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REVIEW

Spatial Navigation: Implications for Animal Models, Drug Development and Human Studies

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Summary

Spatial navigation and memory is considered to be a part of the declarative memory system and it is widely used as an animal model of human declarative memory. However, spatial tests typically involve only static settings, despite the dynamic nature of the real world. Animals, as well as people constantly need to interact with moving objects, other subjects or even with entire moving environments (flowing water, running stairway). Therefore, we design novel spatial tests in dynamic environments to study brain mechanisms of spatial processing in more natural settings with an interdisciplinary approach including neuropharmacology. We also translate data from neuropharmacological studies and animal models into development of novel therapeutic approaches to neuropsychiatric disorders and more sensitive screening tests for impairments of memory, thought, and behavior.

Key words

Memory • Learning • Navigation • Spatial representation • Moving environments • Rats • Animal models • Brain • Neurons

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Introduction to spatial memory

Spatial (place) navigation of rats is one of the most popular behavioral models to examine neurobiological mechanisms underlying learning and memory, decision-making, and other higher cognitive processes (O'Keefe and Nadel 1978). The advantages of spatial tasks arise at many points: navigation is natural for most species, thus facilitating comparative studies (Nekovarova *et al.* 2013). The available sensory information can be controlled (Blahna *et al.* 2011) and navigational tests can be combined with advanced inactivation, electrophysiological, or molecular techniques to see how the brain processes information and gives rise to behavioral actions. Moreover, place navigation constitutes an animal model of human declarative memory (Eichenbaum 2001) or a distinct sub-component of declarative memory (Morris 2013).

In dynamic, real-world settings, both animals and humans often have to interact with moving objects or even whole moving environments. Spatial navigation, especially in such dynamic environments, involves time perception (interval timing; Buhusi and Meck 2005), giving rise to timing strategies and their combinations with place responses (Klement *et al.* 2010). In addition to representations of hidden goals (Morris 1984), recognition of positions of objects in a directly inaccessible space (Klement *et al.* 2010, Levcik *et al.* 2013), continuous updating of changing information (Morris and Frey 1997) such as during navigation by visible, but continuously moving objects (Telensky *et al.* 2009, 2011, Svoboda *et al.* 2012), behavioral flexibility (Burghardt *et al.* 2012), and cognitive coordination of multiple information streams (Wesierska *et al.* 2005, Kubik and Fenton 2005) are important components of navigation in dynamic environments. Together, these processes give rise to highly flexible and purposeful spatial behavior based on internal representations of the

environments in the form of "cognitive maps" (Tolman 1948).

Brain structures participating in spatial memory

The hippocampus is connected in a wider functional network of the hippocampal formation consisting of the hippocampus proper (*Cornu Ammonis*; CA1-4), the dentate gyrus, and the subicular complex (Amaral and Witter 1989). Together with the neighboring entorhinal, perirhinal, and postrhinal cortical areas it is often, especially in human literature, referred to as the medial temporal lobe system (Eichenbaum 2001). The role of the hippocampus in memory has been acknowledged since the seminal report about Henry Gustav Molaison (formerly known as famous patient H. M.), who suffered profound anterograde amnesia of declarative memory after resection of large portions of medial temporal lobes including the hippocampus as a therapy for pharmacoresistant temporal epilepsy (Scoville and Milner 1957). A more specific theory of hippocampal function proposes that it forms a "cognitive map" of the environment, which is particularly useful when navigating to hidden goals, i.e. "place navigation" (Tolman 1948, O'Keefe and Nadel 1978). This influential concept shaped decades of hippocampal studies in animals, although it has also been shown that the hippocampus plays a critical role in anxiety (especially its ventral part; Bannerman *et al.* 2004, Kheirbek *et al.* 2013), and in organizing multiple streams of information (cognitive coordination; Wesierska *et al.* 2005). The hippocampus is also crucial for recognizing familiar places even without any navigational demands (Klement *et al.* 2005) and for recognizing position of objects in inaccessible environment (Levcik *et al.* 2013). Recently, the hippocampus has been suggested to play a role in spatial choice rather than spatial knowledge (Bannerman *et al.* 2012), further underlining the role of neocortex.

