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Prostorová paměť u lidí a její poruchy:

Od animálních modelů ke schizofrenii

Spatial memory in humans and its disorders:

From animal models towards schizophrenia

Disertační práce

Školitel: Mgr. Kamil Vlček, PhD.

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Abstrakt

Prostorové chování zvířat i člověka zahrnuje komplexní systém kognitivních schopností, které vykazují vysokou evoluční homogenitu a jsou nezbytnou součástí každodenního života. Ke studiu prostorové paměti se často využívají úlohy původně vytvořené pro zvířata (zejména potkany). Dnes nejznámější a nejcitovanější úlohou zaměřenou na prostorovou paměť je bezesporu navigace na skrytý cíl v Morrisově vodním bludišti. Méně známý je pak Test aktivního vyhýbání se místu na rotující aréně, neboli Kolotočové bludiště, které testuje navíc i schopnost kognitivní koordinace. Tyto úlohy prokázaly svůj význam nejen s ohledem na identifikaci neurofyziologických podkladů prostorové paměti, ale také ve farmakologickém výzkumu, zejména u animálních modelů neuropsychiatrických onemocnění a při testování účinku léčiv na modelované kognitivní příznaky těchto onemocnění. V této souvislosti se v posledních letech věnuje značná pozornost zejména kognitivnímu deficitu u schizofrenie. Dnes je popsaných několik animálních modelů, které se snaží objasnit příčiny symptomů pozorovaných u schizofrenie, a které vykazují změny v různé míře odpovídající těmto příznakům. Právě kognitivní deficit, který je závažným příznakem schizofrenie, je ve srovnání s pozitivními a negativními příznaky, nejméně ovlivnitelný antipsychotickou medikací. Prediktivní validita animálních modelů schizofrenie (jako predikce odpovědi na léčbu) je proto klíčová pro vývoj nových léčiv zaměřených na terapii kognitivních příznaků. Komparativní výzkum srovnávající schopnosti modelových zvířat a pacientů v podobných úlohách umožňuje validitu modelu ověřit. Oba výše popsané prostorové testy byly ve své původní podobě již v minulosti testované u animálních modelů schizofrenie a potvrdily předpokládaný deficit prostorové paměti a kognitivní koordinace. Cílem této práce proto bylo vytvořit virtuální (počítačové) analogie obou behaviorálních úloh, které by podobné srovnání umožnily prostřednictvím vyšetření skupiny pacientů a zdravých lidí. Tato dizertační práce nejdříve popisuje experiment srovnávající výkon potkanů s animálním modelem schizofrenie, vyvolaným aplikací dizociplinu (MK-801), v reverzních variantách obou prostorových úloh (v měnících se prostorových podmínkách) ve snaze otestovat pracovní paměť a mentální flexibilitu, schopnosti značně narušené u schizofrenie. Následující dva experimenty pak prezentují nálezy virtuálních analogií obou úloh testovaných u pacientů po první epizodě schizofrenního okruhu onemocnění, které potvrzující deficit prostorové paměti a kognitivní koordinace u této skupiny pacientů. Tyto nálezy jsou diskutovány s ohledem na výsledky získané v animálních studiích. V práci je diskutován také význam prostorových schopností ve srovnání s verbálními testy v kontextu kvality života a globálního fungování pacientů, a také z pohledu rostoucího výskytu bilinguality. V závěru práce diskutujeme význam vyvinutých metod z pohledu jejich uplatnění ve vyšetření dysfunkce funkčních oblastí mozku u schizofrenie, zejména vzájemný vztah prefrontální kůry a hipokampu. Výsledky zmíněných studií naznačují, že virtuální prostorové testy můžou být užitečným nástrojem komparativních studií věnovaných kognitivnímu deficitu u schizofrenie a jeho farmakoterapii.

Klíčová slova: *prostorová paměť, schizofrenie, kognitivní deficit, prostředí virtuální reality, test skrytého cíle, oddělené referenční rámce, prefrontální kůra, hipokampus*

Abstract

The spatial behavior of animals and humans involves a complex system of cognitive abilities, which show high evolutionary homogeneity. To study spatial memory tasks originally developed for animals (especially rats) are frequently used. The most cited task focused on spatial memory is undoubtedly the navigation towards the hidden platform in the Morris water maze task. Less well known is the Active place avoidance task on a rotating arena (ie. Carousel maze), a task sensitive towards cognitive coordination. Both tasks have an important role in the process of identification of brain areas crucial for spatial memory, and also in pharmacological research, in particular in animal models of neuropsychiatric diseases used to test the effect of drugs on the modeled symptoms of these diseases. The above-described spatial tasks are primarily applied in modeling of cognitive deficit that presents a crucial symptom of many neuropsychiatric disorders. In recent years considerable attention has been devoted to the research of cognitive impairment in schizophrenia. Today, several animal models are used in attempt to explain the causes of symptoms observed in schizophrenia, showing changes corresponding in various degree also to cognitive symptoms. No specific treatment for cognitive deficit in schizophrenia is currently available, in contrast to positive and negative symptoms. Predictive validity of animal models of schizophrenia is therefore crucial for the development of new drugs aimed at the treatment of cognitive symptoms. Comparative research addressing cognitive abilities of both animal models and patients in a similar tasks, could therefore lead to verification of this validity. Both of the above described spatial tests were in their original form previously been tested in animal models of schizophrenia, and confirmed the expected deficit of spatial memory and cognitive coordination in these models. The aim of this study was therefore to create virtual (computer) analogues of these tasks, which would allow a comparative approach, through examination of patients and healthy subjects. This thesis first describes the experiment testing the performance of an animal model of schizophrenia induced by the application of dizocilpine (MK-801) in reversal versions of both mentioned spatial tasks, in order to assess working memory and learning abilities affected in schizophrenia. Other two experiments present the findings of both virtual analogues tested in the first episode of schizophrenia patients, confirming presence of deficits in spatial memory and cognitive coordination. These results are discussed in context of previous studies in animal model of schizophrenia. Finally, the importance of assessment of spatial abilities is discussed in the context of quality of life and global functioning of schizophrenia patients, and in context of increasing occurrence of bilingualism. The results of the above presented experiments suggest that both virtual spatial tasks present a useful tools for future comparative studies focused on cognitive deficit in schizophrenia and its pharmacological therapy.

Keywords: *spatial memory, schizophrenia, cognitive deficit, virtual reality environment, the hidden goal task, dissociated reference frames, prefrontal cortex, hippocampus*

Content

1 Introduction

1.1 SPATIAL NAVIGATION, LEARNING AND MEMORY

Spatial cognition is a process of determining and remembering spatial positions (of own body and surrounding objects), the directions and distances to other objects in the surrounding space. Navigation process uses this information while maintaining a certain course of trajectory toward planned target position (Jeffery, 2003). Individual processes involved in navigation are closely dependent on each other. For example, the process of distance estimation is based on our ability to perceive depth through binocular and monocular visual and aural cues, however, this ability is based on our previous experiences and thus on memory.

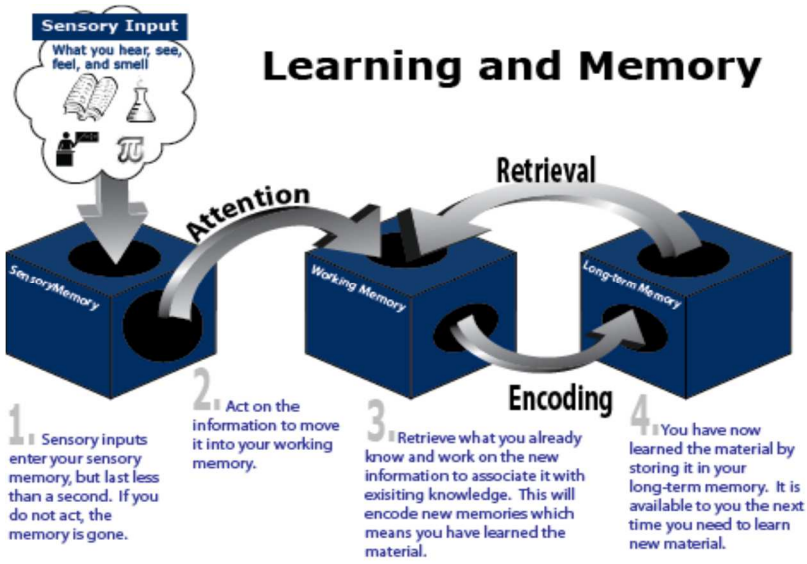


Figure 1. *General model of relationship between individual memory systems (left, adopted from www.lsa.umich.edu).*

Spatial navigation is in fact a very complex behavior that uses a certain extent of all the cognitive functions. This can be illustrated using the schema in Figure 1. If we want to navigate in the environment and find the path to the goal, we must first perceive the information about the environment (stored in sensory memory). Than we have to pay ***attention*** to the surroundings and focus on different sources of information (predominantly visual, auditory or inside information about the own movement). To maintain and process a large amount of information available and choose the ones that are important and useful for orientation, we have to organize it properly. We must first recognize on what object we are looking at, include it in a certain category (for example moving/ changing versus stable elements of the environment) and use only the information that is relevant for us in this specific context. During our own movement the surrounding environment is constantly changing, therefore we cannot effectively navigate without attention, and working memory that allow us to monitor the constantly renewed information. ***Working memory*** allows us for a certain time period to remember some important objects and characteristics of the environment that will be used for consecutive navigation. As human subjects use visual data as a primary source of information, we will be interested

primarily into the capacity of visuo-spatial component of working memory, called the visuo-spatial sketchpad (Baddeley, 1992). Finally, the relevant information is stored in the ***long-term memory*** as a mental representation, so called **cognitive map**, for future navigation in this environment. After some time the navigation process in the familiar environment can be automated and thus processed with lower cognitive demands. Above mentioned memory related cognitive functions will be described in a bigger detail in the next paragraphs.

1.1.1 WORKING MEMORY

Baddeley and Hitch proposed the original *three-component model of* ***working memory*** in 1974 (Baddeley and Hitch, 1974), including visuospatial sketchpad, phonological loop and executive component (see Fig. 2). This model supports both the neuropsyhological and neuroimaging evidence. This model assumes that each component has a limited capacity and is relatively independent of the others. However, the model was updated by Baddeley (Baddeley, 2000) after the model failed to explain the results of various experiments. He proposed an expanded *four-component model* that includes the **episodic buffer** as an additional component. The episodic buffer acts as a 'backup' store which communicates with both long term memory and the components of working memory. It comprises a limited capacity system that provides temporary storage of information held in a multimodal code, which is capable of binding information into a unitary multi-dimensional episodic representation.

The original cognitive theory of working memory (WM) postulates architectural segregation between these components responsible for the short-term active maintenance of information and those responsible for the control and coordination of that information. Cognitive neuroscience research has provided strong evidence that the prefrontal cortex (PFC) serves as an important neural substrate of WM. Braver and Cohen (Braver et al., 2001) proposed a theory postulating that PFC represents and actively maintains context information.

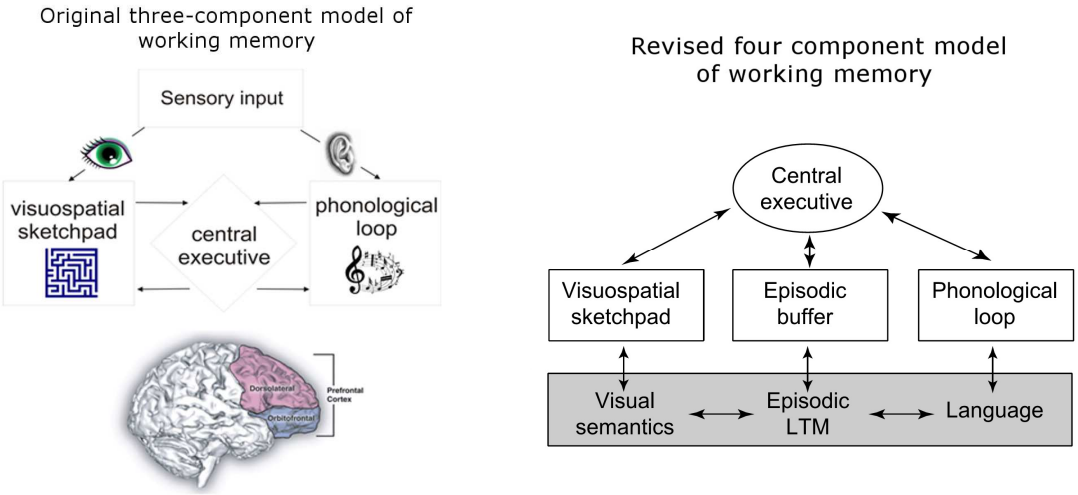


Figure 2. *Flow diagrams of the original model of Working Memory (left) proposed by Baddeley and Hitch (1974) and that contained originally three components, the phonological loop, the visuo-spatial sketchpad, and the central executive. The prefrontal cortex suggested to be responsible for both short-time storage and maintenance of information in WM (bottom left). Revised model includes the episodic component that is affected by crystalized cognitive systems (in shaded rectangle) capable of accumulating long-term knowledge (Baddeley, 2000), in contrast to fluid working memory capacities.*

Maintained representations thus provide a mechanism of control by serving as a top-down bias on the local competitive interactions that occur during processing. As such, they suggest that both storage and control functions are integrated within PFC.

Thus, ***visuo-spatial working memory (VSWM)*** can be defined as the ability to process and store information about the visual identity of an object and its position in space for a short period of time (McAfoose and Baune, 2009).

1.1.2 SPATIAL LEARNING AND LONG-TERM MEMORY

Learning and memory are essential capacities both for humans and animals, as they allow flexible and adaptive behavior in response to slow or sudden changes in the environment, and their principles are shared across species. Extensive research both in lesion studies in animals and clinical studies of brain injured patients have revealed multiple independent memory systems with distinct substrates, specialized for learning of specific material (verbal or visual information, movements, etc.). Long-term memories have been divided to declarative and non-declarative (Kolb and Whishaw, 1995).

Declarative or explicit ('knowing what') memories are conscious and can be voluntarily accessed and verbalized. They can be further divided to semantic and episodic memories. *Semantic* memory refers to facts and rules and basic knowledge about the world (Squire, 2004), while *episodic* memory refers to single events or personal experiences. Episodic memories contain information about the spatial and temporal context of these events, including 'blueprint' of the internal state of the individual during encoding, its emtions, percetions and thoughts (Dere et al., 2008). In a simplified definition episodic memory is a memory for what happened, when (in context of time/ temporal order) and where (spatial context).

Non-declarative or implicit ('knowing how') memories of skills and how to do things, particularly how to use objects or movements of the body (Squire, 2004). These memories are typically acquired through repetition and practice, as they are composed of automatic sensorimotor behaviours that are so deeply embedded that we are no longer aware of them (they are not conscious). Once these "body memories" are learned, they allow us to carry out procedure of motor actions more or less automatically.

Similar disctinction can be done also in the context of spatial memory. In an effort to understand what information both animals and people use when navigating through their environment and what brain areas are engaged in processing and subsequent response of the organism, spatial behavior was categorized into several categories (Jeffery, 2003;O'Keefe, 1978). Since there are several different division systems of spatial behavior, we will focus only on the most common taxonomy in reference to the previously mentioned division of memory systems. Roughly we can distinguish a dichotomy of egocentric (i.e., ego-centered; body-centered) and allocentric (also referred to as exocentric, exo-centered, or environment-centered) spatial strategies suggested by O'Keefe and Nadel (O'Keefe and Nadel, 1978).

Egocentric processes represent the *implicit (procedural) type of long-term memory*, as they are involved during movement in spatial environment and constantly respond to changes in our body position, and then update our position against objects in outer space(Jeffery, 2003). An egocentric strategy refers to the discrimination of a spatial locus with reference to the body, or relative self-movement. This term has been used in at least two ways. Firstly, to refer to the encoding of spatial positions of distal objects by reference to an ego-centered coordinate system, and secondly, in terms of the relationship of the observer to proximal objects,

particularly objects that are within reaching distance (Roche et al., 2005). Egocentric space is important because it includes the region of central space to which sensory processes are most sensitively directed and the use of egocentric coordinates enables the identification of spatial loci in relation to the body midline (Foreman and Gillett, 2008). However, the body midline is always shifting during the movement of an organism and the ego-centered system does not produce a stationary egocentered array.

Egocentric processes involve information from external sources (visual, auditory, tactile and olfactory) and internal somatosensory information. In the absence of external information (navigation without sight), the inertial inputs from the vestibular system and the substrate information from proprioception gain considerable importance (Mittelstaedt and Glasauer, 1991). While navigating in the dark we are talking mostly about the process of path integration or idiothetic navigation (Whishaw, 1998). Such navigation strategy, however, leads to a gradually increasing error in the estimation of distances and it must be from time to time corrected using reference information from external sources (visual, auditory, or tactile), otherwise it leads to a cumulative error.

Allocentric processes represent the *explicit (declarative) type of long-term memory*, and thus constitute more complex method of processing spatial information that is independent on the body position. Spatial information is here integrated in the form of coordinate system, which characterizes the mutual spatial relationships (distances, directions) of the known objects in the environment (Jeffery, 2003). Thus, allocentric space is likely to involve a much greater memory component. It enables to estimate the direction towards the goal position by triangulation method using objects visible around. In contrast to egocentric 'map', the allocentric map is more complex, an allows for easy manipulation with acquired information that can be used to find alternative routes in the environment in case of trajectory to the goal is blocked.

Any traveling requires humans to activate both egocentric and allocentric processes to facilitate spatial knowledge acquisition: person-to-object relations that dynamically change as movement takes place (egocentric referencing) and a more stable object-to-object allocentric strategy that anchors the developing cognitive map (Sholl, 1996). Therefore, both (ego- and allo-centric) processes are mutually cooperating in navigation process to form an internal representation of the environment that Tolman called in 1948 by a term '**cognitive map**' (Tolman, 1948). One of the current models of the process of the cognitive map formation created by Roche is shown in Figure 3 (Roche et al., 2005). According to the traditional theory of 'cognitive mapping' (O'Keefe and Nadel, 1978), the emerging mental map stores information in the form of allocentric coordination system of individual positions of memorized objects. In addition to this theory, there are navigation models showing that remembering the position of the target location can alternatively be saved based on local views (mental images) from a target destination (McNaughton et al., 1989). Spatial relationships between several such points are then stored in the form of a mental representation of individual steps (movements) needed in order to move from one point to another. A cognitive mapping theory (O'Keefe and Nadel, 1978) was first to localize the cognitive maps to the medial temporal lobe, particularly to the hippocampal place cells. This theory was later supported by numerous studies in both animals and human, in brain lesioned patients as well as in healthy volunteers using functional imaging.

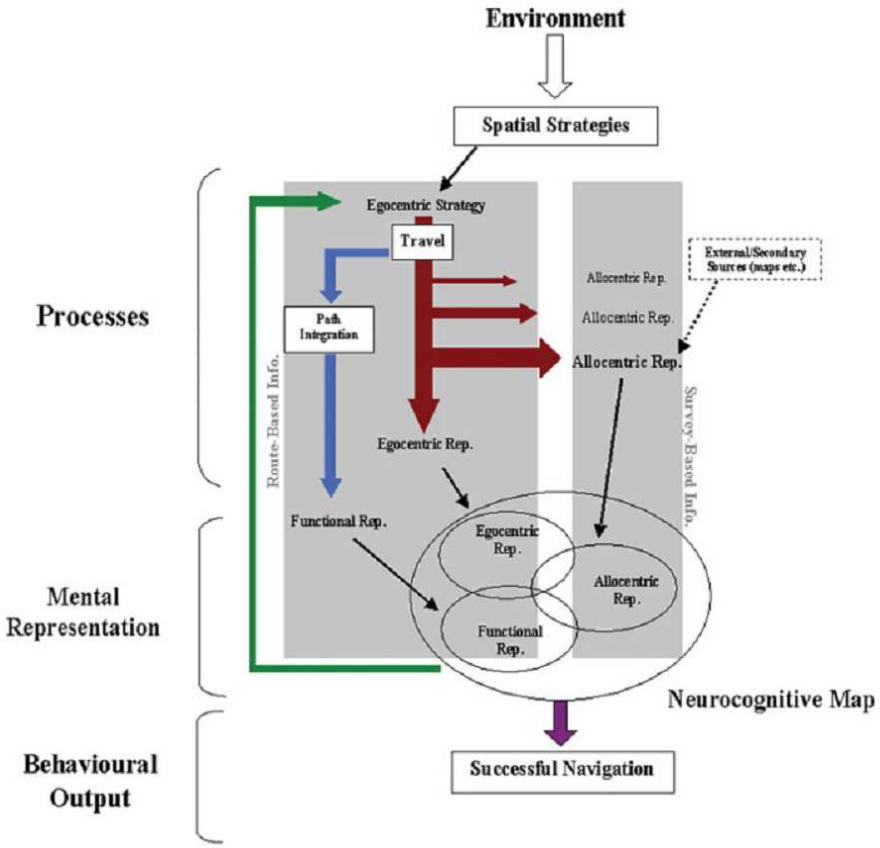


Figure 3. *Schematic diagram representing a cognitive map model by Roche et al. (2005) that outlines how the different navigation processes interact and segregate the different forms of information in producing the unified cognitive map (adopted from Roche et al., 2005).*

1.1.3 ROLE OF REFERENCE FRAMES IN SPATIAL NAVIGATION

The information stored in a form of cognitive map is very complex and includes, at least in some reduced way, the whole three-dimensional space around. An essential feature of any cognitive map is therefore a reference frame, the origin and orientation in space, in the sense of what is above and below, left and right, in front and behind. Spatial decisions can thus be produsedusing several frames of reference (Sun and Wang, 2010).Any conflict between these reference frames can slow down the reaction times needed in order to perform a spatial decision. Translation between individual reference frames should take part mainly in the retrosplenial cortex (RSC), confirmed by the inability to derive directional information from landmark cues (heading disorientation) after RSC damage (lesions) in humans.

Dissociation of reference frames was studied also in animals mostly in moving environments, for example by rotation of some part of the environment. In rats, place avoidance on a rotating arena was applied in order to produce dissociated reference frames of the arena and the surrounding room. Rats demonstrated their ability to code the to-be-avoided area independently, relative to one of the two reference frames (Fenton et al., 1998). The existence of these two representations was supported also on a cellular level, by recording of place cells in the rats` hippocampus (Zinyuk et al., 2000). The partially distinct populations of place cells

for both reference frames imply the existence of their separate spatial representations. Recent recordings of populations of place cells on a rotating arena showed that the place cells that are active together tend to represent locations in the same spatial frame (Kelemen and Fenton, 2010). Similar observations in stable environment with changing spatial configuration showed that the active hippocampal representation seems to switch repeatedly from one reference frame (representation) to another in a form of theta-paced flickering between individual place-cell maps in the hippocampal area CA3 (Jezek et al., 2011).

1.1.4 NEURONAL CORRELATES OF SPATIAL MEMORY

Cognitive functions, responsible for spatial navigation, are dependent on activity of several brain regions creating navigational network involving the following areas: medial temporal lobe (MTL), prefrontal and parietal cortex, the cerebellum, basal ganglia and retrosplenial cortex (Maguire et al., 1998).

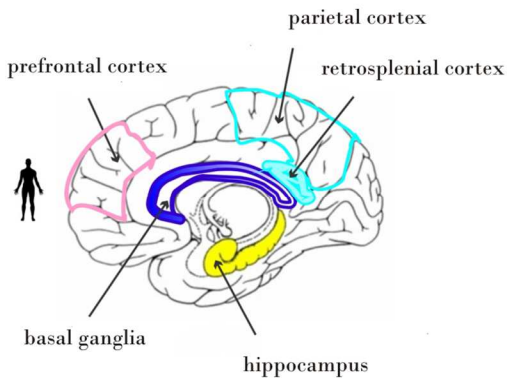
Given that the resulting cognitive map arises from cooperation of several navigation processes, it is very difficult to test them separately and find only the activation of that part of the network that is responsible for some specific process. However, some parts of the navigation network are responsible for spatial learning and memory in general and are shared in all navigation tasks, while some other areas are responsible for simple egocentric navigation (route following) in known environments. For example, if mainly visual stimuli are used to navigate, the visual cortex of the occipital lobe will be activated as well. However, if we utilize auditory or olfactory stimuli during navigation without sight, the specific sensory and association areas will be active.

During navigation using visual information, several areas of the brain are responsible for specific identification of spatial information (see Figure 4). For example, the area responsible for identification and recognition of objects was observed in *lateral occipital complex* and partly in *fusiform gyrus* (includes fusiform face area responsible for identification of faces). Another ventral cortical region specialized for the perception of buildings is located in the right lingual sulcus (Aguirre et al., 1998a). The posterior part of parahippocampal gyrus was active during observation of spatial scenes (Hasson et al., 2003).

If the subject moves during navigation (actively or passively) and thus uses the process of path integration, we can observe the activity of *parietal somato-sensory area in parietal cortex* (Aguirre et al., 1998b). Parietal lobes damage leads to egocentric disorientation (Seubert et al., 2008), as it plays an important role in egocentric space processing. Parietal cortex thus participates also in the estimation of egocentric spatial distances in visual scenes. Given that, in the estimation of distance can take advantage of several possible spatial cues (monocular and binocular), this process activates various regions of dorsal visual stream, including occipital and parietal lobe. Interestingly, while binocular cues activate mostly regions of occipital visual cortex, monocular cues activate the area of intraparietal sulcus, probably requiring higher level of processing, for review see (Berryhill and Olson, 2009).

Crucial is also the function of already mentioned *retrosplenial cortex* (RSC, medial part of the posterior cingulate gyrus, Fig. 4) which cooperates with the structure of hippocampal formation. It is assumed that the area of retrosplenial cortex is responsible for the translation of information between various reference frames, and thus contributes to a shift of attention from egocentric to allocentric framework and vice versa (Fenton et al., 1998;Iaria et al., 2007).

Indeed, lesion of the RSC affected segregation of spatial information in place avoidance task in rats (Wesierska et al., 2009).



Brain area	Role in spatial navigation
Hippocampal formation	Visuo-spatial memory; coding and retrieval of cognitive map
Prefrontal cortex	working memory, planning and decision making, temporal order of spatial information; path integration
Parietal cortex	Visuo-motor coordination, egocentric distance estimation
Retrosplenial cortex (Posterior gyrus cinguli)	Translation of information between reference frames
Basal ganglia	Route following, procedural learning

Figure 4. *Brain areas and their role in the navigation process (adjusted from (Fajnerova, 2011).*

The crucial navigational structure is the same neuronal area as involved in declarative memory formation in general, the hippocampal formation. The ***medial temporal lobe (MTL)***, especially the structures of ***hippocampal formation*** (HF, see Fig. 4) are considered as the most important in the formation of allocentric cognitive map. O'Keefe and Nadel published in (O'Keefe and Nadel, 1978) a book in which they describe the role of hippocampus in coding of spatial information in mammals, resulting in allocentric cognitive map. This theory is based among others also on observation of so called place cells, excitatory pyramidal neurons in Cornus ammonis areas (CA1 and CA3) of the hippocampus, which exhibit spatially selective activity. The activity of the hippocampus was already demonstrated also in many navigation tasks where imaging methods such as PET or fMRI were applied (Epstein and Kanwisher, 1998;Folley et al., 2010;Hartley et al., 2003;Iaria et al., 2009;Maguire et al., 1998;Roche et al., 2005).

