan Bureš – conceptualization of the experimental approach, scientific leadership; Aleš Stuchlík – scientific leadership and writing the article.

The second article extends the methodology further by introducing a programmable robot. Moreover, a role of dorsal hippocampus during mobile cue avoidance is assessed by temporal inactivations of the hippocampus by tetrodotoxin: **Telensky P, Svoboda J, Blahna K, Kubik S, Bures J, Stuchlik A, 2011. Functional**

inactivation of the rat hippocampus disrupts avoidance of a moving object. Proc Natl Acad Sci USA, accepted. Contribution of authors: Petr Telenský and Jan Svoboda – writing the article, analyzing data, performing the experiments; Karel Blahna – performing the experiments; Štěpán Kubík – writing the article, elaboration of main hypotheses; Jan Bureš – elaboration of the concept of the experiment, scientific leadership; Aleš Stuchlík – writing the article, analyzing data, scientific leadership.

The third article reveals an interesting phenomenon of inertial stimuli contribution in acquisition of avoidance behavior on a rotating arena: **Blahna K, Svoboda J, Telensky P, Klement D, 2010. Inertial stimuli generated by arena rotation are important for acquisition of the active place avoidance task. Behav Brain Res 216 (1), 207-213.**

Contribution of authors: Karel Blahna – writing the article, performing experiments, analyzing data; promoting the main idea of experiment; Jan Svoboda – performing experiments, analyzing data, elaboration of the main idea; Petr Telenský – writing the article; Daniel Klement – writing the article, analyzing data, scientific supervision.

The fourth article evaluates contribution of posterior parietal cortex in two variants of place avoidance task: **Svoboda J, Telensky P, Blahna K, Zach P, Bures J, Stuchlik A, 2008. Lesion of posterior parietal cortex in rats does not disrupt place avoidance based on either distal or proximal orienting cues. Neurosci Lett 445 (1), 73-7.** Contribution of authors: Jan Svoboda – writing the article, performing experiments and operations, analyzing data, initialization of the experiment; Petr Telenský – writing the article, analyzing data, assistance with operations; Karel Blahna – assistance with operations; Petr Zach – histological verification of the lesion sites; Jan Bureš – scientific leadership; Aleš Stuchlík – providing theoretical background and scientific leadership.

Contents

I Introduction8
1 Navigation9
1.1 Cognitive mapping hypothesis10
1.2 Categorization of navigation11
1.3 Types of landmarks12
1.4 Behavioral tests studying navigation in stationary environments.....	13
2 Neuroanatomy of spatial behavior17
2.1 Hippocampal formation17
2.2 Function of the hippocampus18
2.3 Functional interventions to hippocampus19
2.4 Place cells21
2.5 Head-direction cells22
2.6 Grid cells23
2.7 Cortical areas26
3 Non-stationary environments29
3.1 Discrete reference-frame dissociating manipulations30
3.2 Continuous dissociating of the environment35
4 Posterior parietal cortex (PPC) of the rat40
4.1 PPC anatomy40
4.2 PPC function in humans and primates43
4.3 PPC function in rodents44
4.3.1 Attention44
4.3.2 Allocentric and egocentric processing45
4.3.3 Electrophysiological studies47
4.3.4 PPC function outlined48
4.3.5 Parieto-hippocampal dialogues49
4.3.6 PPC and head-direction cells50
4.4 Role of rodent PPC in dissociated environments51
II Aims of the thesis53
III Inserted reprints56
IV General discussion57
V Conclusion65
References67
Author's publications not directly relevant to the thesis82

Part I

Introduction

1 **Navigation**

All mobile organisms must be able to adequately organize their individual spatial behavior. The resulting navigational capabilities that have evolved in response to this strong pressure are sometimes quite astonishing despite often being as simple as approaching/avoiding a single stimulus or moving along the axis of a concentration gradient. Although concern is usually centered on "higher" navigational capabilities, basic spatial behavior is an inherent, common feature of any organism makeup and should not be overlooked. The theory maintained in the scientific field for a surprisingly long period of time suggested that an organism's memory of a place in an environment required the storage of its position as a result of a set of stimulus-response mechanisms. This at its core is an example of associative learning in which a guiding stimulus (e.g. turning right at an oak tree) is used to make simple movements. The stimulus (oak tree) elicits a directional response (the right turn). Chaining up associations such as these together can potentially lead to an efficient and rapid route-following behavior even if the individual route is very complex. Despite the obvious logic in these observations, it has been found that associative learning is not the only means by which mobile animals organize spatial behavior.

Against popular opinion at the time, in the 1940s Tolman suggested (Tolman, 1948) that animals (and therefore humans) possess an internal representation of the environment in a map-like form termed a "*cognitive map*". It was not until decades later that Nadel and O'Keefe (1978) formulated a comprehensive and quite influential support for Tolman's mapping hypothesis. A sharp distinction was made between response-based navigation ("*taxon system*", in their terms) and map-based navigation (*locale system*).

1.1 *Cognitive mapping hypothesis*

The purpose of the cognitive map is to store relevant relationships among spatial cues in a given environment. These cues can be used interchangeably; no specific cues are essential, but some minimal subset is necessary. The cognitive map allows the usage of shortcuts even in places never before visited. Its flexibility is thus substantial. However, it is compromised by increased computational and memory demands. When new cues are added to familiar situations, the environmental change will provoke a curiosity-driven exploration and subjects will learn about the new spatial layout. Exploration serves to incorporate new spatial and contextual components into the cognitive map through a “remapping” mechanism.

However, associative learning might still occur in spatial domain, i.e. during localization of a goal based on multiple discrete landmarks. Blocking and overshadowing have been demonstrated. *Blocking* occurs when a second landmark is added near the first one that governs navigation. If the first landmark is removed, the animal will get lost despite the presence of the second landmark (Stahlman and Blaisdell (2009); also documented in humans (Hamilton and Sutherland, 1999)). *Overshadowing* is similar in that it occurs when the memorization of a goal location is based on a compound cue (AB). When one element (A) of the array is missing, the remaining cue (B) exerts hardly any influence over the spatial behavior (Sanchez-Moreno et al., 1999).

Hardt and Nadel (2009) argue that these experiments do not convincingly demonstrate that associative learning also takes place in situations in which we would expect cognitive mapping (i.e. in localization based on an array of cues). Instead, in these situations a map was unlikely to be constructed because not all the cues gained an equal attention. If subjects are provided with the possibility to sufficiently explore the cues, no blocking or overshadowing takes place (but see Stahlman and Blaisdell, 2009).

1.2 **Categorization of navigation**

Egocentric vs. allocentric

The spatial relationships we perceive may be encoded within two principal frameworks. *Egocentric* coding relates the cue position to a certain body part. This is usually the retina, but can also refer to the head, trunk or hand. On the contrary, if a spatial relationship is represented independently of body position then it is referred to as an *allocentric* coding.

Idiothetic vs. allothetic

The aforementioned categorization should not be confused with idiothesis and allothesis, since these refer to the source of the spatial information, not how it is represented.

Idiothesis processes information produced by the animal's active or passive movement. The vestibular signals from semicircular canals (registering angular accelerations) and from otholitic receptors (registering linear accelerations), sometimes supported by optic and/or auditory flow, allow the detection and computation of animal displacement or rotation with respect to an inertial (geo-based) reference frame. This is referred to as *inertial idiothesis*. Similarly, signals from proprioceptors (muscular, juncture or ligament receptors) and efference copies react by relating the subject's locomotion to the ground (*substratal idiothesis*). Integration of the above signals enables the animal to determine its position relative to the previous path (*path integration*). Inertial and substratal idiothesis coincide with each other when the animal moves over a stable substrate, but becomes dissociated when the animal passes over a moving ground or is passively transported. It has however been found that rodents are able to compensate for passive rotations during path integration (Mittelstaedt and Mittelstaedt, 1980).

Navigation based on self-motion generated cues (idiothetic navigation) is considered one of the main modes of way finding, although functionally and

anatomically distinct from allothetic navigation. The precision of this navigation method is prone to degradation in the presence of more complex paths. Recalibration requires reliable positional information provided by an allothetic cue (Etienne et al., 1996; Etienne and Jeffery, 2004). Unless rats are given such a positional fix, they fail to properly monitor their track for paths longer than ca 5 meters (Stuchlik and Bures, 2002).

Allothesis, on the other hand, processes external signals, thus informing the animal about spatial relationships between environmental cues, as outlined in the following section.

1.3 Types of landmarks

Allothetic cues are widely available in any environment and may vary in saliency, stability, relevancy or proximity to a desired goal or route.

Beacons

A beacon refers to a cue that is in close proximity to (or directly indicates) a goal so that the subject animal may be simply guided to the target. As a navigational strategy, guidance only requires the association of the beacon and the goal. An off-beacon is when the cue is not quite spatially identical with the goal, but further away (Mackintosh, 2002). An off-beacon does not prevent the animal from using non-mapping solutions since it can use guidance to off-beacon and then perform a random search. Off-beacons permit a reliable estimation of distance (Collett et al., 1986).

Directional (polarizing, compass) cues

Directional cues contrast beacons in that they do not allow for any distance estimation but instead provide a means of alignment and calibration for an internal sense of direction in the cognitive map (Taube, 2007). The egocentric bearing (angle

between head direction and directional cue) changes very little as the animal moves since the directional cues are the most distal cues available.

Surface (barrier) cues

A salient object that blocks and therefore prevents passage represents a highly relevant kind of cue due to its significant impact on the behavior of several types of neural correlates of spatial representation (O'Keefe and Burgess, 1996; Muller and Kubie, 1987; Solstad et al., 2008). It defines a border of accessible space and allows (as a beacon cue does) a means to estimate distance. Barrier cues are especially emphasized in laboratory conditions in experiments utilizing mazes. Mazes are built up from walls and provide a complete separation of inner space from the outside world, a feature rarely found in nature.

Geometric cues

An array of discrete landmarks or barriers themselves may constitute a geometrical object. If present, geometrical features are readily incorporated into navigation (Cheng, 1986) since they represent salient and easily computable frame of reference. In fact, geometry can overshadow landmark learning under certain circumstances, giving rise to an idea that navigation can be built upon "geometrical modules" (see Cheng (2008) for a review).

1.4 Behavioral tests studying navigation in stationary environments

The cognitive map theory implied that animals use higher ordered mental functions. This consideration stimulated an accelerated development of various types of spatial mazes designed to target particular aspects of spatial cognition. These mazes now provide powerful tools in studying spatial cognition, learning and memory, and their underlying mechanisms using lesions, pharmacological or genetic interventions, as

well as electrophysiological approaches. Unlike the "old-fashioned" complex sets of intertwined corridors, the modern apparatuses usually do not have shapes of mazes and consist of small enclosures or elevated tables, quite dissimilar to its ancestors.

Water maze

In attempt to examine cognitive mapping, Morris (1981) introduced a water maze task (fig. 1A) based on remembering spatial relationships of cues far away from a target. Water maze consists of a smooth and cue-less circular tank (diameter = 1-2 m) filled with water for the most part and containing a shallowly submerged platform which provides a swimming rat the only way how to escape from the water. The rat, even if released into the maze from various starting points will rapidly acquire the platform location (if fixed throughout training) and will swim to it with remarkable accuracy. The target invisibility and absence of any visual, olfactory, tactile or acoustic intramaze cues encourage the animal to utilize landmarks present in the experimental room (i.e. extramaze allothetic cues) to localize the platform. Idiothetic cues play only a minor role that, however, can be emphasized in darkness (e.g. Moghaddam and Bures (1996); Save and Moghaddam (1996)). The place memory is convincingly demonstrated in a "probe trial" in which, despite the platform being no longer present, well-trained animals persevere in searching for the target in the correct location. The water maze takes advantage of its simplicity to distinguish procedural from navigational deficit: A rat unable to locate the submerged platform but able to reach a visible one implies preserved motivational and motor competencies while displaying impaired navigation (Morris, 1981).

"Dry" mazes

Another widely used method in testing spatial behavior is the radial arm maze (Olton and Samuelson, 1976), a device with an elevated central platform, symmetrically surrounded by centrifugally extended arms, each with a hidden piece of food at its end (fig. 1B). Number of the arms varies greatly; its simplest form is a „Y“ maze but more

frequently there are eight arms. The rat must remember, using intramaze or extramaze cues, which arms it has already visited and therefore contains no food, and which arms are still baited (a working memory task). Another variant involves arms that are never baited (a reference memory task). The baited arms may also be determined egocentrically (entry the left adjacent arm).

If we block one corridor in the four arm (= cross-shaped) maze without a central platform present, we get a specific kind of T-maze (fig 1C). This setup allows for an easy assessment of the mutual contribution of (motor) *response* and *place learning* (Packard and McGaugh, 1996). First, a rat is trained to run through the starting corridor and make a specific body turn (e.g. left) at its end to enter the correct (baited) arm. In a probe trial, the rat is forced to start from an opposite, unblocked starting corridor. A rat turning left at the crossroad applies a *response strategy* while a rat turning right displays a *place strategy* because it moves to a location spatially identical to the one in training.

Unlike in the water maze, the rat has only a limited number of spatial choices (equal to the number of arms) in these types of mazes, so they are better suited for testing spatial learning and memory rather than for investigating how animals find their way around. As a dry analogue of the water maze, a hole board is often utilized (Kesner et al., 1989): A featureless circular arena is covered with an array of several tens of small food holes, with only one of them baited. Its position is therefore hard to deduce from intramaze cues and must be determined with respect to landmarks outside the arena.

As a test of idiothethesis, adapted variants of Barnes maze (Barnes, 1979) are usually selected (Save et al., 2001; Whishaw et al., 2001). A rat, having a home base under one of the multiple holes circumferencing a featureless smooth table, searches on its outbound journey for a randomly placed food-pellet under one of multiple cups on the arena (fig 1D). Once the reward found, the rat naturally runs directly to the home base to eat it in safety. While the utilization of allothetic cues is restricted by darkness or by a uniform curtain in the background and by uniformity of arena surface, the homing vector must be computed exclusively on the basis of idiothetic input.

To examine location-specificity of various neural correlates of spatial behavior during recordings of their activity, it is required that the animal locomotes over a surface in a homogenous way. This is achieved by the random scattering of small pellets over the arena surface so that the animal searches for them, finally covering the arena with its tracks. Since this “task” does not involve any goal-directed feature that would have a great impact on neural correlates, a place preference task has been introduced (Rossier et al., 2000). Rats are trained to enter a particular part of the environment in order to release a pellet which subsequently lands at a random place on the arena. Thus, a randomness of tracks in the “searching” phase is preserved.

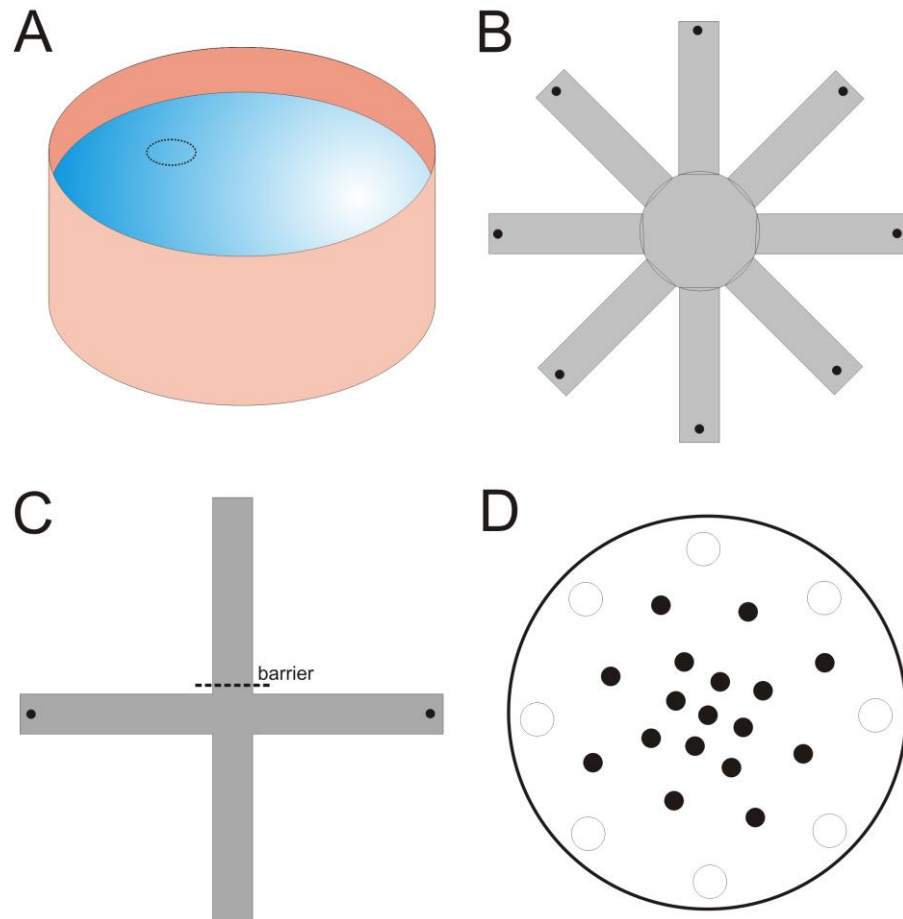


Fig. 1. Examples of mazes used in neuroscience research. (A) Morris water maze. (B) Eight-arm radial maze with central platform. (C) Cross-maze used as T-maze with blockable starting corridors. (D) Adaptation of Barnes maze for testing of idiothesis. From Save et al. (2001).

2 Neuroanatomy of spatial behavior

2.1 *Hippocampal formation*

In a strict sense, the hippocampus proper consists only of fields of Ammon's horn (*cornu ammonis* - CA1, CA2, CA3). Together with the dentate gyrus and subiculum they form a complex termed hippocampal formation (according to Witter and Amaral (2004)), revealing a characteristic shape of two interlocking and mutually reversed "Cs" when cross-sectioned. Since all of these structures are three layered, they are usually classified as an *allocortex*. The adjacent entorhinal cortex (sometimes considered as part of a hippocampal formation) provides a reciprocal connection with neocortex, and conveys the main cortical input to hippocampus.

The basic hippocampal circuitry represents the trisynaptic circuit (fig. 2B). In this unidirectional excitatory loop, the entorhinal cortex sends via a perforant path efferents to the granule cells of the dentate gyrus, from which its mossy fibers project to pyramidal cells of CA3. These in turn, through the Schaffer collaterals, connect to the CA1. The signal from there may return to entorhinal cortex either directly or through the subiculum. Due to the character of its projections, dentate gyrus is believed to play a role during pattern separation, i.e. in separating two similar input patterns into two distinct representations (O'Reilly and McClelland, 1994). The opposite process, a pattern completion, i.e. full retrieval of a representation when only a partial input is available, takes place in CA3 recurrent collaterals considered to be an auto-associating network (Nakazawa et al., 2002).