Several neocortical areas interconnected with the hippocampus are involved in place navigation, including the piriform, perirhinal, and retrosplenial cortices. The retrosplenial cortex (RSC) lies at the "interface" between the hippocampus and neocortical associational areas and it may play a role in integration of egocentric and allocentric information streams (Byrne *et al.* 2007). Indeed, RSC dysfunction impairs navigation in dissociated ego- and allocentric spatial frames (Wesierska *et al.* 2009), pointing to its role in cognitive coordination. Another area involved in navigation and spatial memory is the posterior parietal cortex, which is mainly responsible for egocentric processing (Whitlock *et al.* 2012, but see Svoboda *et al.* 2009). Importance of entorhinal cortex should also be emphasized, given the fact that it provides the main excitatory drive and information input into dentate gyrus, considered a gateway to the hippocampus.

Importantly, neurons within the wider hippocampal network in rodents display a variety of spatially specific activity. Pyramidal neurons in the hippocampus behave as place cells, i.e. they increase their firing rate only when the animal visits a cell-specific place, called the firing-field (O'Keefe and Dostrovsky 1971). Other functional cell types include head direction cells (Taube *et al.* 1990) in the subiculum, RSC, and anterior thalamus, grid cells and border cells in the medial entorhinal cortex (Fyhn *et al.* 2004, Hafting *et al.* 2005) and cells with mixed head direction/place/velocity firing correlates in the RSC (Cho and Sharp 2001). Head direction cells respond when the subject's head is turned in a particular direction, whilst grid cells fire at multiple locations forming a periodic hexagonal grid covering the entire environment. Other cell types respond to spatial boundaries (border cells) or to combinations of spatial variables such as place, head direction, and velocity.

Importantly, the hippocampal formation, specifically the DG, is one of two sites of neurogenesis in the adult brain (Altman and Das 1965). Newly-born neurons in the dentate gyrus are proposed to facilitate learning in the hippocampus by separating overlapping patterns in hippocampal inputs, thus ensuring formation of distinct representations (Sahay *et al.* 2011, Nakashiba *et al.* 2012) and preventing interference of new memories with old ones (Wiskott *et al.* 2006, Winocur *et al.* 2011). Recently, their role has been reformulated to increase "memory resolution" so that cooperation between newly-born, hyperexcitable granule cells and older neurons that code sparsely for salient features increases the amount of detail encoded in hippocampal memories (Aimone *et al.* 2011). Notably, the role of adult neurogenesis in the updating of dynamic environmental features is still controversial, despite recent demonstration of their involvement in behavioral flexibility in mice (Garthe *et al.* 2009, Burghardt *et al.* 2012).

Interestingly, many types of place navigation require the hippocampus or hippocampal formation in general and are disrupted in many brain disorders. We hypothesize that the hippocampus disruption may in fact

be a "apparent link" between several serious brain disorders and cognitive deficits observed in these conditions (Fig. 1).

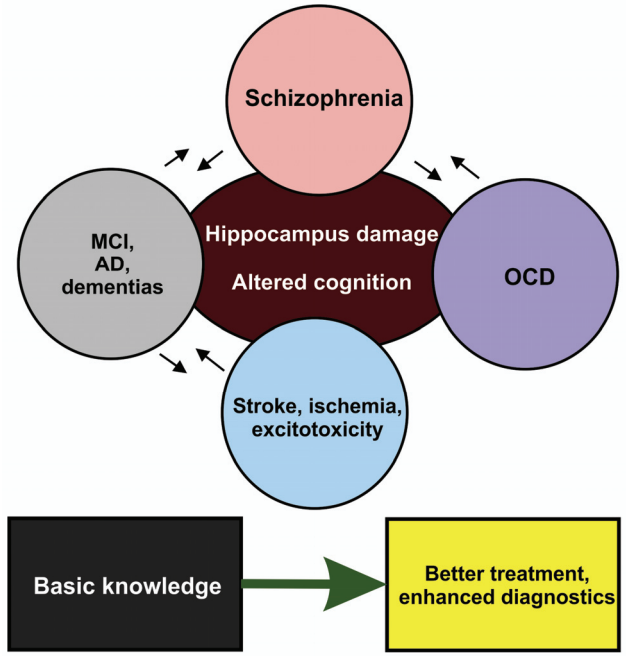

Fig. 1. Schematic illustration of mutual relation of neuropsychiatric disorders to the hippocampal alterations and behavioral and cognitive abnormalities. Our efforts go from understanding of basic processes in animal models to enhanced design and screening of drugs and neurodiagnostics (bottom of the figure). OCD: Obsessive-compulsive disorder, MCI: Mild cognitive impairment, AD: Alzheimer´s disease.