It was confirmed that the bilateral lesions of MTL structures in rats significantly impair spatial abilities, such as allocentric navigation to a hidden goal position in Morris water maze (MWM;(Morris et al., 1982)). Interestingly, navigation in moving environment, such as the Carousel maze on the rotating arena, in the so called also active allothetic avoidance task (AAPA, (Bures et al., 1997)), showed impairment of spatial abilities after unilateral lesion (temporal inactivation) of hippocampus (Cimadevilla et al., 2001). Pre-training unilateral hippocampal inactivation profoundly impaired acquisition and retrieval in the task, while the posttraining inactivation also impaired performance in subsequent sessions. The Carousel maze task seems more sensitive to hippocampal disruption than the standard MWM task because the same unilateral hippocampal inactivation does not impair performance in the hidden goal task. These suggest that the hippocampus not only encodes allothetic relationships amongst landmarks, but it also organizes perceived allothetic stimuli into systems of mutually stable coordinates, requiring greater hippocampal integrity (Cimadevilla et al., 2001). HF indisputable role in spatial cognition even in human have been confirmed in examination of patients with hippocampal lesions (e.g. patient HM). Unilateral (right) parahippocampal cortex lesion led to serious disruption of visuo-spatial memory in both 2D object localization and navigation in the

human version of the hidden object analogy of MWM (Bohbot et al., 1998). Importantly, basic procedural egocentric spatial abilities, such as idiothetic navigation, or path integration in the absence of visual information (Whishaw, 1998) or navigation towards the hidden platform with the stable starting position (Eichenbaum et al., 1990) are not affected by hippocampal lesions, as they are maintained by different brain regions.

The findings of animal studies were confirmed also in the imaging studies in healthy human volunteers that showed MTL activation in various spatial tasks (Gron et al., 2000;Maguire et al., 1998). However, several later studies observed MTL activation only in tasks assessing allocentric navigation (e.g search a hidden place, find a route in new environment, find alternative route in known environment, etc). It turned out that we don't need HF to solve certain spatial tasks requiring usage of already well-learned routes. In such case the network of *corpus nuclei caudate* (*Basal ganglia*, see Fig. 4), insular cortex and extensive area of parietal cortex is activated (Hartley et al., 2003). These areas are probably responsible for maintaining and execution of sequences of actions (movements) leading us to the target position using 'representation of learned route '(action-based navigation,(Hartley et al., 2003)). This type of navigation can be used in everyday navigation, as a process of automatization, a part of procedural learning. However, if during navigation on the previously learned route some obstacle appears, the activity of hippocampus and prefrontal cortex will be observed again, as it is needed for planning of the new alternative route in already familiar environment (Maguire et al., 1998). This dual discrimination of spatial memory can be explained by the well documented case of patient HM, suffering from bilateral hippocampal lesions that led to irreversible disruption of his declarative memory, despite preserved ability of procedural learning (Milner, 1972). This proves the independence of procedural learning on MTL activation. Patient HM was thus able to continuously improve in different procedures and activities (e.g. improvement in the spatial procedure Mirror drawing test), while he never remembered learning/doing them.

Also *prefrontal cortex* (Fig. 4) plays an important role in spatial cognition, as it is involved in both spatial working memory (Goldman-Rakic, 1996), and in executive functioning such as planning and behavioral flexibility, decision-making and strategic choices. In rats, this area, observed mainly in medial prefrontal cortex (MPFC; (Uylings et al., 2003)), is often connected to spatial abilities, probably due to the tight communication with HF. Performance of animals with lesions of the prefrontal cortex was intact in standard allocentric MWM task, but it was disrupted after the removal of some landmarks (Jo et al., 2007). In contrary, MPFC lesion completely disrupts idiothetic navigation (de Bruin et al., 2001) and also leads to weakening performance in tasks that require remembering of a time sequence of spatial locations (Kesner and Holbrook, 1987). It is believed that MPFC participates in in the process of planning and navigation to the goal. The results of these studies further suggest that the hippocampus and MPFC work in parallel, and lesions of MPFC may not necessarily lead to a deficit in spatial cognition tasks that are heavily dependent on a visuo-spatial component of working memory because the hippocampus continues to operate.

Several neurotransmitters including acetylcholine, glutamate, γ-amino-butyric acid (GABA), and catecholamines have been investigated in a variety of memory models, with considerable evidence of extracellular level variations that correlated with changes in neuronal activity during memory formation (Miranda and Bermudez-Rattoni, 2007).

1.2 ASSESSMENT OF SPATIAL COGNITION IN HUMANS

Tests of spatial cognition could be divided into two categories: A) tests ('table-top tasks' and computer tests) presented mostly in two-dimensional (2D) scale and B) navigation tasks (real or virtual) performed in three-dimensional space. These two types of tests differ primarily in the perspective in which the tested person orients, either from the perspective of viewer or first-person perspective, and also in the size of the testing environment.

1.2.1 TWO-DIMENSIONAL PAPER-PENCIL & COMPUTERIZED SPATIAL TESTS

There are many published tasks testing various aspects of spatial cognition. Many traditionalpaper-pencil tasks have been computerized. Kolb and Whishaw distinquish two main categories of spatial tests assessing either visualization or orientation abilities (Kolb and Whishaw, 1995).

1.2.1.1 Visualization tests

Visualization tests evaluate the ability to mentally manipulate, rotate, twist or invert various objects. The underlying ability seems to involve a process of recognition, retention and recall of the presented configuration (Kolb and Whishaw, 1995).

Among the simplest, we can describe the **mental rotation paradigm** (Shepard and Metzler, 1988) of 2D or 3D objects (see Fig.5). This task uses a process of mental transformation (rotation) of visual stimuli. Due to the presentation of the object in both original and rotated position, this test is more dependent on visuo-spatial imagination rather than memory realted processes.

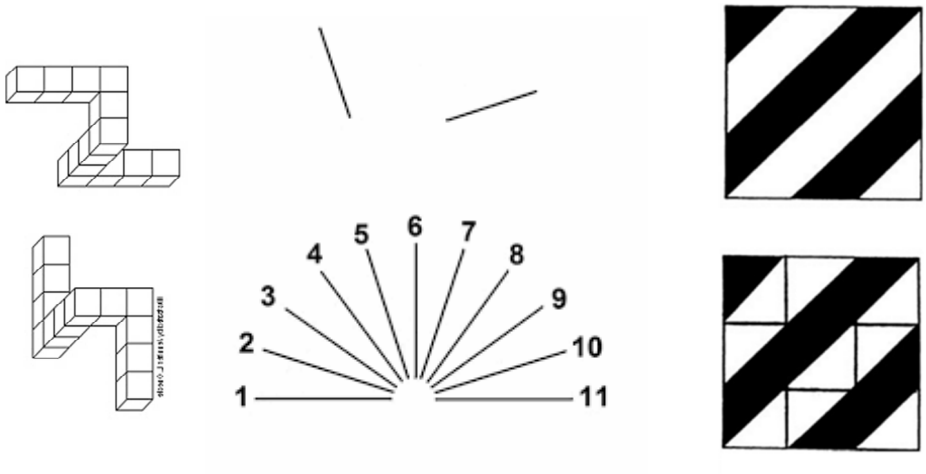


Figure 5. *The illustration of the Mental Rotation tasks based on Shepard and Metzler, 1971) (left); In the Judgement of Line Orientation test -subtest of RBANS battery (Randolf et al., 1998) - subjects are asked to match two angled lines to a set of 11 lines that are arranged in a semicircle and separated 18 degrees from each other (middle); The example trial of the Block design test (WAIS battery) consisting of 9 blocks (above the presented design, below the illustration of the correct result composed of 9 blocks) (right).*

Another test of visualization abilities the **Judgment of Line Orientation** (see Fig.5) – subtest of Repeatable Battery for the Assessment of Neuropsychological Status (Randolph,

1998), was developed by Arthur L. Benton as a standardized test of visuospatial skills commonly associated with functioning of the parietal lobe in the right hemisphere (Benton, 1994). The test measures a person's ability to match the angle and orientation of lines in space (Mitrushina, 2005).

1.2.1.2 Orientation tests

On the other hand, orientation tests evaluate comprehension of the arrangement of elements within a visual stimulus pattern and the aptitude to remain unconfused by the changing orientation in which the spatial configuration may be presented (Kolb and Whishaw, 1995). Kolb ad Whishaw also suggest that inferior temporal damage or hippocampal damage should disrupt performance only on orientation tests, since these tests require both object identification and a spatial-coordinate system.

In here, several tests of **perspective taking abilities** (Perspective taking task, Money Road map test) should be mentioned. The distinction between mental abilities that require a spatial transformation of a perceived object (e.g., mental rotation) and those that involve imagining how a scene looks like from different viewpoints (e.g., perspective taking) are reported by Hegarty and Waller (Hegarty, 2004). Kozhevnikov and Hegarty (Kozhevnikov and Hegarty, 2001) developed and together with Waller adjusted a test of spatial orientation and perspective taking abilities called *Perspective Taking/Spatial Orientation Test*. Here, participants are shown a twodimensional array of objects or a schematic map of a town, and were asked to imagine themselves facing a particular direction within the array or map. They

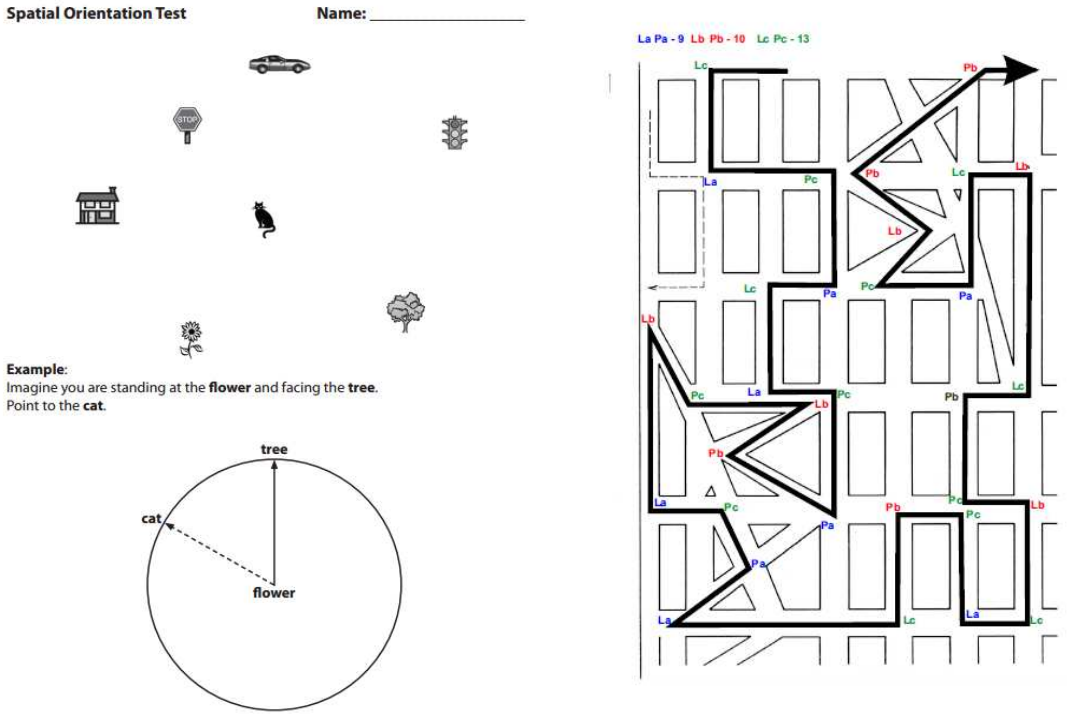


Figure 6. *(left) Perspective Taking/Spatial Orientation Test (Hegarty & Waller, 2004); (right) The Money Road-Map-Test (by Money, Walker, and Alexander 1965) with color coded categories of intersections.*

then indicated the direction to a target object in the array (or landmark in the map) from the

imagined perspective. (A sample item is shown in Fig.6). Verbal reports from the participants indicated that the dominant strategy used to solve the test items was to imagine themselves reoriented with respect to the display, suggesting that the tests are true tests of spatial orientation ability (i.e., depend on egocentric rather than object-based spatial transformations). This conclusion was also supported by systematic errors in which participants confused left/right as well as front/back pointing directions, suggesting that they encoded the locations of the objects with respect to body coordinates.

Similarly, the *Money Road-Map-Test* (RMT; Money, 1965, see Fig.6) assesses specific visuospatial functions, such as mental rotation and perspective taking strategy. This tests measures the total number of errors and time necessary to finish the task. Some authors proposed that tthe total number of errors (out of a total of 32 turns) should be divided into three categories (according to Markova et al, 2015) by the angle of the route before each turn relative to the subject's heading: A) rotation of less than 70 degrees (9 turns), B) rotation of 90 degrees (13 turns), and C) rotation of more than 110 degrees (10 turns).

1.2.1.3 Visuo-spatial neurocognitive tests without mental rotation/ orientation component

Beside these 'typical' spatial tasks, we should mention also other methods used to test specific cognitive abilities (e.g. attention, executive functions or memory) using visuospatial task.

For example, the *Trail Making Test* (TMT- A and B) is widely used to test speed of processing (time measured in part A), and executive functioning (time measured in part B), and working memory or task-switching (B/A ratio) (see Lezak, 1995; Mitrushina et al., 2005; Reitan, 1992). Both parts of the TMT consist of 25 circles distributed over a sheet of A4 paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order as quickly as possible. In Part B, the circles include both numbers (1 – 13) and letters (A – L); and the patient draws lines to connect the circles in an ascending pattern, but alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The direct score of each part is represented by the time of completion of the tasks. In addition, the B-A difference score, the B:A ratio, and the B-A/A proportional score have been used as clinical indicators of certain cognitive operations (working memory), or as specific markers of brain damage (for a review see Periáñez et al., 2007).

Another test developed in order to assesses executive functioning, in particular spatial planning abilities is the The *Key Search Test* (KST; Wilson et al, 1998). This test is one of the six test from the battery called Behavioural Assessment of the Dysexecutive Syndrome (BADS; Alderman et al, 2003). This battery was designed to evaluate the everyday problems arising from Dysexecutive syndrome (DES; Alderman et al, 2003). These six tests assess executive functioning in more complex, real-life situations, which improves their ability to predict day-to-day difficulties of DES. The Key Search test reflects the real-life situation of needing to find something that has been lost. It assesses the patient's ability to plan how to accomplish the task and monitor their own progress using the evaluation of selected spatial strategies and their efficacy.

Other group of tests was developed in order to evaluate visuo-constructive abilities, including visuo-motor functioning and executive functioning, particularly spatial visualization and planning. Here we can mention the *Block-design* test, a subtest of the Wechsler Adult Intelligence Scale (WAIS-III, (Wechsler, 1997) that requires the patient to create a copy of the

pattern presented as 2D design (picture) by arranging the upper side of 4 or 9 blocks (with white, red or red/white sides). This task is used to test constructional apraxia occurring after posterior lesions of frontal cortex (for review see (Darby and Walsh, 2005)), because of the loss of spatial organization of elements, or through the disruption of one or more of the executive steps - intention, programming, regulation or verification (as suggested by Luria and Tsvetkova, 1964, in (Darby and Walsh, 2005)). Performance in this task can be therefore improved after partial programmes are provided. This test is also used to tap spatial visualization ability and visuo-motor coordination. The examined person is asked to use hand movements to rearrange blocks that have various color patterns on different sides in order to match a presented pattern. The items in a block design test can be scores both by accuracy in matching the pattern and by speed in completing each item. Impaired performance on the block design test is indicative of affected functioning of the parietal and frontal lobes. The performance of an individual can be therefore reduced in head injury, Alzheimer's disease, and stroke (Lezak, 2012). Additional evidence suggests impairment in block design performance among schizophrenic and bipolar disorder patient populations.

Patients with constructional apraxia show impaired performance also in the copy of the Rey–Osterrieth complex figure test (RCFT) or the Taylor complex figure. Here examinees are asked to reproduce a complicated line drawing, first by copying it freehand (recognition), and then drawing from memory (immediate and delayed recall). This test was first proposed by Swiss psychologist André Rey in 1941 and further standardized by Paul-Alexandre Osterrieth in 1944. It is frequently used to further explain any secondary effect of brain injury in neurological patients, to test for the presence of dementia, or to study the degree of cognitive development in children. As many different cognitive abilities are needed for a correct performance in this test, the test permits the evaluation of different functions, such as visuospatial constructional ability and visual memory, but was widely used for the evaluation of visuospatial. Recently, the RCFT has been a useful tool for measuring executive function that is mediated by the prefrontal lobe (e.g. Shin et al., 2006; Lezak, 2012).

Finally, spatial tests often used in neuropsychological diagnostics include tests of **visuo-spatial working memory**. These tests examine the ability of the individual to remember the position (or direction, orientation and distance) of several objects in chronological order in a confined 2D or 3D space. The vast majority of these tests, however, uses only two-dimensional space (computer screen or simple plastic and paper surface), and represent a simpler form of spatial orientation.

Typically spatial working memory tests (see Fig.7) include tasks such as:

a) Spatial Delayed-Response Task (SDRT; Piskulic et al., 2007), a behavioral task in which a delay is interposed between when the spatial cue is presented and the subsequent response is permitted. The cue is not present during the delay period so that this spatial information must be stored in memory in order to guide future responding. Alterations in the duration of the delay period adjust the mnemonic load of the task.
b) The n-back task was designed to test working memory function by Wayne Kirchner in 1958. The subject is presented with a sequence of stimuli (letters, numbers, shapes, spatial position, sounds etc.), and the task consists of indicating when the current stimulus matches the one from *n steps earlier* in the sequence. If the task n equals 2 or more, the working memory buffer needs to be updated continuously to keep track of

what the current stimulus must be compared to (Gazzaniga et al., 2009; Lezak, 2012). The simple spatial version of n-back task presents only one item (e.g. square) that appears in different positions on the game board (computer screen) during each turn. The participant has to remember and identify the position of the square N steps back. In the dual-task paradigm (proposed by Susanne Jaeggi et al. in 2003), two independent sequences are presented simultaneously, typically using different modalities of stimuli, such as one auditory and one visual (see Figure 7 left). Meta-analysis of 24 n-back neuroimaging studies have shown that during this exercise the following six brain regions are consistently activated: lateral premotor cortex; dorsal cingulate and medial premotor cortex; dorsolateral and ventrolateral prefrontal cortex; frontal poles; and medial and lateral posterior parietal cortex (Owen et al, 2005).

c) Spatial Span (subtest of the Wechsler Memory Scale III; Wechsler, 1997) or Corsi block test variants are also used to test spatial working memory. In both the real and the computer version of the task is the tested human required to remember and repeat the sequence several blocks/squares (forming 2D grid of 9-10 random spatial positions) in the correct order (tested subsequently after the presentation of the correct sequence).

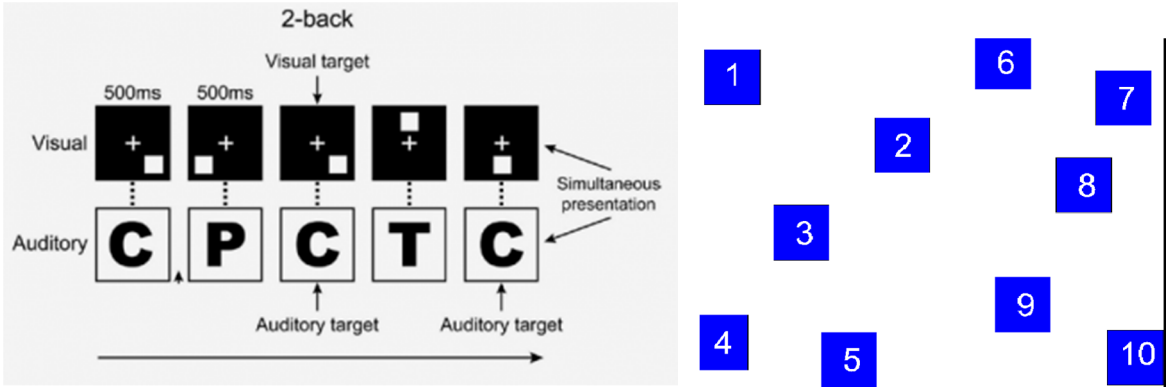


Figure 7. *(left) The example of 'Standard' dual n-back task developed by Dr. Susanne Jaeggi and her colleagues (2008), adopted from http://www.highiqpro.com/2g-nback. (right) The example of the 2D version of the Corsi block test with spatial positions marked by numbers (not visible to tested person).*

1.2.2 NAVIGATION TASKS IN 3D SPACE (FROM ANIMALS TO HUMANS)

For assessment of spatial navigation various spatial tasks have been created, requiring navigation in real or virtual 3D environment (eg. complex maze navigation, navigation inside a building, navigation in virtual city, navigation without the use of sight in real and virtual environments).

Research on spatial cognition in humans is much more diverse than in animals, although some of the frequently used experimental tests are based on animal models. One of the most often used spatial tasks in animal research is the ***Morris water maze*** (MWM; Morris, 1981). This goal-directed task was originally developed for rats and requires them to learn and remember the position of a hidden platform located in a circular swimming pool in relation to distal visual cues (Fig. 8, left). The MWM apparatus is used in three basic versions (shortly described in Vorhees and Williams, 2006) or protocols : 1) the *reference memory protocol*, with the hidden platform placed in a stable position (a measure of place learning); 2) the *reversal*

protocol, with position moved after one week training (reveals whether animals can extinguish their initial learning of the platform's position and acquire a direct path to the new goal position); 3) the *delayed-matching-to-place* (DMP) protocol often referred to as the 'working memory protocol'(Dudchenko, 2004), where the platform position is changing every day and variable inter-trial intervals are used to assess working memory 4) the *probe trial* with the platform removed is usualy applied in the end of the reference protocol.

This test was later used also in aging studies, experiments with brain lesions and to monitor the effects of pharmacological treatment and toxic substances on cognition (particularly in rats). Since 1982 more than 2,500 articles have been published using this model or its variations.

Some real space human MWM analogues have been developed to test the human spatial navigation, mostly in dry circular arenas (Overman et al., 1996; Skolimowska et al., 2011; Bohbot et al., 1998; Stepankova et al, 1999). The development of virtual environments (VE) provided a significant methodological advance, allowing the detailed recording of the subject's behavior, along with easy handling and presentation of stimuli. Several virtual reality versions of the MWM have been designed using the reference memory protocol with a stable goal position (Astur et al., 2004; Goodrich-Hunsaker et al., 2009; Jacobs et al., 1998; Moffat and Resnick, 2002; Mueller et al., 2008; Hanlon et al., 2006) or working memory paradigm (Rodriguez, 2010).

Two different strategies can be used to find hidden goal position in MWM depending on the applied protocol. In egocentric version (with stable starting position) the hidden goal can be located using the distance and direction from the starting position. In the allocentric version of the task, the hidden goal can be found only by deriving its relative position towards diverse points of reference around the arena. The test therefore requires allocentric navigation (orientation using distant orientation cues). Because the start position is randomly changing during the experiment, it is necessary for the subject to carry out a re-orientation of the own position towards the goal position and orientation marks placed around the pool in every trial.

Another very promising task is the test of the *active allocentric place avoidance* (AAPA; Cimadevilla et al., 2000), also called ***Carousel maze*** as it is performed on rotating arena. Due to the arena rotation, two separate frames of reference are dissociated (see Fig. 8, right). The task of the test subject is then to actively avoided 60 ° sector of the arena that is hidden and stable in the room reference frame. For successful avoidance of the punished sector the subject must correctly identify relevant and irrelevant spatial information (Cimadevilla et al., 2001). Thus the animal needs to distinguish the reliable information bound to the stable room frame of reference (mainly visual information) from the misleading infromation tied to the rotating arena (see Fig. 3).

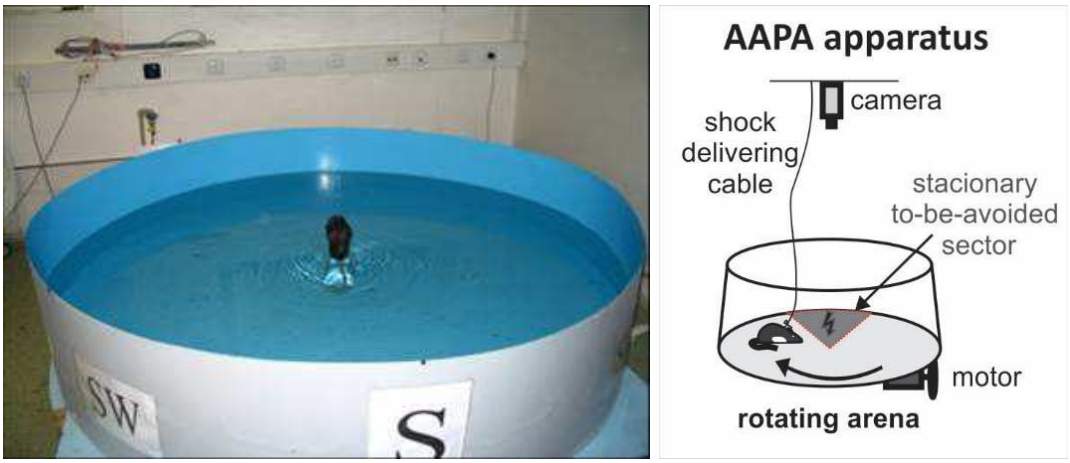


Figure 3. *Morris water maze for rats – with target position placed under the water (left) and schema of the active allothethic place avoidance (AAPA) task on a rotating arena forming two reference frames (stable room frame and moving arena frame) with to-be-avoided sector defined in the room frame (right).*

Real analogies of both previously described tests were developed for testing of human subjects and are both operational in an apparatus build in Prague by our Neurophysiology of Memory group (Institute of Physiology CAS), called the 'Blue Velvet Arena '(BVA; Kalova et al, 2005; Hort et al, 2007; Bohbot et al., 2002; Stepankova et al., 2003). The BVA has a form of an enclosed circular tent with a possible rotation of the floor. Analogue of the MWM hidden goal protocol in BVA was named the Hidden Goal Task (HGT; Kalova et al, 2005), the analogy of the carousel maze is known as the Dissociated task reference frames task (DRF; Vlcek et al., 2006). Both tests were successfully used for testing of spatial deficit in different neuronal diseases, especially in patients with Alzheimerdementia and mild cognitive impairment (MCI, Kalova et al, 2005; Hort et al., 2007).

1.2.3 VIRTUAL REALITY AS A TOOL FOR ASSESSMENT OF MEMORY FUNCTIONS IN HUMANS

Significant methodological shift came with the virtual reality (VR) environments, which was first presented in 1983 (Krueger et al., 1985). Despite certain limitations, as the narrower field of view and absence of actual movement, VR has a lot of advantages. The main advantage of VR is the possibility of easy recording of the behavior and movement of tested subjects in combination with easy accommodation of the environment using a wide spectrum of stimuli, and their easy handling. Thanks to automatic presentation of stimuli the computerized tests in general reach higher time precision than traditional neuropsychological tests (paper-pencil tests) presented by human. It was also shown that the cognitive maps created in 3D VR are comparable to those that develop in real environments (Arthur et al., 1997). For this purpose the maps are often drawn by human subjects after active movement in real or virtual environments, which contained several objects in a defined spatial arrangement.

Virtual reality is related to the concept of *telepresence*, a sense of presence in a virtual environment, introduced in 1980 by Marvin Minsky, who described it as the experience of being in two places at the same time. The greater the degree of reality, or fidelity of the real world

simulation is in the virtual environment, the more the user is pulled into a virtual environment (degree of immersion). Authors therefore try to simulate natural elements of our physical environment (eg. topography, lighting, gravity, avatar movements and actions). Concept of immersion thus reflects the degree of fidelity of the environment (from passive involvement through active control to interactive VR). Immersion can be described in several steps, where the player goes through several phases, beginning with a simple concentration, continues through imaginative engagement to full enthrallement by the virtual world. Apart from spatial immersion, we know also immersion in time (involvement in the plot of the story) and emotional immersion (personal reaction to the characters and events). Very interesting is the 'full immersion', where all our senses are stimulated at the same time. Immersion technology enables us to fool the senses and evoke the impression using various methods (eg. panoramic three-dimensional display, acoustic ambient sounds, and haptic stimuli through the so-called "force feedback" systems and replication of scents and smells). The immersion can be increased by the persuasiveness of visual elements, their interaction with auditory effects (timing) and interactive participation of players.