The rat hippocampal formation may be further subdivided along its longitudinal axis into the dorsal, intermediate and ventral hippocampus, reflecting both their different function and connectivity (Moser et al., 1993; Moser and Moser, 1998).

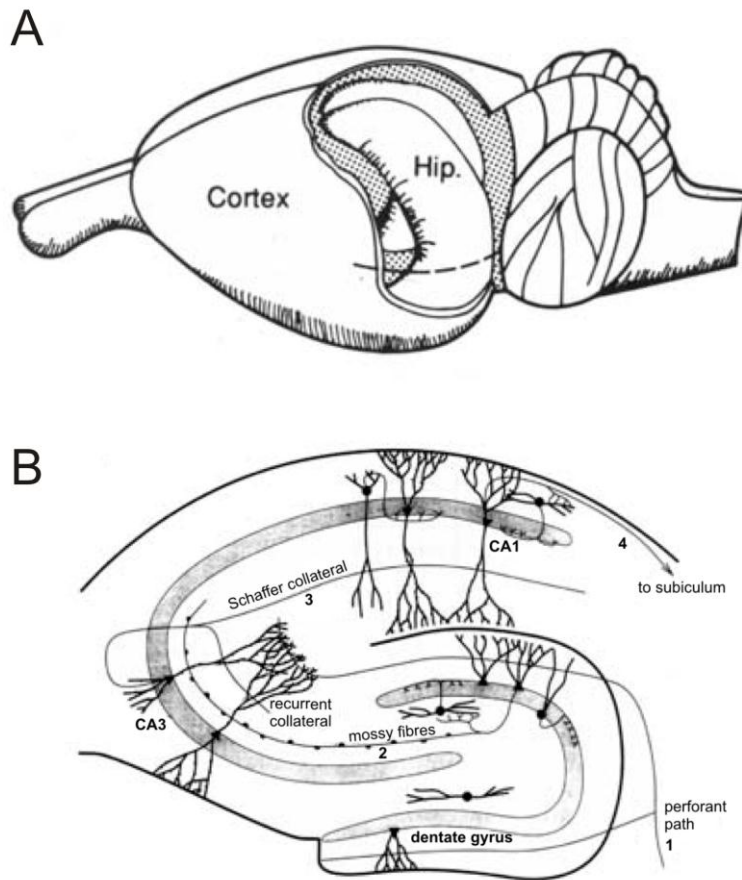


Fig. 2. **(A)** Localization of hippocampal formation (Hip.) in the rat brain. The overlying neocortex was fenestrated to reveal position of the hippocampus. **(B)** Schematic diagram of the trisynaptic circuit, with major components numbered. Adapted from Bischofberger et al. (2006).

2.2 Function of the hippocampus

The first observations of a hippocampal function came from human patients. A notorious case is that of patient H.M. who underwent a bilateral medial temporal removal in order to relieve medically unresponsive epilepsy (Scoville and Milner, 1957). He suffered post-operatively from severe anterograde and limited retrograde amnesia, implying the role of the hippocampus and adjacent structures in mnemonic processes. Later, based on studies in human patients and controlled experiments with monkeys,

such a deficit was explained in terms of disabled encoding of long-term declarative memory (Squire, 1986).

However, studies in rats systematically pointed out a hippocampal involvement in spatial learning and memory, eventually leading to identification of hippocampus with cognitive maps (Nadel and O'Keefe, 1978). The idea that the exclusive role of the rodent hippocampus subsists in spatial cognition seemed too radical to be widely accepted at that time. Instead, several theories attempting to describe hippocampal functioning in more abstract terms rendering both spatial and general mnemonic processes have been proposed, such as multiple-trace (Nadel and Moscovitch, 1997), dual process (Rugg and Yonelinas, 2003) or relational theory (Eichenbaum et al., 1994). The common feature of the current view of hippocampal processing usually points to its implication in episodic (-like) memory (Bird and Burgess, 2008).

2.3 *Functional interventions to hippocampus and spatial learning and memory*

Lesioning hippocampal formation severely impairs various forms of allothetic navigation as demonstrated, for example, by disrupted ability to locate a submerged platform in a water maze (Morris et al., 1982; Sutherland et al., 1983; Dimattia and Kesner, 1988). Furthermore, it also affects both reference and working spatial memory in a radial arm maze (Bouffard and Jarrard, 1988; Jarrard, 1993). The impact of lesions appears to be less devastating when axon-sparing ibotenate lesions are used (Whishaw and Jarrard, 1995). In the plus (cross-shaped) maze procedures, inactivation of the hippocampus disrupts *place learning*, contrasting with impaired *response learning* after striatal lesions (Packard and McGaugh, 1996). Idithetic navigation, tested usually in homing behaviors, seems to be also hippocampus-dependent (Maaswinkel et al., 1999; Whishaw et al., 2001; Save et al., 2001). Restriction of a cortical input by damaging the subiculum and entorhinal cortex does not produce as severe spatial deficits as a

transection of fimbria-fornix, a bundle connecting hippocampus with septum and subcortical structures (Jarrard, 1993; Whishaw and Jarrard, 1995).

On the other hand, the basic procedural and spatial competencies are spared after hippocampectomies. Rats are able to estimate the egocentric distance (Long and Kesner, 1998), swim towards a cued platform (Morris et al., 1982; Dimattia and Kesner, 1988; Sutherland et al., 1983), or locate a hidden platform provided that off-beacon and compass cue are present (Pearce et al., 1998). They even master locating a platform if released from the same start location (Eichenbaum et al., 1990). However, such spatial representation is rather rigid, qualitatively quite different from the proposed flexibility of cognitive mapping.

The participation in spatial processing varies along the septum-caudal axis, with more prominent contribution found in the septal part, i.e. dorsal hippocampus (Fanselow and Dong, 2010; Moser et al., 1993; Moser and Moser, 1998). Interventions aimed at particular subfields of hippocampal formation underlined the requirement of its functional integrity as a whole. Allothetic navigation remains disrupted after a selective, colchicine lesion of dentate gyrus (Jeltsch et al., 2001), or after transection of longitudinally oriented axons of CA3 pyramidal cells (Steffenach et al., 2002).

Investigations focused on particular stages of spatial memory trace formation revealed that temporal inactivation of dorsal hippocampus by AMPA/kainate receptor antagonist LY326325 blocks both encoding and retrieval of the engram (Riedel et al., 1999). However, the exclusive role of the hippocampus in acquiring the allothetic memory has been challenged: Inactivations made by a transient sodium channel blocker lidocaine showed that animals may not acquire the allothetic information during the inactivation per se while possessing the correct engram when tested one day after (Parron et al., 2001). Authors of this study hypothesize that an unknown brain structure latently substitutes the hippocampus in acquiring knowledge about allothetic space; the proper encoding occurs “off-line” after a hippocampal recovery.

2.4 Place cells

Electrophysiological approach led to the discovery of several classes of neural correlates of rat spatial behavior. O'Keefe and Dostrovsky (1971) first found pyramidal neurons in CA3 field that fired whenever the animal occupied a specific part of its environment. Each "place cell" responded to a different place, its "firing field". Such location-dependent activity has also been shown in pyramidal cells in the CA1, and granule cells in the dentate gyrus. The CA3-CA1 firing fields tend to cover uniformly the environment uniformly. Unlike sensory neurons in the brain, discharge of place cells is not directly governed by a single stimulus. Instead, it can be modulated by various signals of various modalities. The firing fields may occasionally appear, disappear or change its position or size, but in a stable environment they can persevere from many weeks to several months (Thompson and Best, 1990). Under light conditions, the visual cues seem to exert much of the control over place cells firings as their firing fields follow rotations of cue cards attached to the wall of the experimental chamber (Muller and Kubie, 1987; fig 3A). However, when the lights are subsequently switched off the firing remains preserved, indicating that the input from idiothesis is sufficient for the rat to self-localize. Place activity does not require any visual information as witnessed by unaltered place cells firing in blind rats (Save et al., 1998). Place cell's discharge is substantially determined by geometric features of the recording apparatus. Firing fields were reported to extend along a wall in line with an extension of a rectangle enclosure (O'Keefe and Burgess, 1996). Place cells can be modulated by many other factors, even non-spatial, including the task requirements (exploration vs. purposeful navigation; Markus et al. (1995)), or the ongoing behavior (Wood et al., 2000). These findings show that place cells receive information about spatial location as well as highly processed information pertaining to the current context. Therefore, they likely provide the animal rather with the notion about the present situation (when, what, where) than exclusively about space (Jeffery, 2007a).

In accordance with the cognitive map theory, change in the experimental environment, or context, usually causes “remapping”, i.e. gaining, losing, or shifting position of the place field. The remapping might be partial. For instance, traversing from one into another visually identical enclosure seems to yield both preserved and remapped place fields (Skaggs and McNaughton, 1998). This suggests that a cognitive map is not necessarily a rigid unitary chart. Rather, its subcomponents are autonomous and reflect various consistent features of the environment. Rhythmic slow activity, or theta rhythm, in the CA1 field of the hippocampus is associated with walking; its amplitude increases with speed. The theta activity appears to be linked with place cells. When restrained animals are moved passively through the environment, the activity of place cells at a given location in the unrestrained condition is practically abolished (Foster et al., 1989). Under self-motion attenuated, the hippocampus behaves as if the rat were moving more slowly, over a smaller distance, making firing fields appear substantially larger (Terrazas et al., 2005). There is still some controversy as to what extent place cells reflect internal awareness of localization. For instance, change in place cell behavior might not be always accompanied by a corresponding change in the spatial behavior of the rat (Jeffery et al., 2003).

2.5 *Head-direction (HD) cells*

A quite different class of spatially tuned neurons was discovered some 15 years after the discovery of place cells. These neurons fire within a narrow (approx. 90 degrees) range of angular direction of the head relative to world centered coordinates, hence they are referred to as head-direction cells (fig. 3B). Though first described in the subiculum (Taube et al., 1990; Taube et al., 1990), they have been also recorded from the anterior and the lateral dorsal thalamic nuclei, lateral mamillary nucleus, striatum, and entorhinal cortex (Taube, 2007). They are usually coupled with place cells, so that their activity also depends predominantly on the visual cues; especially the most distant ones (Zugaro et al., 2001; Yoganarasimha et al., 2006). However, evidence has

accumulated that the head-direction discharge is primarily derived from an idiothetic input. For example, dysfunction of the vestibular apparatus severely disrupts direction-specific firing of HD cells (Stackman et al., 2002) even in the presence of a familiar directional cue. HD signal seems to stem from the dorsal tegmental nucleus, in which neurons sensitive to angular velocity are found. There it propagates via the lateral mammillary nucleus, anterodorsal thalamus and post-subiculum, finally reaching the entorhinal cortex where it provides the grid cells with information about spatial orientation.

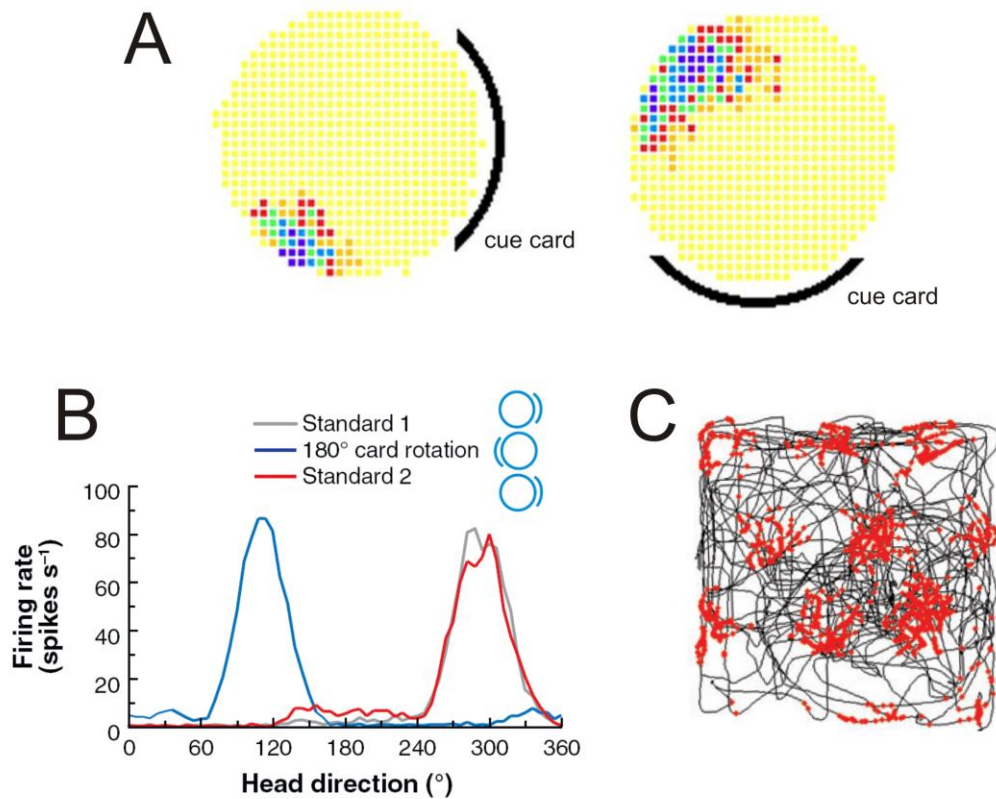


Fig. 3. **(A)** A color-coded firing rate within an arena of a single place cell. Note that the firing field follows the cue rotation (Muller and Kubie, 1987). **(B)** Firing rate of a single head direction cell as a function of direction of the animal's head, and the effect of cue rotation (Taube, 2007). **(C)** Superimposition of sites where a single grid cell generated action potentials (red points) on the track (black line) of an animal placed in a square box, revealing the triangular pattern of firing activity (Moser et al., 2008).

2.6 Grid cells

Finally, a neural substrate that may underlie the internal “sense of metrics” (Jeffery and Burgess, 2006) has been found in the medial entorhinal cortex (MEC) (Hafting et al., 2005). Firing fields of a grid cell constitute a pattern of regularly spaced pinnacles of equilateral triangles (fig. 3C). This grid covers the entire floor of the environment and can extend (while preserving its scale) if the walls of the environment are removed and the animal allowed to explore outside the original boundaries. Anatomically adjacent neurons display grids at similar scales and orientations although their firing may be mutually phase-shifted. The grid orientation changes among sites located a bit further apart. Thus a small region of the MEC contains grid cells that cover the entire maze surface at a particular scale and orientation. Furthermore, the spacing of the grid becomes larger down the dorsocaudal to ventral axis of the MEC. Altogether, grid cells system provides animal with the information as to when it travelled a certain “aerial” distance from a previous spot, suggesting they form a principal element of the path integration system (McNaughton et al., 2006).

The length of an integrated path is determined by angular and linear velocity. Whereas the angular self-motion inputs may reach MEC from the head direction system, the circuitry that convey linear self-motion into the entorhinal cortex has not been determined yet (Jeffery, 2007b). However, linear speed of the animal apparently modulates some of the head-direction cells, grid cells, and their conjunctive cells found in deeper layers of the MEC (Sargolini et al., 2006).

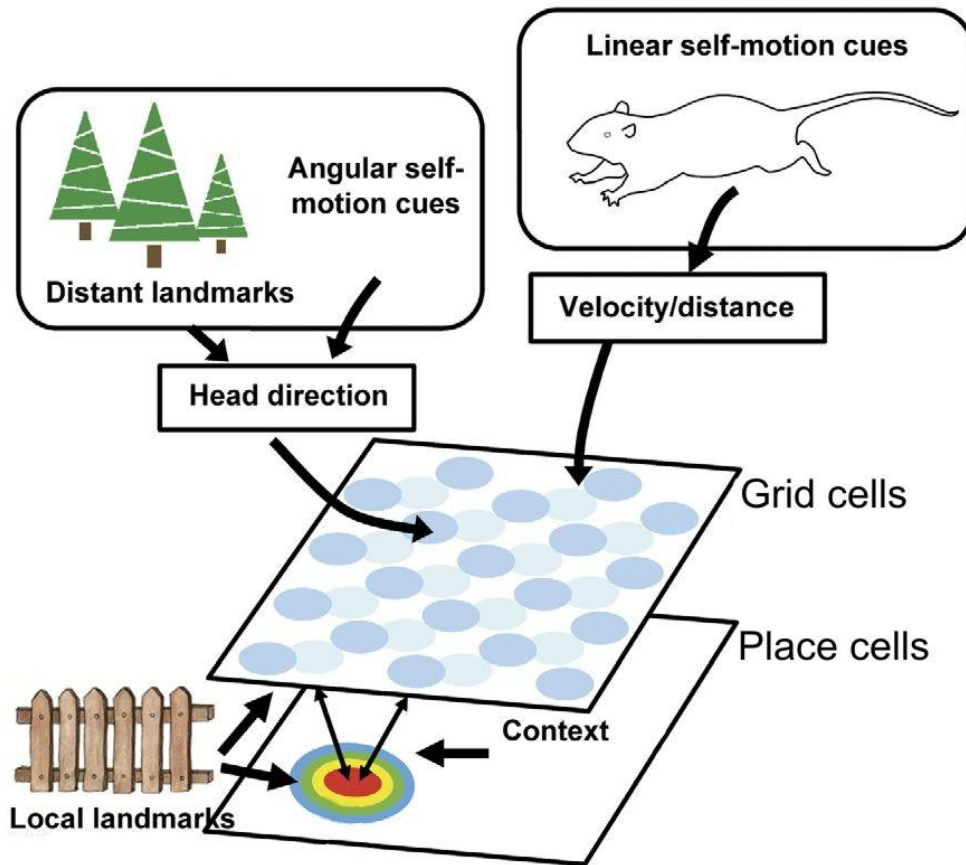


Fig. 4. A diagrammatic representation of inputs leading to generation of signal by grid cells and place cells. Reproduced from Jeffery (2007b).

2.7 Cortical areas

Studies from cellular correlates of spatial behavior suggest that construction of internal spatial representation of the environment is not limited to the hippocampus, or hippocampal formation. The multi-staged cooperation with both subcortical and cortical structures likely occurs. Contribution of these areas is, however, still poorly understood. Much of the theoretical work focused on how and where is the spatial memory stored, proposing a distributed network involving neocortical areas (Frankland and Bontempi, 2005). While a brief sketch of cortical involvement in spatial processing will be provided

here, a detailed review of role of posterior parietal cortex will be given in the last section.