Real world environments often involve multiple frames of reference, which continuously change their relationship. People as well as animals encounter environments consisting of a mixture of relevant and irrelevant information, which can be organized in multiple reference frames (e.g. idiothetic vs. allothetic, own position relative to conspecifics, family, rivals, prey, predators, and moving objects in an environment, vs. relative to the ambient space). Although the need to organize behavior in multiple frames of reference is a common challenge in everyday life, most tests of spatial memory and navigation occur in static environments or involve only one-off changes such as change in goal location or between-session alternations. In contrast, active place avoidance on Carousel (Stuchlik *et al.* 2012, 2013) challenges experimental subjects with two dissociated spatial reference frames of stationary room and rotating arena. They are required to avoid a hidden place defined in a stationary room on a continuously rotating circular arena (extensively reviewed in Stuchlik *et al.* 2013). This behavior critically depends on the hippocampus because inactivation of one hippocampus by injection of voltage-dependent Na^+ channel blocker tetrodotoxin completely abolishes the avoidance (Cimadevilla *et al.* 2001). Follow-up experiments revealed that soma variants of place avoidance on the Carousel depends on hippocampus-dependent cognitive coordination or cognitive control (Wesierska *et al.* 2005, Kubik and Fenton 2005, Kelemen and Fenton 2010) and that this function is distinct from hippocampal role in spatial memory as tested in a water maze (Kubik and Fenton 2005). These findings justify the use of the place avoidance task as a valuable model of a dynamic, real-world environment where multiple frames of reference continuously change their relationship in the study of neurobiology of cognition, cognitive disorders, and their potential therapies (Czéh *et al.* 2001, Stuchlik *et al.* 2004, 2007b, 2008, 2012, 2013, Kubik and Fenton 2005, Stuchlik and Vales 2005, 2006, 2008, Vales and Stuchlik 2005, Kubik *et al.* 2006, Petrasek and Stuchlik 2009, Vales *et al.* 2010, Entlerova *et al.* 2013, Lobellova *et al.* 2013, Zemanova *et al.* 2013).

Schizophrenia and animal models

Schizophrenia is a devastating disease affecting approximately 1 % of world's population. It is one of the most serious neuropsychiatric disorders with enormous human, medicinal and socioeconomic impact. Its symptoms are typically denoted as positive (hallucinations, delusions, disorganization) and negative (social withdrawal, anhedonia, decreased psychomotor tempo). Schizophrenia is also characterized by stable and reproducible cognitive symptoms, as a typical thought disorder. The cognitive deficit is now perceived as primary and the most stable symptom of the disease. It is present before the full onset as well as in remission and also in first-degree relatives of schizophrenic patients, forming a stable and heritable endophenotype. Cognitive deficits in schizophrenia reach multiple domains, ranging from psychomotor functions, verbal fluency, sensorimotor gating (pre-pulse inhibition of acoustic startle; Bubenikova *et al.* 2005), attention, working memory, long-term memory, executive functions and cognitive coordination (reviewed by Phillips and Silverstein 2003, Keefe and Harvey 2012). Importantly, the cognitive deficits are the most resistant to therapeutic interventions since few (if any) substances are capable of alleviating the cognitive symptoms of this disease

(Young *et al.* 2012).

Animal models of brain disorders (reviewed by Jones *et al.* 2011) are indispensable tools in the study of neuropathological mechanisms of those diseases as well as potential novel therapies (Peleg-Raibstein *et al.* 2012). Animal models of schizophrenia range from pharmacological manipulations (acute or chronic application of drugs; Jones *et al.* 2011) to neurodevelopmental (ontogenetic pharmacological, surgical or immunologic manipulations; Wilson and Terry 2010) and a wide variety of genetic models (it should be noted that diverse genetic mutations are interpreted as endophenotypes of schizophrenia (e.g. Willi *et al.* 2010, reviewed by O'Tuathaigh *et al.* 2012). Animal models are usually evaluated in terms of validities: face validity reflects phenomenological resemblance of behavioral alterations, construct validity emphasizes common or similar pathogenesis factors or neural substrate of the alterations, and predictive validity evaluates the explanatory value of the model in relation to interventions (the predictive validity most frequently expresses the sensitivity of the animal model to drugs used as therapeutics in humans) (Ellenbroek and Cools 1990).