However, we should not omit the disadvantages of VR environments. For example, a compression of estimated distances (depth) was repeatedly described in VR environments compared to the real ones. These differences may be due to limitations of the VR, such as narrow field of view (FOV), distortion of angular declination (determining the angle between the visual target and the height of the onlooker's eye) and restrictions of oculomotor cues. Some of these disadvantages can be partly compensated by monocular visual effects that mimic the spatial cuess, such as the size of objects and objects overlay, or by simple shadowing cues presented in relation to the illumination direction. Another major problem is the fixed accommodative distance. Unlike in the real perception of spatial scenes where the eyes automatically refocuse to distance, the viewing distance is fixed while watching VR scenes. This can lead not only to altered perception of depth (to some extent dependent on the accommodation of the eye), but also to faster fatigue and overloading of the visual apparatus.

Another serious problem is also characterized by the absence or limitation of the actual movement and thus the absence of adequate information from the vestibular system. Absence of movement (and motor efforts) is not only an important factor in the distance estimation, but can also be a source of motion sickness (nausea VR). These negative effects (motion sickness with symptoms of drowsiness, headaches, impaired balance and coordination) may arise because of sensory conflict of information from external (visual information about motion in VR) and internal sources (proprioception and the vestibular system informing us of our own motion). During the presentation of VR using head-mounted display (HMD glasses) is the discomfort caused by the curvature of the lenses, which are primarily designed for eyes looking forward, while the head movement is used to control the rotation of FOV. In contrary, in real world we are accustomed to smaller head movements compensated by the eye movements. Paradoxically, even this lack of VR can be used as therapeutic method for dizziness (vertigo) from travel sickness in so called vestibular reeducation, as the VR presentation itself requires adaptation to discrepancies between internal and external information about the movement and thus supports the process of adaptation in real world. The lack of movement is to some extent already successfully addressed by the new technologies that can create a very realistic perception of movement by linking real head movement (HMD) or the whole body (through

application of bikes, treadmills or sensors located on the human body) movement in VR and real world. The key seems to be particularly the involvement of the rotation and tilt of the head and body during movement in VR. But, it should be noted that egocentric navigation processes in VR use not only inner somatic sensory information but also visual information in the form of optical flow (visual changes resulting from the motion of the observer environment, manifesting as apparent motion of the elements of the visual scene and indicating the direction in which the person moves). Therefore, participation idiothetic navigation in VR cannot be fully ignored.

On the other hand, the problem of the absence of movement in VR also represents an indisputable advantage for its research use. Because it allows us to test behavior in large-scale environments, and to investigate the neural correlates (brain activity) of complex behavior and navigation using brain imaging methods (that require the subject to stay still over the experiment). In addition, Sense of 'presence' provided by the VR can lead to greater ecological validity in comparison to standard neuropsychological tests. Finally, VR enables us to create comparable tests for animals and human in form of virtual analogues, and thus enables us to build large-size environments that are proportionally adequate for humans.

1.3 IMPAIRMENT OF SPATIAL ORIENTATION AND MEMORY

1.3.1 TOPOGRAPHICAL DISORIENTATION AND AMNESIA

Topographical Disorientation (TD), also known as Topographical agnosia (Topographagnosia), is a cognitive disorder that results in the individual being unable to orient in one's surroundings due to some neurological cause, such as brain lesion (resulting from a stroke or part of a progressive illness, hemispatial neglect, dementia or Alzheimer's disease) or developmental disorder (Aguirre and D'Esposito M, 1999).

Developmental Topographical Disorientation (DTD) refers to the inability to orient in one's surroundings from childhood despite the absence of any apparent brain damage, neurological condition or general cognitive deficits. Individuals reported to be affected by DTD (Iaria et al., 2009; Bianchini et al, 2010) are unable to generate a mental representation of the environment (cognitive map). Individuals affected by DTD get lost even in very familiar surroundings, such as their house or neighborhood.

Nevertheless, most of the patients develope TD as a result of focal brain damage (Aguirre, D'Esposito M, 1999). This lesion may result to the inability to make use of selective spatial information (such as environmental landmarks) or to orient by means of specific cognitive strategies such as the ability to form a mental representation of the environment (cognitive map). According to the damaged brain area, several types of TD can be classified.

Landmark agnosia is characterised by the inability to use prominent, salient environmental features (such as landmarks) for the purposes of orientation, usually due to lesions in the *lingual gyrus* (Aguirre and D'Esposito M, 1999; Whiteley and Warrington, 1987). Patients with landmark agnosia can distinguish between classes of buildings, but are unable to identify specific buildings, such as their own house or famous landmarks. However, they are able to draw detailed maps and visualize places that were familiar to them before the illness. Nevertheless, they are able to navigate using spatial information and specific details of landmarks such as house number or its color.

Egocentric disorientation is defined as inability to represent the location of objects with respect to the own position (self) that usually occures due to lesions in the *posterior parietal lobe*. While these patients are unable to accurately reach for visual objects or state the relationship between two objects (above, below, left, right, nearer or farther), they experience no difficulty recognizing or naming people or objects (Wilson et al., 2005). These patients are not able to point to locations of targets defined by visual, proprioceptive, or audio input. A frequent demonstration of this disability is that, although the patients can point to a visualized object, they are no longer able to do so with their eyes closed.

Heading disorientation is defined by the inability to represent direction of orientation with respect to external environmental cues. These patients are able to determine their location using landmarks, but are unable to determine which direction to proceed from those landmarks in order to reach their destination, usually due to lesions in the *posterior cingulate cortex*. They are also impaired in map drawing tasks and are unable to describe routes between familiar locations (Aguirre, D'Esposito M, 1999). Also focal brain damage to the *right retrosplenial region* due to a cerebral hemorrhage (described in three case studies) may cause a loss in sense of direction (Takahashi et al, 1997). These patients showed normal visual perception, were able to identify, determine and remember locations of visible objects, but were unable to recall direction from selective familiar landmarks.

Anterograde disorientation or topographical amnesia is marked by the inability to orient in new environments, usually due to lesions in the *parahippocampus* and *medial temporal lobe* (Habib and Sirigu, 1987). These patients are able to navigate through and draw maps only of environments learned at least 6 months before the brain damage (Ross, 1980; Teng and Squire, 1999). This indicates that the hippocampus and surrounding structures of MTL are not needed for the retrieval of spatial maps learned prior to the injury; however, they are essential for the formation of long-term declarative memories, including spatial memories (Teng and Squire, 1999). The study by Bohbot et al. (1998) confirmed the role of the right hippocampus in visuo-spatial memory tasks (object location, Rey-Osterrieth Figure with and without delay) and the left hippocampus for verbal memory tasks (Rey Auditory Verbal Learning Task with delay). However, as only patients with lesions to the right parahippocampal cortex were impaired on the hidden goal task (MWM) with a 30 min delay, showing that parahippocampal cortex itself may play an important role in spatial memory.

1.3.2 SPATIAL MEMORY DEFICIT IN NEUROPSYCHIATRIC DISORDERS

Similar anterograde disorientation is often described in Alzheimer dementia and also in the early stages of Mild Cognitive Impairment (MCI) that is associated with loss of gray matter in the medial temporal regions, including the hippocampus. Spatial disorientation in AD and mild cognitive impairment (MCI), who are at a high risk of developing dementia, are manifested in getting lost in familiar and unfamiliar environments. Spatial disorientation in AD results from an impairment in multiple spatial abilities, including allocentric and egocentric navigation strategies, visuo-spatial perception, or selection of relevant information for successful navigation (Vlcek, 2011; Gazova et al., 2012; Vlček and Laczo, 2014). A study performed in a group of MCI patients found TD in more than 40% of them (Lim, Iaria, 2010). This group also showed significantly impaired functional abilities compared to patients without TD. Patients suffering from mild cognitive impairment (MCI), who are at a high risk of development of

dementia, show impairment in a subset of these abilities, mainly connected with allocentric and egocentric processing. While spatial disorientation in typical AD patients probably reflects neurodegenerative changes in medial and posterior temporal, parietal, and frontal lobes, and retrosplenial cortex (RSC), which is responsible for translation between egocentric and allocentric frames (Vlček and Laczo, 2014), the impairment of spatial navigation in MCI seem to be connected mainly with the medial temporal and also parietal brain changes (Henderson et al., 1989; deIpolyi et al., 2007).

Clinical subtypes of MCI, are mostly distinguished to amnestic and non-amnestic forms, both possibly single or multi domain. This distinction is relevant when considering the outcomes of subjects with MCI. Spatial memory impairment was tested in several MCI subsets in a real space circular arena, an analogy of a Morris water maze (Hort et al, 2007). Depending on the subtest, the subjects could use for navigation either the starting position and thus apply simple egocentric strategy, and/or orientation cues on the wall in subtest focused on allocentric navigation. The AD group and amnestic MCI multi-domain group were impaired in all subtests. The amnestic MCI single-domain group was impaired significantly in subtests focused on allocentric orientation and at the beginning of the egocentric subtest, while non-amnestic MCI performed well in all subtests. These results suggest that the spatial navigation impairment occurs early in the development of AD and can be used for early diagnostics and monitoring of the disease progression of AD. Similar observation was done in study with Four Mountains test assessing amnestic and non-amnestic MCI patients (Moodley, 2014). Laczo et al (2009) proposed also a distinction of two amnestic MCI subsets, hippocampal and non-hippocampal amnestic MCI, based on the pattern of free and cued memory impairment studied in a real space circular arena (analogy of a Morris water maze).

AD is not the only neuropsychiatric disorder observed in connection with spatial cognition. Attention was also paid to spatial ability in schizophrenia. Here, the results pointed out to the impaired ability of allocentric navigation and preserved egocentric navigation (e.g. Weniger and Irle, 2008).

In fact, many neuropsychiatric disorders, especially schizophrenia and mood disorders, provide evidence of disturbances of cognitive functioning, including deficits in memory, executive functioning, attention/information processing, mental flexibility and fluency as core symptoms of the disease. Impaired cognition has been shown to negatively affect daily functioning, sociability, and long-term outcome of these patients. Among the most common disorders with cognitive impairments are those associated with aging such as various forms of dementia and Parkinson's disease as well as psychiatric disorders such obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and schizophrenia. Finally, disorders more typically identified in childhood such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) also present with significant cognitive deficit.

In context of spatial abilities, especially the deficit of visuo-spatial working memory (VSWM), a disruption of the ability to process information about spatial relationships and remember it for short period of time, was described in connection with several neuropsychiatric diseases. Apart from the above mentioned schizophrenia and psychotic disorders, are the disorders of visual-spatial working memory also described in affective disorders (mania and depression), in both children and adults diagnosed with ADHD (Ewijk et al., 2004, Dowson et al., 2014) and autism. In autism, it is assumed that the deficiency of visual attention and working

memory limits the cognitive information processing, thus exacerbating social and communication deficiencies typical of autism (Steele et al., 2007).

In the context of neuropsychiatric disorders, we should also emphasize the role of sleep in spatial memory. Sleep has been found to benefit spatial memory, by enhancing hippocampal-dependent memory consolidation (Ferrara et al., 2008). Hippocampal areas activated in spatial learning while navigating through environment are reactivated during subsequent sleep (Non-REM sleep in particular). It was demonstrated that the actual extent of reactivation during sleep correlated with the improvement in route retrieval and thus memory performance the following day (Peigneux et al., 2004).This is important due to the fact that sleep disorders (insomnia, sleep-related breathing disorders and restless legs syndrome) are part of the symptoms of many neuro-psychiatric disorders, such as alcohol dependence, schizophrenia, depression and anxiety disorders (Spiegelhalder, et al., 2013). It was demonstrated that sleep deprivation hinders memory performance improvement due to an active disruption of spatial memory consolidation (Ferrara et al., 2008). Thus, hippocampal cellular and molecular processes critical for memory consolidation are affected by the amount and quality of sleep attained (Prince and Abel, 2013). Both total and partial SD induce adverse changes in cognitive performance (see review by Alhola and Polo-Kantola, 2007). While partial sleep deprivation was found to influence only attention (especially vigilance), total sleep deprivation impairs also working memory, but in addition it may affect other functions, such as long-term memory and decision-making. The association of sleep impairment with neuropsychiatric disorders is supported by the findings of impaired spatial memory in several neuropsychiatric disorders, mostly affecting visuospatial working memory (VSWM). Deficit of VSWM was therefore proposed as an endophenotype for several disorders such as: attention deficit and hyperactivity disorder ADHD both in children (Sanchez, Lumbreras, 1999; Ewijk et al., 2014) and adults (Dowson et al, 2004); autism spectrum disorder (ASD; Steele et al., 2014; Jiang t al., 2014), bipolar disorders (Pan et al, 2011) and schizophrenia (see review by Piskulic et al., 2007).

1.4 SCHIZOPHRENIA SPECTRUM DISORDER

Schizophrenia is a devastating multifactorial disorder characterized by three categories of symptoms, including **positive symptoms** (such as hallucinations and delusions), **negative symptoms** (e.g. anhedonia and emotional flattening) and **cognitive symptoms**, presented as impairments in several cognitive domains (Andreasen and Flaum, 1991; Owen et al., 2015). Schizophrenia (SZ) is indeed a heterogeneous complex neuropsychiatric disorder, a syndrome defined by peculiar beliefs and sensory experiences, social withdrawal, restricted or inappropriate emotional expression, and disorganized behavior. Apart from the positive, negative and depressive symptoms, also cognitive deficit is considered a stable characteristic of the illness (Green, 1996). The word schizophrenia (translated as ‘splitting of the mind’) comes from the Greek roots schizein (σχίζειν, ‘to split’) and phrēn, phren- (φρήν, φρεν-, ‘mind’). Schizophrenia (historically referred to as dementia praecox) is a chronic and devastating neuropsychiatric disorder, affecting approximately 1% of world's population and having a serious consequences on the patient’s quality of life including social and working abilities (van Os and Kapur, 2009). Schizophrenia is a complex neuropsychiatric disease with

variable symptomatology, traditionally divided into positive and negative symptoms, and cognitive deficits. However, the etiology of this disorder was yet not been fully understood.

Description of states clearly suggesting schizophrenia disorder (reports of irrational, unintelligible, or uncontrolled behavior) can be found in literature since ancient times. However, the first time the French Doctor Philippe Pinel (1745-1826) clearly separated psychological deterioration from other alterations of mental state, such as the idiocy, mania and melancholy in his detailed case report of James Tilly Matthews published in 1809. In the late 19th century, Emil Kraepelin (1856 to 1926) borrowed the term '**Dementia praecox**' ('Dementia précoce' - premature dementia, term used previously by Schule and Pick, argued to be used first in 1852 by the French physician Bénédict Morel) - state of sudden immobilization of mental abilities- for psychotic illness characterized by early onset and prolonged course of deterioration accompanied by hallucinations and delusions. Professor Eugen Bleuler (1857-1939) introduced the concept of '**schizophrenia**' into the professional literature in his monography 'Dementia Praecox oder die Gruppe der Schizophrenien' (Bleuler, 1911; in Libiger, 2002; Kuhn, 2004).

A common feature of all the ebove mentioned theories was a concept of incurable organic disease progressing to dementia image and starting at a young age. Symptom criteria for 'dementia praecox' by Kraepelin took into account that this is the only disease that always leads to mental weakness. Unlike Kraepelin, Bleuler speaks of several diseases ('Schizophrenia Group'). He perceived schizophrenia as a group of diseases characterized by the schism (split) between thoughts, emotions and behavior that does not necessarily lead to decline (dementia). Bleuler accentuated the '**four A's**' as the primary symptoms: sparse Association, Affective disorders, Autism and Ambivalence (Bleuler, 1911; in Libiger, 2002), when diagnosing schizophrenia. As secondary symptoms he proposed delusions and hallucinations.

1.4.1 DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIA SPECTRUM DISORDER

In the early 20th century Professor Kurt Schneider (1887-1967) proposed a hierarchy of first and second order symptoms in pursuit of more accurate specification of symptoms and more accurate diagnosis of **schizophrenia (SZ)**. According to this nomenclature the first order symptoms are not necessary for the diagnosis of SZ, but if they occur, the diagnosis is certain. This 1st order symptoms include sounding ideas, hearing voices in the form of a conversation or discussion, hearing voices that comment own actions, experiences of physical influence, withdrawing and insertion of ideas - thought broadcasting, delusional perception, and all the other experiences to be affected by someone else will, emotions, and impulses. Symptoms of 2^{nd} order include the sensory delusions, delusional ideas, helplessness, perplexity, depressed and euphoric mood, experiences and emotional impoverishment, etc. The criteria by Schneider helped to unite the diagnostic criteria for schizophrenia (Libiger, 2002).

Most of the more recent attempts to classify schizophrenia are based on symptoms dimension, based on the prevailing symptoms, such as positive (delusions, hallucinations, sparse association, behavior disorder) or negative (flattening of affect and emotions, emotional and social withdrawal, impoverishment of speech, puzzling thought, abulia, anhedonia, and impaired abstract thinking, etc.) (Crow, 1985; Andreasen, 1999). Individual subtypes of schizophrenia are characterized by a set of dominating symptoms. Besides the categories of positive and negative symptoms some new categories were added, such as disorganization, affective symptoms and cognitive deficits.

Current psychopathological concept of schizophrenia follows the concept proposed by Kraepelin, Bleuler and Schneider. The diagnostic criteria for schizophrenia of the two classification systems used worldwide: the International Classification of Diseases (ICD), according to the World Health organization, and in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM) are very similar. Both systems are based on the phenomenological approach, however, ICD-10 (10^{th} revision) places greater emphasis on Schneider first order symptoms. An important difference between the two classifications is a condition in DSM-IV (4^{th} revision) that requires the presence of any symptoms for at least 6 months (including prodromal phase and residual period), while the ICD-10 criteria for duration of the symptoms is at least one month. Another difference relates to the DSM-IV criterion B, which implies the presence of a social or occupational dysfunction as part of a schizophrenia diagnosis.

Both classification systems were currently revised (DSM-V, ICD-11). The objective of these revisions is to change the concept of disease based on the latest findings, accepting that schizophrenia is not a single disease with a single etiology or pathophysiological process, with consensus in the basic clinical symptoms. Several changes to the classification criteria of schizophrenia and other primary psychotic disorders have been proposed in both classification systems (Rethelyi, 2011; Gaebel et al., 2013; Tandon, 2013). Key considerations regarding DSM-V and ICD-11 are summarized by Tandon and Maj (2008).

Specific changes in the definition of schizophrenia according to DSM-V include elimination of the classic subtypes, addition of unique psychopathological dimensions, clarification of cross-sectional and longitudinal course specifiers, elimination of special treatment of Schneiderian 'first-rank symptoms', better delineation of schizophrenia from schizoaffective disorder, and clarification of the relationship of schizophrenia to catatonia (Tandon et al, 2013). The International Classification of Diseases includes schizophrenia to the category F20-29 together with schizoaffective, schizotypal, delusional and acute psychotic disorders. In view of the considerable variation of the course of schizophrenic disorders it is desirable (especially for research purposes) to specify the pattern of course of the illness. If registered for psychiatric care in an acute onset of symptoms, schizophrenia spectrum disorder patients will often meet the diagnostic criteria for F23.X Acute and transient psychotic disorders. Only later they are diagnosed as schizophrenia F20.X. The boundary between these two categories is therefore very narrow.

The differential diagnostics is crucial, as it is necessary to exclude others psychotic conditions, in particular toxic organic etiology. They can be quite unambiguously diagnosed using a detailed medical history, psychological tests, laboratory tests and thorough somatic examination. Diagnosis of Schizophrenia is usually excluded if primary brain disease is established or if the symptoms are due to other disease or somatic use of psychoactive substances.

1.4.2 EPIDEMIOLOGY

Results of epidemiological studies consistently indicate whole lifetime prevalence of diseases between 1-1.5%. This means that approximately one person in a hundred fulfils the diagnostic criteria for schizophrenia (Kaplan et al., 1994; Messias et al., 2007). Disease more often affects women, but it begins few years earlier in men (Libiger, 2002). In men schizophrenia starts typically between 15 and 25 years of age, while for women it is between

25 and 35 years (Sham et al., 1994). Late-onset and early onset of schizophrenia in childhood (even before the 10th year of age) are rare. The category of late-onset schizophrenia now includes also number of patients formerly diagnosed as paraphrenias.

1.4.3 ETHIOPATHOGENESIS

Despite progress in genetics, biochemistry, neurophysiology and neurochemistry schizophrenia etiology remains unknown. Many abnormalities described support different hypotheses and push the boundaries of our knowledge and understanding. However, none of these hypotheses can yet serve as a universal etiopathogenetic model of schizophrenia in order to be recognized as a diagnostic marker. Nevertheless, the important influence of some environmental and genetic factors in the development of this complex disorder has been demonstrated as risk factors of schizophrenia, such as growing up in urban environment, immigration, cannabis, male gender and perinatal events (hypoxia, infectious diseases in the prenatal period, stress and malnutrition) (Kaplan, 1994).

1.4.3.1 Biological factors

Genetics

Increased incidence of schizophrenia in families, studies on twins and adoption studies suggest a strong genetic component of this disease. Various epidemiological studies have shown that while the prevalence of disease in the general population is about 1%, the risk of a child whose one parent suffers from schizophrenia is 12%, in case of both parents ill is the risk 40% and in the identical twins 47% (Kaplan et al., 1994; Tsuang, 2000). Relatives of patients with schizophrenia are also at greater risk for other psychiatric diseases. Meta-analysis study in twins estimated the heredity of 81% (Sullivan et al., 2003).

Candidate genes and alleles that could be responsible for the manifestation of the disease, include polymorphisms of genes for dopamine and serotonin receptors, serotonin transport gene, HLA proteins, and in particular gene polymorphisms enzymes controlling the synthesis and degradation of some important neurotransmitters (e.g. catechol-O-methyltransferase, tryptophan hydroxylase). Recently, the role of the gene for dysbindin is studied as one of the candidate genes for schizophrenia, as dysbindin plays important role in the potentiation of synaptic plasticity of neurons and in the transmission of information in areas of dorsolateral prefrontal cortex and hippocampal formation (Verébová and Horacek, 2010). Nevertheless, it appears that the transmission of genetic predisposition to schizophrenia is subject to polygenic inheritance. Expression of disease symptoms is considered to be a result of the mutual interaction between the inner disposition (genetic load, vulnerability) and external factors (Tiwari et al., 2010).

Perinatal complications and neurodevelopment

A number of studies found a link between the development of schizophrenia and perinatal complications or prenatal insult exposure. Several observations in history gave rise to a so-called viral or infectious theory of schizophrenia, however, these findings support the neurodevelopmental hypothesis of schizophrenia (Weinberger, 1995). This hypothesis, same as the classical concept of schizophrenia as a neurodegenerative disease (disease begins progressively and leads to gradual deterioration), assumes nonspecific disorder of nervous system during early development (Leipzig, Weinberger, 1993). The cause of such disorders in

prenatal, perinatal and early postnatal period may be a viral infections, as well as metabolic disorders or malnutrition and other factors. The developmental hypothesis coud be supported also by the findings of cognitive deficit in schizophrenia.

Morphological and functional brain abnormalities

Historically Kraepelin understood "dementia praecox" as a result of damage to the cortex, particularly in the frontal and temporal lobe. Nonspecific pathological changes in the brains of patients with schizophrenia have been shown first in autopsy findings, and were later confirmed by various imaging methods. Typically extension of lateral brain ventricles, expansion of brain folds and cortical atrophy are mentioned (Shenton et al., 2010). These abnormalities occur in approximately 50% of patients, they are usually associated with a predominance of negative symptoms and worse therapeutic response. Findings of cortical atrophy and histopathological abnormalities in cytoarchitecture are presented as evidence for the hypothesis of Schizophrenia as a disorder of pruning of nerve synapses. Important is the interconnection of cortico-thalamo-cerebral circuits that are responsible for synchronization of movements and coordination of motor-thought sequences, resulting in cognitive dissymmetry.

Application of imaging techniques, such as structural MRI and CT confirmed the following morphological abnormalities in schizophrenia patients: extension of lateral ventricles and the third ventricle, reduced volume of the cerebral cortex (frontal, prefrontal, temporal), limbic system (hippocampus, parahippocampal gyrus) and subcortical structures (thalamus, corpus callosum, basal ganglia) (Shenton et al., 2010). Magnetic resonance spectroscopy (MRS) used to examine biochemical abnormalities, demonstrated reduced production and increased breakdown of phospholipid membranes in the frontal lobes and reduced concentration of N-acetylaspartate (marker of neuronal activity) in temporal areas, particularly the hippocampus in SZ. Positron emission tomography (PET) and single photon emission tomography (SPECT), used to monitor the metabolism and regional perfusion, and to visualize receptor systems, demonstrated reduction in anterior-posterior, cortico-subcortical and left-right gradient, reduction in metabolic activation in frontal cortex and in 50% of cases also resting hypofrontality. Frontal abnormalities are usually associated with negative symptoms, while temporal with hallucinations and delusions.

Functional magnetic resonance imaging (fMRI) monitoring the functional changes in schizophrenia by detecting changes in blood flow during the activation during the resting state or by specific stimuli (e.g. cognitive tests) confirmed several areas associated with the cognitive deficit in schizophrenia that include mainly changes in the dorsolateral prefrontal cortex, limbic system, hippocampus, parahippocampal gyrus, cingulate gyrus, thalamus and basal ganglia. Most prominent are the changes in DLPFC and hippocampus, related to working memory and long-term (episodic) impairments in schizophrenia (Kraguljac et al, 2013).

Triple network dysfunction

Over the past few years the focus of neuroimaging research has shifted from the localization of task-related neural activity towards functional connectivity within and between organized cerebral networks. Also recent review on functional magnetic resonance imaging in schizophrenia suggests that alternations are not isolated to a few brain regions, but are characterized by abnormalities within large-scale brain networks (Kraguljac et al., 2013).

A lot of data based on temporal coupling of fMRI responses during rest and context/stimulus-dependent activations has identified a triple large-scale brain network model

consisting of the default mode network (DMN), salience network (SN) and central executive network (CEN) (Menon, 2011). It is widely accepted that coordination of these networks plays a key regulatory role in organizing neural responses underlying fundamental brain functions (Nekovarova et al, 2014).

The DMN shows decreased activation during cognitive task performance relative to resting-state or internally focused tasks and is implicated in self-referential internal mentation (Andrews-Hanna, 2012). Its subsystems include cortical midline structures, i.e. medial prefrontal cortex (mPFC), posterior cingulate cortex and adjacent ventral precuneus, along with the medial, lateral and inferior parietal cortex and a part of the medial temporal lobe. The second network - CEN - engaged in externally oriented attention during demanding cognitive tasks, includes primarily the dorsolateral prefrontal cortex (DLPFC), and posterior parietal cortex (PPC) (Menon and Uddin, 2010). In general, cognitive states that activate the DMN typically deactivate the CEN and a vice versa. The last large-scale salience network (SN), composed of the anterior cingulate and the anterior insula, mediates selection of salient external and interoceptive signals (Menon and Uddin, 2010; Sridharan et al., 2008).

Accumulating evidence from neuroimaging studies in healthy individuals indicates that SN causally influences anticorrelated activation of DMN and CEN and plays a general role in switching between these two networks upon salient stimuli mediated by midbrain dopaminergic input (Menon and Uddin, 2010). The aberrant orchestration within the triple network model has been suggested as a backbone for some clinical and cognitive features of various psychiatric and neurological disorders (Menon, 2011).

Numerous resting-state and stimulus-evoked (task-related) fMRI measurements in patients with schizophrenia compared to healthy controls repeatedly showed aberrant functional connectivity within and between DMN, SN and CEN (Kasparek et al., 2013; Moran et al., 2013; Orliac et al., 2013; White et al., 2013; Guo et al., 2014; Manoliu et al., 2014). Those results converge on the conclusion that SN dysfunction may be causative to triple network dysfunction inherent to the illness (Palaniyappan et al., 2012). Indeed, based on nonpsychiatric lesion studies, it was clearly shown that structural SN integrity plays a crucial role in the fine-tuned orchestration of the other two major brain networks (Zhou et al., 2010). This gains particular importance considering concentration of the most often reproduced structural deviations in schizophrenia in regions of insula and ACC, which represent key hubs of SN. A prominent gray matter reduction within these structures has been consistently and robustly reported in the meta-analyses of morphometric MRI studies (Glahn et al., 2008; Ellison-Wright and Bullmore, 2010; Bora et al., 2011; Shepherd et al., 2012). ACC and insula gray matter volume reduction precede the occurrence of the first psychotic symptoms and thus represent candidates for trait symptoms of the disease.