Perirhinal and postrhinal cortex

Perirhinal and postrhinal cortices provide a major source of cortical input to the hippocampal complex. Perirhinal cortex projects preferentially to the lateral entorhinal cortex and postrhinal cortex projects preferentially to the MEC (Burwell and Amaral, 1998). Surprisingly, perirhinal lesions usually produce no spatial deficits. They do not affect delayed alternation in a T-maze (Ennaceur et al., 1996), working memory variant of radial arm maze (Ennaceur and Aggleton, 1997), and reference memory in water maze (Burwell et al., 2004). If occasionally reported, the spatial deficits are mild and transient (Liu and Bilkey, 1998; Liu and Bilkey, 2001; Aggleton et al., 2004), probably reflecting general working memory rather than a specific spatial impairment (Jarrard et al., 2004). The contribution of postrhinal cortex to allothetic processing appears to be more significant (Liu and Bilkey, 2002) as would be predicted from its connection to MEC. However, combined post- and peri-rhinal cortex lesions also largely fail to affect spatial processing (Bussey et al., 1999). Furthermore, though postrhinal lesion may reduce coherence of CA1 firing fields they do not alter their location specificity (Nerad et al., 2009).

Retrosplenial cortex (RSC)

RSC (misleadingly also referred to as posterior cingulate) is quite large and cytoarchitecturally heterogenous neocortical area along the cerebral midline. It either receives direct projections from hippocampal formation (subicular complex) or is connected indirectly, via reciprocal fibers from postrhinal cortex. Thalamic projections include both afferents from and efferents to the lateral dorsal thalamic nucleus and the anterior thalamic nuclei known to contain HD cells. Furthermore, RSC receives input from visual areas and connects reciprocally to posterior parietal cortex and anterior cingulate (Vann et al., 2009). RSC lesions impair performance in standard spatial

memory tasks, including learning the fixed (Vann and Aggleton, 2002; Whishaw et al., 2001) or daily-changing (Whishaw et al., 2001) location of a platform in a water maze, and performance in working memory tasks in a radial-arm maze (Vann and Aggleton, 2002). Lesion-induced impairments have also been reported in tasks designed to tax the use of directional information (Pothuizen et al., 2008) or the use of idiothetic information for path integration (Whishaw et al., 2001). However, idiothetic navigation may be spared after RSC lesion (Zheng et al., 2003; Wesierska et al., 2009). RSC contains HD cells (estimated 10% of total number) with properties quite similar to the others found in the head-direction cell network (Cho and Sharp, 2001). Thus, RSC plays an important yet still not fully understood role in combining the idiothetic and allothetic signal and planning goal-directed motion, a role complementing or parallel to that of posterior parietal cortex.

Prefrontal cortices

The prefrontal cortices are considered to be central for cognitive and executive functions as well as for mediating a working memory. In the rat, medial prefrontal cortex (mPFC, a putative analogue of primate dorsolateral cortex (Uylings et al., 2003)) appears to be associated with spatial processes under certain conditions. Beside multiple cortical and subcortical projections, mPFC densely communicate with hippocampus (Ferino et al., 1987). Animals with lesions centered to mPFC, however, perform well in allothetic navigation in a water maze (Lacroix et al., 2002; Rawson et al., 2010; Jo et al., 2007) unless they face pattern a completion challenge (a partial cue removal) (Jo et al., 2007). Instead, lesioned animals completely fail to locate platform by idiothetic means (de Bruin et al., 2001).

Inactivation of mPFC does not permit an adaptation to an “extra dimensional shift”, i.e. when cues of one modality (e.g. space) became irrelevant and rat must follow cues of another modality (e.g. odor) (Ragozzino, 2007). On the contrary, intradimensional shift (a change of a goal within one modality) does not require mPFC. That is in agreement with findings that lesioned rats are only mildly impaired during a

“reversal” in water maze (Lacroix et al., 2002). Unit recordings from mPFC revealed neurons of similar characteristics as place cells. They fired during place preference task, with most of the firing fields located at the goal area (Hok et al., 2005). Prefrontal area provides an important source of signal for hippocampal place cells; ablation of mPFC results in disrupted place cells activity (Kyd and Bilkey, 2003). It is hypothesized that mPFC may participate in spatial processes by goal-directed planning, a process that apparently recruits both working memory and a selection of relevant strategy. However, as mPFC and hippocampus may work in parallel, mPFC lesions do not necessarily yield spatial deficits.

3 Non-stationary environments

As we experience on a daily basis space around us is not a rigid scene and undergoes both short- and long-term changes, so the brain must cope with two antagonistic demands. First, the perceived changes might be considered minor and/or irrelevant for ongoing spatial behavior and hence should be suppressed or excluded from the corresponding spatial representation. Second, they might be considered relevant enough to bring about a reorganization of the initial spatial representation. The first is likely accomplished by process of pattern completion, the second by pattern separation.

These assumptions are firmly embedded in the cognitive map hypothesis (Nadel and O'Keefe, 1978), predicting that a disappearance of a cue yields no effect on a map-based navigation. Conversely, adding a salient cue, or changing context elicits a substantial change in map-like representation.

However, an animal is not only confronted with a particular change in the environment (whether spatial or non-spatial) but occasionally also with fractionating its environment into independent and coherent subsets which move relative to each other and deserve to be spatially attended (e.g. a duck on a floating island vs. a stationary beacon). These coherent subsets may be regarded as individual reference frames. Such dissociating situations are even more frequently encountered in modern life of humans (e.g. travelling in a train vs. stable surroundings). Even a single moving object within a stable environment may be conceptualized as a distinct reference frame. But do these assumptions correspond to brain representations of fractionated environments or single moving objects? Although the reference frame dissociating situations are not uncommon in neuroscience research, assessment of spatial representation with respect to a single moving object is somehow neglected, partially due to a lack of appropriate behavioral test.

3.1 *Discrete reference-frame dissociating manipulations*

Distinct manipulations with environmental features leading to dissociation of reference frames, such as various cue or maze rotations, translations or shape modifications are widely used to examine as to how these features exert control over the rat's spatial behavior and/or its cellular correlates. These manipulations usually occur discontinuously as discrete events, without the possibility for the animal to experience them. Therefore, the animal typically faces a sudden conflict between a current spatial configuration and the expected one.

Manipulations with a single object or an array of objects

Rotation a single distal cue in a symmetrical environment is readily followed by corresponding rotation of firing fields (Muller and Kubie, 1987) even if it does not match with idiothetic information (Jeffery, 1998). However, if the rotating cue is directly experienced as unstable, i.e. is moving in sight of the animal, its control over spatial behavior entirely ceases. This can be reverted if the animal first experience the cue stability for several sessions. Then the firing field will follow the cue rotation even if the cue is visibly mobile (Jeffery, 1998).

The proximal cues (except for beacons), however, do not display as strong control as distal ones (Save and Poucet, 2000; Shapiro et al., 1997). An array of proximal cues providing the only correct reference frame for locating the reward will govern the spatial behavior only after intensive training (Collett et al., 1986; Biegler and Morris, 1996; Save and Poucet, 2000). The subtle control is even more suppressed if rats can directly experience that location of an array of proximal cues changes relative to the rest of the environment from trial to trial (Biegler and Morris, 1993; Biegler and Morris, 1996). It is not then surprising that in rats performing goal-undirected chasing for randomly scattered pellets on an arena with centrally placed objects, a single rotation of them does not evoke corresponding rotation of recorded firing fields (Cressant et al., 1997). Yet, animals do not neglect proximal landmarks. For example they respond by

increased exploration to an inter-trial change in spatial configuration or displacement of the objects (Goodrich-Hunsaker et al., 2005; Save et al., 1992a, b). Furthermore, Gothard et al. (1996a) even managed to reliably record place cells' firing as coupled to unstable (moving from trial to trial) intramaze landmarks. Rats were intensively trained to shuttle between a variably placed box and two variably placed landmarks inside a large arena, some cells fired in stable spatial relationships to the box, whereas others fired in relation to the landmarks.

The capacity of intramaze objects to exert control over place fields grows as the objects are brought closer to the maze periphery (Cressant et al., 1997). Such peripheral landmarks may even surpass distal cues. In a double rotation study, Renaudineau et al. (2007) reported that 25% of the recorded place cells followed a clockwise proximal cues rotation while only 9% followed a counter-clockwise distal cue rotation. Most of the cells, however, remapped. Subsequent restoration of the original maze layout was accompanied by a re-establishment of the previous place fields locations.

Maze position manipulations

The maze itself may also constitute a distinct frame of reference delimited by the walls which are also strong determinants of either navigational behavior or place cells discharging (Hamilton et al., 2007; Hamilton et al., 2008; O'Keefe and Burgess, 1996). However, it should be noted here that many authors describe maze walls in terms of proximal cues, making the terminology rather confusing. The genuine proximal (=intramaze) objects are such that they may be approached from any direction. The number of spatial views experienced is therefore substantially higher than in the case of, e.g. apparatus walls. Therefore the brain "computations" considered to determine the location appear to be quite demanding (Benhamou and Poucet, 1998). These are the likely reasons why the intramaze objects hardly exert any control over the rat's navigation and why a rat prefers navigation based on landmarks that cannot be viewed from the other side. Nevertheless, quite distant objects do not provide accurate distance information because of minimal parallax. Therefore maze walls represent near-ideal tool

for determining a target location: they are close enough to enable distance estimation, yet impassable, i.e. preventing from an abundance of views.

In principle, two basic spatial manipulations with the maze can be made, translation or rotation.

If a maze is repeatedly translated within a room so that some of its parts may overlap across sessions (for one such an instance see fig. 5-1), place cells usually maintain their firing according to reference frame of the maze (Knierim and Rao, 2003; Siegel et al., 2008) while HD cells retain their alignment bound to the room coordinates (Yoganarasimha and Knierim, 2005). This is particularly true for corridor-like mazes. On arenas, few place cells' discharge may remain determined by extramaze cues. However, most of place cells respond to translation, regardless of the maze type, by remapping.

Behavioral studies conducted in water maze confirmed dissociability of maze-derived and room-derived spatial information. If a water maze tank is shifted in a probe trial within a room so as the target location occurs in the opposite quadrant of the pool, the well-trained rats search for the platform in a place corresponding to the pool reference frame (Hamilton et al., 2007; fig. 5-2), indicating the distal cues provide directional information but the accurate platform location is derived from distance to the maze wall (Hamilton et al., 2007). If the tank is filled up almost to the rim, rats demonstrate navigation exclusively by distal cues. Interestingly, this is also true when the maze manipulation is performed during early acquisition, suggesting the dominance of maze reference frame evolves gradually (Hamilton et al., 2009).

The pattern of results encountered after maze rotations is more complex. Rotation of background cues in a symmetrical environment results in corresponding and conjunctive rotation of place cells and HD cells (Muller and Kubie, 1987; Knierim and Rao, 2003; Yoganarasimha and Knierim, 2005). Provided that the local cues are enhanced, a subset of place cells tend to be tied to the maze frame (Shapiro et al., 1997; Cressant et al., 1997; Yoganarasimha et al., 2006) while HD cells almost exclusively keep firing in line with distal cues (Yoganarasimha et al., 2006). If a rat is present on arena during the rotations, inertial stimuli play an important role in determining both place

cells and HD cells discharge. Inertial stimuli may compensate for the rotation so that a place cell can keep its signal according to a pre-rotational reference frame (Wiener et al., 1995) which is in accord with behavioral evidence that gerbils are able to compensate for rotation while path integrating (Mittelstaedt and Mittelstaedt, 1980).

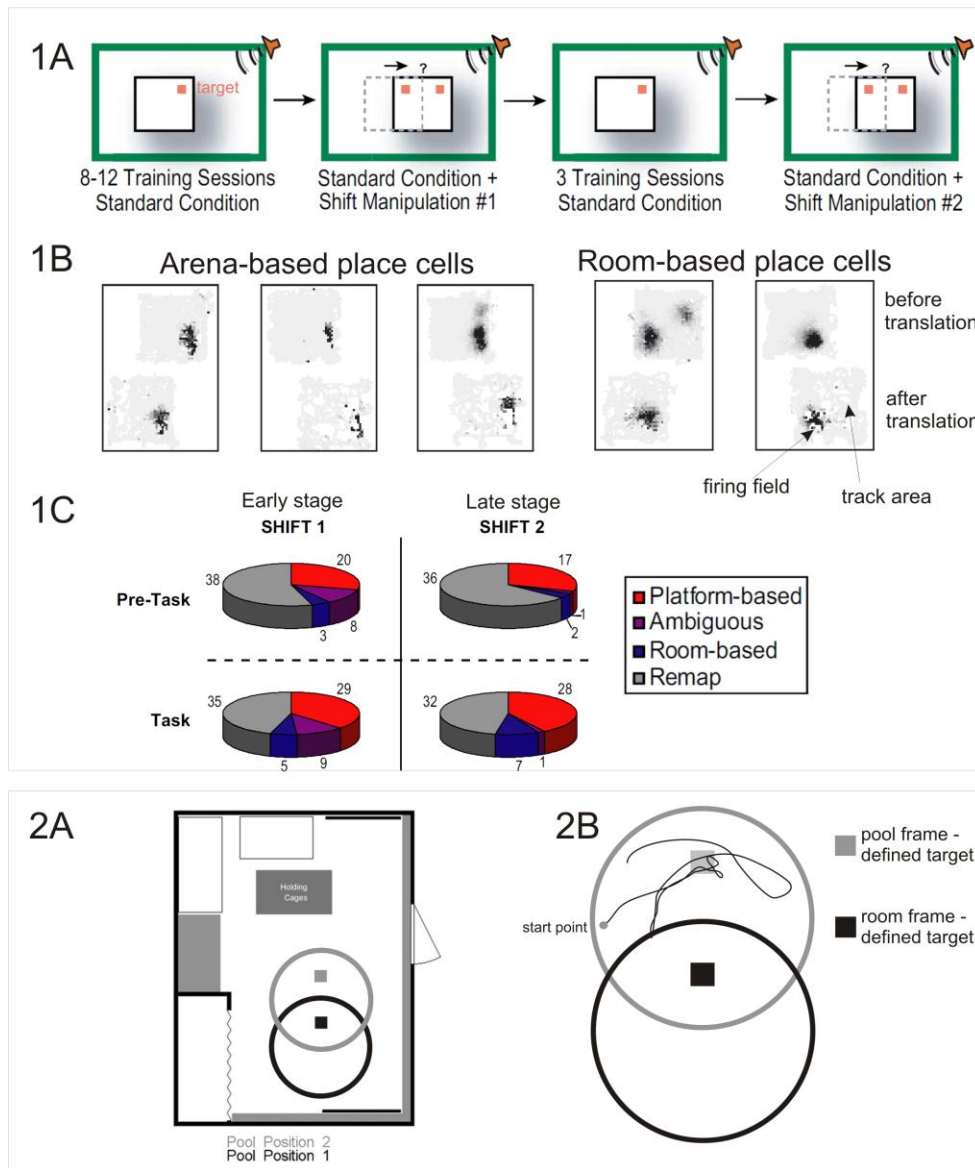


Fig. 5. Effect of maze translation on place cells activity (1) and navigation in water maze (2). Rats were trained in a modified version of a place preference task (1A) to run to an unmarked place on the arena (red square) after a beep, and pause there, in order to let release a food pellet scattering randomly over arena. In probe trials (at an early [SHIFT1] and late [SHIFT2] stage of acquisition) the maze was translated to either right or left side, with no reward delivered during unit recordings. Typical examples of firing fields (black parts of the gray track area) from probe trials are shown in (1B) (upper part=before, lower

part=after translation). Three illustrations on the left show arena-based place cells, two illustration on the right display room-based place cells. Panel **(1C)** shows proportions and numbers of place cells types before and during learning the task. In another experiment **(2A)**, rats were intensively trained to locate an underwater platform (black square) in water maze (large black circle). In a probe trial with no platform present, the maze was translated towards the centre of the room (large gray circle). An illustrative path **(2B)** of the probe-trial rat indicates that upon release the animal accurately headed to a location defined by water maze walls (gray square), rather than searching for the platform in its original location, as defined by room coordinates (black square). Compiled from Siegel et al. (2008) and Hamilton et al. (2007).

In most situations, the perceived conflict between a previously concordant reference frame and a novel dissociated environment results in remapping of place cells. Noteworthy, if rats are exposed to spatial dissociations of maze and its surroundings repeatedly, their place cells tend to develop and maintain quite new representational layout allowing to pursuit both room-based and maze-based references frame independently (Shapiro et al., 1997; Siegel et al., 2008).

Conflict between allothesis and idiothesis

A distinct reference frame can be built upon idiothetic input. Gothard et al. (1996b) examined the effect of repetitive discrepancy between idiothetic and allothetic information. Rats shuttled on a narrow linear track between two rewarded ends - a fixed and a movable slide box (fig. 6). When a rat ran towards the fixed end, a slide box was displaced a bit closer along the track, making the returning rat a mismatch between expected and actual distance of the track. Again, one class of place cells retained their firing relative to the starting point (hence idiothesis) while numerous place cells fired in relation to the moving box. The authors also computed a population vector analysis to construct a “mapping” from each full-length track to the shortened track. For small mismatches, the vector moved smoothly through intervening coordinates until the mismatch was corrected. For large mismatches, it jumped abruptly to the new coordinate, indicating a switch from a room reference frame to a reference frame based on idiothesis.

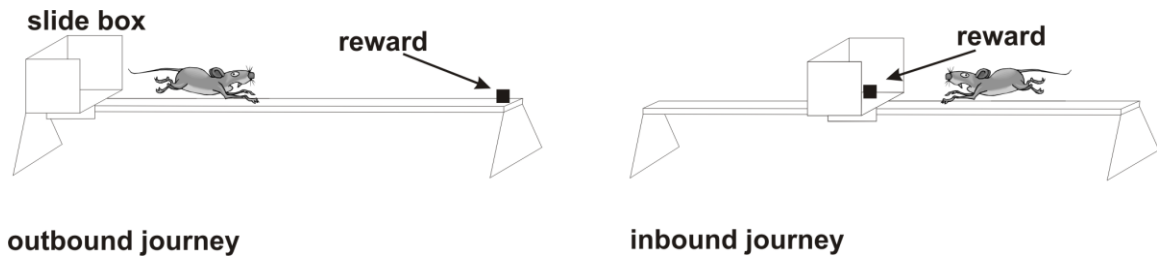


Fig. 6. The allothesis and idiothesis dissociating task employed by Gothard et al (1996b).