Cognitive deficits in an animal model of schizophrenia

Administration of MK-801 (dizocilpine, a high affinity non-competitive NMDA receptor antagonist) to rats and mice produces typical behavioral alterations analogous to selected symptoms of schizophrenia. Moreover, MK-801 and other non-competitive NMDA-receptor antagonist elicit acute psychosis in healthy humans and exacerbate symptoms in schizophrenic patients (Newcomer and Krystal 2011) demonstrating strong face validity of the pharmacological model of schizophrenia by systemic administration of NMDA receptor antagonists. This model is rooted in the glutamatergic hypothesis of schizophrenia. It posits that dysregulation of the glutamatergic neurotransmission is the primary cause of the disease. MK-801 causes dose-dependent hyperlocomotion, social deficit, stereotypies and general behavioral primitivization (Nilsson *et al.* 2001). Hyperlocomotion in animal models of schizophrenia is considered analogous to positive symptoms in humans and attributed to increased dopaminergic activity in mesolimbic circuits. Importantly, MK-801 (and most NMDA receptor antagonists) also produces a reproducible cognitive deficit and it meets the criteria of a cognition impairer (van der Staay *et al.* 2011). It impairs inhibitory avoidance, navigation in the Morris water maze (MWM) and object recognition. Our results accumulated over almost 10 years suggested that the acute dose for induction of cognitive deficit in rats of the Long-Evans strain from the breeding colony of the Institute of Physiology in Prague lies between 0.08 and 0.15 mg/kg (depending on behavioral factors and cognitive demands of the task) and is very close to dose threshold for hyperlocomotion.

Stuchlik *et al.* (2004) compared the effect of MK-801 (0.1 and 0.2 mg/kg) on performance of Long Evans rats in the MWM (Morris *et al.* 1984, Stuchlik *et al.* 2007a) with its effect on the place avoidance on Carousel. The lower dose (0.1 mg/kg) only retarded learning in the MWM, the higher dose (0.2 mg/kg) severely disrupted performance in both tasks. A profound deficit manifested in the MWM where rats were completely unable to find the escape platform in any of the 60-s swims. Inability to avoid a place and escape shocks was accompanied by hyperlocomotion in the place avoidance task. A follow-up study (Stuchlik and Vales 2005) examined the effects of two doses of MK-801 on the place avoidance task with pretraining. The lower dose (0.15 mg/kg) only affected new place avoidance in a new environment, whereas the higher dose (0.20 mg/kg) also impaired reinforced retrieval in the familiar environment. Dose-dependence study examining the effect of MK-801 (0.05-0.15 mg/kg) on behavioral flexibility demonstrated the adverse effects of even low doses (0.08 mg/kg) on reversal learning in both place avoidance on Carousel and Morris water maze (Lobellova *et al.* 2013). The highest dose (0.15 mg/kg) also impaired swimming towards visible platform and increased swimming speed. MK-801 (0.12 and 0.15 mg/kg) also impaired visuospatial working memory and increased locomotion in a modification of the place avoidance task where the location of the to-be-avoided place is changed daily (Zemanova *et al.* 2013), called allothetic place avoidance alternation (Dockery and Wesierska 2010, Dockery *et al.* 2011). Vales and colleagues (2006) compared the effects of three doses of MK-801 (0.1, 0.2 and 0.3 mg/kg) on place avoidance on Carousel in two outbred strains of rats, Long-Evans and Wistar from the Institute of Physiology breeding colony. In addition, the lowest dose (0.1 mg/kg) was also tested in a short-term memory version in the MWM with daily changing platform position. Wistar rats proved to be more

sensitive to the low dose (0.1 mg/kg) in place avoidance task, but short-term memory in water maze was not disturbed by this dose of MK-801.

The predictive validity of the acute MK-801 animal model was also tested on the Carousel (Bubenikova-Valesova *et al.* 2008). The place avoidance deficit induced by low dose of MK-801 (0.1 mg/kg) was reversed by multi-receptor atypical antipsychotic risperidone and also by ritanserin, an antagonist of 5-HT2A/2C receptors. In contrast, a classical antipsychotic haloperidol did not prevent the place avoidance deficit, but markedly reduced locomotion at higher doses. Interestingly, administration of both antipsychotics alone (without MK-801), but not ritanserin, significantly impaired place avoidance compared to saline-only treated rats (Bubenikova-Valesova *et al.* 2008). Vales *et al.* (2010) investigated the effects modulating glutamatergic neurotransmission by metabotropic glutamate receptor (mGluR) agonists, in search of new therapeutic options for schizophrenia. Agents stimulating mGluR5 such as ACPD ((1S,3R)-1-amino-1,3-cyclopentanedicarboxylic acid), DFB (3,3'-difluorobenzaldazine) etc. showed beneficial effects, whilst agents acting at mGluR2/3 did not. This finding supports the notion that mGluR represent a promising treatment target (reviewed by Herman *et al.* 2012). On a similar note, 3alpha5beta-pregnanolone glutamate (PG), a patented neuroprotective steroid derivative, efficiently reversed cognitive deficit induced by MK-801 without affecting locomotion (Vales *et al.* 2012).