A transition to psychosis and further chronicity is associated with additional morphological changes in the adjacent regions of the mediofrontal cortex and the temporal lobe. (Chan et al., 2011). Further, an impaired anti-correlated relationship between task-positive CEN and task-negative DMN due to SN malfunction may be phenotypically expressed as major symptoms of schizophrenia, such as auditory verbal hallucinations (Manoliu et al., 2014), delusions of reference (Menon et al., 2011), and cognitive dimension of schizophrenia (Elvevåg and Goldberg, 2000).

It has been suggested that a lack of optimal DMN suppression during cognitive task engagement may be a source of the general cognitive impairment (Anticevic et al., 2012). In previous

literature it has been proven that in healthy controls the magnitude of task-induced deactivation within the DMN positively correlates with cognitive performance (McKiernan et al., 2003; Li et al., 2007). In schizophrenia, reduced suppression of the DMN during various cognitive tasks represents a constant finding (Meyer-Lindenberg et al., 2005; Garrity et al., 2007; Harrison et al., 2007; Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009; Nygård et al., 2012; Anticevic et al., 2013; Fryer et al., 2013). Therefore, a breakdown in coordinated suppression of DMN activity may impair the overall performance across various cognitive domains in schizophrenia (Nekovarova et al, 2014).

Biochemical abnormalities

Neurotransmitters, carriing signals between neurons in the synapses and their binding site receptors, are without doubt the most studied substances in schizophrenia (Horacek et al., 2006). Attention is focused especially on the monoamines and their influence on human behavior. Dopamine is associated with one of the oldest hypothesis of schizophrenia, the dopamine theory (Carlsson et al., 2006). This hypothesis was based on evidence of the mechanism of action of classic antipsychotics, which is the blockade of dopamine, in particular postsynaptic D2 receptors. This theory is supported by the dopamine agonists or reuptake inhibitors (amphetamine or cocaine) induced psychosis. From the original concept of higher level of dopamine release at synapses and increased dopaminergic transmission, attention concentrated to a density of postsynaptic D2 receptor. Dopamine is also important neurotransmiter regulating neuronal response to external stimulation. Simply, the model explains the relationship between signal and noise: the increased dopaminergic transmission increases their ratio, while the depletion of dopamine leads to its reduction (Horáček et al., 2002).

Serotonin has been linked to schizophrenia etiopathogenesis already in the 50s years of 20th century, based on the similarity of schizophrenic psychoses and psychoses induced by hallucinogens such as lysergic acid diethylamide (LSD), a potent serotonin agonist. The role of serotonin in the creation and development of schizophrenia was recently revived by the introduction of the second-generation antipsychotics with significant affinity for serotonin receptor and high ratio blockade between the serotonin 5HT2 and dopamine D2 receptors. The complexity of the interrelationships among the neurotransmitter systems is illustrated in the fact, that serotonin has an inhibitory effect on dopaminergic and glutamatergic receptors.

Glutamate, the excitatory neurotransmitter, is in recent years also in the center of attention of the schizophrenia research (Carlsson et al., 1999). It is based primarily on the model of phencyclidine psychosis. Phencyclidine (PCP) and other substances, e.g. ketamine or MK-801, are competitive antagonists of N-metyl-D-aspartate (NMDA) glutamate receptors, and their administration results in psychosis similar to schizophrenia (Bubenikova-Valesova, et al., 2008). Alterations of glutamatergic system of the brain have been documented in schizophrenia patients in both *in vivo* and *post mortem* examinations (Kerwin et al., 1990; Egerton and Stone, 2012). Glutamate is an important neuromodulator of signal transmission in the cortex and subcortical nuclei. Its mutual coordination with the dopaminergic transmission system, and gamma-aminobutyric acid is studied as well.

Noradrenaline, particularly its metabolite 3-methoxy-4 hydroxyphenylglykol and metabolizing enzyme monoamine oxidase, have been extensively studied in schizophrenia. Some authors reported decreased activity of noradrenergic neurons in the locus coeruleus after long-term use of antipsychotics.

Similarly gamma aminobutyric acid, an inhibitory neurotransmitter, is studied for its significant interaction with glutamate system. Recent findings indicate that schizophrenia is associated with multiple pre- and post-synaptic abnormalities in parvalbumin basket cell class of GABAergic neurons that weakens their inhibitory control of pyramidal cells. This hypothesis suggests that NMDAR hypofunction at parvalbumin GABAergic interneurons is sufficient for schizophrenia-like effects (Nakazawa et al, 2012).

The interaction between various neurotransmitter systems with a key role of thalamus as a filter of cortical stimulation are a base for Carlssons' model of schizophrenia (Carlsson, 1995). This model is based on the idea that the cortex is constantly being bombarded by stimuli from the outside world, and if not filtered or sorted by thalamus, they would create noise.

Among other substances, the interest focuses on the role of neuropeptides (endorphins cholecystokinin, neurotensin, and endocannabinoids). Despite all the abnormalities described earlier in the text, the role of these substances in the brains of SZ patients and in the etiopathogenesis remains unknown (Horacek et al., 2006).

1.4.3.2 Psychological and social factors

Even that for understanding of the etiology and pathogenesis of schizophrenia the meaning of most of the psychological and social factors recedes into the background, they can't be entirely disregarded, both in terms course and prognosis of disease, and particularly in terms of a complex therapeutic approach. Attention is primarily devoted to failures of communication within the family, although the older concept of. 'schizophrenogenic mother' (overprotective, emotionally cold) introduced by Frieda Fromm-Reichmann in 1984 that is now completely deserted. The families of patients with SZ are typically described by ambiguous communication, for example when a different content of a verbal or nonverbal communication is presented, or that verbal language conceals a variety of meanings often ambiguous. Examined is the extent of expressed emotions, such as excessive criticism, hostility, but also warmth, and emotional commitment towards the patient. In families with high expressed emotion higher number of relapses has been described (Kaplan et al., 1994).

1.4.4 PROGRESS AND COURSE OF ILLNESS

The course of the disease is very diverse, from sporadic episodes over repeated attacks with varying degrees of functional impairment between relapses to the progressive, long-term chronic course of illness (Libiger, 2002). The beginning of the illness may be acute (from full health without warning signs) or slow. In many individuals with a gradual development, we can observe discrete changes already in the premorbid period, often in the form of reduced performance in neuropsychological tests. The following prodromal period is characterized with more salient unspecific symptoms (behavioral changes, changes of motivation, thoughtfulness, touchiness, perceptual distortions, sleep disturbances etc.). After different length of prodromal stage, follows the full manifestation of the disease in acute episode, with fully expressed symptomatology of the relevant subtype. Further progress is variable (Watt et al., 1983): single episode followed by recovery (assumed in 22% of patients), or recurrent acute episodes of illness either with return to premorbid level between episodes (35%), with partial remission after each episode (8%), or with increasing residual symptoms between individual episodes (35%). According to prognosis, the least favorable variant is a chronic course (witch acute episodes or without them) to progressively deepening disabilities. Severe functional impairment

is observed after the first episode of the disease, and over time with each additional episode disability deepens in a large portion of patients. In addition, the relapse risk increases with the number of previous relapses (Robinson et al., 1999). It appears that the greatest variability in the disease is during the first 5-10 years, after then the course tends to be more stable.

Predictors of unfavorable course and outcome of schizophrenia is a history of psychotic illness among first instance relatives (in contrary, history of affective disorder is predictive of a favorable course), probably also birth complications (the relationship was not unequivocally confirmed), poor premorbid social adaptation, cognitive disorders, neurodevelopmental differences and structural brain abnormalities such as an enlarged ventricle, reduced volume of the hippocampus, male gender, younger age at beginning of the disease, insidious progression of the disease, low socioeconomic status, substance abuse and possibly the length of the untreated psychosis. Favorable course is associated with the presence of psychosocial stress and living in an ethnic minority (Murray, Van Os, 1998; Robinson et al., 1999).

1.4.5 THERAPY

Antipsychotic therapy remains the main treatment method of schizophrenia (see below). Electroconvulsive therapy (ECT) is usually reserved for therapeutically resistant or catatonic patients (Luchini et al, 2015). However, ECT is criticized for its adverse effects on memory function. The non-pharmacological treatment such as psychosocial intervention (psychotherapy, social training, psychoeducation, cognitive remediation, etc.) benefits of pharmacological treatment and complements the comprehensive approach to the disease.

The prerequisite for successful treatment is undoubtedly the insight of the patient and his perspective towards treatment and illness. This implies patients' recognizing of the fact that he/she suffers from a mental disorder, collaboration in treatment and its acceptance, and an ability to recognize unusual mental events as abnormal (Cooke et al., 2005). Study by Monteiro et al. (2008) showed that poorer attention, impaired abstract thinking and consequently disrupted ability of judgment prevent adequate utilization of introspection capability, which is important for full insight of the illness. Besides the psychopathology and its effective treatment, the insight is also related to stigmatization of the illness in the society (Lysaker et al., 2007).

A wide range of antipsychotic drugs that differ in their mechanism of effect and the profile of side effects are currently available. In addition to classical antipsychotics, a large number of new antipsychotics emerged in last years referred to as second-generation antipsychotics. The antipsychotic activity of classical antipsychotics is based on the blockade of dopamine D2 receptor (Meltzer, Stahl, 1976). Evidence of their effectiveness in treating the positive symptoms comes from numerous controlled studies and extensive clinical experience with their administration. However, they are less effective in treating the negative and affective symptoms. They shorten the length of psychotic episodes, however, they are less effective in preventing relapses. A large number of adverse side effects can often lead to the nonadherence in patients (Konley and Kelly, 2005; Dibonaventura et al., 2012). The most typical side effects include neurological and endocrine disorders, extrapyramidal symptoms (EPS): Parkinsonism, dystonia, dyskinesia, and akathisia. From a wide range of other adverse effects (antihistaminic, anticholinergic, antiadrenergic and others) potentially lethal neuroleptic malignant syndrome deserves to be mentioned. Some authors suggest also antidopaminergic deficit syndrome with prominent negative and depressive symptoms as the side effects of antipsychotics treatment.

Second generation antipsychotics, sometimes also referred to as new or atypical antipsychotics, are a heterogeneous group of psychotropic drugs, which when compared with conventional antipsychotics, defines especially good tolerance (especially absence of EPS) and clinical efficacy not only in positive but also in negative, affective and in cognitive symptoms; and therapeutic efficacy in resistant patients with schizophrenia (Krausz, 2002). Their onset dates from the reintroduction of clozapine in the 80s of the 20th century. The most common side effects are sedation, weight gain and anticholinergic effects (Casey, 1996). Zotepine and clozapine can dose-dependently induce seizures. Therapy by clozapine is associated with a potentially lethal complication, agranulocytosis with hypersalivation. Recently discussed in connection with certain antipsychotic drugs of second generation are metabolic disorders such as impaired glucose tolerance, including the development of diabetes, and lipid metabolism disorders.

1.5 COGNITIVE DEFICIT IN SCHIZOPHRENIA

The neuropsychological background of the cognitive deficit in schizophrenia is a quickly developing area in psychology and attracts a lot of attention. Schizophrenia is now well-recognized as a neurodevelopmental disorder with a trajectory that begins in utero, evolves in the first decades of life through a multidirectional interplay among genetics, environmental, and stochastic influences, resulting at maturity in disturbed patterns of brain structure, connectivity, and activation (Lewis and Levitt, 2002; Marenco and Weinberger, 2000). These abnormalities are often subtle, but they affect widely acting neurotransmitter systems (e.g., dopamine, glutamate, GABA) and abnormalities are represented in critical neural hubs, including the prefrontal cortex and hippocampal formation (Callicot et al., 2000; Meyer-Lindenberg et al, 2005; Weinberger et al, 1992). Given this neurodevelopmental nature of schizophrenia, it is no surprise that cognitive performance is also broadly disrupted in schizophrenia.

The impairment of cognitive functions is considered to be a characteristic and permanent manifestation in patients with schizophrenia disorder (Andreasen, 1999). In 1998, Heirichs and Zakzanis published the first large-scale-meta-analysis of cognitive deficit findings in schizophrenia (Heinrichs and Zakzanis, 1998), documenting a far-reaching global cognitive impairment with an overall mean of 0.92 standard deviations relative to community comparison groups (Heinrichs, 2005). Although the extent of cognitive decline in schizophrenia has considerable inter-individual variability, it has been shown that the overall performance in neuropsychological tests is more than 1 SD lower in schizophrenia when compared to the healthy population (Keefe et al., 2005; Reichenberg et al., 2009, see Fig. 9). This deficit has been demonstrated in 82-84 % of the patients (Reichenberg et al., 2009) and was shown to be stable in time.

An important amount of research in SZ has examined the relationship between cognition and variety of clinical factors including age of onset, symptomatology, severity, duration, medication, functional outcome, and QOL (Bilder, 2000;Mesholam-Gately, 2009;Heinrichs, 1998). Cognitive deficits are a significant predictor of functional outcome - ability to perform specific activities of daily living (Green, 1996; Harvey et al., 1998; Green et al., 2000, 2004), and are current targets for psychopharmacological treatment (Hyman and Fenton, 2003).

The MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative identified seven crucial cognitive areas typically influenced in

schizophrenia: attention, psychomotor speed, working memory, logical thinking, problems solving, social cognition, and verbal and visuo-spatial learning and memory (Green et al, 2004). Neurocognitive deficit thus represents a reliable feature, with moderate to large effect size on global functioning across all cognitive domains (Milev, 2005).

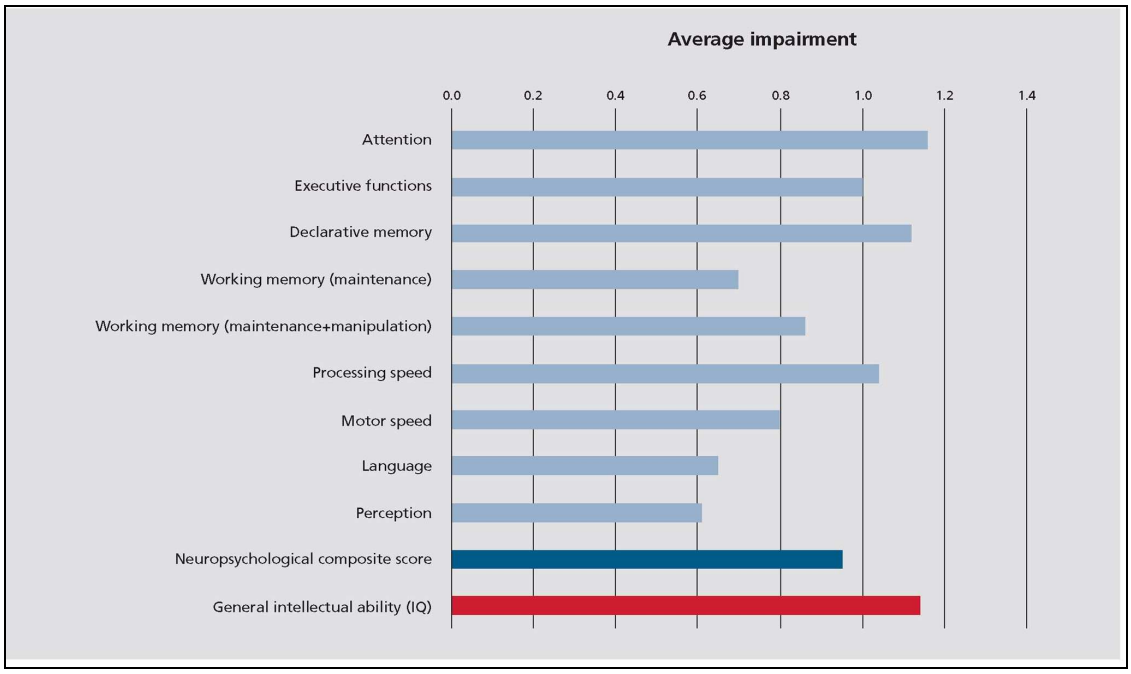


Figure 9. *Neuropsychological performance profile of schizophrenia. Summary of results from meta-analytic studies presented in effect-size units (median effect size was calculated from available meta-analyses) (adopted from Reichenberg, 2010).*

The issue investigation of cognitive functions in schizophrenia is complicated by considerable heterogeneity of deficit among the patients. According to the experience of reviews and meta-analysis (Dickinson et al., 2007; Palmer et al., 2009) some investigators found significant deficit in some certain areas and some reported general deficit. Moreover about 20% of patients manifest almost normal functioning of cognitive functions as well as functioning in every-day life ('high-functioning' group), based on their premorbid IQ and education (Allen et al., 2003). However, it is certain, that cognitive measures could predict further success in work and social life more than just psychiatric symptoms (Green et al., 2004).

Besides deficit in attention, cognitive symptoms in schizophrenia include two main clusters (see Fig. 9):

1) **Executive functions** associated with the prefrontal cortex (deficits in problem solving, verbal fluency and working memory (Morris et al, 1995; Park and Holzman, 1992; Shallice et al, 1991, etc.),
2) **Long-term memory** associated with medial temporal lobe (both verbal and visuo-spatial; Achim and Lepage, 2005; Aleman et al, 1999; Kraguljac et al., 2013; Ranganath et al., 2008).

Some authors argue (Aleman et al, 1999; Boyer et al, 2007) that disturbed executive functioning is not specific feature of schizophrenia, as it is described in various neuropsychiatric disorders, such as depression (Fossati et al, 1999), obsessive compulsive disorder (Greisberg and McKay, 2003) or attention deficit hyperactivity disorder (Willcutt et al, 2005), suggesting that although prefrontal impairment is one of the major features of schizophrenia, it is not specific to the disorder (Boyer et al, 2007). On the other hand, long-term memory impairments, are equally if not more salient feature of the impaired cognitive profile in schizophrenia (Aleman et al, 1999). In addition, these impairments have been found to be correlated with dysfunctional outcomes in the daily living of people with schizophrenia (Green et al, 1996), and seems to be the best predictor of overall psychosocial well-being in these patients (Green et al, 2000). Aleman and his collegues (1999) compared more than 70 studies comparing SZ patients with healthy population and concluded in their meta-analysis that impairments of long-term memory are not secondary to frontal attentional dysfunction or executive abnormalities, as suggested in previous studies. This idea was supported by experimental studies (Holthausen et al, 2003). Furthermore, neither medication status nor severity of psychopatology were associated with memory impairment (Aleman et al, 1999). Some authors even report that spatial and verbal memory and verbal learning showed effect sizes nearing 3 standard deviations below normal performance, compared with abstraction and mental flexibility that had effect size approaching 1SD (Saykin et al, 1991).

1.5.1 LONG-TERM MEMORY DEFICIT IN SCHIZOPHRENIA

Schizophrenia patients have been show to be impaired in both verbal and visual long-term memory (Aleman et al, 1999; Holthausen et al, 2003), even that the explicit memory is mostly tested by verbal methods. They perform quite poorly on explicit memory tasks including both memory subsystems - semantic (memory for isolated facts) and episodic (memory for whole events) (Clare et al, 1993; Goldberg et al 1998; Holthausen et al, 2003; Tamlyn et al, 1992). In contrast, the implicit memory (such as repetition priming and procedural learning) seems to be unimpaired in SZ (Kornetsky et al, 1959; Danion et al., 2001), and subtle impairment was observed only in the presence of increased psychotic symptoms, probably due to the lack of motivation and changes in psychomotor speed (Exner et al, 2006). Interestingly, the explicit memory deficit in schizophrenia is similar to that found in patients with medial temporal lobe lesions (Duffy and O'Carroll, 1994), however, they are considerably less severe than that caused by degeneration in organic amnesia (Heinrichs et al, 1994).

In terms of separate neuroal processes involved in memory formation (encoding, storage and retrieval), patients with schizophrenia are reported to be impaired both in encoding (associated with medial temporal lobe dysfunction) and retrieval parts of the process (associated with frontal lobe dysfunctions) (for review see Aleman 1999; Boyer et al, 2007). They are most impaired in the learning of new information, connected to issuficient encoding (Holthausen et al, 2003). Gold and Goldberg (Gold et al, 2004; Goldberg et al, 2003) suggest encoding processes to be central to memory impairments in schizophrenia, while storage and retrieval procedures are mostly found to be unimpaired (e.g. Brown et al, 1994; Bacon et al., 2007; Holthausen et al, 2003; Egeland et al, 2003; Paulsen et al, 1995). However, only minority of studies have examined recognition in schizophrenia. Meta-analysis by Achim and Lepage (2005) found noticeable differences in encoding and retrieval between controls and schizophrenia subjects in the left inferior prefrontal cortex.

In the light of these findings, the complementary perspective involving the role of temporo-frontal (HPC-PFC) network could provide a more accurate explanation of the cognitive deficits in schizophrenia (Boyer et al, 2007). This is supported by the existence of connections of the medial temporal lobe to the frontal lobe are repeatedly shown in animal studies (Kawashima et al, 2006; Thierry et al, 2000), involving the projection of information from the hippocampus to the prefrontal cortex (Gabbott et al, 2002; O'Mara et al, 2000). This HPC-PFC pathway represents one of the major factors in learning and memory (Laroche et al, 2000) and thus abberant HPC-PFC connectivity could explain cognitive deficits (both in working and long-term memory) in schizophrenia.

1.5.2 VISUO-SPATIAL DEFICIT IN SCHIZOPHRENIA

Patients with schizophrenia exhibit impaired performance at all levels of spatial cognition, from simple visual perception to complex navigation in spatial environments.

1.5.2.1 Visual Perception in Schizophrenia

Schizophrenia is linked to problems in low- and high-level visual information processing. Butler et al. (2005, 2008) studied the early-stage visual processing in schizophrenia, measuring rate response of neurons on visual-evoked potentials. More concretely the study focused on magnocellular pathway, which leads visual information from the thalamus to the visual cortex and then to the dorsal visual system mediated by NMDA. Patients with schizophrenia showed significantly lower responses of magnocellular cells, lower contrast sensitivity and impaired motion processing than the control group (see also Chen et al., 1999). From these results authors concluded dysfunction within low-level visual pathways involving thalamo-cortical radiations, especially contrast sensitivity, which was in turn related to deficiency in high-level visual processing.

However, SZ patients show particular difficulties also in high-level visual information processing. This is mainly connected to object identification tested by incomplete object recognition (for example, one object covered by another object), or the perceptual proximity (e.g. in the fragmented pictures test). This ability is closely related to information integration, thus to ventral visual system functioning (Doniger et al., 2001). The difficulties were also found in perception organization and placing perceived into context (Butler et al., 2008).

A study investigating simple eye-movements in SZ in order to discriminate schizophrenia cases from control subjects showed reasonable predictive validity of similar tests (Benson et al, 2012). Eye movements were recorded during smooth pursuit, fixation stability, and free-viewing tasks. A group, of schizophrenia patients differed from control subjects on almost all eye-movement tests, including horizontal pursuit, visual scanpath, and fixation stability; but the fixation dispersal during free viewing was the best single discriminator (see Figure 10). Effects were stable over time, and independent of sex, or medication. This study demonstrated very good predictive validity of the applied methods, showing that simple viewing patterns can detect eye-movement abnormalities in SZ that can discriminate schizophrenia cases from control subjects with exceptional accuracy (ranging from 87 to 98.3% depending on the applied model).

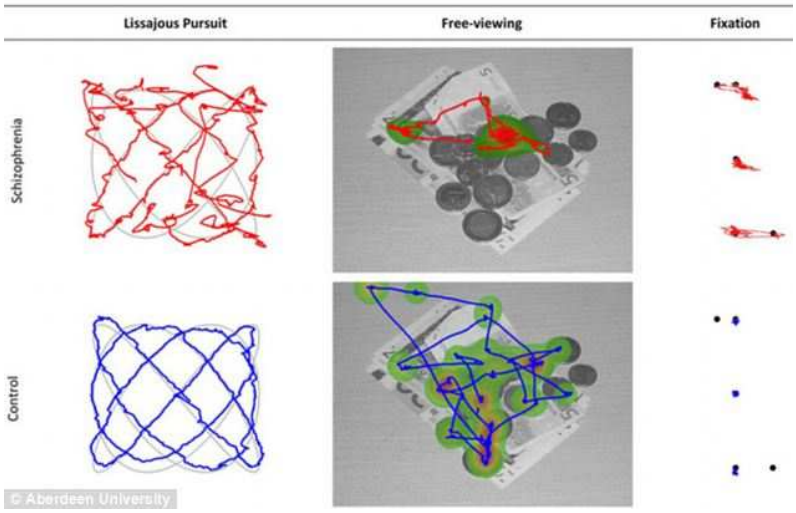


Figure 10. *Illustration of simple eye movement tests (Lissajous pursuit, free-viewing and fixation) and their results in SZ and healthy controls (adopted from Benson et al, 2012)*

*1.5.2.2 **Mental rotation and perspective taking***

Schizophrenia patients are slower and less accurate in mental rotation of letters and objects (de Vignemont et al., 2006). Longer reaction times measured in patients can be explained by an overall slowing of mental processes in schizophrenia and impaired visuo-spatial sketchpad and centrally executive component involved in the working memory during imagination of motor movements (Baddeley, 1992).

Spatial navigation abilities have been tested also in more complex virtual environments not directly based on animal studies. Landgraf et al (2010) tested spatial orientation in allocentric and egocentric reference frame in a complex virtual environment of a palace square (Landgraf et al., 2010). Here, participants had to make a decision as to which of two trash cans was closest to themselves (viewer-centered, egocentric), to a ball (object-centered, unstable allocentric), or to a palace (landmark-centered, stable allocentric). The results of the study imply that schizophrenia patients' adoption of an egocentric perspective is preserved. However, their allocentric estimations are inaccurate, and their switching between ego and allo-centric reference framework is significantly delayed. Thus, adopting an allocentric point of reference and switching between egocentric and landmark-centered perspectives are impaired in schizophrenia.

1.5.2.3 Spatial memory and executive functioning

Declarative memory and executive functioning- planning and organization - in SZ

Declarative memory is also often reported as deficient in SZ. While verbal declarative memory deficits in schizophrenia are well documented, visual declarative memory is less studied. Complex figures, such as RCFT and Taylor figure (Meyers and Meyers, 1995; see Fig. 11) are often used to test both, visuo-spatial memory and executive functioning (organization of the copied material) that is mediated by the prefrontal lobe (e.g. Shin et al., 2006; Lezaky, 2014) in patients with SZ. A study comparing chronic SZ and chronic bipolar psychotic disorder with healthy controls (Seidman et al, 2003) demonstrated that SZ patients are significantly more impaired in RCFT test than controls on both copy accuracy and organisation, and recall accuracy. While the bipolar patients performed at an intermediate level between controls and SZ patients. This data suggest that the visual memory disorder in SZ is characterized by combined organizational processing impairments (construction of the copied material) and retention difficulties. In addition, decline in visual memory function progresses with duration of illness (Seidman, 2003).