3.2 Continuous dissociating of the environment

Although the study of Gothard et al. (1996b) investigated a repeated yet discrete mismatch between idiothetic input and exteroceptive cues, there had been still an apparent lack of experiments investigating continuous separation of the spatial representational framework. Nevertheless, the above mentioned experiments yielded three principal findings: 1) the initial dissociation of the environment causes partial remapping; however, this event-related disruption stabilizes as the dissociation is experienced repeatedly, 2) representation can be likely bound to any arbitrary reference frame, 3) rarely yet distinctly, a place cell can respond to two reference frames simultaneously.

To shed light on these issues, an assay enabling a continuous dissociation of maze-related and room-related reference frame has been introduced (Bures et al., 1997a, b). Foraging rats were at first exposed to a stable arena. Under this circumstance, the idiothetic (or arena-based) cues are in a good agreement with the cues provided by the space outside the maze. However, a subsequent continuous rotation of the arena puts the two sources of spatial information in conflict. Place cells recordings revealed that most of the cells disintegrated their firing after the onset of rotation. Few of them followed the arena rotation, few of them retained stable place field according to room coordinates. The rotation itself did not account for the disruptive effect on place cells because if the onset of the rotation was followed by switching off the lights most of the place cells preserved their firing, reliably anchored to the arena surface. The minority of

cells that fired in reference frame either of the arena or the room provided a clue about possibly independent spatial representations: one following the rotation of the arena surface, the other anchoring its coordinates to the stable room environment. Such dual representation can be further emphasized in a relevant navigational task (Zinyuk et al., 2000), i.e. during performance of place preference task (Rossier et al., 2000). Place cells of the “navigators” were less sensitive to the onset of the rotation, so that only about one fourth had their firing fields disrupted. Their discharge was tightly anchored to stationary room frame representing the relevant frame of reference. At the same time, slightly fewer place cells fired according to navigation-irrelevant arena frame. Importantly, there was a near-equal number of cells that had their place field bound to both arena and room frames.

Place avoidance paradigms

Though initially devoted to neurophysiology recordings (Bures et al., 1997b), the place avoidance task has been standardized as to methodological procedures and eventually expanded to various behavioral, pharmacological and lesion experiments. Generally, it requires a rat to avoid a directly unperceivable, sector-shaped place on a elevated circular arena, since entering the sector is punished by a mild electrical foot-shock. The principal feature of the task is represented by the fact that the arena disc can be continuously rotated relative to its central vertical axis. Rotating the arena produces a segregation of previously concordant spatial information into two different frames of reference – the arena frame (AF) of reference that slowly rotates, and room frame (RF) of reference which remains fixed relative to the room. Then, we can choose as to which reference frame the punished sector will be defined in. In most cases, the sector is fixed to RF. This variant is called Active Allothetic Place Avoidance (AAPA) since a rat must compensate for the arena rotation otherwise it would be passively transported into the (fixed) punished region. To solve this task, a rat must navigate using extramaze allothetic cues such as doors, shelves, windows etc. and abandon navigation based on intramaze allothetic cues (scent marks, tactile cues) and/or idiothesis. In other words,

rat must first segregate previously concordant spatial information into two independent coherent representations, arena- and room- based. Subsequently, the arena-bound cues must be considered as navigation-irrelevant. Such process is formally framed in concept of cognitive coordination (Wesierska et al., 2005; Kubik and Fenton, 2005; Phillips and Silverstein, 2003).

Since cognitive coordination belongs to one of the processes significantly impaired in schizophrenic patients, AAPA provides a convenient behavioral tool to assess the effects of various antipsychotics in a rat model of schizophrenia-like symptoms (Bubenikova-Valesova et al., 2008; Vales et al., 2006; Vales et al., 2010).

In healthy animals, the presence of two segregated, independent spatial representations can be demonstrated in several ways. If rats trained to avoid a sector on a stable arena are subjected to an extinction session (no shocks) on a rotating arena in darkness, they subsequently display apparent avoidance as if it continued in the arena frame. However, the avoidance in the absence of the reinforcer gradually ceases. If the lights are subsequently switched on, rats instantly avoid a putative sector according to room cues. Thus, although arena frame memory extinguished, the room frame memory remained intact (Bures et al., 1997a). Even more explicit demonstration is provided by a “double avoidance” task (Fenton et al., 1998; Kelemen and Fenton, 2010). In these situations rats are required to simultaneously avoid both arena-bound and room-bound sectors. Despite the obvious considerable demands on coordination of the representations, attention, and proper timing of the escape behavior, rats confidently master this task within few sessions (Kelemen and Fenton, 2010).

The double avoidance and AAPA tasks are critically dependent on functional integrity of the hippocampus (Wesierska et al., 2005; Cimadevilla et al., 2000; Kubik and Fenton, 2005; Kelemen and Fenton, 2010). Even unilateral inactivation of dorsal hippocampus can prevent the rat successfully performing AAPA (Cimadevilla et al., 2001), a result hypothesized to reflect the inability to segregate rather than inability to maintain multiple representations of space (Kubik and Fenton, 2005). Ensemble recordings from CA1 neurons in animals performing the double avoidance task revealed

that, as a whole, the system switches from room frame to arena frame representation in few seconds intervals with higher probability to attend to a given representation if its corresponding sector is closely approaching (Kelemen and Fenton, 2010). Variants of place avoidance that do not tax cognitive coordination (e.g. AF+ in darkness) seem to be unaffected by disrupted function of hippocampus (Wesierska et al., 2005).

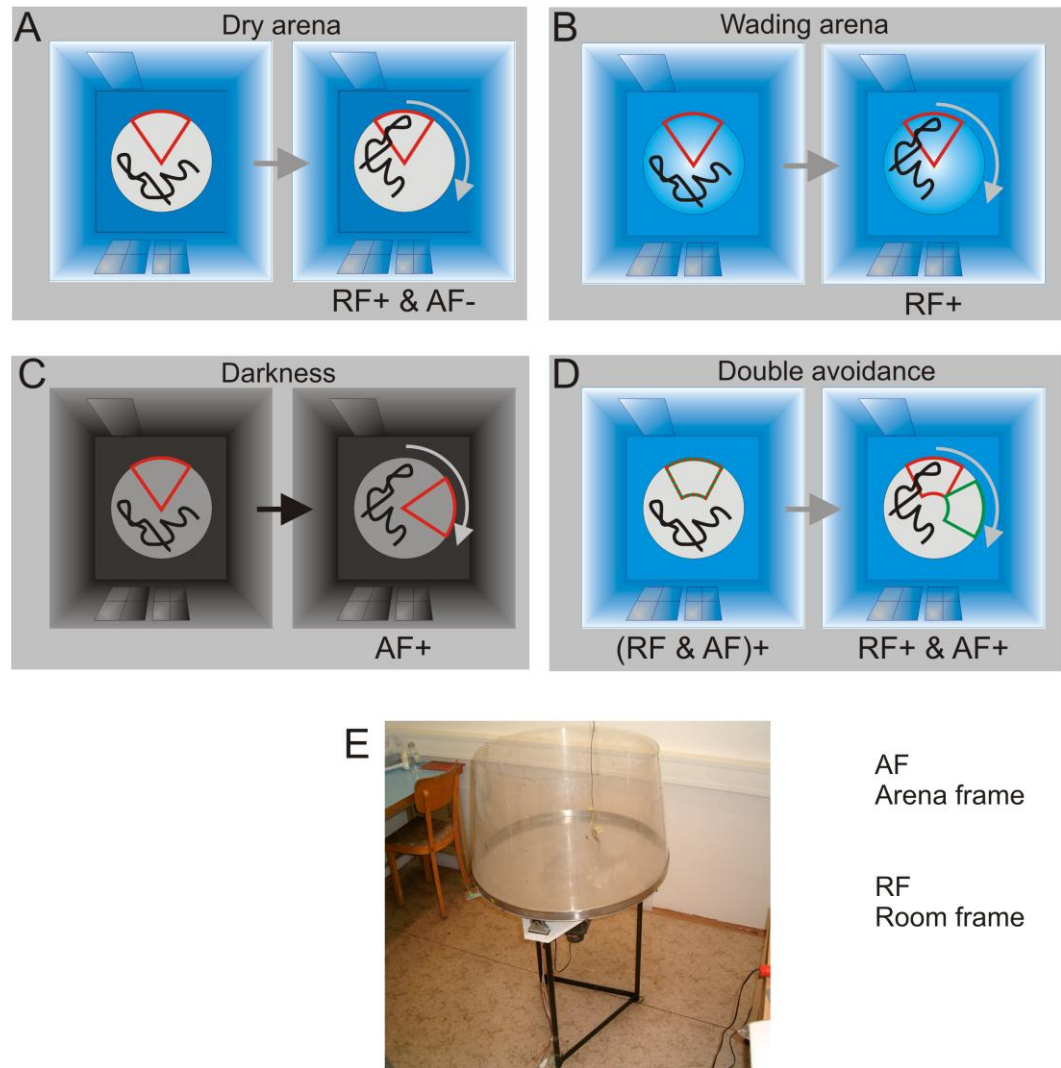


Fig. 7. Examples of the most commonly used variants of place avoidance task. **(A)** Arena rotates from the beginning of the experiment, with a shock sector (red) anchored to room coordinates. Thus the rats must treat cues (illustrated as putative odor traces) bound to AF as irrelevant and navigate solely according to RF (RF+&AF-). This setup is referred to as Active Allothetic Place Avoidance. **(B)** The same as A except that the arena surface is covered by shallow water to reduce availability of odor or tactile cues, hence no arena-bound cues to be suppressed are present (except for idiothesis) (RF+). **(C)** The arena rotates in darkness; the sector is anchored to the arena. Rats navigate according to AF (AF+). Due to the darkness, there is no requirement to suppress RF-based cues. **(D)** Rats are at first trained on stable arena. They can navigate using both AF or RF bound cues since both reference frames overlap [(AF&RF)+]. The arena then begins to rotate, with one sector left anchored to the RF (red) and the other to AF (green). Rats must simultaneously use both AF and RF bound cues but in separate, mutually discordant navigations (AF+ RF+). This is referred to as double avoidance. To make the escape accomplishable, central parts of the shock sectors are withdrawn. **(E)** Standard place avoidance apparatus, photo courtesy of Ms. Lenka Řezáčová.

4 Posterior parietal cortex (PPC) of the rat

4.1 PPC anatomy

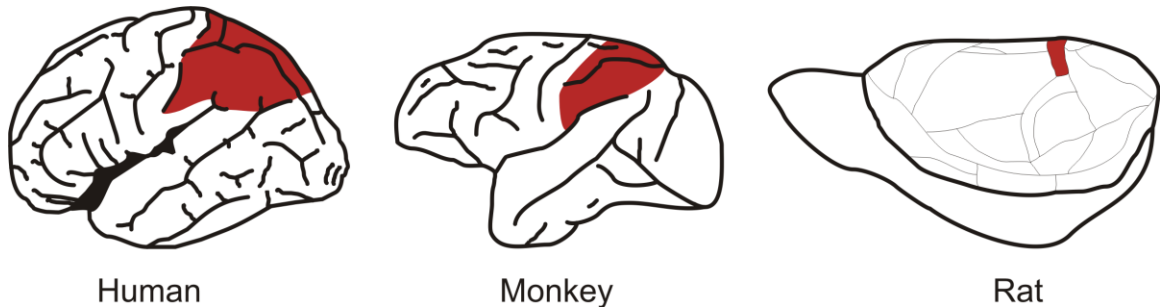


Fig. 8. Illustration of PPC extent relative to the brain surface in human, monkey, and rat. Compiled from Reep and Corwin (2009).

The PPC lies between the rostral primary somatosensory areas (which are also overlaying PPC laterally) and the caudal secondary visual areas, while the retrosplenial cortex adjoins medially (figs. 8, 9). As multimodal information converges in the PPC region, it is often referred to as associative (Thinus-Blanc et al., 1996). It had not been long determined as to which part (if any) of the rat parietal cortex is analogous to primate PPC, since its cytoarchitecture in rodents makes it difficult to clearly distinguish it from adjoining cortices, especially at caudal part. PPC has thus been traditionally regarded as the most rostral part of secondary visual cortex and labeled OC2M and OC2L in neuroanatomy atlas of Paxinos. However, using retrograde tracers to examine thalamo-parietal connections, a putative analogue of primate PPC was delineated in late 1980s.

This area, like primate PPC, receives thalamic input exclusively from the posterior, lateral dorsal and lateral posterior nuclei (Kolb and Walkey, 1987; Reep et al., 1994; Chandler et al., 1992) but not from the somatosensory ventrobasal nucleus and visual dorsal lateral geniculate nucleus. The associative nature of PPC is reflected in its numerous cortical projections. It receives afferents from striate, extrastriate, and

somatosensory cortex, while input from posterior cingulate and medial frontal cortex (anterior cingulate, frontal eye fields) seems to be reciprocal (Kolb and Walkey, 1987). Also auditory area sends substantial number of afferents to PPC. Noteworthy, there is a direct afferentation from cerebellum, emphasizing the possible role of PPC in motoric processes (Giannetti and Molinari, 2002). Although PPC does not directly connect to hippocampus (fig. 10), it is widely accepted that hippocampo-parietal communications are crucial for some aspects of spatial information processing. The signal into hippocampus can pass via retrosplenial cortex or postrhinal cortex. A small parietal projection also reaches medial part of entorhinal cortex (Burwell and Amaral, 1998).

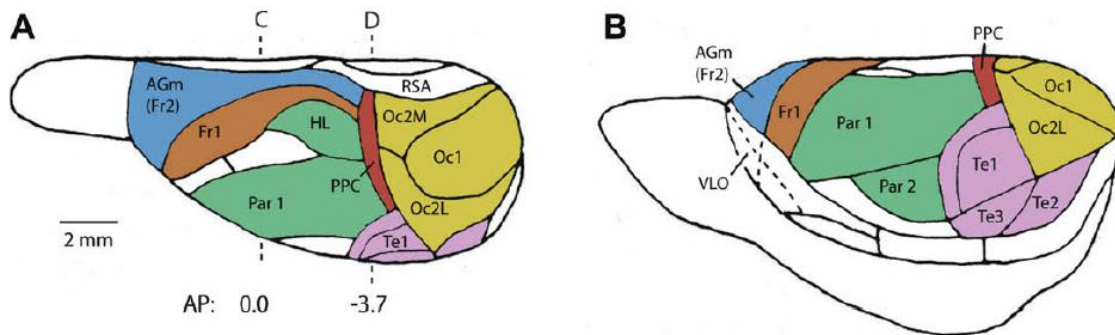


Fig. 9. Dorsal (A) and lateral view (B) of the left hemisphere of a rat brain with depicted parcellation of the neocortex. Fr – frontal, Oc – occipital, Par – parietal, Te – temporal cortex, RSA – retrosplenial area. C – bregma level, D – PPC level. AP – anteroposterior distance from bregma. Reproduced from Reep and Corwin (2009).

The cytoarchitectonics of PPC can be identified by the presence of thin layers II and III, a small but well-defined layer IV, and densely packed layers V and VI (Kolb and Walkey, 1987). The PPC lacks rich neurotransmitter heterogeneity. Beside glutamatergic (kainate, NMDA, AMPA) and GABAergic (A and B) receptors, cholinergic (M1, M2, nicotinic), 5-HT (1A, 2) and adrenergic (α 2h) receptors have been also detected in low densities (Palomero-Gallagher and Zilles, 2004). Cholinergic efferents thought to play some roles in attention stem from the nucleus basalis magnocellularis of the basal forebrain.

Despite detailed anatomical studies, the exact extent of the PPC region is still a matter of debate. Early anatomical attempts demarcated an area ranging 2-6 mm

posterior to bregma and 1.5-5.5 mm laterally to midline (Kolb and Walkey, 1987), which soon became a “gold standard” in the majority of studies employing PPC lesions. However, a comprehensive inspection of the parieto-thalamic connectivity resulted in confining PPC area into a strip 3.4-4.4 mm posterior to bregma and extending 1.5-4.5 mm laterally (Reep et al., 1994; Reep and Corwin, 2009; fig. 9A). It is possible to further divide PPC into at least two subregions since its medial part communicates with agranular medial frontal cortex and dorsocentral striatum, while its lateral part is connected with dorsal periphery of the dorsocentral striatum (Palomero-Gallagher and Zilles, 2004; Reep and Corwin, 2009). However, no systematic study has examined their potentially different functions yet.

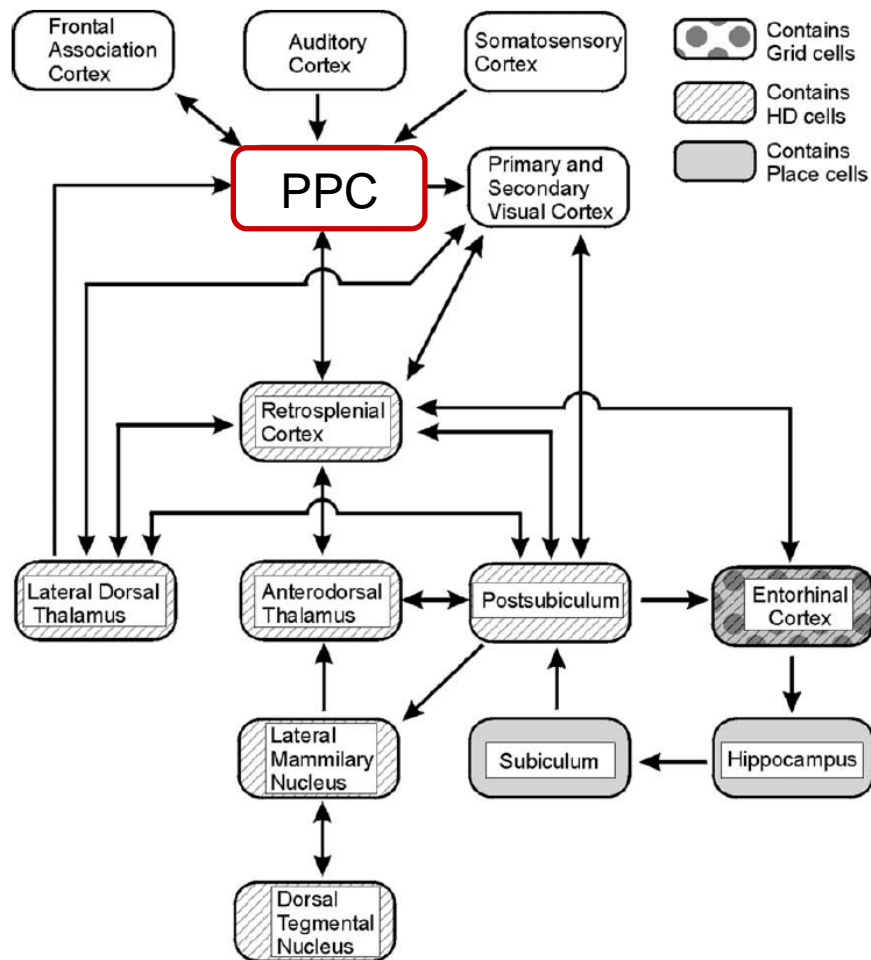


Fig. 10. Scheme of main connections of PPC and structures containing neural correlates of spatial representation. Reproduced from Calton and Taube (2009).