Deficits in spatial navigation and behavioral flexibility in other animal models

We have recently established an animal model of obsessive-compulsive disorder (OCD) by D2 sensitization by quinpirole in our laboratory (unpublished observations). OCD is a chronic and partly heritable behavioral disorder with strong anxiety component. Its lifetime prevalence is estimated about 1-3 % (Stein 2002). OCD is marked by recurrent intrusive thoughts called obsessions and repetitive uncontrollable behaviors termed compulsions, the latter often reported to neutralize obsessions and reduce anxiety (Stein 2002). OCD negatively affects quality of life and may even completely dominate the life of affected patients. Furthermore, a significant proportion of patients fail to respond to established treatments. The first choice treatments for OCD are selective serotonin re-uptake inhibitors (SSRI) and cognitive-behavioral therapy. A tricyclic antidepressant clomipramine is also used. The pathophysiology of OCD is still unknown. Dysfunction of the fronto-striatal circuits including orbitofronto-striato-thalamic system was associated with the expression of symptoms and the illness. This theory has been revised and newly includes dorsolateral prefronto-striatal system together with the parietal and prefrontal cortices, representing a substantial extension of the proposed circuit (Menzies *et al.* 2008, Koprivova *et al.* 2009). Neurochemical abnormalities in OCD affect several neurotransmitter/receptor systems (serotonergic, dopaminergic, glutamatergic, and GABAergic). OCD has been associated with dysfunction of the serotonergic system, based mainly on the responsiveness of the disease to serotonergic drugs such as SSRI and clomipramine. Some evidence pointed to the role of dopamine, based on clinical studies showing benefits of atypical neuroleptics in treatment and on animal model (Szechtman *et al.* 1994, 1998, 2001). However, recent evidence has emphasized the role of glutamate dysregulation in fronto-striatal systems, including hyperactivity of glutamatergic system in orbitofrontal cortex (OFC), caudate nucleus, and other areas.

The animal model of OCD is based on sensitization of rats with quinpirole, a dopamine D2/D3 receptor agonist. Rats sensitized to quinpirole display behavior in an open-field arena that meets performance criteria for compulsive checking proposed in the literature (Szechtman *et al.* 1994, 1998, 2001). Indeed, motor rituals after chronic administration of quinpirole resemble several behavioral OCD symptoms to a remarkable extent, which adds to the face validity of this model (Szechtman *et al.* 1991, 1994, 1998, 2001, Eilam *et al.* 2005, 2012, Albelda and Joel 2012). Rats chronically treated with quinpirole display a striking preoccupation with one or two places in the arena and return there repeatedly, a pattern of behavior that resembles the spatiotemporal structure of OCD checking (Eilam *et al.* 2005). This compulsive-like behavior is context-dependent, similarly to OCD patients. Clomipramine (a tricyclic antidepressant commonly used in OCD treatment) attenuates the quinpirole-induced compulsive checking, supporting the predictive validity of this animal model (Szechtman *et al.* 2001). Construct validity of the model is supported by amelioration of checking behavior by lesions of the orbitofrontal cortex and the nucleus accumbens core (NAc), presumed parts of the OCD-circuit (Dvorkin *et al.* 2010). This study suggested that

OFC may support the goal-directed activity (checking of objects, i.e. "focus") while NAc may be responsible for "vigor" of motor performance. Indeed, the quinpirole rat model has been proposed and validated as a useful framework for the conceptualization of human OCD psychopathology in patients (Eilam *et al.* 2012). Preliminary studies have established this animal model in our laboratory and found no deficit in initial acquisition of place avoidance on the Carousel in quinpirole-sensitized animals compared to controls, but revealed significant impairment in reversal learning after relocation of the to-be-avoided place (Hatalova *et al.*, unpublished data).