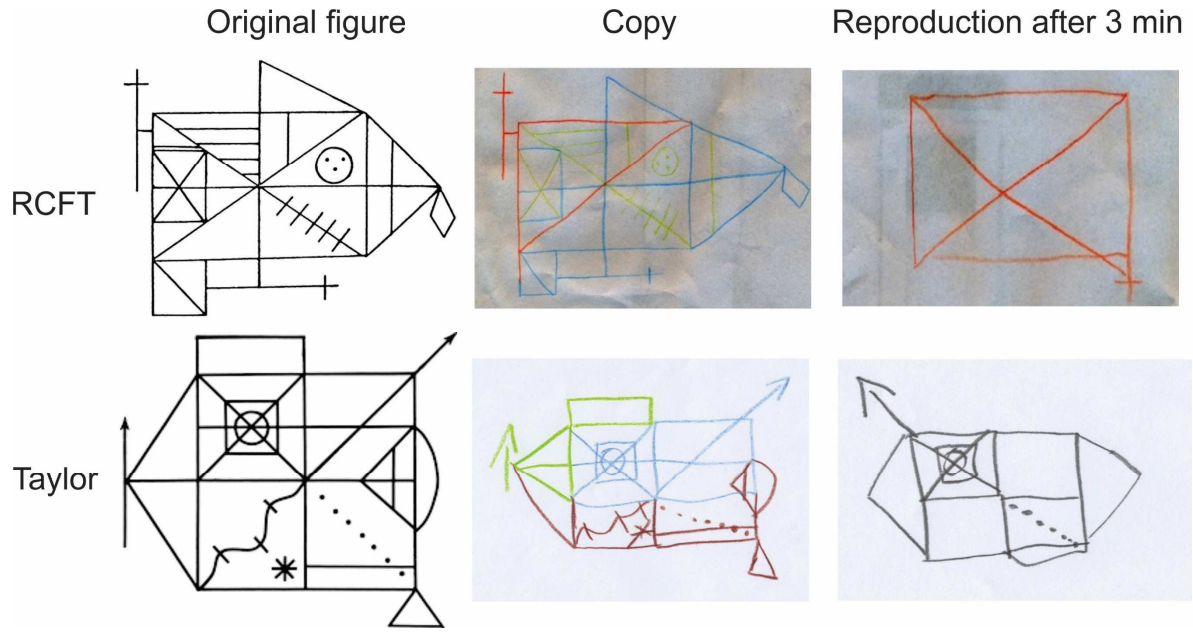


Figure 11. *(left) The design of the Rey–Osterrieth (RCFT) and Taylor complex figure test; (middle, right) Examples (21 year old women, and 20 year old men, schizophrenia scpectrum disorder) of the incorrect organization of the copied material (presented in the color coded order of copied details) not following the logical pattern (middle), resulting in later reproduction error (right) in schizophrenia patient (obtained during assessments performed in this thesis). Illustrations were obtained in the experimental part of the study.*

Another test sensitive towards deficit in visuo-constructive abilities mediated by frontal lobe is the *Block-design* (WAIS subtest). This task is used to test disorganization of spatial elements or the disruption of one or more of the executive steps - intention, programming, regulation or verification (as suggested by Luria and Tsvetkova, 1964). Several studies suggest

impairment in block design performance among schizophrenic and bipolar disorder patient populations (Lezak, 2012).

Executive functioning, in particular spatial planning abilities, tested using the *Key Search Test* (BADS; Alderman et al, 2003), also showed impaired planning of spatial strategies and monitoring of the own progress in schizophrenia (Evans et al., 1997). For illustration of spatial strategies see Fig.12.

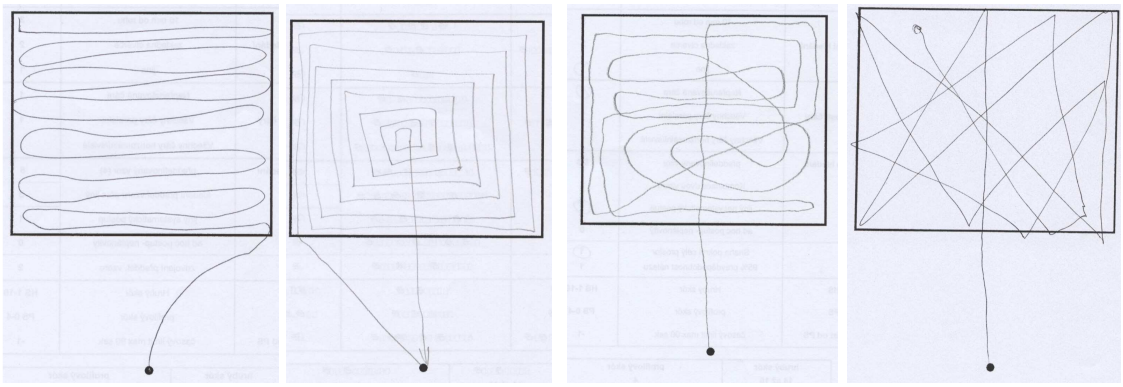


Figure 12. *Illustration examples of typical strategies used by healthy volunteers (2 left images) and SZ patients with deficit in spatial planning abilities (2 images on the right) obtained during neuropsychological assessments performed in the experimental part of this thesis.*

Spatial working memory

The deficit of **working memory**, as the restricted capacity system necessary for the short term storage and manipulation of information that sub-serves goal directed action, intention and thought (Goldman-Rakic, 1996; Baddeley, 1996), was well documented in schizophrenia both in verbal and visuo-spatial tests. It seems that schizophrenia is a disorder primarily characterized by the deficit in organization and processing of information at a central executive component of working memory (Longevialle-Henin et al., 2005). That is the reason why the negative symptoms manifest themselves at processing both verbal and visuo-spatial information, with a consequent mistakes in remembering. WM is considered an objective marker of function of prefrontal cortical (PFC), specifically the dorsolateral prefrontal cortex (DLPFC), areas that are modulated by cortical and subcortical dopaminergic projections. Importantly, this brain-behavior model of WM impairment in SZ has good explanatory power for both animal and human models of the disorder (Goldman-Rakic, 1994; Goldman-Rakic, 1996; Baddeley, 1996). According to Piskulic, WM dysfunction model of schizophrenia is possible to induce experimentally in animals (non-human primates and rodents); at least for non-verbal or spatial information (Piskulic, 2007).

Impairment of **visuospatial working memory (VSWM)** performance in SZ was demonstrated using various methods (see meta-analyses by Lee and Park, 2005; Piskulic et al., 2007; Dreher et al., 2001). Three main types of tests that have been most frequently applied by a large majority of the SWM studies (according to Pisculic, 2007): 1) the delayed-response task (DRT) or Spatial Span, 2) self-ordered searching paradigm (CANTAB subtest; Computerized Executive Golf Task) and 3) the n-back paradigm. The first group of tests (DRT and spatial span task in forward version) require that spatial information be held briefly in memory, but not

manipulated. The remaining two categories, however, require both maintenance and manipulation of incoming spatial information, and are therefore superior and more sensitive for the assessment of SWM function. Thus, some of the tests are weaker, less sensitive, than the others as they are not engaging all processes involved in SWM function (Piskulic, et al., 2007).

Context-memory, cognitive coordination and attractor states in Schizophrenia

The core or main cause for cognitive disorganization and complex cognitive deficit observed in schizophrenia could be the impairment of cognitive coordination (i.e. neural control of cell population activity in time and context) (Phillips and Silverstein, 2003). This impairment should include inappropriate perceptual associations and beliefs, deficits in an ability to integrate contextual information as well as impaired discrimination between relevant and irrelevant information (Hemsley, 2005). Contextual information plays an important role in memory deficits in SZ. Schizophrenia patients show impaired contextual processing abilities while maintaining perception and memory processes (Cohen et al, 1999; Penn et al, 2002). Contextual binding involves a deeper type of encoding using contextual features (such as spatial relationships or temporal order), shown to be important for processing of episodic memories (Danion et al, 1999). Binding processes allow us to combine different contextual elements into a complete memory representation and provide us the knowledge that certain features (content and context) have co-occurred (Chalfonte and Johnson, 1996). Studies applying memory binding tasks, such as remembering of both target (words, objects or faces) and their spatial position or some other context feature such as temporal context (Rizzo et al.,1996; Burglen et al, 2004; Gold et al, 2004) indicated that the memory for target or spatial information alone is unimpaired in SZ, relative to the ability to bind target and spatial information together. Medial lobe structures, particularly hippocampus, play a critical role in this type of contextual binding (Eichenbaum, 2000).

According to another but related model (Rolls, 2012), instability of neuronal cortical attractor states, due to general reduction of firing rates of glutamatergic neurons, contributes to cognitive as well as negative schizophrenia symptoms. This instability results in interfusion of working memory items and poor ability to allocate attention. Findings in animal models of schizophrenia support this suggestions. The hypersynchrony theory claims that the cognitive deficit in psychosis results from increased coactivity specifically between neurons which normally do not fire together. TTX-induced cognitive disorganization on rotating circular arena disrupted ability to segregate relevant associations in rats and led to coactivity (hypersynchrony) of hippocampal pyramidal cells discharge (Olypher et al., 2006). Such hypersynchrony could produce the excessive associations observed in schizophrenia by reduced separation between representations of unrelated events and contexts in the hippocampus. Later observations of MK-801 (NMDA receptor blocker) induced impairment of spatial coordination in carousel maze (Stuchlik et al., 2004) and elimination of contextual specificity (increased similarity) of IEG expression in hippocampal CA1 ensembles (Kubik et al., 2014) also supported the hypersynchrony theory. The impaired ability to identify context using task-relevant information stored in a working memory, involving PCF hypofunction, was described also in schizophrenia patients. Similar observations have been done in all task-switching paradigms related to dysfunction of medial and lateral PFC areas (Jamadar et al., 2010). No studies yet involved the processes of switching between spatial reference frames in dynamic

environments applied to schizophrenia patients. These findings point towards the importance of PFC-hippocampus connectivity in etiology of schizophrenia.

1.5.2.4 Spatial navigation in schizophrenia – from animals to humans

Spatial navigation abilities, especially the goal-directed navigation offers a powerful paradigm for studying neural system interactions during complex human behavior (Spiers and Maguire, 2006) and animal models of neuropsychiatric disorders. The neurobiology of various cognitive processes including perception, motivation, planning, memory and decision making at molecular, cellular, and systems level have been introduced using spatial navigation tasks in the rodent models (Burgess, 2008; Moser et al., 2008). The neurotransmitter dopamine and glutamate, important targets in schizophrenia research, play a dominant role in the modulation of the neuroanatomical structures and networks engaged in navigation (Penner and Mizumori, 2012). Several core brain regions that are involved in successful goal-directed navigation in humans including the hippocampus, prefrontal cortex and striatum (Aguirre et al., 1996; Astur et al., 2002; Bohbot et al., 2004; Hartley et al., 2003; Iaria et al., 2003; Maguire et al., 1998; Spiers and Maguire, 2006; Wolbers and Hegarty, 2010), are also strongly implicated in the pathophysiology of schizophrenia (Weinberger et al., 1986; Goldberg et al., 1987; Heckers and Konradi, 2002).

Optimal navigation is associated with the ability to flexibly switch between allocentric and egocentric strategy, and those between the hippocampal and striatal networks (Hartley et al., 2003; Iaria et al., 2003; Etchamendy and Bohbot, 2007). Also the ability to integrate wayfinding networks with prefrontal cortex working memory and executive functions (Maguire et al., 1998; Hartley et al., 2003) are essential for successful navigation in space. Evidence of impaired spatial memory and navigation have been reported in schizophrenia, and also in animal model of schizophrenia (see below). Visuo-spatial information that leads to the mental representation of space, the cognitive map, may contain errors and inaccuracies. Recalling from such cognitive maps can then impair spatial orientation at various levels.

In schizophrenia research, the mostly used virtual reality (VR) navigation paradigms are mainly focused on specific neural structures or cognitive domains, and therefore tend to be based on environments used in rodent models, within a paradigm of trial and error learning (Astur et al., 2004; Hanlon et al., 2006, 2012; Folley et al., 2010). With respect to MWM task, only the classic reference memory version of the hidden goal paradigm was tested in the virtual environment, in contrast to navigation to a visible target (Hanlon et al., 2006). This study demonstrated significant behavioral deficits in schizophrenia manifested in longer latency and a long search trajectory in hidden goal trials, but preserved visible target navigation. Other studies show spatial memory deficits in tasks that require extensive exploratory activity prior to testing to ensure familiarity with landmark locations (Weniger and Irle, 2008; Spieker et al., 2012).

Traditionally used ‘paper-and-pencil’ or simple computer tests to assess cognitive deficit in schizophrenia, are not comparable with the behavioral tasks used in animal research and such limitation can be shown in a low predictive validity of the animal models of schizophrenia (Pratt, Winchester, Dawson, and Morris, 2012). Considerable attention is therefore devoted to the assessment of spatial navigation abilities in schizophrenia and in animal models of this disorder, since spatial behavior and spatial memory can be measured using similar methods in various species. Rats are commonly used as models of schizophrenia.

One of this models uses neonatal ventral hippocampal lesion (NVHL), an experimental lesion in the ventral hippocampal area of rats created shortly after birth. Adult rats with NVHL show typical indicators of schizophrenia such as hypersensitivity to psychostimulants, reduced social interactions and impaired prepulse inhibition, working memory and set-shifting (Lipska, Weinberger, 2000; Lipska et al, 2002; Marquis et al., 2008; Brady, 2009). This research indicates that spatial memory may be adversely affected by neonatal damage to the hippocampus in a way that closely resembles schizophrenia. Schizophrenia is thought to stem from neurodevelopmental problems shortly after birth (Lewis et al., 2002).

Similar to schizophrenia, hippocampally impaired rats also failed to use environmental context in spatial learning tasks resulting in difficulty completing the radial arm maze and the Morris water maze (Silva-Gomez et al., 2003; Levin et al., 2006). Interestingly, this observations are similar to that reported in AD and amnestic MCI patients.

Some analogues of animal tasks have been already tested also in schizophrenia patients. Virtual Morris Water Maze has been previously applied only in the reference memory protocol in SZ (Hanlon et al., 2006; Folley et al., 2010). This task has been shown in human and non-human animal studies to be hippocampus-dependent. SZ patients traveled further and took longer to find the hidden platform (hippocampal-dependent version) over training blocks and spent less time in the correct quadrant during a probe trial. However, there was no deficit in the visible-platform condition (relying on cued-navigational abilities).

Another analogue, the virtual eight-arm radial maze (RAM), showed learning and memory impairments in SZ, as this task relies on intact prefrontal and hippocampal functions. Here, subjects attempted to learn to retrieve four rewards each located in separate arms. As expected, subjects with SZ used more time and traveled more distance to retrieve rewards, and made more reference and working memory errors, and retrieved fewer rewards than HC. Impaired virtual RAM performance in SZ is consistent with studies that examined RAM performance in animal models of SZ. These findings motivate the development of human analogues of animal spatial tasks for application in comparative clinical research.

Weniger and Irle (2008) tested SZ patients in egocentric navigation using complex virtual maze and allocentric navigation in complex virtual park (open scene with landmarks). This study demonstrated deficit of allocentric navigation using landmarks in contrast to preserved egocentric navigation using routes in SZ (Weniger and Irle, 2008). Stronger disorganized symptoms of schizophrenia subjects were significantly related to more errors on the virtual maze. It is concluded that egocentric spatial learning adds to the many other implicit cognitive skills being largely preserved in schizophrenia. Wilkins et al. (2013) showed strategy-dependent impairment in schizophrenia using virtual maze, where schizophrenia subjects demonstrated deficit in hippocampal spatial strategy, but not in the response strategy (associated with caudate function).

1.5.2.5 Visuospatial vs. verbal cognitive deficit in relation to quality of life in SZ

Even that abnormalities in cognitive functions are considered to be one of the key components in schizophrenia, studies focusing on specific relationships among the cognitive domains or relationships inside the domains and their influence on daily functioning are limited (Harvey, 2012). One of the most neglected areas is the comparison of the impact that visuospatial (VIS) and verbal (VERB) abilities have on global functioning and QOL. Focused research of VIS functions can help provide a better understanding of neuropsychological

patterns of heterogeneity in SZ. In addition, since VIS functions are less biased by language skills, research in this area can enlarge the neuropsychiatric field (Paradis 2008). Furthermore, VIS functions are an important tool for comparative research on animal models of SZ (Fajnerova et al. 2014).

One of the main reasons why visuospatial functions did not receive much attention as an independent entity in the research of SZ was the negative impact of the first-generation (typical) antipsychotic treatment on some motor and visuospatial functions (e.g. psychomotor retardation; Arana 2000;Meltzer and McGurk 1999;Bilder et al. 1992;Spohn and Strauss 1989). With the development of second generation (atypical) antipsychotics (AP), the risk of neurological side effects seemed reduced. Moreover, findings of slightly positive effects of some atypical AP on cognitive deficit were reported in SZ (e.g. Houthoofd, Morrens, and Sabbe 2008;Peuskens, Demily, and Thibaut 2005) and these findings were supported by results in an animal model of SZ (Bubenikova et al. 2005). However, when atypical antipsychotics were directly compared with the typical ones, no differences were found in either psychomotor functions or other cognitive areas (Keefe et al. 2007;Jones et al. 2006;Lewis and Lieberman 2008). Another limitation related to the study of VIS functions is that not all studies use a separate model of verbal and visuospatial functions. Usually, both VERB and VIS functions are included in the same cognitive domain (e.g. memory domain) or in the total IQ score; alternatively, they are studied as isolated variables. The question how much (if at all) the AP medication affects the motor and VIS functions when compared with the verbal functions, and to what degree the visuospatial functions impact daily functioning and the quality of life requires more research.

Visuospatial (VIS) impairment can negatively affect various daily activities from the most common, such as watching TV or reading a book, to the most complex, including social interactions (visual recognition of social signals) and recognition of territorial boundaries (interpersonal space) (Cummings and Mega 2003). SZ subjects exhibit impaired performance in a wide range of VIS functions, from the most basic level of visual perception to more complex visuospatial processing and navigation abilities (e.g. Butler et al. 2005;Stuve et al. 1997;Doniger et al. 2001;Piskulic et al. 2007;Cocchi et al. 2009;Landgraf et al. 2010;Weniger and Irle 2008;Folley et al. 2010;Hanlon et al. 2006;Fajnerova et al. 2014). This decline in VIS performance is already present in first episode schizophrenia and performance further deteriorates over time, predicting poor outcome (Stirling et al. 2003). Cross-sectional studies in subjects with late-life schizophrenia report impairment in visuospatial ability, alongside with executive and verbal fluency deficit. Moreover, longitudinal studies suggest that cognitive decline in late-life schizophrenia may first affect VIS abilities (Rajji and Mulsant 2008). It was also demonstrated that VIS tasks related to attention, memory and planning predict improvements on psychosocial functions, such as autonomy in daily living, treatment compliance, and social competence in subjects with psychosis (Prouteau et al. 2005). Given the significance of VIS functions in our daily life, it is expected that visuospatial tests would be good predictors of functional outcome in SZ.

Functional capacity and quality of life (QOL) play a key role in the study of the course, treatment efficacy and other factors related to functional outcome in SZ. Both functional capacity and QOL are negatively associated with clinical symptoms (Gaite et al. 2005b;Malla

and Payne 2005;Milev et al. 2005;Makara-Studziñska, Wo³yniak, and Partyka 2011). Negative symptoms are more strongly related to poor QOL and psychosocial functioning in SZ outpatients (Rocca et al. 2009;Eack and Newhill 2007), whereas general psychopathology shows a consistent negative relationship with QOL across all study samples and treatment settings (Eack and Newhill 2007;Rocca et al. 2009). Findings about the influence of positive symptoms are heterogenous, with the relationship towards negative and general symptomatology being more evident, varying only in the extent of influence (Eack and Newhill 2007;Rocca et al. 2009).

In terms of cognition, the current state of the literature did not enable drawing any conclusions about specific cognitive constructs related to global functioning and QOL. Some studies have documented a relationship between measured general cognitive ability (IQ index) and global functioning or QOL (Tzeng, Lung, and Chang 2004;Chaplin et al. 2006;Leeson et al. 2009), while other studies also point out the importance of specific neuropsychological domains. The results of these studies are very heterogeneous, depending on the measures used in the assessment. Despite the heterogeneity of measures, the deficit in executive functions appears to be the most evident and burdensome, and is most related to impairment of global functioning and QOL in SZ (Bilder et al. 2000;Reed et al. 2002). In addition, lower QOL is related to the deficit in verbal memory (Fiszdon et al. 2008;Matsui et al. 2008;Ritsner 2007). As was stated previously, VIS and VERB functions are usually combined in a single domain or IQ score. Thus, the role of VIS functions in global functioning and QOL remains unclear.

1.6 ANIMAL MODELS OF SCHIZOPHRENIA

Developing reliable predictive animal models for complex psychiatric disorders, such as schizophrenia, is essential in order to increase our understanding of the neurobiological basis of the disorder, mechanisms underlying this disease, and its symptoms (for review see Jones et al., 2011; Bubenikova-Valesova et al., 2008; Carlsson et al., 2004). Animal models of schizophrenia represent an important tool also for development of novel antipsychotic agents with improved therapeutic efficacy, and for verification of their effect on positive and negative symptomatology, and cognitive deficits in schizophrenia. Most of the currently used therapeutics for schizophrenia have been tested with the help of animal models. Animal models of schizophrenia represent experimentally-induced analogies of selected symptoms of the disease that do not represent the full manifestation of this typically human disorder. It is due to the obvious difficulty in modeling symptoms like hallucinations and delusions in animals. Instead, animal models do mimic observable behavioral manifestations of the disease, and scientists thus rely on observing this behavioral changes following specific experimental manipulations, usually evaluated in terms of validities (Bubenikova-Valesova et al., 2008). Construct validity reflects the agreement of the real disease and the animal model in terms of pathogenesis and (possible) causes (Ellenbroek and Cools, 1990). Face validity emphasizes similarities of the symptomatology; and finally the predictive validity of the model relates to the response to drugs used as therapeutics on human subjects (Jones et al., 2011, see Fig.13).

The use of animal models helps to improve understanding of the neurochemical and structural CNS changes that precipitate development of schizophrenia, rather than focusing on treating the symptoms, is a prerequisite to enable new more effective therapeutic strategies to be developed (Jones et al., 2010). Most rodent models have behavioural phenotype changes that

resemble ‘positive-like’ symptoms of schizophrenia, probably reflecting altered mesolimbic dopamine function, but fewer models also show altered social interaction, and learning and memory impairment, analogous to negative and cognitive symptoms of schizophrenia respectively. All available animal models of schizophrenia fit into four different induction categories: developmental, drug-induced, lesion or genetic manipulation. In these chapter we will focus only on Pharmacological models of schizophrenia.

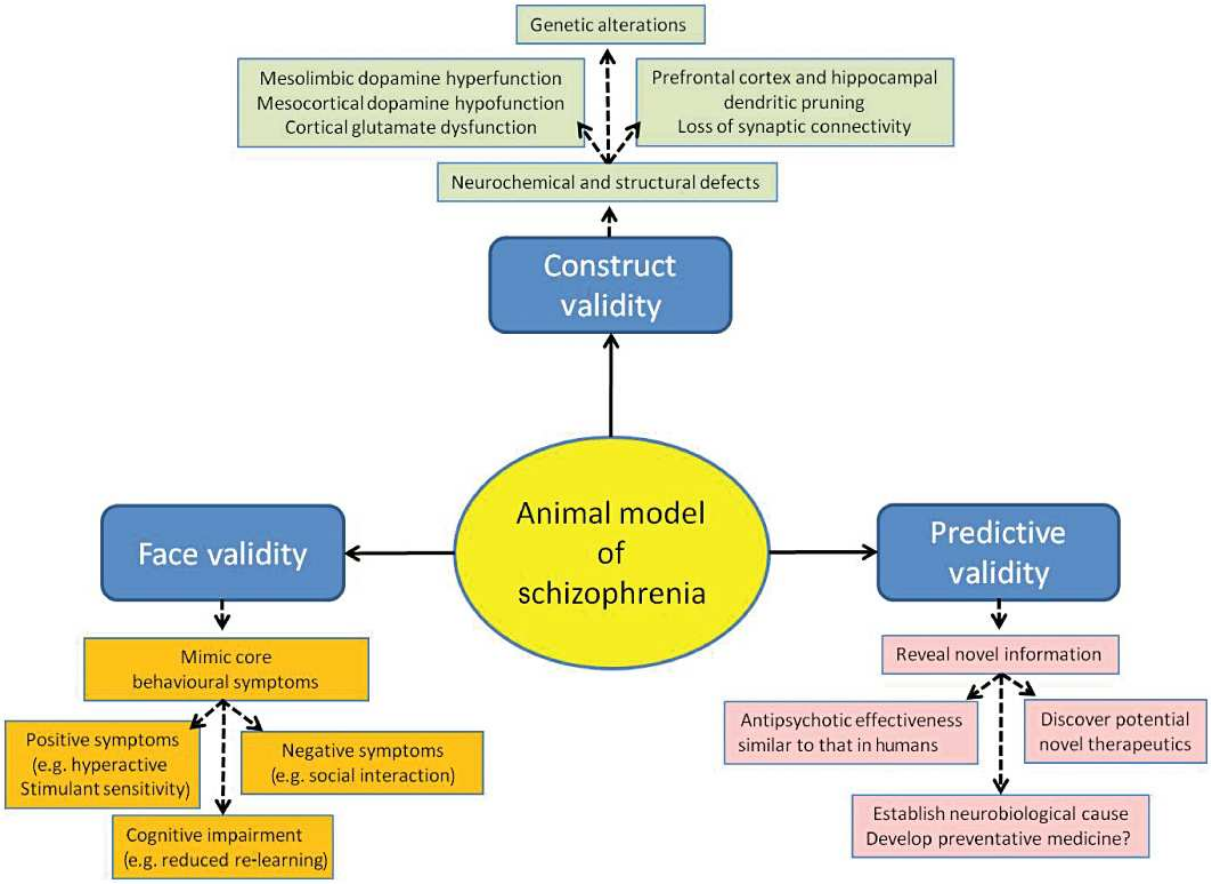


Figure 13. *Schematic diagram of the key behavioural, neurochemical and structural changes expected be present and to have translational relevance to the three core symptom domains of schizophrenia in an animal model of the disorder (adopted from Jones et al., 2011).*

1.6.1 DOPAMINE MODEL OF SCHIZOPHRENIA

A dopamine dysregulation with hyperfunction of the mesolimbic dopamine system was the original theory underlying the basis of schizophrenia (Murray et al., 2008), therefore the first animal models were developed on the basis of pharmacological manipulation trying to mimic this feature. Amphetamine-induced psychosis was first described in the 1950s with a clinical picture of positive symptoms of SZ: auditory hallucinations and persecutory delusions. In rodents, chronic amphetamine administration induces a persistent sensitization, exaggerating the hyperactivity caused by acute amphetamine application (Robinson and Becker, 1986), which is thought to more robustly model symptoms than a single injection (Featherstone et al., 2007). Pre-administration of a low dose of either haloperidol or clozapine prevents the induction of such sensitization (Meng et al., 1998).

In general, chronic amphetamine induces positive psychotic-like changes, but does not replicate the negative or cognitive symptoms seen in schizophrenia (Jones et al., 2011).

Nevertheless, amphetamine sensitization may be accompanied by deficits in PFC-dependent cognitive tasks, such as impairments in the attentional shift and reversal learning in the set-shifting tasks (Fletcher et al., 2005; Featherstone et al., 2008). Furthermore, clozapine, and to a lesser extent haloperidol, attenuates this amphetamine-induced impairment in attention (Martinez and Sarter, 2008). However, repeated amphetamine administration has no effect on delayed alternation tasks (Stefani and Moghaddam, 2002). Hippocampal- dependent cognition also appears to be spared, as repeated amphetamine has no effect on acquisition or retention of spatial visual learning and memory in the Morris water maze (Featherstone et al., 2008). Thus, cognitive impairment following chronic amphetamine appears to be restricted only to some PFC-dependent tasks.

1.6.2 GLUTAMATERGIC MODEL OF SCHIZOPHRENIA

An important role of the glutamatergic neurotransmitter system in the etiopathogenesis of schizophrenia (Jones et al., 2011) has been supported by extensive findings on various levels from molecular interactions up to the structural layout of neuronal network in the human brain (Goff and Coyle, 2001; Javitt, 2012).