4.2 PPC function in humans and primates

In a neurological context, the PPC is often associated with the phenomenon of hemispatial neglect (Halligan et al., 2003; Husain and Nachev, 2007). Patients sustaining damage in the area of the right parietal-temporal-occipital junction demonstrate a remarkable deficit in directed attention. In the most severe cases, the patients shave only the right (ipsilesional) side of their face or attempt to dress only the right side of the body. The deficit is not just a lack of responsiveness to sensory stimulation but also a deficit in the cognitive representation of space. When asked to describe a mental representation of a well-known scene, neglect patients describe objects only in the right side of space. When asked to reverse the spatial perspective, they now describe objects on the right side of the reversed perspective and cannot describe the previously described objects (Bisiach and Luzzatti, 1978).

Bilateral PPC lesions are obviously rare, yet well characterized. The Balint syndrome (Balint, 1909) is associated with the inability to attend and/or to perceive more than one object at a time (simultagnosia) and inability to accurately reach toward an object (optic ataxia).

Though the neglect syndrome can be induced in primates by lesioning or otherwise injuring their PPC (Valenstein et al., 1982; Crowne and Mah, 1998), much of the work illuminating the role of PPC took advantage of electrophysiological recordings: typically performed on head- or trunk-restrained animal attending a visual stimulus on a computer screen. Numerous studies have demonstrated that neuronal firing in the PPC area can be related to various reference frames, either egocentric (retina, head, hand, or trunk) or allocentric (Snyder et al., 1998; Cohen and Andersen, 2002), suggesting that PPC acts as "translator" between various frames, providing a computational framework for motor actions (Cohen and Andersen, 2002).

Human and primate PPC data combined suggest that PPC participates in what has been collectively referred to as "vision for action", a dorsal stream in neocortex that is engaged in visual attention and transforms visual-spatial information into a code

applicable in construction of motor plans (Goodale and Milner, 1992). PPC has been proposed to participate in at least three distinct functional systems: grasping, reaching, and eye movements planning (Culham and Valyear, 2006; Andersen and Buneo, 2002). Recently, an issue of mnemonic contribution of PPC has been raised as, in spite of only mild memory deficits seen after PPC injury, this cortical region repeatedly displays its significance in brain imaging studies involving both short-term and long-term memory, particularly of episodic type (Olson and Berryhill, 2009; Cabeza et al., 2008). Directly addressing the issue of PPC role in spatial cognition, Burgess (2008) proposed that PPC provides a “window” performing spatial updating of egocentric location which is further transformed into an allocentric representation residing in medial temporal lobe.

4.3 *PPC function in rodents*

The function of PPC is still poorly understood in rodents as many experiments have yielded contradictory results. This might be partially due to the fact that PPC was not defined until late 1980s which resulted in using different coordinates of lesion among laboratories. Surprisingly, this practise has persevered to these days. However, there is currently a general consensus that rat PPC plays two principal, though rather vaguely defined roles: it is part of a network mediating directed attention and represents one of the principal brain sites contributing to spatial learning and memory.

4.3.1 *Attention*

As a logical consequence of the neglect phenomenon, several research groups sought to establish if unilateral neglect can be replicated in rodents as this would provide a tool in modeling such a debilitating brain dysfunction (Reep et al., 2004). Indeed, rats with injuries aimed to PPC in one hemisphere or with controlled unilateral lesions of this site do not respond to multimodal stimuli (King and Corwin, 1992; King and Corwin, 1993). However, the attention deficit seems to be mild and transient, and

not always inducible. Follow-up studies revealed that PPC represents only one element of a distributed network mediating directed attention. This network comprises of PPC agranular medial cortex (a putative analogue of primate frontal eye fields), dorsocentral striatum and lateral posterior thalamic nucleus (Reep and Corwin, 2009). This is consistent with human studies because injuries to the aforementioned brain sites may also produce a hemispatial neglect. The cholinergic afferentation in rodent PPC seems to be important in surprise-induced attention enhancement (Bucci et al., 1998) or in modulating attention for new learning (Maddux et al., 2007).

4.3.2 Allocentric and egocentric processing

Early attempts to identify the role of PPC led to its implication in spatial processes. Specifically, impaired allocentric navigation contrasted with egocentric spatial processing left unaffected after a bilateral PPC lesion (Kesner et al., 1989). It was repeatedly found that lesioned rats cannot find submerged platform in watermaze (Kolb et al., 1994; Kolb and Walkey, 1987; Dimattia and Kesner, 1988), or locate the correct hole in the cheese-board task (Kesner et al., 1989) as efficiently as control rats. The observed deficit correlates with the lesion extent. If the affected area involves, in addition to PPC, much of the somatosensory cortex both rostrally and laterally (Dimattia and Kesner, 1988) the impairment is even pronounced compared to the hippocampectomized animals. However, lesions limited to the currently defined PPC area yield only a moderate disruption of allocentric navigation (Kolb and Walkey, 1987). Detailed analysis of the swimming paths revealed that operated rats do retain some allocentric capabilities. They look to swim to the correct quadrant but fail to accurately direct their path towards a goal. Motor disturbances do not account for the deficit since lesioned rats have no difficulty to swim to a visible platform. PPC plays a role in both acquisition and retention of allocentric information (Save and Moghaddam, 1996). However, evidence has accumulated that PPC lesions do not always lead to detectable allocentric impairment in water maze (Save and Poucet, 2000; Mogensen et al., 1995;

Compton et al., 1997). The purely allocentric theory of PPC function hence did not stand on a solid ground, disproved also by the fact that PPC lesions were later reported to affect egocentric processing.

In a two experiments, Save and colleagues demonstrated PPC's involvement in path integration on a dry arena. They trained rats to forage for food pellets placed randomly inside one of seventeen holes on a clean circular arena (Save et al., 2001; Parron and Save, 2004; see also fig 1D). Once the animal found the pellet, it ran immediately and directly to its home-base cage, located at the arena circumference. Since the cage was underneath the arena surface (hence invisible for the animal) and a black curtain beyond the arena space provided no extramaze cues, rats were encouraged to follow the path integration-based homing vector while navigating on the inbound trip. PPC lesion impaired efficient homing even though not severely. Specifically, heading angles during the onset of the return trips were not as accurate as that of control rats. Likewise, animals often erroneously tried to jump into "dummy" cages attached regularly spaced around the arena to mask the home cage position. The inaccuracy of the return runs increased with complexity of the outbound trips (Save et al., 2001). Navigation based on self-motion cues is also disabled in the corresponding variant of water maze. Save and Moghaddam (1996) trained rats to reach a platform in darkness, with a start-goal relative position fixed. Lesioning the PPC again resulted in inaccurate trajectories so that lesioned rats could not even learn the task. The path integration is not the only manifestation of egocentric coding of space. However, as noted earlier, behavioral tests based on a simple egocentric response, such as the egocentric version of the radial maze (Kolb et al., 1994; Kesner et al., 1989) or memorizing the egocentric distance (Long and Kesner, 1998) have not proved PPC involvement at all. On the contrary, more egocentric information-demanding test as memorizing the route in Hebb-Williams maze led to a significant impairment (Rogers and Kesner, 2006).

The results discussed above give somewhat ambiguous results leading to a general and rather trivial suggestion that PPC plays a role in demanding spatial

calculations needed for execution of accurate spatial response. Can its role be conceptualized more specifically? Or the scarcity in rodent literature does not allow for formulating a more specific hypothesis?

Save and Poucet (1998, 2000) put forward the idea originally conceived in primate experiments that PPC transforms egocentric into allocentric coding and vice versa. They noticed that PPC lesioned rats did not properly respond especially to spatial cues occurring in the proximity to their body (eg., Save et al., 1992a; Save and Poucet, 2000). For example, lesioned rats experience difficulties in locating submerged platform in water maze when only intramaze landmarks are available to them. Conversely, if they can use extramaze landmarks, their performance is equal to that of control rats (Save and Poucet, 2000). Save and Poucet hypothesize that PPC associates idiothetic and visuospatial information in order to translate egocentrically perceived spatial relationships into allocentric representations. In turn, PPC also accomplishes an inverse task: translation of allocentric spatial representations into body-centered coordinates required for planning of the goal-directed movement. The "translator" is busier when it "calculates" near-space relationships since proximal objects provide greater variability of spatial views than distal landmarks; their parallax changes only little as the animal locomotes.

4.3.3 Electrophysiological studies

A greater insight into the allocentric/egocentric transformational role of PPC would be provided by unit recordings from parietal neurons. However, electrophysiological studies are rare, partially due to the technical difficulties in recording from parietal cortex. Both allocentrically and egocentrically responding neurons have been identified in rodent PPC. Surprisingly, allocentric neurons were detected using auditory stimuli (Nakamura, 1999). They responded to one of six speakers placed around a restrained animal performing a delayed-match to sample task.

The specific speaker-preferred firing remained preserved in spite of rotating the body axis of the restrained animal.

In radial maze, PPC neurons have been shown to fire in conjunction with specific locomotor actions, such as turns, and a particular place (Chen et al., 1994a, b); few neurons displayed head-direction-like specificity which was furthermore retained in darkness. A significant number of neurons was modulated by passive rotations, suggesting PPC's role in integration of angular displacement, i.e. path integration (Chen and Nakamura, 1998). Recent recordings demonstrated quite a remarkable behavior; they signaled a position according to progression on a well-known route (Nitz, 2006). For example, one neuron fired whenever a rat, just after the onset, occurred before a first right turn, during both outbound and return journey. Thus a set of PPC neurons seems to inform the rat about its location within a given route according to body spatial responses, which may serve as "intrinsic landmarks". Importantly, this route position firing is not anchored to any allothetic cue which makes it distinct from place cells.

4.3.4 PPC function outlined

Though extracellular recordings from PPC neurons did not substantially accelerate progress on revealing the role of PPC, several theories attempting to characterize PPC functioning in some detail have been recently proposed.

Whitlock et al. (2008) elaborated on the translation between egocentric and allocentric reference frame and emphasized the position of PPC just before a route plan is going to be developed. They suggested that signals generated by place cells and grid cells, inherently allocentric, reach PPC through postrhinal and retrosplenial cortices, with an alternative - via mPFC. Then it undergoes translation into the body-based coordinates necessary for planning the next movement in a navigational sequence.

Calton and Taube (2009) went even further. According to them, PPC may manipulate with space as we manipulate with objects. PPC integrates the perception of space in the immediate vicinity (i.e. spatial orientation) with more distant spatial

representations, both of them provided by place cells and the path integration system. Thus, a part of the cognitive mapping system resides in PPC. Then the signal may be combined with neocortically generated signals (both spatial and non-spatial) in order to accurately formulate a route to the goal (so-called route planning), or at least the heading of immediate path (trajectory planning).

On the contrary, Nitz (2009) underscored the ability of PPC to code information in any arbitrary frame of reference. Since rodents often limit their locomotion to several regularly visited routes only, PPC allows for constructing route-centered representation (Nitz, 2006). The hippocampus may then restrict utilization of behavioral sequences linked to such route-based representation to relevant places only. Projections to secondary sensory and motor cortices as well as superior colliculus could serve as a unifying framework for activity within these structures so that the detection of navigation-relevant cues and the timing of locomotor actions are optimized. As a result, PPC activity would have a great impact on an animal's ability to quickly move in an uninterrupted fashion along a complex path.

In more general terms, Kesner (2009) defines the role of PPC as a structure involved in perceptual and long-term spatial memory.

4.3.5 Parieto-hippocampal dialogues

Since a mutual relationship between the hippocampal complex and PPC is the critical point in most of the assumptions, the cooperation of these brain sites has been tested in more detail. In the most parsimonious view, both structures might contribute to spatial knowledge in parallel, or they may work in series. To test this hypothesis, Rogers and Kesner (2007) made unilateral lesions of hippocampus and PPC, located either ipsilaterally or contralaterally to each other, and examined their impact on an array of spatial tasks known to be dependent on functional integrity of both structures. An assumption made is that the right and left hemispheres operate in parallel. If the cooperation between hippocampus and PPC does take place, then disrupted

performance after contralateral (but much less severe after ipsilateral) ablations should occur. Indeed, in the majority of tasks (object-place paired-associate learning, dry-land water maze task) the crossed lesions produced significant spatial deficits while processes known to be independent on PPC or hippocampus such as single discriminations of places or objects were unaffected. This ruled out a non-specific impairment due to the lesion.

Another approach employed by Save et al. (2005) examined an effect of bilateral thermocoagulation lesions on place cell activity. On a circular arena with a curtain obscuring distal visual cues, and with three salient objects placed intra-maze at the periphery, they found near-identical place cell characteristics in control and lesioned rats. Nevertheless, firing fields of lesioned rats (unlike that of controls) did not follow the ninety-degrees rotation (carried out in the absence of the rat) of the arena. Furthermore, removal of the objects (in the presence of the rat) was not accompanied by preserved position of firing fields controlled by idiothetic input; rather they became aligned according to unintentional distal cues. This study thus confirmed a close cooperation between PPC and hippocampus, and emphasized the role of PPC in processing of proximal space-related spatial information.

4.3.6 PPC and head-direction cells

As it is reasonable to expect that lesions to PPC may also affect the HD system, neurons from anterodorsal thalamic nucleus were recorded in case of bilateral PPC lesions (Calton et al., 2008). Likewise, their electrophysiological characteristics (peak and background firing rate, signal-to-noise ratio, directional firing range, directional information content and anticipatory time intervals) remained unaffected. Moreover, despite the lesions, they could still be controlled by a directional visual landmark (a cue card attached to a wall). Likewise, they preserved heading while the animal locomoted from a familiar into an unknown enclosure, suggesting unimpaired control by idiothesis.

4.4 Role of rodent PPC in dissociated environments

Despite many theories suggested, their common feature in both primates and rats points to the fact that PPC acts as a translator between various reference frames (Save et al., 1998; Save and Poucet, 2009; Nitz, 2009; Calton and Taube, 2009; Cohen and Andersen, 2002). In non-stationary environments, this function might even be emphasized. Since healthy rats are capable to simultaneously maintain two separate spatial representations, each anchored to a different reference frame, a role of PPC during this process (besides the well-known hippocampal-dependence) is just prompting. The failure of rotating the intramaze objects to elicit a corresponding rotation of firing fields in rats with bilateral PPC lesion (Save et al., 2005) suggests the involvement of PPC in modulating the proximal space-based reference frame. Unfortunately, this is the only observation made in dissociated environments.

Since retrosplenial cortex (RSC) receives dense input from PPC, and is believed to act as a switch for a PPC signal being conveyed towards hippocampus (and vice versa), a study of (Wesierska et al., 2009) provides some clues on the putative PPC function in dealing with non-stationary environments. They used several variants of place avoidance task to examine RSC lesion. The operated rats performed well on the arena frame task, suggesting they had no difficulty to represent proximal space. Furthermore, they displayed no impairment in the room frame task variant, when they were presented with distal room cues only. They were, however, impaired, when both proximal and distal spatial information was brought into conflict by rotating the arena in light, and only distal information become relevant for solving the task (= AAPA variant), indicating RSC plays a role in cognitive segregation. These results suggest that RSC is incorporated into a network segregating spatial information into independent coherent representations and assessing their relevance according to a given task. Therefore, at least this process would also occur in PPC. Moreover, a failure to detect deficit in arena frame does not necessarily imply that PPC does not carry that kind of representation. Instead, PPC might be the principal site feeding the intramaze relationship information

into the overall representation of the environment, as suggested in other experiments (Save and Poucet, 2000; Save et al., 1992; Rogers and Kesner, 2006; Save et al., 2005). The hippocampus itself, although arena-frame representation is reflected in it, is not crucial for performing the arena frame task, hence the putative structure must be located elsewhere in the brain.

Part II
Aims of the thesis

To develop a moving object-related spatial task

Rats have been demonstrated to maintain two mutually discordant yet coherent spatial representations, each anchored to a different frame of reference. However, substantially easier and more natural situations such as those representing spatial representations towards a moving object (predator, conspecific) have not been modeled yet under controlled laboratory conditions. This is rather surprising in the context of more than thirty years of intense research in the field of spatial learning and memory. We therefore attempted to modify the aversively-motivated place avoidance task so that the to-be-avoided sector will be centered onto a mobile “landmark” represented by another rat. Will a rat be able to continuously avoid a mobile object, represented by its conspecific? Such novel behavioral task would then allow for testing brain structures and mechanisms underlying the object-based avoidance behavior.

To assess the role of rotation (inertial stimuli) on place avoidance performance

The AAPA task has been employed in numerous pharmacological, genetical, lesion, or electrophysiological studies in the past decade. However, it remains unclear as to what specific spatial processes occur while solving the task. We addressed the question whether inertial stimuli arising from arena rotation represent a key component in the acquisition. We hence plan to compare an acquisition in a cue-controlled AAPA with a modified task in which the controlled extramaze cues will be rotating around a stationary arena with the punished sector defined with respect to the cues.

Role of posterior parietal cortex in a place avoidance task

The PPC has been proposed to participate in the transformation of spatial information between various reference frames in order to formulate a goal-directed locomotion. Thus, it is reasonable to expect its crucial involvement in constructing and maintaining an appropriate spatial representation according to any arbitrary frame of reference. Since PPC has been suggested to be crucial for path integration and

processing information from near space, we will examine the effect of PPC bilateral lesions on acquisition of the arena frame variant of the place avoidance task. Furthermore, the AAPA variant encompasses segregation of spatial information into irrelevant arena-based and relevant room-based. This segregation might be also reasonably expected to be processed in PPC. Thus, the PPC lesion of PPC will also be examined in the AAPA variant.