Drug development

Searching for novel drugs potentially useful for therapy of CNS damage belongs to most intensively investigated topics in contemporary pharmacology and neuroscience (Fig. 2). Significant advances have been achieved in the field of development and screening of new neuropsychiatric therapeutics based on steroidal compounds naturally occurring in the brain and exerting endogenous neuroprotective activity (Korinek *et al.* 2011). This research is done in a cooperation of more institutions including Department of Cellular Neurophysiology, Institute of Physiology, Institute of Organic Chemistry and Biochemistry, AS CR, Prague Psychiatric Center etc. An example of such promising compound is PG (see above), a synthetic analogue of pregnanolone sulfate, which is a naturally neuroprotective neurosteroid. The proposed mechanism of its action is blockade of extrasynaptic, tonically-activated NMDA receptors and thereby prevention of excessive glutamate action on neurons. Given these premises, we expect the effect of the designed drugs on normal signal transmission between neurons to be minimal. The role of neurosteroids in the pathogenesis of a number of neuropsychiatric diseases and evaluation of their therapeutic potential has been in focus of biomedical research for the last decade. A number of experimental studies documented their potential in treating several CNS diseases, including neurodegenerative disorders, multiple sclerosis, affective disorders, alcoholism, pain, insomnia, and schizophrenia using animal models (Morrow 2007). The basic goal of this research is obtaining neuroprotective drugs with minimal side effects, i.e. with the most favorable benefit/risk ratio.

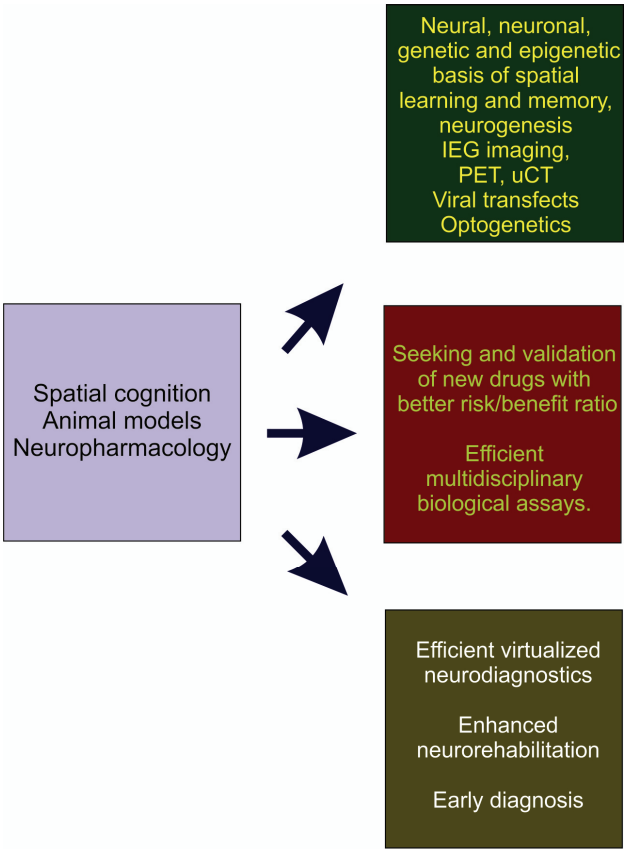

Fig. 2. Outline of future plan of the laboratory. From general interest in spatial cognition, animal models and pharmacology, we continue in three directions: detailed study of brain substrate of cognition, including genetics and epigenetics, neurogenesis and immunohistochemistry, immediate-early gene (IEG) imaging, neuroimaging in whole animals (PET – positron emission tomography, uCT – micro-computed tomography) and viral transfects and optogenetics in the long-term focus. Another direction is seeking and validation of new drugs and efficient assays of biological action of selected substances. The third direction points to more efficient and informative neurodiagnostics, outputs for neurorehabilitation and cognitive training.