1.6.2.1 Phencyclidine models of schizophrenia

In recent years, increasing evidence supports the idea that dysfunction of the glutamatergic system is a primary pathophysiological change seen in schizophrenia (Olney and Farber, 1995; Coyle, 2006; Konradi and Heckers, 2003). The exact etiology of SZ disease is unknown, yet neurodevelopment-related changes in the glutamatergic system in the brain are suspected to play an important role (Kantrowitz and Javitt, 2012). The importance of the glutamate system was underlined also by the finding that the application of non-competitive antagonists of NMDA subtype of glutamate receptors, such as phencyclidine (PCP) and ketamine, induces delusions and hallucinations (typical for acute psychosis) and progressive withdrawal and poverty of speech (resembling the negative symptoms) in otherwise healthy humans (for review see Bubenikova-Valesova, et al., 2008). Additionally, both acute low-dose and chronic recreational use of PCP impair cognitive performance (Javitt and Zukin, 1991). Furthermore, in both stabilized chronic and acute schizophrenic patients, PCP reignites and exacerbates positive symptoms (Javitt and Zukin, 1991).

As PCP induces in humans several symptoms similar to those seen in schizophrenia, it has been used to attempt to produce a pharmacological rodent model of schizophrenia inducing the following behavioral changes after acute or chronic PCP administration (for review see Jones et al., 2011; Bubenikova-Valesova et al.,2008): hyperlocomotion, social withdrawal, and impairment of both PPI and cognition in rodents. Additionally, early PET scans suggested that recreational PCP abuse was accompanied by deficits in the temporal and frontal lobes, which confirms the changes seen in schizophrenic patients (Hertzmann et al., 1990). Thus, it has been suggested that chronic PCP use may be applied in order to more accurately mimic the symptoms of schizophrenia (Jentsch and Roth, 1999).

Glutamatergic hypothesis of schizophrenia (Javitt and Zukin, 1991; Carlsson et al., 2001) presumes that by inhibition of NMDA receptors, the mesolimbic dopaminergic system becomes secondarily activated which in turn causes psychosis. Besides affecting the dopamine system, blockade of NMDA receptors reduces the firing rate of fast-spiking inhibitor interneurons in the frontal cortex (Homayoun and Moghaddam, 2007). Acute NMDA inhibition

causes disinhibition of neurotransmitter systems, while long-term exposure to NMDA antagonists causes a decrease of brain activity (Jentsch and Roth, 1999). Chronic or subchronic administration of NMDA receptor antagonists produces various changes, such as the facilitation of the NMDA synaptic current while depressing the extra-synaptic NMDA current and hypofunction of GABAergic neurotransmission (Yu et al., 2002). The above-mentioned changes in neurotransmitter systems are associated with behavioural changes, such as impairment of cognitive functions and information processing following chronic NMDA administration reported in several studies (Vales et al., 2006; Stefani and Moghaddam, 2002; Rujescu et al., 2006; Bubenikova-Valesova et al. 2008).

Neurodevelopmental hypothesis of the origin of schizophrenia assumes that a disorder in pre- or perinatal development of the brain will result in manifestation of the disease in early adulthood (Weinberger, 1996; Lipska and Weinberger, 2002). Neurodevelopmental model of schizophrenia based on early NMDA receptor inhibition (Ikonomidou et al., 1999) indicating that administration of the NMDA receptor antagonists (dizocilpine or phencyclidine) in late fetal and early postnatal period of life in the rat will increase neuronal death by apoptosis, due to excitotoxic effects (Deutsch et al., 2001). The increased death of neurons by apoptosis during the early phase of CNS development may result in decreased ability of neuronal damage by programmed death, reported in chronic patients with schizophrenia (Jarskog, 2006).

Finally, the genetic model inspired by a hypothetical NMDA dysfunction in SZ is based on a decrease in expression of the NR1 subunit or of other NMDA receptor subunits (Mohn et al., 1999) and causes behavioral abnormalities, including increased motor activity and stereotypy and deficits in social interactions.

1.6.2.2 MK-801 (dizocipline) model of schizophrenia

Another glutamatergic animal model of schizophrenia-like behavior is induced in adult animals by application of MK-801 (dizocilpine), a non-competitive antagonist of NMDA-subtype of glutamate receptors. This model does not have construct validity, as it is based on the acute effects of a drug and contains no developmental component, especially when applied to adult animals. Yet this model shows a good predictive validity (Bubenikova-Valesova et al, 2008), and importantly the model exhibits a substantial phenomenological face validity since it induces schizophrenia like behaviour in animals with numerous changes resembling symptoms observed in affected human subjects (van der Staay et al., 2011). Due to its time feasibility, this model is often used to predict the effect of substances with potential antipsychotic properties (Bubenıkova et al., 2005; Large, 2007).

It has been shown that MK-801 produces hyperlocomotion (which was analogized to positive symptoms based on increased activity of mesolimbic dopaminergic circuits; Nilsson et al., 2001), social flattening (Rung et al., 2005), and perhaps most importantly a deficit in various cognitive domains (van der Staay et al., 2011). MK-801 has been described to fulfill the criteria of a ‘cognition impairer’, and by carefully titrating the dose, researchers can induce behaviors resembling those present in schizophrenia patients (Bubenikova-Valesova et al., 2008). MK-801 has shown to induce a deficit in acquisition in the Morris water maze, object recognition task, inhibitory avoidance, and other tests of relational and spatial memory including the active place avoidance task (van der Staay et al., 2011; Stuchlik and Vales, 2005). At least some deficits resulting from the administration of NMDA antagonists (including MK-801) can be alleviated by pre-training (Saucier et al., 1996). Nevertheless, a deficit in the re-acquisition of

the active place avoidance task induced by MK-801 (0.15mg kg^{-1}) has shown to be resistant to previous experience with the task under no influence of the drug (Stuchlik and Vales, 2005).

Importantly, deficits in cognitive flexibility (Han et al., 2012) and managing of multiple information streams and changed contingencies are documented in many schizophrenia patients (Phillips and Silverstein, 2003), who often display general problems in distinguishing relevant information from irrelevant information (Ellenbroek and Cools, 1990). Indeed, alterations of cognitive control, behavioral flexibility and adapting to changed conditions were detected in animal models of schizophrenia in various experiments (e.g., Morice et al., 2007; Broberg et al., 2008; Amitai and Markou, 2010). It is known that alterations in the function of the prefrontal cortex may contribute or even play a substantial role in disrupted flexibility observed in schizophrenia and schizophrenia animal models (Gruber et al., 2010).

2 Aims of the thesis

Complex neuropsychiatric disorders, such as schizophrenia, create significant challenges to both clinical and preclinical researchers. Animal models of schizophrenia provide valuable information for the development of novel therapeutic options that may benefit patients with schizophrenia. This dissertation thesis aims to demonstrate the usefulness of the comparative research enabling to build a bridge between animal models and neuropsychiatric patients by application of comparative methods testing spatial abilities (navigation and spatial memory) both in animal model and schizophrenia patients.

Preclinical part:

- ***Assessment of spatial memory using two behavioral tasks in animal model of schizophrenia induced by MK-801 – Experiment I***

  As mentioned above, animal models of schizophrenia offer reasonable insight into neuropharmacological processes underlying schizophrenia and thus provide important information for development of new antipsychotic drugs. The study demonstrates the behavioral impairment in a glutamatergic animal model of schizophrenia induced by MK-801 (dizocilpine), a non-competitive antagonist of NMDA glutamate receptors, previously demonstrated to produce cognitive-like symptoms in injected animals. In order to address the both deficit in spatial memory and mental flexibility in schizophrenia, this study employed two established behavioral tests of spatial navigation, the *Morris water maze* and an *Active place avoidance task* (Carousel maze) in reversal paradigms, and evaluated their sensitivity to the effects of MK-801 upon changed contingencies in this reversal configuration. The obtained results are discussed in context of comparative data reported from virtual variants of the two spatial tasks.

Clinical part:

The aim of the human part of the thesis was to compare the previously reported behavioral results in the animal model of schizophrenia (including Animal part I) with the behavior of human subjects suffering from schizophrenia disease. In order to achieve this we have developed two virtual reality tests for humans based on previous animal research: virtual Morris water maze (Experiment II) and virtual Carousel maze (Experiment III). This was crucial in order to provide information about the predictive validity of the applied pharmacological animal model of schizophrenia. Both paradigms have been adjusted to single day protocols in order to test human subjects in one day session. Virtual tests have been applied in a group of first episode of schizophrenia spectrum disorder (FES) patients, evaluated once they were stabilized at the end of their psychiatric hospitalization in partial symptomatic remission state, and in a group of healthy volunteers (see Experiment II and III). The aim of these experiments was to evaluate the sensitivity of newly-developed spatial tasks to assess cognitive deficit in schizophrenia.

Both methods have been designed in order to test at least partly different cognitive abilities, therefore we present them as separate experiments. Nevertheless, please note that both methods have been assessed in the same group of patients and healthy volunteers in order to

enable some comparison of their results. For these reason, part of the methods presented in experiment II are applicable in Expriment III as well.

Finally, we attempt to elucidate on the impact of visuospatial (VIS) deficit in comparison with verbal (VERB) deficit on global functioning and quality of life (QOL) in FES patients (see Experiment IV).

Aims of individual experiments:

- ***Development of two novel virtual reality tests for human subjects based on animal research: Morris water maze and Carrousel maze, and their application as a tool for assessment of spatial memory in schizophrenia patients in comparison to healthy control group – Experiments II and III***

  In order to assess complex spatial abilities, including memory and executive functioning, in schizophrenia and compare our results with the data obtained previously in animal models of this disease, we designed two virtual reality tasks adopted from the animal research: 1) the *Morris water maze* (MWM) and 2) the *Carousel maze* paradigm (active place avoidance task). Both virtual reality (VR) environments have been created using the Unreal Tournament game engine editor that allowed us to build large-scale and/or moving environments similar to those used in animals. Reference memory versions of the virtual reality MWM were already applied in chronic schizophrenia. Thus, our aim was to extend the current comparative research by attempting to incorporate several MWM variants (including delayed-matching to place) into a small test battery named the "virtual Four Goals Navigation" (vFGN) task. On the other hand, rotating arena paradigms have not yet been tested in schizophrenia. Thus our aim was to develop the virtual analogue of the Carousel maze, so called Active Allocentric Place Preference (vAAPP) task. This tasks are aimed to test both spatial memory and/or cognitive coordination in schizophrenia.

  Complex cognitive deficit is well demonstrated in chronic schizophrenia patients. Several studies report impairment in cognitive functioning of schizophrenia patients already after the first episode of psychotic symptoms, here referred as First Episode Schizophrenia (FES) patients. In order to test spatial memory deficit in early stages of schizophrenia, and to demonstrate the sensitivity of the comparative methods towards this deficit, both newly-developed comparative virtual tests have been applied in a group of FES patients. All patients were assessed once they were stabilized at the end of their first psychiatric hospitalization in partial symptomatic remission state and their performance was compared to a group of matched healthy volunteers (HC group). First, the FES group performance was compared to the healthy controls group (HC group) in various standard neurocognitive tests in order to demonstrate the complex cognitive impairment in early stages of the disease. Variable methods, both verbal and visuospatial, were chosen in order to evaluate all main cognitive domains (attention and vigilance, processing speed, working and long-term memory, and executive functioning). Also new standard methods not yet reported in schizophrenia were applied.

  Experiment II presents the data obtained in a group of FES patients in the newly-developed vFGN task, and Experiment III demonstrates the results of the vAAPP task in the same group of FES patients and HC. In order to assess the usefulness of both methods in future preclinical studies, we compare the data obtained in the vFGN and vAAPP tasks with the previously published animal studies.

- ***Comparison of visuospatial and verbal abilities in first psychotic episode of schizophrenia spectrum disorder: impact on global functioning and quality of life- Experiment IV***

  To our knowledge, no study to date has described the extent to which visuospatial functions affect everyday life of schizophrenia patients, in contrast to the effect of verbal abilities. The aim of this study was thus to elucidate on the impact of visuospatial deficit in comparison with verbal deficit on global functioning and quality of life (QOL) in FES patients. In order to understand their impact together with possible significance of clinical symptoms and antipsychotic medication, we analyzed a cumulative model of verbal and visuospatial neurocognition performance, with medication, and positive, negative and general symptoms on QOL and global functioning using multiple linear regression analysis.

3 Experimental data

3.1 PRECLINICAL PART:

3.1.1 EXPERIMENT I. - SPATIAL MEMORY AND MENTAL FLEXIBILITY IN ANIMAL MODEL OF SCHIZOPHRENIA

3.1.1.1 Aims

This study aimed to address the deficit in mental flexibility in animal model of schizophrenia. In order to achieve this, the study employed two established behavioral tests of spatial navigation in rodents, an active place avoidance task (AAPA) and the Morris water maze (MWM), and evaluated their sensitivity to the effects of MK-801 (dizocilpine) upon changed contingencies in the reversal configuration (changing rules). The present study aimed at testing the hypothesis that MK-801 application would result in a deficit of flexibility in spatial reversal. Moreover, this study employed both well-established behavioral tests of spatial navigation and evaluated their sensitivity to the effects of MK-801 upon changed contingencies in the reversal configuration. Finally, this study sought to determine dose-dependency of these effects in both tasks using five different doses of MK-801 (see Methods).

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3.1.1.2 Methods:

Drugs

MK-801 (dizocilpine maleate) was purchased from SigmaAldrich, Czech Republic. It was dissolved in saline (0.95% NaCl) at concentrations 0.05 mg ml^{-1}, 0.08 mg ml^{-1}, 0.10 mg ml^{-1}, 0.12 mg ml^{-1} and 0.15 mg ml^{-1}. MK-801 solution was injected at doses of 0.05 mg kg^{-1}, 0.08 mg kg^{-1}, 0.10 mg kg^{-1}, 0.12 mg kg^{-1} and 0.15 mg kg^{-1}. Control group was administered with a sterile saline solution at a volume 1 ml kg^{-1}. All animals obtained the same volume in an injection per kg of body weight.

Apparatuses and behavioral procedures

Active place avoidance task (Carousel maze)

The active place avoidance apparatus (Vales and Stuchlik, 2005; Stuchlik et al., 2008; Blahna et al., 2011; Prokopova et al., 2012) is a smooth metallic arena (82 cm in diameter), enclosed with a 30-cm-high transparent Plexiglas wall and elevated 1 m above the floor. Extra-maze landmarks (door, posters, and shelves) in the room were kept in the same positions throughout the study. At the beginning of each session, a rat was placed in the center of the arena, which rotated constantly at one revolution min^{-1}. An unmarked 60-degree to-be-avoided sector was defined in the coordinate frame of the room in the North of the four arbitrarily

defined compass directions (acquisition sessions) and was changed to the South in the final two days (reversal sessions); i.e., there were five daily sessions in total (see later). The rat could rely solely on the distal room-frame landmarks to locate the sector (Bures et al., 1997). This sector is defined by the computer-based tracking system (Tracker, Biosignal Group, USA), which records the position of the rat (indicated by an infrared light emitting diode that was fastened on a latex harness between rat's shoulders) at a sampling rate of 25 Hz. Another infrared diode, placed on the periphery of the arena, indicates arena rotation. The trajectories were digitized and recorded on a PC, allowing off-line reconstruction and analysis of the animal's trajectory (Track Analysis, Biosignal Group, USA) both in the coordinate frame of the room and in the coordinate frame of the rotating arena.

Whenever a rat entered the sector for more than 300 ms, constant-current regulated electric foot-shocks (AC, 50 Hz, 200-600 μA) were delivered at 1200-ms intervals up to the moment a rat left the sector. The shocks were administrated through the above-described subcutaneous needle connector implanted on the back of the rat standing on the grounded floor. Since the highest voltage drop of the current passing through the rat was at the high-impedance contact between the paws and the metal floor, the rats presumably perceived the shocks in their paws. The appropriate current was individualized for each rat in order to elicit a rapid escape reaction but prevent freezing (fear-related immobility). This aversive procedure has been shown to be efficient and safe in previous studies (Vales and Stuchlik, 2005; Wesierska et al., 2005; Stuchlik et al., 2008; Prokopova et al., 2012). Since the arena rotated, the rat had to move actively away from the shock in the direction opposite to arena rotation, otherwise it was passively transported into the shock sector. Five daily sessions of active place avoidance testing, separated by 24-h inter-trial intervals, were conducted in the light phase of the day. The initial three sessions were designated as acquisition sessions which were followed by two reversal sessions (see below).

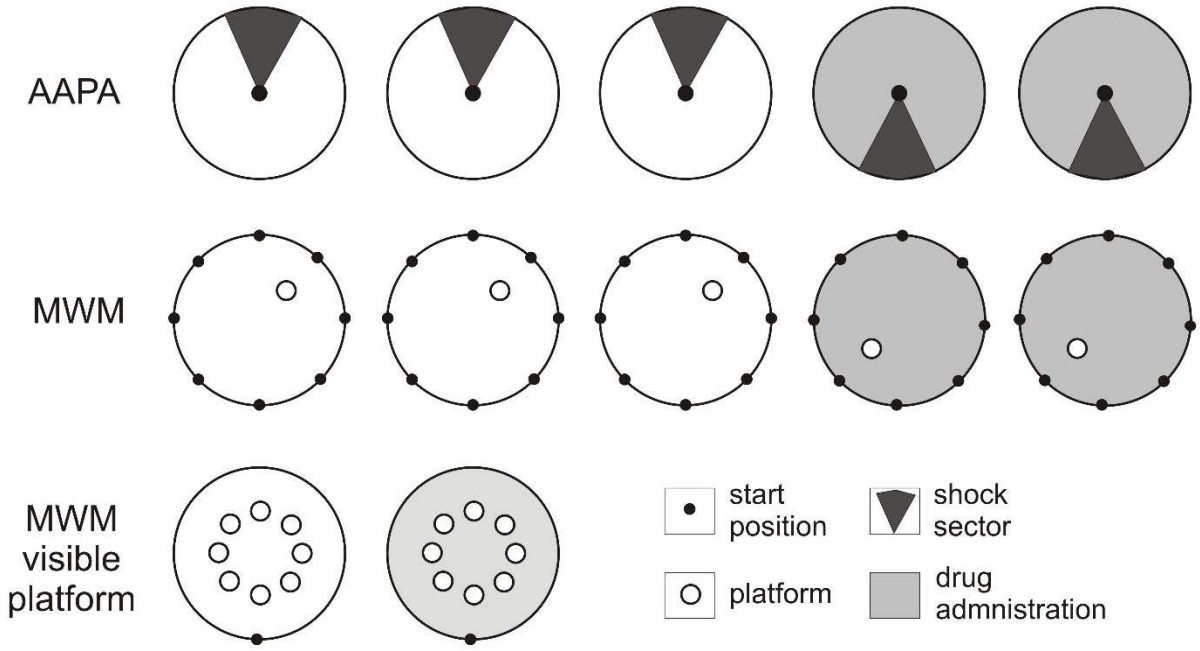

Figure 14. *Schematic drawing of experimental design. In the active place avoidance experiment, three acquisition sessions with the to-be-avoided sector in the North (all animals obtained saline) were followed by two reversal*

sessions with the sector in the South. Saline (control group) or the drug (experimental groups) was administered prior to the reversal sessions. In the hidden platform experiments in the MWM, three sessions with platform located in the NE were followed by two sessions with the platform in the SW after the application of saline or drug. Starting positions varied pseudo-randomly in this experiment and each session consisted of eight swims (not shown). In the visible platform version of the MWM, the start position was always fixed to the South position and the platform position varied pseudo-randomly between swims. The first session was with saline application, the second was preceded by administration of the drug (or saline in the case of controls). MWM VP - visible platform test in the Morris water maze.

Morris water maze

The Morris water maze (MWM; Morris, 1981; Stuchlik et al., 2007) consists of a grey circular pool (180cm in diameter) filled with water at a temperature of 21±2ºC to a depth of 35cm. The water was rendered opaque by adding a small amount of non-toxic white paint (Primalex, PPG Deco, Czech Republic). The maze was located in a room providing an abundance of extra-maze cues. Swimming trajectories were monitored by an overhead camera connected to a digital tracking system and data acquisition program (Tracker, Biosignal Group, USA). The maze contained a transparent plastic platform (10 cm in diameter) located in the center of quadrants that were labeled arbitrarily based on compass directions.

In the visible platform sessions of the task (two daily sessions), the animal underwent 10 swims in 15-min intervals, always being released from the South of the pool. The platform position was chosen pseudo-randomly from eight locations for each swim. The order of platform positions varied between the two sessions.

In the hidden platform testing, the rats were released for eight swims per day, separated by 15-min intervals from the following start positions: S, W, SE, NW, E, SW, NE, N, to ensure a rat was learning spatial location of the platform and not the path itself. These start positions varied pseudo-randomly within every day and this sequence varied for each daily session. The platform was positioned in the center of NE quadrant in the initial three acquisition sessions of the hidden-platform phase and it was relocated to SW for the subsequent two daily reversal sessions. In total, there were five daily sessions of the hidden-platform testing in the MWM. Probe trials (60-s swims with the platform removed from the pool) were administered after the final acquisition session, and first and second reversal sessions, respectively, to reveal the memory trace for the current platform location.

Design of the study, measured parameters and data analysis

The design of the study is shown schematically in Fig.14. Saline was applied to all animals (1 ml/kg) 30 min prior to start of the testing during three initial acquisition sessions in active place avoidance and the MWM. After the third acquisition sessions, animals were assigned randomly to control group and groups with MK-801. The drug (or saline in case of the controls) was applied only in the reversal sessions 30 min prior to the start of active place avoidance testing and 30 min prior to the first swim in the hidden platform version of the MWM. In the visible platform experiment in the MWM, all animals were applied with saline 30min prior to the initial swim in the first session (10 swims) and with saline or drug 30 min before the first swim in the second session (10 swims). The intervals between injections of MK-801 and probe trials on the reversal days were 140 min.

Separate groups of animals were used for active place avoidance reversal experiment, visible platform version of the MWM and spatial reversal in the MWM. In the active place

avoidance testing, a control group (n = 20) and groups with five above-mentioned doses were used: 0.05 mg kg^{-1} (n = 9), 0.08 mg kg^{-1} (n = 8), 0.10 mg kg^{-1} (n = 8), 0.12 mg kg^{-1} (n = 8) and 0.15 mg kg^{-1} (n = 8). In the visible platform experiment in the MWM, all groups had n = 10. In the reversal experiment in the MWM, all groups also consisted of 10 rats.

In the active place avoidance task, an offline analysis program (Track Analysis, Biosignal Group, USA) measured and evaluated **total distance** traveled per session (measured as a sum of linear distances between points selected every second in the coordinate frame of the arena) which reflected only the active movement excluding passive arena rotation. Spatially-selective parameters included the number of entrances into the to-be-avoided sector (**number of errors**) per session, maximum time without shock (**maximum time avoided**) and **percentage of the total time per session in the target quadrant**. The target quadrant in the active place avoidance task was defined as a 60-degree sector of the arena, which corresponded to the to-be-avoided sector and dwelling time in this sector was expressed as relative percentage of the total time (20 min). Procedural performance in the task (efficiency of escape reaction) was measured by total number of shocks (which were repeated upon staying in the sector; see above) divided by the number of errors; this parameter is henceforth referred to as **skill learning index**. The total distance reflected the locomotor activity (forced by arena rotation and presence of the room-frame-fixed sector), and the number of errors and maximum time avoided served as cumulative measures of within- and between-session improvements. In the MWM, an off-line program (Track Analysis, Biosignal Group, USA) evaluated **total distance** (m) **to find the platform** in each swim; this measure corrects for possible changes in swimming speed. In the probe trials, we evaluated the **percentage of the total time spent in the target quadrant**, which was defined as a 90-degree sector of the Morris water maze centered at the actual platform position. We used an initial 30-s interval of the probe trial as the most sensitive time period (unpublished observations; note that upon failing to find the platform in the previous position at the beginning, animals often explore other parts of the maze).

Since the animals were randomly divided into treatment groups after the completion of initial three acquisition sessions in both active place avoidance and the MWM, only the reversal sessions in the place avoidance and water maze were analyzed for putative differences between groups. Data from the reversal sessions of the active place avoidance had skewed (non-normal) distribution in all measured parameters; therefore we transformed all the values with a common logarithm. Prior to this transformation, a constant of '1' was added to all values to ensure that the resultant values are not less than zero. The same transformation was applied to the total distance to reach the platform in the MWM, which also had skewed distribution. Data from the active place avoidance were analyzed with a two-way ANOVA (groups x sessions) with repeated measures on sessions. Groups served as a between subject-factor. Data from the reversal sessions in the MWM were analyzed with a general linear model (three-way ANOVA: groups x sessions x swims with repeated measures on sessions and swims). Groups again served as a between-subject factor. Percentages of time in the target quadrant in the probe trials were analyzed with a two-way ANOVA (groups x sessions) with repeated measures on sessions. Data from the probe trials were not logarithmically transformed prior to analysis. Data from the second day of the visible platform test in the MWM were also not transformed and were analyzed with a two-way ANOVA (groups x swims; repeated measures on swims. Note that only saline was applied on the first day and animals were randomly divided into groups hereafter). A Newman-Keuls post-hoc test followed the ANOVA when appropriate.

Significance was accepted at $p \leq 0.05$. All statistical calculations were done in Statistica 8 (StatSoft, Czech Republic)

*3.1.1.3 **Results***

Visual observation of the rats did not suggest any signs of severe sensorimotor deficit after application of saline or MK-801 at the above-mentioned doses. Animals treated with MK-801 showed mild hyperactivity in the active place avoidance task, which was confirmed by an analysis of the total distance (see next paragraph). In the MWM, rats treated with 0.15 mg kg^{-1} of MK-801 sometimes continued swimming after finding and climbing onto the platform, suggesting an impaired procedural functions; moreover, the highest dose also increased swimming speed in the visible platform test (*data not shown*). Mild ataxia was observed only rarely after the highest dose.

Reversal learning in the active place avoidance

There was a significant effect of MK-801 on the total distance in active place avoidance (Fig. 15A). A two-way ANOVA (groups x sessions) revealed a significant main effect of groups ($F(5,55) = 24.93$; $p < 0.001$), sessions ($F(1,55) = 6.85$; $p < 0.05$) but not an interaction between these factors ($F(5,55)$; $p > 0.05$). A Newman-Keuls post-hoc test computed on the group factor showed that significant hyperlocomotion was seen after doses 0.08, 0.10, 0.12 and 0.15 mg kg^{-1} but not after the dose 0.05 mg kg^{-1}.

Analysis of the numbers of errors showed that it was affected by MK-801 treatment (Fig. 15B). A two-way ANOVA (groups x sessions) with repeated measures on sessions showed a significant main effect of groups ($F5,55) = 9.71$; $p < 0.001$), sessions ($F(1,55) = 26.36$; $p < 0.001$) and interaction between both factors ($F(5,55) = 3.21$; $p < 0.05$). A post-hoc test performed on the groups factor revealed that only groups treated with 0.15 mg kg^{-1} ($p < 0.001$), 0.12 mg kg^{-1} ($p < 0.01$) and 0.08 mg kg^{-1} ($p < 0.05$) of MK-801 differed from controls; groups treated with 0.05 mg kg^{-1} and 0.10 mg kg^{-1} of MK-801 did not differ from controls (both $p > 0.05$). A Newman-Keuls post-hoc test of the interaction showed that only groups treated with 0.15 MK-801 differed from controls on the initial reversal day ($p < 0.05$), whilst other groups did not differ. On the second reversal day, there was a difference between groups treated with 0.12 mg kg^{-1} and 0.15 mg kg^{-1} of MK-801 (both $p < 0.05$). The performance of the control group improved between both reversal sessions ($p < 0.05$).