Part III

Inserted reprints

- Telensky P, **Svoboda J**, Pastalkova E, Blahna K, Bures J, Stuchlik A., 2009. Enemy avoidance task: a novel behavioral paradigm for assessing spatial avoidance of a moving subject. *J Neurosci Meth* 180 (1), 29-33.
- Telensky P, **Svoboda J**, Blahna K, Kubik S, Bures J, Stuchlik A. 2011. Functional inactivation of the rat hippocampus disrupts avoidance of a moving object. *Proc Natl Acad Sci USA*, accepted.
- Blahna K, **Svoboda J**, Telensky P, Klement D, 2010. Inertial stimuli generated by arena rotation are important for acquisition of the active place avoidance task. *Behav Brain Res* 216 (1), 207-213.
- **Svoboda J**, Telensky P, Blahna K, Zach P, Bures J, Stuchlik A, 2008. Lesion of posterior parietal cortex in rats does not disrupt place avoidance based on either distal or proximal orienting cues. *Neurosci Lett* 445 (1), 73-77.

Part IV
General discussion

Studies of spatial cognition in rodents have become a fruitful branch in neuroscience, providing insights into fundamental processes of spatial learning and memory and their neuronal substrate. A spatial layout of the environment is reflected in internal representations, formed by organized discharging of the neurons. In non-stationary environments, where coherent subsets of cues may move with respect to each other, rats are able to create multiple representations, each anchored to a reference frame formed by a particular stimuli subset (Siegel et al., 2008; Shapiro et al., 1997; Renaudineau et al., 2007; Gothard et al., 1996a, b). These multiple representations can be expressed even simultaneously, e.g. on a continuously rotating arena (Zinyuk et al., 2000; Kelemen and Fenton, 2010; Fenton et al., 1998).

In the present thesis, we demonstrated that rats are capable to organize their spatial behavior with respect to a single non-stationary object. We introduced a novel behavioral task (Telensky et al., 2009) in which a rat was foraging for pasta pellets on a circular arena while continuously maintaining a safety distance from the other rat (“enemy”); whenever the mutual distance between the two rats dropped below 25cm, the subject rat was punished by a mild electric foot-shock. We found that, in spite of considerable unpredictability of the enemy's locomotion, the subject rats significantly reduced number of entrances into the punished zone from approximately 65 to 15, after 16 training sessions. A detailed analysis of the avoidance behavior revealed that the subjects adopted a strategy to stay close to the apparatus wall (thigmotaxis), thus minimizing the probability of the enemy encounter. However, when the enemy approached close enough, the subjects chose a spatially appropriate escape route. The situations leading to shocks were caused by an active locomotion of the enemy, not by the subject. In particular, they occurred when the enemy rapidly approached the subject.

This experiment clearly demonstrates that a continuously moving navigationally relevant intramaze object may gain control over the subject's spatial behavior. Thus, we do not confirm data that unstable proximal yet navigationally relevant landmarks cannot gain such a control (Biegler and Morris, 1993), or that the control is only possible after

an intense training (Collett et al., 1986; Biegler and Morris, 1996). The essential issue concerns the way the moving object is represented in the brain with respect to the environment. Both electrophysiological evidence from monkeys and observation of neglect patients demonstrate that the brain possess the capability to build and retain object-centered spatial representations (Olson and Gettner, 1995; Olson and Gettner, 1996). Up to date, the only attempt to find such a neural correlate in rat hippocampus, a structure implicated in spatial representational processes in rodents (Nadel and O'Keefe, 1978), failed to identify a coherently framed object-related activity recorded from CA1 neurons; the rats were trained to maintain a certain distance from a mobile remote-controlled toy (car) in order to get reward delivered by intracranial stimulation (Ho et al., 2008). This study may have inadvertently stressed the important issue of the task motivations. Whereas the above experiments used intramaze cues associated with a positive reinforcement, our task is aversive in nature. As we can imagine, most natural situations in which an animal encounters moving stimuli is rather aversive (predator attack), particularly in rodents. We can thus expect that a brain is pre-wired to be employed preferentially in representations of moving objects that act as threatening stimuli (predator silhouettes, odors) or are associated with an aversive stimulus. In laboratory conditions, presentation of moving intramaze threatening object reliably elicits a properly oriented escape reaction (Ellard and Eller, 2009).

To make our task more feasible, we replaced the enemy rat with a programmable robot which allowed making the path of the “enemy” object more predictable. We found that within the same experimental design, the rats displayed a faster decrease of the shocks received and reached the asymptotic level of learning already after five 20min sessions (Telensky et al, 2011). Although this setup led to a rapid acquisition, suggesting only moderate requirements on the continuous avoidance behavior, bilateral inactivation of dorsal hippocampus by sodium channel blocker tetrodotoxin severely disrupted the performance which was restored next day when only saline was injected into the hippocampi. This demonstrated that the process of maintaining a safety distance, and both temporary and spatially organizing the escape

route when the "enemy" object is approaching substantially depends on functional integrity of dorsal hippocampus. Such a finding is in contrast with a failure to detect in this brain site any neural correlates of representation to a moving, navigationally-relevant intramaze object (Ho et al., 2008). Furthermore, this experiment revealed that avoidance of a stationary object is hippocampus-independent, a finding that is in accord with other experiments that demonstrated preserved egocentric distance estimation after hippocampal damage (Long and Kesner, 1998). This finding is even more convincing if we take into account the fact that the object was experienced as non-stationary throughout the training (its position was changing in the middle of each training session) and was even dislocated once during the TTX session. Taken together, these data suggest that a spatially relevant (at least aversively-associated) moving object should be encoded within hippocampal representational system. It therefore remains questionable and so far highly speculative as to whether moving object indeed constitutes its own reference frame or is incorporated as a dynamic cue within the framework of inertial (geo-based) reference frame. Several studies have demonstrated that hippocampus possesses the capability of encoding position of the animal with respect to an object that moves from trial to trial besides the representation of the stationary world (Gothard et al., 1996a, b).

Other parts of the thesis dealt with a different type of non-stationary environment. If a substantial part of the environment moves with relative to the rest, a previously concordant spatial layout is dissociated into separate reference frames. This situation is for example modeled in the AAPA task (Fenton et al., 1998). One of the aims of the thesis was to determine whether perceiving an inertial instability supports navigation in AAPA. In the standard version of the task, the rats placed on a slowly rotating arena must avoid a sector which remains stable relative to stationary surroundings. In the modified version, the situation is inversed. Rats are placed on a stationary arena and must avoid a sector bound to surrounding cues slowly rotating around the arena. Rats were not able (except for one) to solve the modified version unless they were pre-trained in the standard version of the task (Blahna et al., 2011).

Contrary to the first set of experiments, we report that rats are not readily able to avoid an unmarked place defined by moving cues. However, in this case, the cues were represented by extramaze cue cards attached to a curtain beyond the arena perimeter. This is an important finding as many studies have shown that distal cues control firing of both HD cells and place cells (Muller and Kubie, 1987; Taube et al., 1990). However, the orienting system is primarily based on the idiothetic input (Taube, 1998; Taube, 2007). Thus a rat may be continuously assessing to as which cues are unstable relative to the inertial reference frame. If they are evaluated as unstable, their control over the representational alignment disappears (Jeffery, 1998). Furthermore, the inertial stimuli may keep the animal attentive (Smith et al., 2010). Attention is a prerequisite for a proper implementation of perceived cues into a map-like representation (Hardt and Nadel, 2009). In order to specify the relative contribution of inertial stimuli, additional experiments must be carried out. The observed distinction between standard and modified AAPA task provides a promising tool for clarifying the role of perceived instability on rat's spatial behavior or its neural correlates. So far, studies in this field have not examined the effect of continuous rotating either the distal cue or the arena itself (Sharp et al., 1995; Jeffery, 1998).

Next aim of the thesis focused on elucidating the role of the PPC in arena-based or room-based reference frame navigation. Rats were first trained in AF+ variant of the place avoidance task. Both lesioned and control rats successfully learned to avoid the prohibited sector in darkness while searching for randomly scattered barley grains (Svoboda et al., 2008). PPC lesions usually disrupt idiothetic navigation (Save et al., 2001; Moghaddam and Bures, 1996) or allothetic navigation based on intramaze cues (Save and Poucet, 2000), both of which are crucial in solving AF+ task. In most of the cases, however, the authors claim that instead of the overall inability to locate a goal the parietal operates displayed inaccurate trajectories towards it. The to-be-avoided sector in place avoidance occupies a substantial amount of arena surface, so the rat does not have to be so precise to locate it. Thus, consistently with other studies (Kesner et al., 1989; Long and Kesner, 1996; Long and Kesner, 1998), we provide an evidence

that PPC dysfunction does not disable simple allocentric or egocentric processing that do not tax accurate goal-directed behavior (Svoboda et al., 2008). Furthermore, we demonstrated that parietal rats can even acquire AAPA version as well as control, a surprising finding in context of disrupted cognitive coordination in retrosplenial cortex lesioned rats (Wesierska et al., 2009). Thus it appears that cognitive coordination, a process dependent on functionality of both hippocampi (Cimadevilla et al., 2001), is mediated only up to one synapse before PPC.

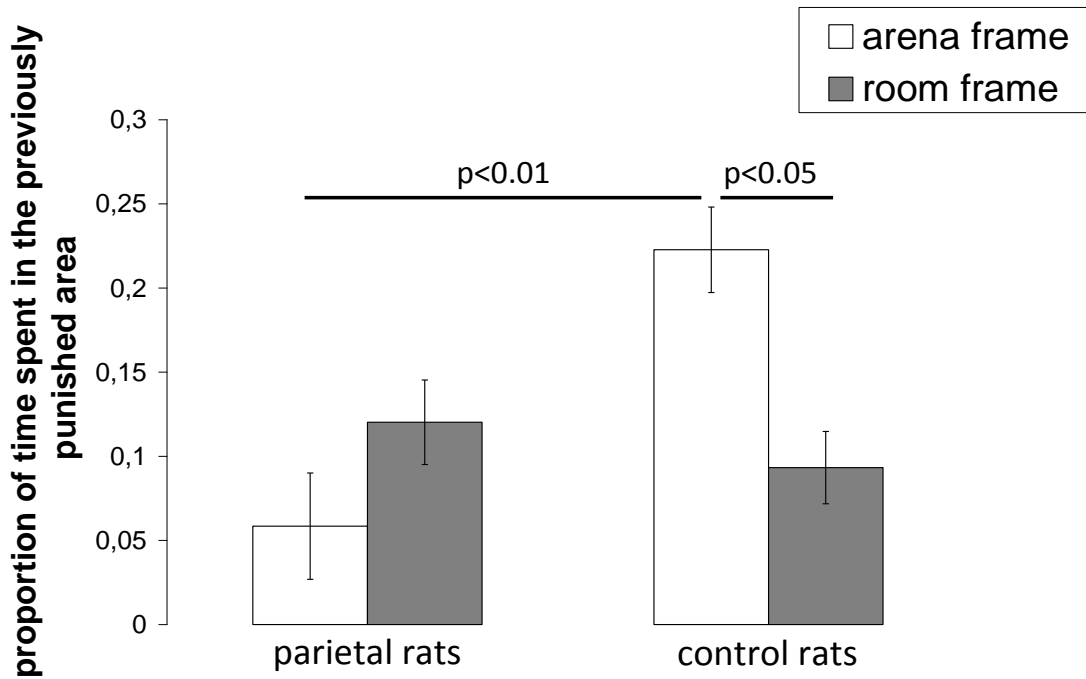


Fig. 11. Differences in occupancy of a previously punished area in parietal and control rats during an extinction session in a "preferential challenge" session. Control rats stopped avoiding a sector defined in arena frame and spent in it an amount of time approx. corresponding to chance value (0.25) while still displaying avoidance in the room frame. PPC lesioned rats, however, were displaying preserved avoidance in both frames, stronger in the arena frame.

To further investigate the role of PPC we assessed its contribution during a "preferential challenge". We trained both sham operated (n=8) and PPC lesioned (n=8) rats to search for barley grains in seven 20min session on a stable arena in light. The

punished sector remained stationary and both arena frame and room frame constituted one concordant frame of reference. Both groups displayed an equally rapid acquisition of the task. In session 8, after ten minutes of standard avoidance, the arena started to rotate and the shock-delivery device was switched off. The previously overlapping reference frames therefore dissociated, leaving the rat with no feedback for the rat as to which reference frame it should expect to be the prohibited sector. We measured the time a rat spent in arena- or room-related places to which the putative sector dissociated (fig. 11). Control rats demonstrated preserved avoidance in room frame but not in arena frame, which is in accord with a long-held notion that distal cues dominate over proximal ones in spatial representations (Save and Poucet, 2000; Zugaro et al., 2001; Cressant et al., 1997). To the contrary, parietal rats rather maintained their avoidance behavior in both frames simultaneously. These results support our previous finding that a PPC lesion does not prevent the rat from locating a goal either in relation to arena cues or room cues. However, they clearly demonstrate that PPC modulates the relative weight assigned to the room reference frame. To sum up, although PPC is implicated in translations between egocentric and allocentric coordinates, and presumably also in other coordinate systems (Save et al., 1998; Burgess, 2008; Nitz, 2006; Nitz, 2009) we found that it is not necessary for encoding and maintaining a spatial representation related to arena frame or room frame. Rather it plays a marginal role during their coordination, minor enough to be insignificant in AAPA where arena frame navigation is suppressed.

Although lesioning techniques were found to be a useful tool for elucidating the contribution of a particular brain structure or pathway to spatial learning and memory, their utilization is limited. The results should be interpreted with care as standard procedures do not examine in detail a secondary degeneration around the lesion site itself. Likewise, we are completely unaware as to what reorganization processes might occur in impacted networks.

Also one ought to note that, as already discussed in the Introduction, the lesioning techniques and PPC lesion sites vary greatly between research groups despite

the fact that PPC area has been delineated quite rigorously (Reep et al., 1994; Reep and Corwin, 2009). Our approach was to lesion an area which is common for nearly all of the PPC experiments found so far in literature. However, the lesion is apparently not limited to PPC and extends beyond its borders, particularly in the rostral direction. In spite of that, for the sake of a nomenclature, we keep labeling it “PPC lesion”.

Part V
Conclusion

Rats are capable of organizing their spatial behavior in non-stationary environments with regard to multiple reference frames, specifically:

1. We developed a behavioral task that introduces a navigationally relevant moving object as a potential source of a new reference frame. Rats demonstrated their capability to adopt a successful distance-based avoidance behavior, with learning becoming more rapid when the trajectory of the moving object was more predictable. This capability, however, requires intact dorsal hippocampus.

2. Although we demonstrated that rats do utilize continuously moving cues for locating a directly unperceivable "punished" area, we furthermore revealed that, surprisingly, such cues exert hardly any control over navigation in place avoidance paradigm, unless the rats are provided with inertial stimuli during acquisition, indicative of instability of their environment. Once acquired, the cues controlled the spatial behavior reliably, in spite of restored stability of the inner environment.

3. The posterior parietal cortex (PPC) plays neither a significant role in navigation based on non-visual intramaze cues, nor in the process of cognitive segregation leading to navigation by extramaze allothetic cues. However, PPC appears to be important for the development of preference for distal cues in navigation, a process quite common in healthy rats.

References

Aggleton, J. P., Kyd, R. J., Bilkey, D. K., 2004. When is the perirhinal cortex necessary for the performance of spatial memory tasks? *Neurosci Biobehav Rev* 28 (6), 611–624.

Andersen, R. A., Buneo, C. A., 2002. Intentional maps in posterior parietal cortex. *Annu Rev Neurosci* 25, 189–220.

Balint, R., 1909. Paralysis of the soul "blindness", optic ataxia, spatial disorder of attention. *Monatsschrift fur Psychiatrie und Neurologie* 25, 51–81.

Barnes, C. A., 1979. Memory deficits associated with senescence: A neurophysiological and behavioral-study in the rat. *J Comp Physiol Psychol* 93 (1), 74–104.

Benhamou, S., Poucet, B., 1998. Landmark use by navigating rats (*Rattus norvegicus*): Contrasting geometric and featural information. *J Comp Psychol* 112 (3), 317–322.

Biegler, R., Morris, R. G. M., 1993. Landmark stability is a prerequisite for spatial but not discrimination-learning. *Nature* 361 (6413), 631–633.

Biegler, R., Morris, R. G. M., 1996. Landmark stability: Studies exploring whether the perceived stability of the environment influences spatial representation. *J Exp Biol* 199 (1), 187–193.

Bird, C. M., Burgess, N., 2008. The hippocampus and memory: insights from spatial processing. *Nat Rev Neurosci* 9 (3), 182–194.

Bisiach, E., Luzzatti, C., 1978. Unilateral neglect of representational space. *Cortex* 14 (1), 129–133.

Bischofberger, J., Engel, D., Frotscher, M., Jonas, P., 2006. Timing and efficacy of transmitter release at mossy fiber synapses in the hippocampal network. *Pflugers Arch* 453 (3), 361–372.

Blahna, K., Svoboda, J., Telensky, P., Klement, D., 2010. Inertial stimuli generated by arena rotation are important for acquisition of the active place avoidance task. *Behav Brain Res* 216 (1), 207–213.

Bouffard, J. P., Jarrard, L. E., 1988. Acquisition of a complex place task in rats with selective ibotenate lesions of hippocampal formation: combined lesions of subiculum and entorhinal cortex versus hippocampus. *Behav Neurosci* 102 (6), 828–834.