PG crosses the blood-brain barrier, preferentially inhibits tonically-activated NMDA receptors, does not induce psychotomimetic symptoms (such as hyperlocomotion and sensorimotor gating deficit), and reduces excitotoxic damage to brain tissue and consequent behavioral impairment in rats. Specifically, PG significantly ameliorated neuronal damage in the dentate gyrus and subiculum and improved place avoidance on the Carousel after bilateral NMDA-induced lesions to the hippocampus (Rambousek *et al.* 2011). These findings point to therapeutic potential of PG in treating disorders caused by NMDA receptor overactivation (Rambousek *et al.* 2011). Despite being a use-dependent NMDA receptor antagonist, it also exerts a paradoxical "antipsychotic-like" effect in an animal

model of schizophrenia by acute systemic MK-801. The procognitive properties were evaluated using place avoidance on the Carousel. In addition to the place avoidance behavior, we evaluated effects of PG on locomotor activity and anxiety. PG alone altered neither spatial learning nor locomotor activity in control animals. In the model animals, PG reversed the MK-801-induced cognitive deficit without reducing hyperlocomotion. The highest dose of PG also showed mild but significant anxiolytic properties. Taken together, PG acts to restore normal brain functioning and these results may facilitate development of new drugs to improve cognitive functioning in schizophrenia (Vales *et al.* 2012).

Spatial navigation deficits in Alzheimer's disease, mild cognitive impairment, and other brain disorders

Another line of research in our laboratory focuses on alterations in spatial navigation in cognitively impaired patients, mainly due to Alzheimer's disease (AD), schizophrenia, or temporal lobe epilepsy. AD is a neurodegenerative disorder, which affects first and foremost the mediotemporal structures, especially the hippocampus and the parahippocampal gyrus. Episodic memory deficit is a hallmark of the disease, although spatial memory impairment in real space, such as in a hospital lobby, has also been repeatedly reported. A human analogue of the Morris water maze, called Blue Velvet Arena (BVA), has been used in our laboratory for a long time to distinguish allocentric and egocentric spatial deficits. In a Hidden Goal Task in the BVA, the subjects are required to locate either a directly imperceptible goal using two landmarks (allocentric subtest) or their own position (egocentric subtest). We found a deficit in allocentric but not egocentric memory in a group of AD patients using the BVA task, together with a deficit in remembering the presentation order of several locations (as assessed by sequential order in a spatial memory test) (Kalova *et al.* 2005). In another group of patients we observed impaired spatial navigation in BVA in amnestic patients with single-domain mild cognitive impairment (MCI), presumably due to their memory deficit. Their navigational impairment was limited only to allocentric, but not the egocentric navigation (Hort *et al.* 2007). This specificity suggests that the critical factor affecting the patients' performance was memory for spatial configurations, rather than visuospatial perceptual functions, which would be required in either test. Impairment of allocentric spatial navigation was found also in the hippocampal subtype of amnestic MCI patients (Laczo *et al.* 2009) and in amnestic MCI APOE ε4-positive patients (Laczo *et al.* 2011). Strong correlation between the right hippocampal volume and allocentric navigation efficiency in BVA was found in MCI and AD patients using total brain and hippocampal volumetric MRI (Nedelska *et al.* 2012). This relationship marks the role of the right hippocampus in spatial navigation and likely results from hippocampal atrophy associated with development of AD. Importantly, the link between right hippocampal volume and navigation was observed also in a computerized overhead 2D version of Morris water maze suitable as a clinical diagnostic test for AD.

In parallel, spatial tests in virtual reality environment have been implemented as virtual analogies to real tasks to study spatial cognition independent of locomotion and to facilitate cross-species comparisons (Klement and Bures 2000, Pastalkova *et al.* 2003, Nekovarova and Klement 2006, Nekovarova *et al.* 2006a, Klement *et al.* 2010). These tests were successfully used in rats with reversible inactivations (Levcik *et al.* 2013a) and pharmacological interventions (Levcik *et al.* 2013b) as well as in non-human primates and humans (Nekovarova *et al.* 2006b, 2009, 2013, reviewed in Klement *et al.* 2008). Virtual tests have significant advantages: the stimuli, timing, and other factors of the experimental design can be easily adjusted; their results can be straightforwardly compared between various animal species and people; and cognitive component can be studied without potentially confounding locomotor (ambulatory) activity. In addition, the virtual test can be used in electrophysiological and in some pharmacological studies where motor functions could be affected and potentially confounding the results.

Conclusions

The Laboratory of Neurophysiology of Memory has a long-standing interest in learning and memory with special focus on spatial navigation as a model of declarative memory in both healthy and diseased brain. The basic branch of research targets the neuronal and neurochemical mechanisms of navigation in dynamic environments and, using the data from the animal models of disease, this research is translated into development of neuropharmacological *in vivo* screening, new therapeutic approaches, and novel real and virtual diagnostic tests for patients with neuropsychiatric disorders (Fig. 2).

Conflict of Interest

There is no conflict of interest.

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