Analysis of the maximum time avoided showed, again, a difference as a result of the MK-801 application (Fig. 15C). A two-way ANOVA (groups x sessions) showed a significant main effect of groups ($F(5,55) = 8.72$; $p < 0.001$), sessions ($F(1,55) = 9.63$; $P < 0.01$) but only a trend for an interaction between both factors ($F(5,55) = 2.18$; $p = 0.07$). A post-hoc test performed on the group factor revealed that application of MK-801 at the doses 0.12 mg kg^{-1} and 0.15 mg kg^{-1} impaired performance in this measure ($p < 0.05$, 0.01, respectively). Control group improved performance from the first to the second reversal session ($p < 0.05$).

Percentage of time in the target quadrant was altered as a result of the application of MK-801 (Fig. 15D). A two-way ANOVA revealed a significant main effect of groups ($F(5,55) = 7.27$; $p < 0.001$), sessions ($F(1,55) = 11.44$; $p < 0.005$) but no interaction between these two factors ($F(5,55) = 1.69$; $p = 0.15$). A Newman-Keuls post-hoc test on the factor of groups showed that groups receiving 0.08 mg kg^{-1} ($p < 0.05$), 0.12 mg kg^{-1} ($p < 0.01$) and 0.15 mg

kg^{-1} ($p < 0.001$) of MK-801 showed impairment in this parameter. No difference was seen after 0.05 mg kg^{-1} MK-801 application ($p < 0.44$), and a trend for worsening was detected only after 0.10 mg kg^{-1} of MK-801 ($p = 0.08$). It therefore appears that the percentage of time in a target quadrant is a sensitive measure of spatial performance.

The skill learning index, indicative of procedural functions (i.e., an escape reaction from the to-be-avoided sector upon first shock), was affected by MK-801 application in a more complicated fashion than the mere group factor (Fig. 15E). A two-way ANOVA failed to show an effect of groups ($F(5,55) = 0.85$; $P > 0.05$), sessions ($F(1,55) = 0.26$; $P > 0.05$), but interestingly, it revealed an interaction between these two factors ($F(5,55) = 4.37$; $P < 0.01$). This interaction suggested that skill learning index improved over two reversal sessions in some groups, but not others. Analysis of the interaction showed that this index improved (decreased) between the two reversal sessions in groups treated with saline (control group) and 0.15 mg kg^{-1} of MK-801, and remained similar in animals treated with 0.05 mg kg^{-1} and 0.08 mg kg^{-1} of MK-801, or even increased (worsened) in groups treated with 0.10 mg kg and 0.12 mg kg^{-1} of MK-801. However, generally, this index was relatively low and barely exceeded the value of 2 (e.g., 2 shocks per 1 error) in the reversal sessions. Moreover, the interaction term was very subtle and none of the interactions was confirmed by a Newman-Keuls post-hoc test calculated on the interaction.

Reversal learning in the Morris water maze

Reversal learning (cognitive flexibility) in the MWM was affected by treatment with MK-801 (Fig. 16A). Regarding the total distance to reach the platform, a general-linear-model three-way ANOVA (groups x sessions x swims) with repeated measures on the last two factors showed significant main effects of groups ($F(5,51) = 16.25$; $p < 0.0001$), sessions ($F(1,51) = 82.00$; $p < 0.0001$) and swims ($F(7,357) = 25.05$; $p < 0.0001$). Moreover, interactions were detected between groups and swims ($F(35,357) = 2.27$; $p < 0.0005$) and between sessions and swims ($F(7,357) = 5.62$) but not between groups and sessions ($F(5,510 = 0.53$; $p > 0.05$). There was also a significant triple interaction between groups, sessions and swims ($F(35,357) = 1.47$; $p < 0.05$).

Importantly, a Newman-Keuls post-hoc test calculated on the group factor showed that groups treated with 0.05 mg kg^{-1} and 0.08 mg kg^{-1} MK-801 did not significantly differ from the control group, but groups treated with 0.10 mg kg^{-1}, 0.12 mg kg^{-1} and 0.15 mg kg^{-1} of MK-801 differed from control rats. All groups improved in shortening the distance to reach the platform between the two reversal sessions (i.e., absence of an interaction between groups and sessions). A post-hoc analysis of the interaction term group x swims showed that while controls and animals treated with 0.05 mg kg^{-1}, 0.08 mg kg^{-1}, 0.10 mg kg^{-1} and 0.12 mg kg^{-1} improved with each successive swim, no between-swim improvement was seen in the group treated with the highest dose (0.15 mg kg^{-1}). A post-hoc analysis of the triple interaction revealed that control rats and the groups treated with 0.05 mg kg^{-1} and 0.08 mg kg^{-1} of MK-801 improved between swims in both of the two consecutive reversal sessions. Groups treated with 0.10 mg kg^{-1} and 0.12 mg kg^{-1} of MK-801 improved only in the second reversal session, and the group treated with the highest dose failed to improve between swims at all.

Results of the probe trials showed a strong preference for the target quadrant on the final acquisition day (after saline; see Fig. 16B). A two-way ANOVA conducted on the time in the target quadrant (groups x sessions) involving the final acquisition session and first and second reversal sessions showed a significant main effect of groups ($F(5,52) = 7.41$; $p < 0.0001$), an

effect of sessions ($F(2,104) = 19.23$; $p < 0.0001$) and a significant interaction between these factors ($F(10,104) = 4.66$; $p < 0.001$). A post-hoc analysis of the interaction showed that while control group and groups treated with 0.05 mg kg^{-1} and 0.08 mg kg^{-1} MK801 did not decrease the preference for the target quadrant in the first reversal session (the group treated with 0.08 mg kg^{-1} MK-801 even increased the target preference in the second reversal session), groups treated with 0.10 mg kg^{-1}, 0.12 mg kg^{-1} and 0.15 mg kg^{-1} decreased this preference for the target quadrant in the probe trial in the first reversal session (Fig. 16C). In the second reversal session, however, the preferences of all groups were again generally high, returning to values obtained prior to treatment (Fig. 16D).

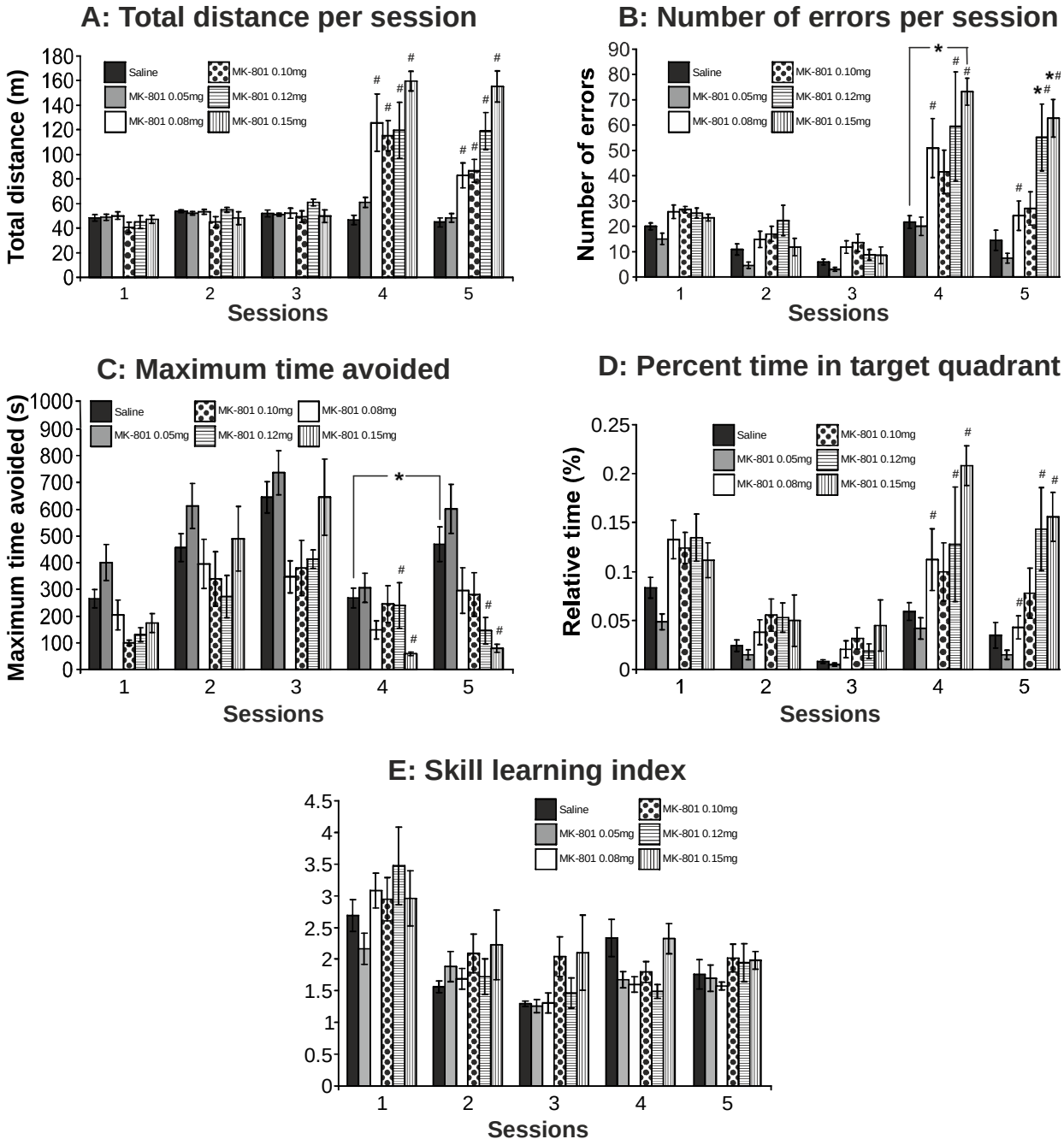

Figure 8. Panel A: *Effect of MK-801 on the total distance in the active place avoidance task. Note that all doses of MK-801 except the lowest one 0.05 mg kg^{-1}) increased locomotion.* ***Panel B:*** *Effect of MK-801 on the number of errors. there was a worsening of this parameter after MK-801 at doses 0.08 mg kg^{-1}, 0.12 mg kg^{-1} and 0.15 mg kg^{-1}.* ***Panel C:*** *Effect of MK-801 on maximum time avoided. Disruption of this parameter was detected at doses 0.12 mg kg^{-1} and 0.15 mg kg^{-1}. Control groups improved between the two reversal sessions.* ***Panel D:*** *MK-801 and percentage of time in the target sector. Doses 0.08 mg kg^{-1}, 0.12 mg kg^{-1} and 0.15 mg kg^{-1} impaired performance measured by this parameter.* ***Panel E:*** *Effect of MK-801 on the skill learning index. There was no significant main effect of MK-801 on this parameter. Annotation: # $p < 0.05$ in the main effects of the drug, * $p < 0.05$ in the interaction term.*

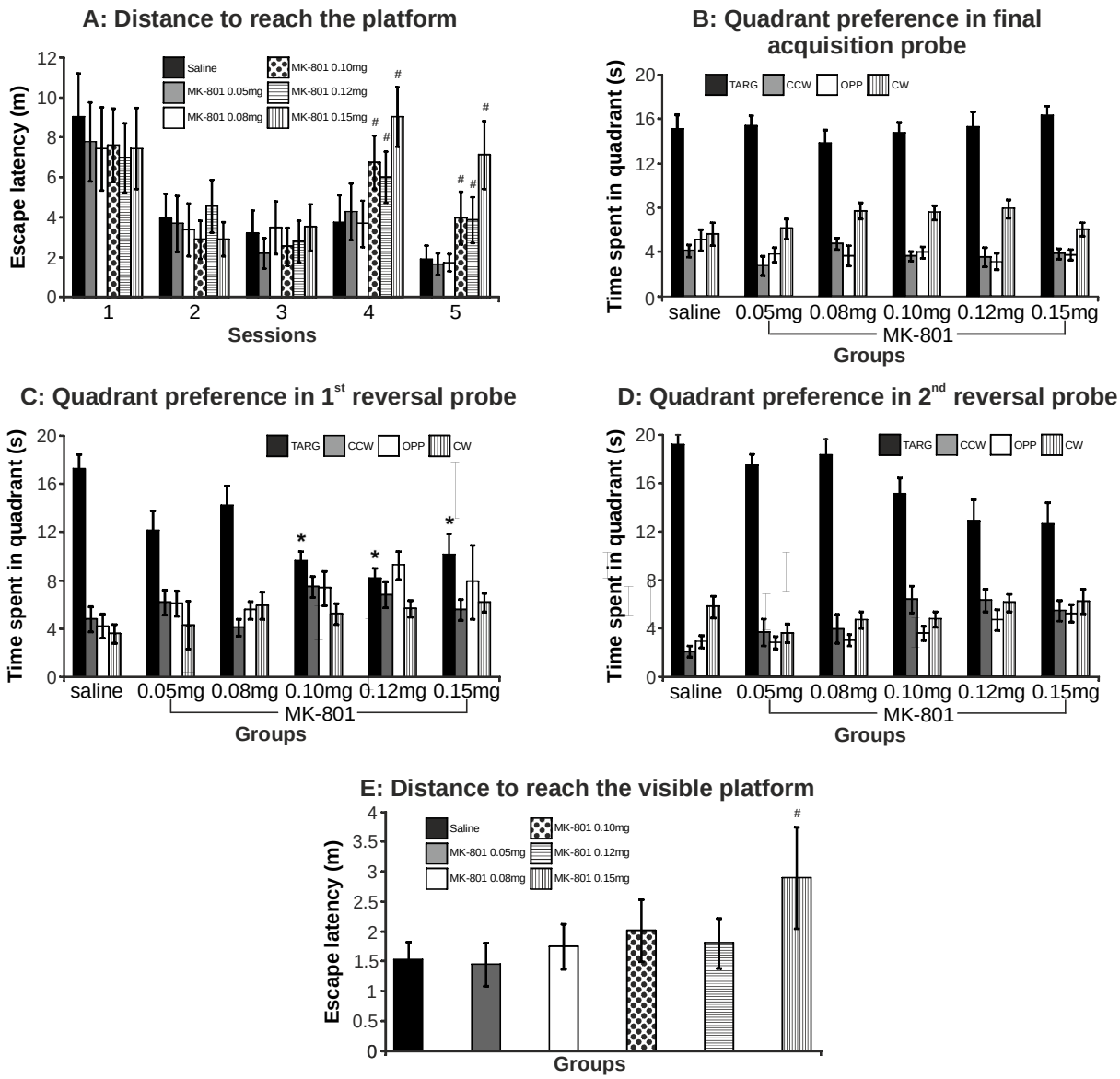

Figure 9. ***Panel A:*** *Effect of MK-801 on the total distance to reach the platform in the reversed hidden platform experiments in the MWM. Doses 0.10 - 0.15 mg kg−1 impaired reversal learning measured by this parameter.* ***Panel B:*** *Performance in the first probe trial, conducted after the final (third) acquisition sessions and expressed as time in the target quadrant. All groups (still receiving saline at this stage) display a strong preference for the target quadrant.* ***Panel C:*** *Time in the target quadrant in the second probe trial, conducted after the first reversal session. Preference for the target quadrant is significantly decreased by MK-801 at doses 0.10 mg kg−1, 0.12 mg kg−1 and 0.15 mg kg−1.* ***Panel D:*** *Target quadrant preference in the probe trial conducted after the second reversal sessions. All groups again show strong preference for the correct quadrant.* ***Panel E:*** *Total distance to reach the visible platform in the second sessions of visible platform testing was only increased by 0.15 mg kg−1 MK-801. Annotation: # $p < 0.05$ in the main effect, * p* **< 0.05 in the interaction term.**

Visible platform testing in the Morris water maze

All animals adopted a strategy of swimming towards the platform in the first reversal session, which was manifested as gradually decreasing distances to reach the platform in consecutive swims (*data not shown*). After random assignment to treatment groups, there were differences between them on the second day of the visible platform following application of saline or MK-801 (Fig. 16E). A two-way ANOVA (groups x swims, groups as an independent factor; repeated measures on swims) showed a significant main effect of groups ($F(5,47) = 8.93$; $p < 0.0001$), swims ($F(9,423) = 5.84$; $p < 0.001$) but no interaction between these factors ($F(45,423) = 0.73$; $p > 0.05$). A Newman-Keuls post-hoc analysis of the factor of swims revealed that the total distance in the first swim significantly differed from the remaining swims (all $Ps < 0.05$), suggesting a within-session improvement. Post-hoc analysis of the groups revealed that animals treated with the highest dose had a significantly longer total distance compared to control rats ($p < 0.05$) and also all other treatment groups ($p < 0.05$), suggesting that only highest dose caused significant impairment of navigation to the visible platform.

3.1.1.4 Discussion

Results of this work showed that the reversal learning of adult male rats in the active place avoidance task and the Morris water maze is sensitive to systemic treatment with MK-801, a non-competitive (open-channel) blocker of NMDA receptors. MK-801 was administered in the same sessions as spatial contingencies were changed; therefore the present study did not test the effect of the drug on learning (or acquisition) of the tasks. The impairments of reversal performance were consistently evident after the dose of 0.10 mg kg^{-1} was administered, and some deficits (such as that in percentage of time in a target quadrant in the place avoidance task or number of errors) were seen even at the lower dose of 0.08 mg kg^{-1}. MK-801-induced impairments were seen in both tasks. These data extend our knowledge of behavioral deficits in this animal model of schizophrenia-like behavior in several aspects.

First, in the active place avoidance task, the doses which caused disruption of spatial reversal performance appear to be lower than those prerequisite to impair acquisition in this task suggesting a preferential sensitivity of the reversal configuration to MK-801 (Stuchlik et al., 2004; Stuchlik and Vales, 2005, Vales et al., 2006). For example, our previous study (Stuchlik et al., 2004) showed a deficit in the active place avoidance acquisition at a dose 0.20 mg kg^{-1} but not 0.10 mg kg^{-1} (a lower dose; however, disrupted acquisition in the MWM). A subsequent study (Stuchlik and Vales, 2005) has suggested a dose of 0.15 mg kg^{-1} as a threshold for the impairment of acquisition of the active place avoidance task in Long-Evans rats. However, there have been also observations suggesting the dose 0.10 mg kg^{-1} might impair the acquisition of active place avoidance (Vales et al., 2010), more specifically, the level of final asymptotic performance (Vales et al., 2010).

Secondly, in the reversal experiment conducted in the Morris water maze, we consistently observed deficits beginning at the dose 0.10 mg kg^{-1}. Such a finding is in agreement with our previous experiments (Stuchlik et al., 2004), which showed a deficit in MWM acquisition after the same dose. This suggests that in the MWM, the dose thresholds of MK-801 for disruption of performance in acquisition vs. reversal configuration are equivalent. Interestingly, a recent study (van der Staay et al., 2011) and an older report (McLamb et al., 1990) suggested that even lower doses (as low as 0.05 mg kg^{-1} or 0. 07 mg kg^{-1}) can be efficient

in impairing MWM acquisition. This suggests that Long-Evans rats from our breeding may have lower sensitivity to MK-801 than other rat lines and this is also corroborated by a previous finding by our research group (Vales et al., 2006), which showed a lower sensitivity to MK-801 of Long-Evans compared to Wistar rats.

Furthermore, previous studies (Saucier et al., 1996) also suggested that in the MWM, it is very difficult to separate the navigational deficits induced by NMDA-receptor antagonists from procedural impairments and that such deficits may be eliminated by non-spatial pretraining to the rules of the task. Our present results are not entirely consistent with these data as we show here that only the dose 0.15 mg kg^{-1} impaired the swimming towards a visible platform. However, the present study has involved pretraining the rats to a visible platform procedure with the application of saline (day 1 of the visible platform testing), and this familiarization with procedure might have alleviated the dose sensitivity on performance in the second day. Moreover, the swimming speed of our rats in the visible platform test in the MWM was increased only in the groups treated with the highest dose of MK-801 (*data not shown*). It, therefore, appears that doses of MK-801 between 0.10 mg kg^{-1} and 0.12 mg kg^{-1} affect primarily navigational rather than sensorimotor functions, specifically in the MWM in our strain (note that contrarily to the MWM, in active place avoidance, the hyperlocomotion was seen at lower doses; see above).

The present results clearly demonstrate that MK-801 at relatively low doses affects behavioral flexibility tested by reversal configuration. Such results are consistent with previously published findings obtain in different paradigms and models. The study by Chadman and colleagues (2006) showed that MK-801 administered at similar doses negatively influences reversal learning in juvenile rats (postnatal days 21-30) in a T-maze and found that doses 0.06 mg kg^{-1} and 0,10 mg kg^{-1} selectively impaired reversal in the T-maze. Importantly, this effect was demonstrated to be independent of behavioral sensitization and state-dependent learning (Chadman et al., 2006). Moreover, the effect of MK-801 on this discrimination reversal learning was found to be mediated by NMDA-receptor blockade in the hippocampus (Watson and Stanton, 2009a), dorsomedial striatum (Watson and Stanton, 2009b) and medial pre-frontal cortex (Watson and Stanton, 2009c) in weaned rats. Based on these findings, it is conceivable that the deficit seen in the present study might have been mediated by a blockade of glutamate receptors in these structures, although, the dose 0.15 mg kg^{-1} could have also induced an overall psychotomimetic state accompanied by overall impairments involving procedural, sensory and motivational functions. Higher doses of MK-801 were required to abolish the reversal learning in an allocentric reversal task in the 8-arm radial maze in an older study by Bischoff and Tiedtke (1992). A study by Beninger et al. (2009) showed a deficit in the MWM reversal learning in MK-801-treated rats (however, at much higher dose than 0.50 mg kg^{-1}), and our results confirm this finding. Interestingly, Caramanos and Shapiro (1994) demonstrated that MK-801 impaired reversal learning in the radial-arm maze at a broad dose range, but it did not exert an effect upon working memory in female rats (for a limited role of NMDA receptors in working memory; see Steele and Morris, 1999; Vales et al, 2006). Additionally, another work (Harder et al., 1998) detected impairment in acquisition and reversal of a visuospatial task in marmoset monkeys.

In the light of present results in active place avoidance, a question might be raised, to what extent the MK-801-induced hyperlocomotion (found in all doses except the lowest one, i.e., 0.05 mg kg^{-1}) contributed to the spatial deficit in active place avoidance reversal. Increases in locomotion are conventionally observed after application of this drug (Nilsson et al., 2001,

Stuchlik et al., 2004, Stuchlik and Vales, 2005; Beninger et al., 2009) but at considerable higher doses compared to the ones used in the present study (see also Vales et al., 2006, who found no hyperlocomotion in the place avoidance at 0.10 mg kg^{-1} of MK-801 in Long-Evans strain). We therefore propose, that hyperactivity observed in the present study at relatively low doses of MK-801 could be the result of an increased number of shocks obtained due to the changed spatial contingencies and due to higher cognitive demand (possibly together with a moderate hypoglutamatergia). Such interpretation would be supported by the fact that in the visible platform test in the Morris water maze, an increase in the swimming speed was seen only after the highest dose (i.e., 0.15 mg kg^{-1}; *data not shown*). Note that hyperactivity found in the MWM after this dose i) is consistent with the previous results obtained in the arena (Stuchlik and Vales, 2005) and ii) occurred in the task where pre-drug sensory and motor demands and behavioral load after the application of the drug are similar (i.e., first and second sessions of the visible platform test in the MWM, respectively). It should also be pointed out that the highest dose used in this study could also mildly interfere with the shock perception, however this option seems improbable due to the absence of the main effect of drug application upon the skill learning index (see Results).

This study provides the first evidence for disrupted cognitive flexibility in the active place avoidance task and Morris water maze in an MK-801 induced animal model of schizophrenia-like behavior. Furthermore, the present data suggest higher sensitivity of active place avoidance task in reversal configuration than the MWM, which underlines the importance of the task in searching for novel treatments for cognitive deficits in schizophrenia.

The present study provides clear evidence for a deficient visuospatial working memory in the allothetic place avoidance alternation task in an animal model of schizophrenia induced by MK-801. Such a deficit; however, may be eliminated by intact pretraining to the rules of the task. Increased locomotion accompanies this behavioral alteration and is present in both naive and pretrained animals despite the presence of memory differences.

3.2 CLINICAL PART:

3.2.1 EXPERIMENT II – ASSESSMENT OF SPATIAL MEMORY IN VIRTUAL ANALOGUE OF MORRIS WATER MAZE (STABLE ARENA)

3.2.1.1 Aims

The aim of this experiment was to extend the current comparative research by attempting to incorporate several MWM variants into a small test battery named the 'virtual Four Goals Navigation' (vFGN) task. The vFGN task is completed in a virtual analogue of the real BVA apparatus designed previously by our group (Stepankova et al., 1999). The presented study describes the newly-developed vFGN task and presents first data obtained in a group of patients after the first episode of schizophrenia psychosis in comparison to a group of healthy volunteers, in order to express its sensitivity toward the present cognitive deficit. To minimize possible effects of sex, age and education level, both groups were carefully matched according to these variables. In order to assess the usefulness of the vFGN task in preclinical studies, we compare the data obtained in the vFGN task with the previously published animal studies.

On the basis of animal and human literature, we hypothesized that the schizophrenia patients would perform worse compared to healthy controls in the vFGN task in terms of: a) impaired spatial learning during the Reference memory (RM) session; and b) decreased working memory and mental flexibility performance in the Delayed-matching-to-place (DMP) session. Since several studies described sex differences in spatial abilities of rodents (e.g. Roof and Stein, 1999; Cimadevilla et al., 2004) and humans (e.g.Sandstrom et al., 1997; Astur et al., 1998; Astur et al., 2004), we hypothesized to find similar differences in our subjects as well. In addition, the effect of age variable was analyzed in order to understand how the age affects performance in the vFGN task and if this effect is same in both groups. Moreover, the effect of several clinical parameters, such as the duration of untreated psychosis, general functioning (GAF score), clinical symptoms (PANSS scores) and antipsychotic medication (dose calculated in chlorpromazine equivalents), was evaluated in the group of patients.

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3.2.1.2 Methods

Subjects (Experiment II and III)

Twenty-nine patients (17 males and 12 females) after the first psychotic episode with schizophrenia symptoms were recruited for the study. All patients have been diagnosed with schizophrenia or related psychotic disorders according to ICD-10 criteria (Paranoid Schizophrenia F20.0: n=3; Undifferentiated Schizophrenia F20.3: n=1; Simplex Schizophrenia F20.6: n=1; Acute psychotic disorder: F23.0: n=4; F23.1: n=18; F23.2: n=2). They were recruited in the early remission phase during their first psychiatric hospitalization (therefore considered to be first-episode psychotic patients with schizophrenia symptoms, FEP) with a variable duration of untreated psychosis (DUP, 6.4 ± 13 months). DUP defined as the duration of untreated but clearly presented psychotic symptoms, was obtained from the detailed interview with the patients and family members. All of the patients were tested prior to the end of their hospitalization. In order to cover the whole spectrum of the first episodes of schizophrenia, both early and late onset patients were recruited for the study (in the age between 18 and 35 years).

The patients were individually matched to healthy volunteers (n = 29; see Table 1) in terms of sex, age (within 2 years difference), education level and gaming experiences (both within 1 level of difference). Healthy subjects were recruited from the same socio-demographic background via a local advertisement. To provide sufficient homogeneity of the examined group, most of the recruited participants were regular users of computer devices with none or mild gaming experience. The inclusion criteria for both groups were: i) no history of neurological disease or loss of consciousness longer than 10 minutes; and ii) native in Czech/Slovak language. The main exclusion criterion for the control subjects was personal history of any psychiatric disorder. All tested subjects signed a written informed consent approved by the Ethics Committee.

Clinical and neuropsychological assessment (Experiment II and III)

All of the patients completed a psychiatric interview prior to the experiment in order to obtain information about their current symptoms using the Positive and Negative Symptoms Scale (PANSS; Kay et al., 1987) and the GAF (Global Assessment of Functioning) scale (Jones et al., 1995). Only stabilized patients who mainly scored 3 points or lower in their individual scores were recruited for the experiment. All of the patients were treated by second generation antipsychotics (olanzapin, risperidon and amisulpirid). The dose of antipsychotic medication was calculated in chlorpromazine (CPZ) equivalents (according to Andreasen et al., 2010;Woods, 2003). For details on the clinical parameters see Table 1.