- Bubenikova-Valesova, V., Stuchlik, A., Svoboda, J., Bures, J., Vales, K., 2008. Risperidone and ritanserin but not haloperidol block effect of dizocilpine on the active allothetic place avoidance task. *Proc Natl Acad Sci USA* 105 (3), 1061–1066.
- Bucci, D. J., Holland, P. C., Gallagher, M., 1998. Removal of cholinergic input to rat posterior parietal cortex disrupts incremental processing of conditioned stimuli. *J Neurosci* 18 (19), 8038–8046.
- Bures, J., Fenton, A. A., Kaminsky, Y., Rossier, J., Sacchetti, B., Zinyuk, L., 1997a. Dissociation of exteroceptive and idiothetic orientation cues: effect on hippocampal place cells and place navigation. *Philos Trans R Soc Lond B Biol Sci* 352 (1360), 1515–1524.
- Bures, J., Fenton, A. A., Kaminsky, Y., Zinyuk, L., 1997b. Place cells and place navigation. *Proc Natl Acad Sci USA* 94 (1), 343–350.
- Burgess, N., 2008. Spatial cognition and the brain. Vol. 1124 of *Ann N Y Acad Sci*. pp. 77–97.
- Burwell, R. D., Amaral, D. G., 1998. Perirhinal and postrhinal cortices of the rat: Interconnectivity and connections with the entorhinal cortex. *J Comp Neurol* 391 (3), 293–321.
- Burwell, R. D., Saddoris, M. P., Bucci, D. J., Wiig, K. A., 2004. Corticohippocampal contributions to spatial and contextual learning. *J Neurosci* 24 (15), 3826–3836.
- Bussey, T. J., Muir, J. L., Aggleton, J. P., 1999. Functionally dissociating aspects of event memory: The effects of combined perirhinal and postrhinal cortex lesions on object and place memory in the rat. *J Neurosci* 19 (1), 495–502.
- Cabeza, R., Ciaramelli, E., Olson, I. R., Moscovitch, M., 2008. The parietal cortex and episodic memory: an attentional account. *Nat Rev Neurosci* 9 (8), 613–625.
- Calton, J. L., Taube, J. S., 2009. Where am I and how will I get there from here? A role for posterior parietal cortex in the integration of spatial information and route planning. *Neurobiol Learn Mem* 91 (2), 186–196.
- Calton, J. L., Turner, C. S., Cyrenne, D.-L. M., Lee, B. R., Taube, J. S., 2008. Landmark control and updating of self-movement cues are largely maintained in head direction cells after lesions of the posterior parietal cortex. *Behav Neurosci* 122 (4), 827–840.
- Chandler, H. C., King, V., Corwin, J. V., Reep, R. L., 1992. Thalamocortical connections of rat posterior parietal cortex. *Neurosci Lett* 143 (1-2), 237–242.

- Chen, L. L., Lin, L. H., Barnes, C. A., McNaughton, B. L., 1994a. Head-direction cells in the rat posterior cortex. 2. contributions of visual and ideothetic information to the directional firing. *Exp Brain Res* 101 (1), 24–34.
- Chen, L. L., Lin, L. H., Green, E. J., Barnes, C. A., McNaughton, B. L., 1994b. Head-direction cells in the rat posterior cortex. 1. anatomical distribution and behavioral modulation. *Exp Brain Res* 101 (1), 8–23.
- Chen, L. T. L., Nakamura, K., 1998. Head-centered representation and spatial memory in rat posterior parietal cortex. *Psychobiology* 26 (2), 119–127.
- Cheng, K., 1986. A purely geometric module in the rats spatial representation. *Cognition* 23 (2), 149–178.
- Cheng, K., 2008. Whither geometry? Troubles of the geometric module. *Trends Cogn Sci* 12 (9), 355–361.
- Cho, J. W., Sharp, P. E., 2001. Head direction, place, and movement correlates for cells in the rat retrosplenial cortex. *Behav Neurosci* 115 (1), 3–25.
- Cimadevilla, J. M., Fenton, A. A., Bures, J., 2000. Functional inactivation of dorsal hippocampus impairs active place avoidance in rats. *Neurosci Lett* 285 (1), 53–56.
- Cimadevilla, J. M., Wesierska, M., Fenton, A. A., Bures, J., 2001. Inactivating one hippocampus impairs avoidance of a stable room-defined place during dissociation of arena cues from room cues by rotation of the arena. *Proc Natl Acad Sci USA* 98 (6), 3531–3536.
- Cohen, Y. E., Andersen, R. A., 2002. A common reference frame for movement plans in the posterior parietal cortex. *Nat Rev Neurosci* 3 (7), 553–562.
- Collett, T. S., Cartwright, B. A., Smith, B. A., 1986. Landmark learning and visuospatial memories in gerbils. *J Comp Physiol A* 158 (6), 835–851.
- Compton, D. M., Griffith, H. R., McDaniel, W. F., Foster, R. A., Davis, B. K., 1997. The flexible use of multiple cue relationships in spatial navigation: A comparison of water maze performance following hippocampal, medial septal, prefrontal cortex, or posterior parietal cortex lesions. *Neurobiol Learn Mem* 68 (2), 117–132.
- Cressant, A., Muller, R. U., Poucet, B., 1997. Failure of centrally placed objects to control the firing fields of hippocampal place cells. *J Neurosci* 17 (7), 2531–2542.
- Crowne, D. P., Mah, L. W., 1998. A comparison of hemispatial neglect from posterior parietal and periarculate lesions in the monkey. *Psychobiology* 26 (2), 103–108.

- Culham, J. C., Valyear, K. F., 2006. Human parietal cortex in action. *Curr Opin Neurobiol* 16 (2), 205–212.
- de Bruin, J. P. C., Moita, M. P., de Brabander, H. M., Joosten, R., 2001. Place and response learning of rats in a morris water maze: Differential effects of fimbria fornix and medial prefrontal cortex lesions. *Neurobiol Learn Mem* 75 (2), 164–178.
- Dimattia, B. D., Kesner, R. P., 1988. Spatial cognitive maps - differential role of parietal cortex and hippocampal formation. *Behav Neurosci* 102 (4), 471–480.
- Eichenbaum, H., Otto, T., Cohen, N. J., 1994. Two functional components of the hippocampal memory system. *Behav Brain Sci* 17 (3), 449–472.
- Eichenbaum, H., Stewart, C., Morris, R. G. M., 1990. Hippocampal representation in place learning. *J Neurosci* 10 (11), 3531–3542.
- Ellard, C. G., Eller, M. C., 2009. Spatial cognition in the gerbil: computing optimal escape routes from visual threats. *Anim Cogn* 12 (2), 333–345.
- Ennaceur, A., Aggleton, J. P., 1997. The effects of neurotoxic lesions of the perirhinal cortex combined to fornix transection on object recognition memory in the rat. *Behav Brain Res* 88 (2), 181–193.
- Ennaceur, A., Neave, N., Aggleton, J. P., 1996. Neurotoxic lesions of the perirhinal cortex do not mimic the behavioural effects of fornix transection in the rat. *Behav Brain Res* 80 (1-2), 9–25.
- Etienne, A. S., Jeffery, K. J., 2004. Path integration in mammals. *Hippocampus* 14 (2), 180–192.
- Etienne, A. S., Maurer, R., Seguinot, V., 1996. Path integration In mammals and its interaction with visual landmarks. *J Exp Biol* 199 (1), 201–209.
- Fanselow, M. S., Dong, H. W., 2010. Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron* 65 (1), 7–19.
- Fenton, A. A., Wesierska, M., Kaminsky, Y., Bures, J., 1998. Both here and there: Simultaneous expression of autonomous spatial memories in rats. *Proc Natl Acad Sci USA* 95 (19), 11493–11498.
- Ferino, F., Thierry, A. M., Glowinski, J., 1987. Anatomical and electrophysiological evidence for a direct projection from ammons horn to the medial prefrontal cortex in the rat. *Exp Brain Res* 65 (2), 421–426.

- Foster, T. C., Castro, C. A., McNaughton, B. L., 1989. Spatial selectivity of rat hippocampal neurons: dependence on preparedness for movement. *Science* 244 (4912), 1580–1582.
- Frankland, P. W., Bontempi, B., 2005. The organization of recent and remote memories. *Nat Rev Neurosci* 6 (2), 119–130.
- Giannetti, S., Molinari, M., 2002. Cerebellar input to the posterior parietal cortex in the rat. *Brain Res Bull* 58 (5), 481–489.
- Goodale, M. A., Milner, A. D., 1992. Separate visual pathways for perception and action. *Trends Neurosci* 15 (1), 20–25.
- Goodrich-Hunsaker, N. J., Hunsaker, M. R., Kesner, R. P., 2005. Dissociating the role of the parietal cortex and dorsal hippocampus for spatial information processing. *Behav Neurosci* 119 (5), 1307–1315.
- Gothard, K. M., Skaggs, W. E., McNaughton, B. L., 1996a. Dynamics of mismatch correction in the hippocampal ensemble code for space: Interaction between path integration and environmental cues. *J Neurosci* 16 (24), 8027–8040.
- Gothard, K. M., Skaggs, W. E., Moore, K. M., McNaughton, B. L., 1996b. Binding of hippocampal CA1 neural activity to multiple reference frames in a landmark-based navigation task. *J Neurosci* 16 (2), 823–835.
- Hafting, T., Fyhn, M., Molden, S., Moser, M. B., Moser, E. I., 2005. Microstructure of a spatial map in the entorhinal cortex. *Nature* 436 (7052), 801–806.
- Hamilton, D. A., Akers, K. G., Johnson, T. E., Rice, J. P., Candelaria, F. T., Redhead, E. S., 2009. Evidence for a shift from place navigation to directional responding in one variant of the Morris water task. *J Exp Psychol Anim B* 35 (2), 271–278.
- Hamilton, D. A., Akers, K. G., Johnson, T. E., Rice, J. P., Candelaria, F. T., Sutherland, R. J., Weisend, M. P., Redhead, E. S., 2008. The relative influence of place and direction in the Morris water task. *J Exp Psychol Anim B* 34 (1), 31–53.
- Hamilton, D. A., Akers, K. G., Weisend, M. P., Sutherland, R. J., 2007. How do room and apparatus cues control navigation in the morris water task? Evidence for distinct contributions to a movement vector. *J Exp Psychol Anim B* 33 (2), 100–114.
- Hamilton, D. A., Sutherland, R. J., 1999. Blocking in human place learning: Evidence from virtual navigation. *Psychobiology* 27 (4), 453–461.
- Hardt, O., Nadel, L., 2009. Cognitive maps and attention. Vol. 176 of *Progress in Brain Research*. pp. 181–194.

- Ho, S. A., Hori, E., Kobayashi, T., Umeno, K., Tran, A. H., Ono, T., Nishijo, H., 2008. Hippocampal place cell activity during chasing of a moving object associated with reward in rats. *Neuroscience* 157 (1), 254–270.
- Hok, V., Save, E., Lenck-Santini, P. P., Poucet, B., 2005. Coding for spatial goals in the prelimbic/infralimbic area of the rat frontal cortex. *Proc Natl Acad Sci USA* 102 (12), 4602–4607.
- Husain, M., Nachev, P., 2007. Space and the parietal cortex. *Trends Cogn Sci* 11 (1), 30–36.
- Jarrard, L. E., 1993. On the role of the hippocampus in learning and memory in the rat. *Behav Neural Biol* 60 (1), 9–26.
- Jarrard, L. E., Davidson, T. L., Bowring, B., 2004. Functional differentiation within the medial temporal lobe in the rat. *Hippocampus* 14 (4), 434–449.
- Jeffery, K. J., 1998. Learning of landmark stability and instability by hippocampal place cells. *Neuropharmacology* 37 (4-5), 677–687.
- Jeffery, K. J., 2007a. Integration of the sensory inputs to place cells: What, where, why, and how? *Hippocampus* 17 (9), 775–785.
- Jeffery, K. J., 2007b. Self-localization and the entorhinal-hippocampal system. *Curr Opin Neurobiol* 17 (6), 684–691.
- Jeffery, K. J., Burgess, N., 2006. A metric for the cognitive map: Found at last? *Trends Cogn Sci* 10 (1), 1–3.
- Jeffery, K. J., Gilbert, A., Burton, S., Strudwick, A., 2003. Preserved performance in a hippocampal-dependent spatial task despite complete place cell remapping. *Hippocampus* 13 (2), 175–189.
- Jeltsch, H., Bertrand, F., Lazarus, C., Cassel, J. C., 2001. Cognitive performances and locomotor activity following dentate granule cell damage in rats: Role of lesion extent and type of memory tested. *Neurobiol Learn Mem* 76 (1), 81–105.
- Jo, Y. S., Park, E. H., Kim, I. H., Park, S. K., Kim, H., Kim, H. T., Choi, J. S., 2007. The medial prefrontal cortex is involved in spatial memory retrieval under partial-cue conditions. *J Neurosci* 27 (49), 13567–13578.
- Kelemen, E., Fenton, A. A., 2010. Dynamic grouping of hippocampal neural activity during cognitive control of two spatial frames. *PLoS Biol* 8 (6).
- Kesner, R. P., 2009. The posterior parietal cortex and long-term memory representation of spatial information. *Neurobiol Learn Mem* 91 (2), 197–206.

- Kesner, R. P., Farnsworth, G., Dimattia, B. V., 1989. Double dissociation of egocentric and allocentric space following medial prefrontal and parietal cortex lesions in the rat. *Behav Neurosci* 103 (5), 956–961.
- King, V. R., Corwin, J. V., 1992. Spatial deficits and hemispheric asymmetries in the rat following unilateral and bilateral lesions of posterior parietal or medial agranular cortex. *Behav Brain Res* 50 (1-2), 53–68.
- King, V. R., Corwin, J. V., 1993. Comparisons of hemi-inattention produced by unilateral lesions of the posterior parietal cortex or medial agranular prefrontal cortex in rats: neglect, extinction, and the role of stimulus distance. *Behav Brain Res* 54 (2), 117–131.
- Knierim, J. J., Rao, G., 2003. Distal landmarks and hippocampal place cells: Effects of relative translation versus rotation. *Hippocampus* 13 (5), 604–617.
- Kolb, B., Buhrmann, K., McDonald, R., Sutherland, R. J., 1994. Dissociation of the medial prefrontal, posterior parietal, and posterior temporal cortex for spatial navigation and recognition memory in the rat. *Cereb Cortex* 4 (6), 664–680.
- Kolb, B., Walkey, J., 1987. Behavioral and anatomical studies of the posterior parietal cortex in the rat. *Behav Brain Res* 23 (2), 127–145.
- Kubik, S., Fenton, A. A., 2005. Behavioral evidence that segregation and representation are dissociable hippocampal functions. *J Neurosci* 25 (40), 9205–9212.
- Kyd, R. J., Bilkey, D. K., 2003. Prefrontal cortex lesions modify the spatial properties of hippocampal place cells. *Cereb Cortex* 13 (5), 444–451.
- Lacroix, L., White, I., Feldon, J., 2002. Effect of excitotoxic lesions of rat medial prefrontal cortex on spatial memory. *Behav Brain Res* 133 (1), 69–81.
- Liu, P., Bilkey, D. K., 1998. Perirhinal cortex contributions to performance in the morris water maze. *Behav Neurosci* 112 (2), 304–315.
- Liu, P., Bilkey, D. K., 2001. The effect of excitotoxic lesions centered on the hippocampus or perirhinal cortex in object recognition and spatial memory tasks. *Behav Neurosci* 115 (1), 94–111.
- Liu, P., Bilkey, D. K., 2002. The effects of NMDA lesions centered on the postrhinal cortex on spatial memory tasks in the rat. *Behav Neurosci* 116 (5), 860–873.
- Long, J. M., Kesner, R. P., 1996. The effects of dorsal versus ventral hippocampal, total hippocampal, and parietal cortex lesions on memory for allocentric distance in rats. *Behav Neurosci* 110 (5), 922–932.

- Long, J. M., Kesner, R. P., 1998. Effects of hippocampal and parietal cortex lesions on memory for egocentric distance and spatial location information in rats. *Behav Neurosci* 112 (3), 480–495.
- Maaswinkel, H., Jarrard, L. E., Whishaw, I. Q., 1999. Hippocampectomized rats are impaired in homing by path integration. *Hippocampus* 9 (5), 553–561.
- Mackintosh, N., 2002. Do not ask whether they have a cognitive map, but how they find their way about. *Psicologica* 23, 165–185.
- Maddux, J. M., Kerfoot, E. C., Chatterjee, S., Holland, P. C., 2007. Dissociation of attention in learning and action: Effects of lesions of the amygdala central nucleus, medial prefrontal cortex, and posterior parietal cortex. *Behav Neurosci* 121 (1), 63–79.
- Markus, E., Qin, Y., Leonard, B., Skaggs, W., McNaughton, B. L., Barnes, C. A., 1995. Interactions between location and task affect the spatial and directional firing of hippocampal neurons. *J Neurosci* 15, 7079–7094.
- McNaughton, B. L., Battaglia, F. P., Jensen, O., Moser, E. I., Moser, M. B., 2006. Path integration and the neural basis of the 'cognitive map'. *Nat Rev Neurosci* 7 (8), 663–678.
- Mittelstaedt, M. L., Mittelstaedt, H., 1980. Homing by path integration in a mammal. *Naturwissenschaften* 67 (11), 566–567.
- Mogensen, J., Pedersen, T. K., Holm, S., Bang, L. E., 1995. Prefrontal cortical mediation of rats place learning in a modified water maze. *Brain Res Bull* 38 (5), 425–434.
- Moghaddam, M., Bures, J., 1996. Contribution of egocentric spatial memory to place navigation of rats in the morris water maze. *Behav Brain Res* 78 (2), 121–129.
- Morris, R. G. M., 1981. Spatial localization does not require the presence of local cues. *Learn Motiv* 12 (2), 239–260.
- Morris, R. G. M., Garrud, P., Rawlins, J. N. P., O'Keefe, J., 1982. Place navigation impaired in rats with hippocampal-lesions. *Nature* 297 (5868), 681–683.
- Moser, E., Moser, M. B., Andersen, P., 1993. Spatial-learning impairment parallels the magnitude of dorsal hippocampal-lesions, but is hardly present following ventral lesions. *J Neurosci* 13 (9), 3916–3925.
- Moser, M. B., Moser, E. I., 1998. Functional differentiation in the hippocampus. *Hippocampus* 8 (6), 608–619.
- Muller, R. U., Kubie, J. L., 1987. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *J Neurosci* 7 (7), 1951–1968.

- Nadel, L., Moscovitch, M., 1997. Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr Opin Neurobiol* 7 (2), 217–227.
- Nadel, L., O'Keefe, J., 1978. *Hippocampus as a cognitive map*. Oxford University Press, Oxford.
- Nakamura, K., 1999. Auditory spatial discriminatory and mnemonic neurons in rat posterior parietal cortex. *J Neurophysiol* 82 (5), 2503–2517.
- Nakazawa, K., Quirk, M. C., Chitwood, R. A., Watanabe, M., Yeckel, M. F., Sun, L. D., Kato, A., Carr, C. A., Johnston, D., Wilson, M. A., Tonegawa, S., 2002. Requirement for hippocampal CA3 NMDA receptors in associative memory recall. *Science* 297 (5579), 211–218.
- Nerad, L., Liu, P., Bilkey, D. K., 2009. Bilateral NMDA lesions centered on the postrhinal cortex have minimal effects on hippocampal place cell firing. *Hippocampus* 19 (3), 221–227.
- Nitz, D., 2009. Parietal cortex, navigation, and the construction of arbitrary reference frames for spatial information. *Neurobiol Learn Mem* 91 (2), 179–185.
- Nitz, D. A., 2006. Tracking route progression in the posterior parietal cortex. *Neuron* 49 (5), 747–756.
- O'Keefe, J., Burgess, N., 1996. Geometric determinants of the place fields of hippocampal neurons. *Nature* 381, 425–428.
- O'Keefe, J., Dostrovsky, J., 1971. Hippocampus as a spatial map. Preliminary evidence from unit activity in freely-moving rat. *Brain Res* 34 (1), 171–177.
- Olson, C. R., Gettner, S. N., 1995. Object-centered direction selectivity in the macaque supplementary eye field. *Science* 269 (5226), 985–988.
- Olson, C. R., Gettner, S. N., 1996. Brain representation of object-centered space. *Curr Opin Neurobiol* 6 (2), 165–170.
- Olson, I. R., Berryhill, M., 2009. Some surprising findings on the involvement of the parietal lobe in human memory. *Neurobiol Learn Mem* 91 (2), 155–165.
- Olton, D. S., Samuelson, R. J., 1976. Remembrance of places passed - spatial memory in rats. *J Exp Psychol Anim B* 2 (2), 97–116.
- O'Reilly, R. C., McClelland, J. L., 1994. Hippocampal conjunctive encoding, storage, and recall: avoiding a trade-off. *Hippocampus* 4 (6), 661–682.

- Packard, M. G., McGaugh, J. L., 1996. Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiol Learn Mem* 65 (1), 65–72.
- Palomero-Gallagher, N., Zilles, K., 2004. *Isocortex*. Elsevier Academic Press, San Diego, pp. 729–757.
- Parron, C., Poucet, B., Save, E., 2001. Re-evaluation of the spatial memory deficits induced by hippocampal short lasting inactivation reveals the need for cortical co-operation. *Behav Brain Res* 127 (1-2), 71–79.
- Parron, C., Save, E., 2004. Evidence for entorhinal and parietal cortices involvement in path integration in the rat. *Exp Brain Res* 159 (3), 349–359.
- Pearce, J. M., Roberts, A. D. L., Good, M., 1998. Hippocampal lesions disrupt navigation based on cognitive maps but not heading vectors. *Nature* 396 (6706), 75–77.
- Phillips, W. A., Silverstein, S. M., 2003. Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behav Brain Sci* 26 (1), 65–+.
- Pothuizen, H. H. J., Aggleton, J. P., Vann, S. D., 2008. Do rats with retrosplenial cortex lesions lack direction? *Eur J Neurosci* 28 (12), 2486–2498.
- Ragozzino, M. E., 2007. The contribution of the medial prefrontal cortex, orbitofrontal cortex, and dorsomedial striatum to behavioral flexibility. Vol. 1121 of *Ann N Y Acad Sci*. pp. 355–375.
- Rawson, T., O’Kane, M., Talk, A., 2010. The medial prefrontal cortex and memory of cue location in the rat. *Neurobiol Learn Mem* 93 (1), 132–136.
- Reep, R. L., Chandler, H. C., King, V., Corwin, J. V., 1994. Rat posterior parietal cortex: topography of corticocortical and thalamic connections. *Exp Brain Res* 100 (1), 67–84.
- Reep, R. L., Corwin, J. V., 2009. Posterior parietal cortex as part of a neural network for directed attention in rats. *Neurobiol Learn Mem* 91 (2), 104–113.
- Reep, R. L., Corwin, J. V., Cheatwood, J. L., Van Vleet, T. M., Heilman, K. M., Watson, R. T., 2004. A rodent model for investigating the neurobiology of contralateral neglect. *Cogn Behav Neurol* 17 (4), 191–194.
- Renaudineau, S., Poucet, B., Save, E., 2007. Flexible use of proximal objects and distal cues by hippocampal place cells. *Hippocampus* 17 (5), 381–395.
- Riedel, G., Micheau, J., Lam, A. G. M., Roloff, E. V., Martin, S. J., Bridge, H., de Hoz, L., Poeschel, B., McCulloch, J., Morris, R. G. M., 1999. Reversible neural inactivation reveals hippocampal participation in several memory processes. *Nat Neurosci* 2 (10), 898–905.

- Rogers, J. L., Kesner, R. P., 2006. Lesions of the dorsal hippocampus or parietal cortex differentially affect spatial information processing. *Behav Neurosci* 120 (4), 852–860.
- Rogers, J. L., Kesner, R. P., 2007. Hippocampal-parietal cortex interactions: Evidence from a disconnection study in the rat. *Behav Brain Res* 179 (1), 19–27.
- Rossier, J., Kaminsky, Y., Schenk, F., Bures, J., 2000. The place preference task: A new tool for studying the relation between behavior and place cell activity in rats. *Behav Neurosci* 114 (2), 273–284.
- Rugg, M. D., Yonelinas, A. P., 2003. Human recognition memory: a cognitive neuroscience perspective. *Trends Cogn Sci* 7 (7), 313–319.
- Sanchez-Moreno, J., Rodrigo, T., Chamizo, V. D., MacKintosh, N. J., 1999. Overshadowing in the spatial domain. *Anim Learn Behav* 27 (4), 391–398.
- Sargolini, F., Fyhn, M., Hafting, T., McNaughton, B. L., Witter, M. P., Moser, M. B., Moser, E. I., 2006. Conjunctive representation of position, direction, and velocity in entorhinal cortex. *Science* 312 (5774), 758–762.
- Save, E., Buhot, M. C., Foreman, N., Thinusblanc, C., 1992a. Exploratory activity and response to a spatial change in rats with hippocampal or posterior parietal cortical lesions. *Behav Brain Res* 47 (2), 113–127.
- Save, E., Guazzelli, A., Poucet, B., 2001. Dissociation of the effects of bilateral lesions of the dorsal hippocampus and parietal cortex on path integration in the rat. *Behav Neurosci* 115 (6), 1212–1223.
- Save, E., Moghaddam, M., 1996. Effects of lesions of the associative parietal cortex on the acquisition and use of spatial memory in egocentric and allocentric navigation tasks in the rat. *Behav Neurosci* 110 (1), 74–85.
- Save, E., Paz-Villagran, V., Alexinsky, T., Poucet, B., 2005. Functional interaction between the associative parietal cortex and hippocampal place cell firing in the rat. *Eur J Neurosci* 21 (2), 522–530.
- Save, E., Poucet, B., 2000a. Hippocampal-parietal cortical interactions in spatial cognition. *Hippocampus* 10 (4), 491–499.
- Save, E., Poucet, B., 2000b. Involvement of the hippocampus and associative parietal cortex in the use of proximal and distal landmarks for navigation. *Behav Brain Res* 109 (2), 195–206.
- Save, E., Poucet, B., 2009. Role of the parietal cortex in long-term representation of spatial information in the rat. *Neurobiol Learn Mem* 91 (2), 172–178.

- Save, E., Poucet, B., Foreman, N., Buhot, M. C., 1992b. Object exploration and reactions to spatial and nonspatial changes in hooded rats following damage to parietal cortex or hippocampal-formation. *Behav Neurosci* 106 (3), 447–456.
- Save, E., Poucet, B., Foreman, N., Thinus-Blanc, C., 1998. The contribution of the associative parietal cortex and hippocampus to spatial processing in rodents. *Psychobiology* 26 (2), 153–161.
- Scoville, W. B., Milner, B., 1957. Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosur Ps* 20 (1), 11–21.
- Shapiro, M. L., Tanila, H., Eichenbaum, H., 1997. Cues that hippocampal place cells encode: Dynamic and hierarchical representation of local and distal stimuli. *Hippocampus* 7 (6), 624–642.
- Sharp, P. E., Blair, H. T., Etkin, D., Tzanetos, D. B., 1995. Influences of vestibular and visual-motion information on the spatial firing patterns of hippocampal place cells. *J Neurosci* 15 (1), 173–189.
- Siegel, J. J., Neunuebel, J. P., Knierim, J. J., 2008. Dominance of the proximal coordinate frame in determining the locations of hippocampal place cell activity during navigation. *J Neurophysiol* 99 (1), 60–76.
- Skaggs, W. E., McNaughton, B. L., 1998. Spatial firing properties of hippocampal CA1 populations in an environment containing two visually identical regions. *J Neurosci* 18 (20), 8455–8466.
- Smith, P. F., Darlington, C. L., Zheng, Y. W., 2010. Move it or lose it-is stimulation of the vestibular system necessary for normal spatial memory? *Hippocampus* 20 (1), 36–43.
- Snyder, L. H., Grieve, K. L., Brotchie, P., Andersen, R. A., 1998. Separate body- and world-referenced representations of visual space in parietal cortex. *Nature* 394 (6696), 887–891.
- Solstad, T., Boccara, C. N., Kropff, E., Moser, M. B., Moser, E. I., 2008. Representation of geometric borders in the entorhinal cortex. *Science* 322 (5909), 1865–1868.
- Squire, L. R., 1986. Mechanisms of memory. *Science* 232 (4758), 1612–1619.
- Stackman, R. W., Clark, A. S., Taube, J. S., 2002. Hippocampal spatial representations require vestibular input. *Hippocampus* 12 (3), 291–303.
- Stahlman, W. D., Blaisdell, A. P., 2009. Blocking of spatial control by landmarks in rats. *Behav Processes* 81 (1), 114–118.

- Steffenach, H. A., Sloviter, R. S., Moser, E. I., Moser, M. B., 2002. Impaired retention of spatial memory after transection of longitudinally oriented axons of hippocampal CA3 pyramidal cells. *Proc Natl Acad Sci USA* 99 (5), 3194–3198.
- Stuchlik, A., Bures, J., 2002. Relative contribution of allothetic and idiothetic navigation to place avoidance on stable and rotating arenas in darkness. *Behav Brain Res* 128 (2), 179–188.
- Sutherland, R. J., Whishaw, I. Q., Kolb, B., 1983. A behavioral-analysis of spatial localization following electrolytic, kainate-induced or colchicine-induced damage to the hippocampal-formation in the rat. *Behav Brain Res* 7 (2), 133–153.
- Svoboda, J., Telensky, P., Blahna, K., Zach, P., Bures, J., Stuchlik, A., 2008. Lesion of posterior parietal cortex in rats does not disrupt place avoidance based on either distal or proximal orienting cues. *Neurosci Lett* 445 (1), 73-77.
- Taube, J. S., 1998. Head direction cells and the neurophysiological basis for a sense of direction. *Prog Neurobiol* 55 (3), 225–256.
- Taube, J. S., 2007. The head direction signal: Origins and sensory-motor integration. *Annu Rev Neurosci* 30, 181–207.
- Taube, J. S., Muller, R. U., Ranck, J. B., 1990a. Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative-analysis. *J Neurosci* 10 (2), 420–435.
- Taube, J. S., Muller, R. U., Ranck, J. B., 1990b. Head-direction cells recorded from the postsubiculum in freely moving rats. II. Effects of environmental manipulations. *J Neurosci* 10 (2), 436–447.
- Telensky, P., Svoboda, J., Blahna, K., Kubik, S., Bures, J., Stuchlik, A., 2011. Functional inactivation of the rat hippocampus disrupts avoidance of a moving object. *Proc Natl Acad Sci USA*, accepted.
- Telensky, P., Svoboda, J., Pastalkova, E., Blahna, K., Bures, J., Stuchlik, A., 2009. Enemy avoidance task: a novel behavioral paradigm for assessing spatial avoidance of a moving subject. *J Neurosci Meth* 180 (1), 29-33.
- Terrazas, A., Krause, M., Lipa, P., Gothard, K. M., Barnes, C. A., McNaughton, B. L., 2005. Self-motion and the hippocampal spatial metric. *J Neurosci* 25 (35), 8085–8096.
- Thinus-Blanc, C., Save, E., Poucet, B., Foreman, N., 1996. Effects of parietal cortex lesions on spatial problem solving in the rat. *Behav Brain Res* 81 (1-2), 115–121.

- Thompson, L. T., Best, P. J., 1990. Long-term stability of the place-field activity of single units recorded from the dorsal hippocampus of freely behaving rats. *Brain Res* 509 (2), 299–308.
- Tolman, E., 1948. Cognitive maps in rats and men. *Psychol Rev* 55, 189–208.
- Uylings, H. B. M., Groenewegen, H. J., Kolb, B., 2003. Do rats have a prefrontal cortex? *Behav Brain Res* 146 (1-2), 3–17.
- Valenstein, E., Heilman, K. M., Watson, R. T., Vandenabell, T., 1982. Non-sensory neglect from parietotemporal lesions in monkeys. *Neurology* 32 (10), 1198–1201.
- Vales, K., Bubenikova-Valesova, V., Klement, D., Stuchlik, A., 2006. Analysis of sensitivity to MK-801 treatment in a novel active allothetic place avoidance task and in the working memory version of the Morris water maze reveals differences between Long-Evans and Wistar rats. *Neurosci Res* 55 (4), 383–388.
- Vales, K., Svoboda, J., Benkovicova, K., Bubenikova-Valesova, V., Stuchlik, A., 2010. The difference in effect of mGlu2/3 and mGlu5 receptor agonists on cognitive impairment induced by MK-801. *Eur J Pharmacol* 639 (1-3), 91–98.
- Vann, S. D., Aggleton, J. P., 2002. Extensive cytotoxic lesions of the rat retrosplenial cortex reveal consistent deficits on tasks that tax allocentric spatial memory. *Behav Neurosci* 116 (1), 85–94.
- Vann, S. D., Aggleton, J. P., Maguire, E. A., 2009. What does the retrosplenial cortex do? *Nat Rev Neurosci* 10 (11), 792–802.
- Wesierska, M., Adamska, I., Malinowska, M., 2009. Retrosplenial cortex lesion affected segregation of spatial information in place avoidance task in the rat. *Neurobiol Learn Mem* 91 (1), 41–49.
- Wesierska, M., Dockery, C., Fenton, A. A., 2005. Beyond memory, navigation, and inhibition: Behavioral evidence for hippocampus-dependent cognitive coordination in the rat. *J Neurosci* 25 (9), 2413–2419.
- Whishaw, I. Q., Hines, D. J., Wallace, D. G., 2001a. Dead reckoning (path integration) requires the hippocampal formation: evidence from spontaneous exploration and spatial learning tasks in light (allothetic) and dark (idiothetic) tests. *Behav Brain Res* 127 (1-2), 49–69.
- Whishaw, I. Q., Jarrard, L. E., 1995. Similarities vs differences in place learning and circadian activity in rats after fimbria-fornix section or ibotenate removal of hippocampal cells. *Hippocampus* 5 (6), 595–604.

- Whishaw, I. Q., Maaswinkel, H., Gonzalez, C. L. R., Kolb, B., 2001b. Deficits in allothetic and idiothetic spatial behavior in rats with posterior cingulate cortex lesions. *Behav Brain Res* 118 (1), 67–76.
- Whitlock, J. R., Sutherland, R. J., Witter, M. P., Moser, M. B., Moser, E. I., 2008. Navigating from hippocampus to parietal cortex. *Proc Natl Acad Sci USA* 105 (39), 14755–14762.
- Wiener, S. I., Korshunov, V. A., Garcia, R., Berthoz, A., 1995. Inertial, substratal and landmark cue control of hippocampal ca1 place cell-activity. *Eur J Neurosci* 7 (11), 2206–2219.
- Witter, M., Amaral, D., 2004. *Hippocampal formation*. Elsevier Academic Press, San Diego, pp. 729–757.
- Wood, E. R., Dudchenko, P. A., Robitsek, R. J., Eichenbaum, H., 2000. Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron* 27 (3), 623–633.
- Yoganarasimha, D., Knierim, J. J., 2005. Coupling between place cells and head direction cells during relative translations and rotations of distal landmarks. *Exp Brain Res* 160 (3), 344–359.
- Yoganarasimha, D., Yu, X. T., Knierim, J. J., 2006. Head direction cell representations maintain internal coherence during conflicting proximal and distal cue rotations: Comparison with hippocampal place cells. *J Neurosci* 26 (2), 622–631.
- Zheng, Y., Pearce, J. M., Vann, S. D., Good, M., Jenkins, T. A., Smith, P. F., Aggleton, J. P., 2003. Using idiothetic cues to swim a path with a fixed trajectory and distance: Necessary involvement of the hippocampus, but not the retrosplenial cortex. *Behav Neurosci* 117 (6), 1363–1377.
- Zinyuk, L., Kubik, S., Kaminsky, Y., Fenton, A. A., Bures, J., 2000. Understanding hippocampal activity by using purposeful behavior: Place navigation induces place cell discharge in both task-relevant and task-irrelevant spatial reference frames. *Proc Natl Acad Sci USA* 97 (7), 3771–3776.
- Zugaro, M. B., Berthoz, A., Wiener, S. I., 2001. Background, but not foreground, spatial cues are taken as references for head direction responses by rat anterodorsal thalamus neurons. *J Neurosci* 21 (14), art. no.–RC154.

Author's publications not directly relevant to the thesis

Rambousek L, Bubenikova-Valesova V, Kacer P, Syslova K, Kenney J, Holubova K, Najmanova V, Zach P, **Svoboda J**, Stuchlik A, Chodounska H, Kapras V, Adamusova E, Borovska J, Vyklicky L, Vales K, 2011. Cellular and behavioural effects of a new steroidal inhibitor of the N-methyl-D-aspartate receptor $3\alpha5\beta$ -pregnanolone glutamate. *Neuropharmacology*, accepted.

Vales K, **Svoboda J**, Benkovicova K, Bubenikova-Valesova V, Stuchlik A, 2010. The difference in effect of mGlu2/3 and mGlu5 receptor agonists on cognitive impairment induced by MK-801. *Eur J Pharm* 639 (1-3), 91-98.

Bubenikova-Valesova V, **Svoboda J**, Horacek J, Sumiyoshi T, 2010. Effect of tandospirone, a serotonin-1A receptor partial agonist, on information processing and locomotion in dizocilpine-treated rats. *Psychopharmacology* 212 (2), 267-276.

Bubenikova-Valesova V, **Svoboda J**, Horacek J, Vales K., 2009. The effect of a full agonist/antagonist of the D1 receptor on locomotor activity, sensorimotor gating and cognitive function in dizocilpine-treated rats. *Int J Neuropsychopharmacol* 20, 1-11.

Bubenikova-Valesova V, Stuchlik A, **Svoboda J**, Bures J, Vales K., 2008. Risperidone and ritanserin but not haloperidol block effect of dizocilpine on the active allothetic place avoidance task. *Proc Natl Acad Sci USA* 105 (3), 1061-1066.

Stuchlik A, Rehakova L, Rambousek L, **Svoboda J**, Vales K, 2007. Manipulation of D2 receptors with quinpirole and sulpiride affects locomotor activity before spatial behavior of rats in an active place avoidance task. *Neurosci Res* 58 (2), 133-139.