Our neuropsychological battery consists of following 6 (11) tests focusing on both the visuospatial and the (verbal) functions (see Table 2).

TABLE 1. PATIENTS WITH SCHIZOPHRENIA WERE INDIVIDUALLY MATCHED WITH HEALTHY CONTROLS FOR SEX, AGE (WITHIN 2 YEARS), EDUCATION LEVEL AND GAMING EXPERIENCE (BOTH WITHIN ONE LEVEL OF DIFFERENCE).

Demographic variable	**Group mean (SD)**		**Group differences**	
	Schizophrenia patients (SZ)	**Healthy Controls (HC)**	Mann-Whitney U	p-value
N	29	29		
Sex (M : F)	17 : 12	17 : 12		
Age	25.8 ± 6.2	25.7 ± 5.4	419.5	0.994
Education level (1-6)	3.1 ± 1.6	3.7 ± 1.2	323	0.131
Gaming experience (0-2)	1.1 ± 0.7	0.6 ± 0.5	258	0.012
Clinical assessment	**SZ**	**HC**		
PANSS score	56 ± 16	-		
PANSS-positive	13.6 ± 6	-		
PANSS-negative	15 ± 6	-		
PANS-general	27 ± 7.7	-		
GAF	64 ± 20.5	-		
Duration of illness	12 ± 20.8	-		
DUP	6.4 ± 13	-		
Hospitalization duration	30 ± 12	-		
Medication (CPZ equivalents)	426 ± 145	-		

SZ - patients with schizophrenia; **HC -** healthy controls; **Education level:** 1 = less than high school, 2 = started high school, 3 = completed high school, 4 = started university, 5 = completed university, 6 = started postgraduate studies; **Gaming experience:** 0 = none, 1 = mild, 2 = good; **PANSS** - Positive and Negative Symptoms Scale; **GAF**– Global of Assessment of Functioning; **DUP** - duration of untreated psychosis.

TABLE 2. LIST AND BRIEF DESCRIPTION OF (A) VISUOSPATIAL AND (B) VERBAL NEUROPSYCHOLOGICAL TESTS APPLIED IN THE THESIS.

A. VISUOSPATIAL NEUROPSYCHOLOGICAL TESTS				
Test	**Monitored cognitive function**	**Test outputs**	**References**	**Test description**
Trail Making Test (TMT A & B)	Psychomotor speed (A); visuospatial working memory (B); mental flexibility (B/A)	Time A (sec) Time B (sec) Ratio B/A	(Reitan, 1985); (Preiss, 2006)	Chaining a sequence of numbers (A) or alternatively numbers and letters (B) that are randomly distributed on a single paper
Rey-Osterrieth (Taylor) Complex Figure Test (RCFT)	Visuospatial organization, constructional functions and visual memory	Raw score for copy trial (RCFT-copy), reproduction after 3 (RCFT-3) and 30 minutes (RCFT-30)	(Osterrieth, 1944;Taylor, 1969;Preiss, 2012)	Copy and reconstruction of figure after 3 and 30 minutes
Key Search Test (KST)	Executive functions	Raw scores of strategy	BADS (Wilson, 1996)	Strategy of exploration of 2-dimensional space (2D square shape)
Money Road-Map Test (RMT)	Spatial orientation	Raw scores for number or errors/32; A, B and C error types	(Money, 1965)	Ability to determine right/left turns on crossroads in 2D view of a simple maze/city
Spatial Span (SS)	Visuospatial working memory	Raw scores: total (forward + backward)	PC version adjusted from the Corsi block test in (PEBL, 2012) according toto WMS-III (Wechsler, 1997)	Repeating a sequence of spatial positions presented in 2D plane, forward or backward
PEBL Perceptual Vigilance Task (PVT)	Vigilance and attention	Number of lapses (RT over 500 ms) or longer sleep attacks, average RT speed	PEBL battery (PEBL,2012; pebl.sourceforge.net) (Dinges, 1985;Loh, 2004)	Response to stimulus appearing in the variable time interval (1-9 seconds) during 10 minutes

B. VERBAL NEUROPSYCHOLOGICAL TESTS				
Test	**Monitored cognitive function**	**Test outputs**	**References**	**Test description**
Auditory Verbal Learning Test (AVLT)	Verbal learning and memory	Learning curve and total number of words (AVLT-I-V); immediate recall (AVLT-VI) delayed recall (AVLT-30) Number of confabulations and repetitions	A.Rey (1964); (Preiss, 2012)	Repeated recall of 15 words with interference trial (B) and delayed recall after 30 min
Verbal Fluency Test (VFT)	Psychomotor speed and mental flexibility	Number of words for phonemic (total of three trials) and semantic fluency	(Preiss, 2012)	Speaking aloud words beginning with letters N, K, P or naming category of animals during 1 minute
Digit Span (DS)	Attention (forward), verbal working memory (backward)	Raw scores: total (forward + backward)	WAIS-III (Wechsler, 1997); Czech version (Cernochová, 2010)	Repeating list of numbers forward and backward
Similarities (Sim)	Verbal conceptualization	Raw score – correct responses		Describe similarities between pair of words

Pre-training of motor control / Common for Experiment II and III

Prior to the task, all of the participants underwent a short (5 min long) pre-training of movement control using the gamepad device (see time schedule in Fig. 17A). The forward movement was controlled by the forward press of the left or right joystick (according to the handedness of the participant) of the gamepad device (a forward joystick press started the movement and a release stopped it), but the backward movement was blocked. The left/right turning of the view was controlled by the left and right press of the same joystick. Afterwards, the participants performed a simple task in a complex virtual labyrinth maze (see Fig. 17B) with instructions to 'follow the route highlighted by six objects (stars) on each crossroad and get to the end of the route as fast as possible'.

Figure 17. *The pre-training task: (A) The gamepad apparatus used to control movement and bearing in the virtual space, with the green button used to mark direction toward the goal position (here in white); (B) A map of the virtual complex maze and the route followed during the pre-training and first-person view of this environment.*

Software and apparatus - Virtual Environment

The virtual scene was displayed on a 24" LCD monitor using the Unreal Tournament game engine (UT2004; Epic Games, 2004). A Java software toolkit called *'SpaNav'* (Šupalová, 2009) was programmed to configure an experimental setup and to record detailed experimental data for further analysis. A three-dimensional circular arena was designed as a virtual model of the *Blue Velvet Arena (BVA)* apparatus, an arena enclosed by a white curtain wall and with floor covered with a gray carpet (Stepankova et al., 2003), with the utmost realism. Because the virtual environment enabled us to enlarge the size of the virtual arena, an arena 20 times larger than the original BVA apparatus (2.8 m in diameter) was used. Three orientation cues were located in the arena near the circular wall. These objects were fully colored and had various rotational shapes. The goal location had a circular shape with a red border and occupied about 10% of the arena diameter (see Figure 18). The tested subject moved through the virtual maze in a first person view. In order to facilitate movement in VE for participants without gaming experience, only one stick of the gamepad device (Logitech F310) was used, enabling only forward/backward movement and left/right rotation.

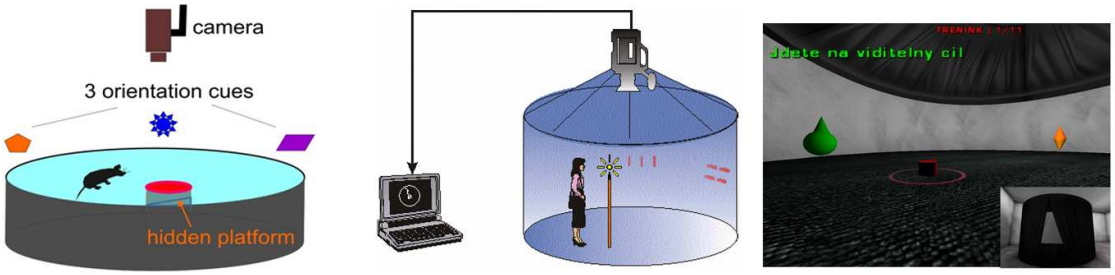

Figure 18. *Morris water maze - MWM paradigm: model of the original MWM apparatus for rats (left); The model of a real MWM analogue called Blue Velvet Arena adopted from Laczo et al, 2009 and Kalova et al., 2005 (middle); Virtual version, the vFGN task in an enclosed dry arena` view of the virtual tent from inside (with two orientation cues and vsible goal position placed on the arena floor) and from outside (smaller picture) (adjusted from Fajnerova et al., 2014) (right).*

Design of the Virtual Four Goals Navigation (vFGN) task - virtual analogue of MWM

After completing the pre-training, all of the tested subjects performed the virtual Four Goals Navigation (vFGN) task. In each trial of the vFGN task the subjects were required to find a hidden circular goal placed on the arena floor using the direct trajectory to the goal. Each trial started by moving towards a pseudorandom starting position displayed as a red sphere near the arena wall (see Figure 19A). Then, three orientation cues were visualized in the arena. At this moment, the subject's movement was blocked at the starting position and only rotational movements were enabled. Apart from the first trial when the goal position was unknown, the subject was instructed to point towards the hidden goal position using the yellow cross in the middle of the screen (see Figure 19B) and then press the green button on the gamepad (in all standard, probe and control trials) to activate his or her movement. Thereafter, the 60 s time limit for locating the hidden goal began. After entering the correct area, the goal became visible and a short beeping sound was played. If the goal was not found within the 60 s time limit, it became visible (see Figure 19C) and a short warning beep was played. The subject was then instructed to enter the visible goal position. Upon entering the goal area, the movement was blocked in the middle of the goal position and the participant had 10 s to remember the goal position for consecutive trials using only rotational movements (see Figure 19D). This 'learning time' represented the analogy of an animal standing on a platform for several seconds after each trial.

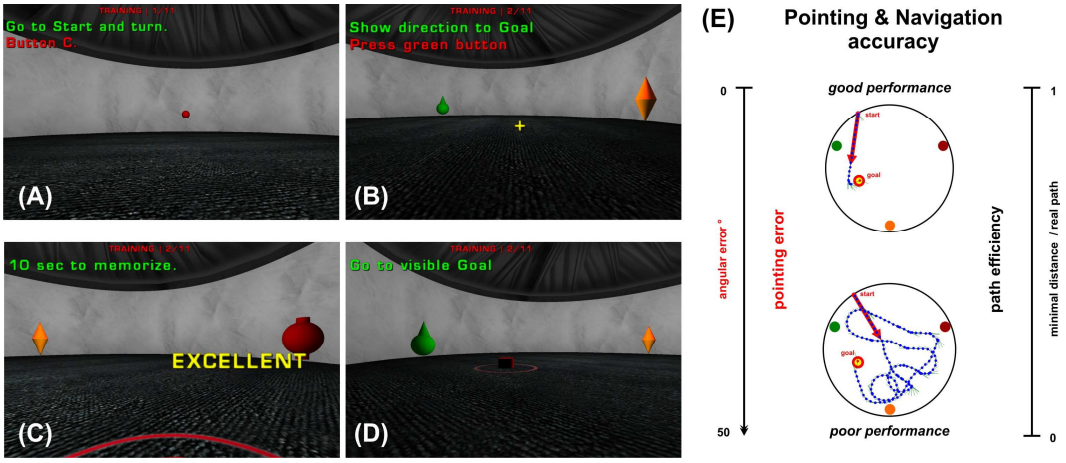

Figure 19. *Virtual version of the BVA apparatus from inside– one trial procedure. Figures A-D demonstrate the experimental parts of the trial using the first-person preview from the vFGN task. The short instructions used to remind it to the participants was translated to English. (A) The starting position presented as a red sphere. (B) Two visible orientation cues (from a set of 3 cues with various shapes and colors) and yellow cross in the middle of the screen used to point towards the hidden goal direction. (C) Goal position visualized after 60 sec trial time limit. (D) Movement blocked after the entrance to the goal position. Enabling only rotational movement in 10 sec memorizing. (E) Illustration of the two parameters measured in all (except probe) trials. Lateral axis present the interval of values gained in both parameters. The central pictures illustrate good and poor performance in the vFGN task. Trajectories (line of blue points) from both tested groups are presented as an overview scheme of the spatial configuration in one hidden goal trial. The red arrow illustrates the pointing error parameter. The trajectory length is transformed to path efficiency parameter.*

The vFGN task consisted of two parts: the Reference memory and the Delayed-matching-to-place sessions; both administered successively in one day protocol (Time schedule in Figure 20A).

Part I - Reference memory (RM) session completed at the beginning of the vFGN task, was designed according to the original reference memory protocol (Morris, 1984;Morris et al., 1982;Morris, 1981). Similar to other human MWM analogues (Astur et al., 2002; Jacobs et al., 1998) the task was shortened into one day protocol to test spatial learning and memory by monitoring the performance improvement in 11 consecutive trials (see Figure 20B). In the 'first search' trial (T1) the participants were instructed to find the hidden goal location on the arena floor by free exploration of the arena and to remember it for the following trials using the three orientation cues. In the following standard trials T2-T5 and T7-T10, displayed as four blocks of two trials in Figure 3 and 4, the subjects were required to look for the hidden goal repeatedly while starting from pseudo-randomized starting positions. One probe trial (T6) was inserted in the middle of the RM session in order to test the effect of extinction process as a sort of interference in the course of learning (inspired by the human learning tasks). This probe trial was aimed at memory precision and confidence (by evaluating the time spent in the goal proximity) while the goal was inactivated. The final CONTROL trial (T11) used the navigation towards the visible goal and served as a test of secondary effects generated by impairment of vision and motor abilities.

Part II - Delayed-matching-to-place (DMP) session. In order to prevent any transfer from the RM session, the color and the shape of the orientation cues were changed for the

following DMP session. The DMP session was designed as a working memory protocol constructed by combining two different animal protocols for assessment of working memory adapted for humans. The DMP session consists of three consecutive phases (graphically depicted on Figure 20C):

1) The **ACQUISITION** phase involved nine trials with the goal placed successively in three various positions (A, B or C) in relation to three distal orientation cues. The goal was moved after each three trials (see Figure 20C). It was based on a modified *reversal protocol* of the MWM, in which the goal position is changed over the days used to test mental flexibility (Garthe et al., 2009;Lipp et al., 1998;Lobellova et al., 2013;Vorhees and Williams, 2006) and/or working memory (Morris et al., 1986). Unlike in rats, the change in goal position was separated not by days of testing but by an announcement to the subjects, in order to test their memory for spatial sequence (ABC) in the subsequent phases.

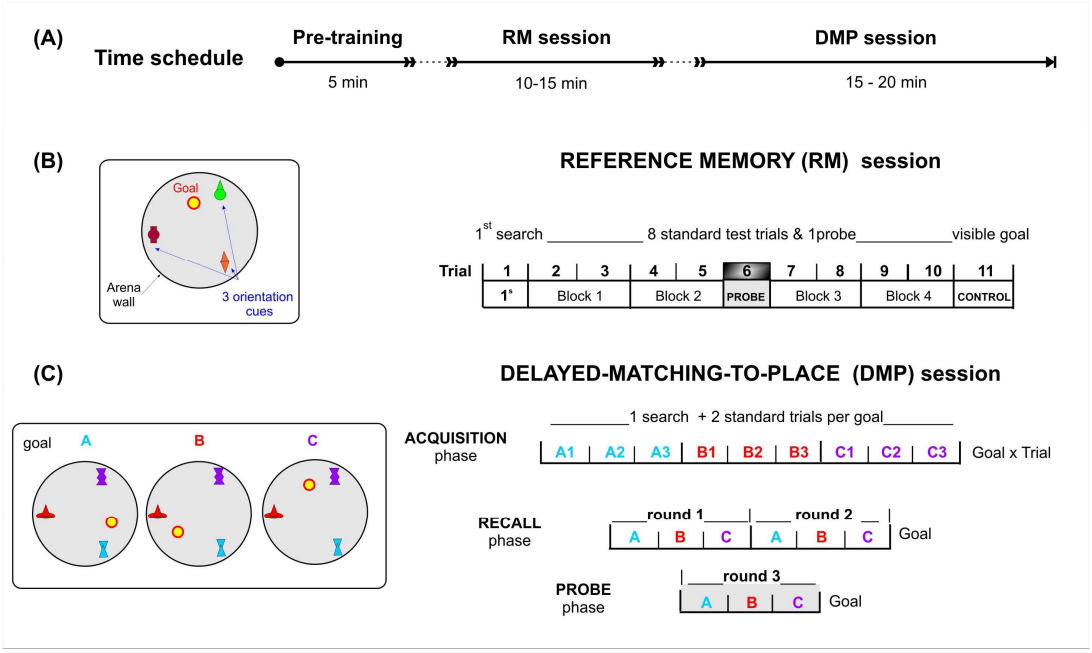

Figure 20. *The virtual Four Goals Navigation (vFGN) task: (left) spatial configurations with goal positions used in two sessions and (right) time scheme of individual parts of the task. (A) REFERENCE MEMORY session with a stable goal position over 11 trials. T1 – 1st search trial; Block 1-Block 4 – pairs of standard trials with repeated search for hidden goal; T6 – probe trial with inactivated goal position; T11 – control trial testing navigation towards a visible goal. (B) DELAYED-MATCHING-TO-PLACE session with goal in 3 possible positions ordered in a spatial sequence (A, B, C). ACQUISITION phase - each goal position is repeated in 3 consecutive trials (9 trials in total); Recall phase - two rounds of the spatial sequence (6 trials in total); Probe phase - one spatial sequence ABC with inactivated goal positions (3 trials).*

2) The **RECALL** phase together with the Acquisition phase represents a modified version of the DMP paradigm (for review see Dudchenko, 2004; also in O'Carroll et al., 2006;Steele and Morris, 1999; Morris et al., 1986) designed for assessment of the working memory functions in rodents using delayed recall. Our task was designed to test spatial memory processes by evaluating the performance decline measured between the Acquisition and the Recall phase. To increase the difficulty and adapt the task for human participants, the task

combined the DMP protocol applied in rats with the spatial sequence encoding in the Corsi Block Test (developed by Corsi in 1972) used in many variants to test spatial working memory in humans (Fischer, 2000). This modified protocol required them to retrieve the correct sequence of three goal positions (ABC) previously learned in the Acquisition trials and identify them successively (according to instructions) in two consecutive rounds (see Figure 20C).

3) The **PROBE** phase, involving three trials with inactivated goal position, was conducted directly after the Recall phase as a final third round of the spatial sequenced recall (see Figure 20C). The probe trials, with a removed hidden platform adopted from the animal studies, provide an important demonstration of memory processes in terms of spatial bias (Morris et al., 1982;Morris et al., 1990;Sutherland et al., 1983;Whishaw, 1991). In rats probe trials are usually conducted in the reference memory protocols, but sometimes after reversal condition as well (Lobellova et al., 2013).

Measured parameters and data analysis

Latency to find the goal and distance traveled to reach it are usually measured in standard trials in animals (for review see D'Hooge and De Deyn, 2001) and in human studies (Folley et al., 2010;Hanlon et al., 2006;Moffat, 2009). In our study the latency parameter was not evaluated, since the decision about the correct goal position was already done while pointing to it. Therefore we address the spatial performance in all trials except probes using the *pointing accuracy* later referred to as the ***pointing error***. This parameter was recorded at the moment when the subject stands on the starting position and points toward the hidden goal by pressing one of the gamepad keys. It was calculated as the absolute angular difference between the pointed and linear direction towards the goal position and its value decreases with growing precision in pointing performance (see Figure 19E).

The distance parameter expresses the *navigation accuracy* and it is referred to as ***path efficiency*** (abbr. ***path eff***) with the range of 0 to 1. It was calculated as a ratio between the minimal possible path length (the actual distance between the start and the goal position) and the real distance traveled by the subject, using the following formula: path eff = $path_{min}$ / $path_{real}$ (see Figure 19E). Contrary to the standard *distance* parameter its value increases with the precision of navigation and enables us a direct comparison between individual trials by considering the possible minimal distance.

In addition, we measured two common parameters in all of the probe trials: ***goal quadrant preference*** calculated as a proportion of the overall trial time spent in the goal quadrant (arena quadrant containing the hidden goal in its center); and ***number of entrances*** calculated as number of crossings through the inactivated goal position.

To analyze the data recorded in SpaNav, a custom-made PHP program called drf2track was used to produce primary data tables and trajectory pictures. Further statistical analysis was performed using the Statistica software (Statistica v.9, StatSoft, Czech Republic). The group differences in the demographic variables (age, education level and gaming experience) are calculated using non-parametric Mann-Whitney U Test. Identical method was used to analyze the raw scores obtained in neuropsychological tests. The group and sex differences in individual parts of the vFGN task were calculated using the GLM repeated measure analysis of variance with two categorical predictors (group x sex). Significant interactions were analyzed using a Newman-Keuls post hoc test. A correlation analysis was performed separately for both groups between the age variable and the spatial performance of individual subjects averaged for

individual parts of the vFGN task. The t-test for independent groups was used to compare the groups in a single visible goal trial and in a single probe trial in the RM session. The t-test for single means against a reference constant was used in order to show that the quadrant preference measured in probe trials is different from the chance level (0.25). The effect of clinical characteristics (age of illness onset, DUP, PANSS and GAF scores and antipsychotic medication calculated in CPZ equivalents) on averaged performance in the vFGN task was calculated using forward stepwise multiple linear regression analysis (with F to enter set to 1.00 and F to remove to 0). The overall level of significance was set to 0.05.

3.2.1.3 RESULTS

The groups did not differ significantly in any of the demographic parameters, except the gaming experiences, where patients showed to be more experienced than the healthy controls (see Table 1). As expected, group of patients showed significantly lower cognitive performance on all neuropsychological tests, except the forward Digital and Spatial Span task performance (see Table 3). The modification from 3D to 2D version of the Spatial Span could cause lower sensitivity of the test in comparison to other standard methods. Group differences measured in individual parts of the vFGN task are graphically depicted as performance curves for all of the evaluated parameters (see Figure 4 to 8).

Neuropsychological battery

Results obtained using the standard neurocognitive battery have been tested for possible group differences in order to determine the cognitive deficit in the group of schizophrenia patients. As expected according to the previous studies, most of the tests showed significant group differences, suggesting that the first episode schizophrenia patients tested in our study are impaired in all assessed cognitive domains (see Table 3).

TABLE 3. GROUP DIFFERENCES OBTAINED IN THE BATTERY OF STANDARD NEUROCOGNITIVE TESTS

Neurocognitive assessment	**Raw data (Average ± SD)**		**Group differences (SZ and HC)**
	SZ	***HC***	***Mann-Whitney U test***
PVT-lapses	9±9	2±4	111 ***
Verbal fluency phonological	38±12	47±9	174.5 ***
Categorical fluency	19.5±5.5	29±5	56.5 ***
Trial making test			
TMT - *A*	38±12	26±8	155 ***
TMT – *B*	97±42	50±12	91.5 ***
Auditory verbal learning test			
AVLT –I-V	49±11	60±7	156 ***
AVLT-VI interference	9.5±3	13±2	101 ***
AVLT - 30 min	9±3	13±2	79 ***
Rey/Taylor Complex Figure			
RCFT –copy	32.5±3	36±1	138***
RCFT -3min	17±7	26±5	105 ***
RCFT - 30 min	18±7	26±5	117 ***
Spatial Span (WMS-III) –			
forward	8.5±2	9±1.4	322 ns
backward	7.5±2.5	9±1.4	218.5 *
Digit Span (WAIS-III) –			
forward	9±2	10±2	295 ns
backward	5±2	8±2	143.5 ***
Similarities (WAIS-III)	22±5	28±2	114.5 ***
Key Search test	11±3	13±2	314.5 ns
Money Road map test	4±5	1±2.6	243 **

Group differences in the vFGN task

RM session 1.

To analyze the group differences in the RM session a GLM analysis was performed with the group as one of the main factors (group x sex) and block (pairs of standard trials) as a repeated measure factor. This analysis showed impaired learning performance of the schizophrenia group in both measured parameters (see Figure 21). While a robust effect of the group factor was identified in the pointing error parameter ($F(1, 54) = 9.5$; $p < 0.01$), a significant interaction (block x group) was found in path efficiency parameter ($F(3,162) = 6.2$; $p < 0.001$). A post hoc test on this interaction revealed that the groups differed in path eff (on level $p < 0.01$) in the second block of trials (T4 and T5). Interestingly, the navigation performance in healthy controls improved significantly in the beginning of training between the first two blocks of trials ($p < 0.001$), while in the group of patients similar improvement occurred later on after the completion of probe trial in the middle of the training (only blocks completed before the probe trial showed lower performance than blocks completed after the probe trial; $p < 0.05$). Block as repetition factor was significant in both tested parameters ($p < 0.001$).

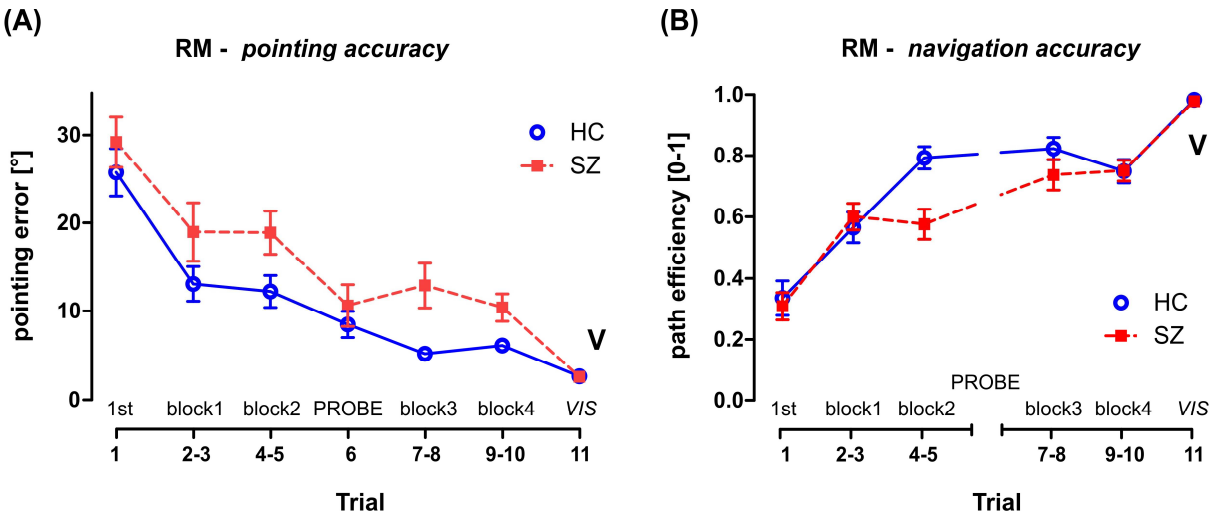

Figure 21. *Reference Memory (RM) session group performance. (A) The pointing error (mean ± SEM) and (B) the path efficiency (mean ± SEM) in individual trials and/or blocks of trials. The probe trial T6 is not depicted in path efficiency parameter, the control trial T10 is marked by V (as visible).*

To compare the ***first search trial (T1)*** of the RM session with the remaining standard trials, another GLM analysis was performed on all RM trials, individually. The post-hoc test performed on trials showed that the first trial (T1) differed significantly from all of the following standard trials in the RM session ($p < 0.05$) in both of the measured parameters, demonstrating fast learning of the goal position after one learning episode.

The ***visible goal trial (T11***, marked as V in Fig. 21) used as a control of visuo-motor functioning at the end of the RM session showed minimal interpersonal variability. No group effect was revealed by the t-test for two independent samples in either of the parameters; in pointing error ($t(56) = 0.57$; $p = 0.57$) or in path eff parameter ($t(56) = 0.09$; $p = 0.93$).

One ***probe trial (T6)*** was inserted in the middle of the RM session (see Figure 22) to assess spatial memory by evaluating the goal quadrant preference. While the control subjects spent 75 ± 11% of the trial time in the correct arena quadrant, the mean value in the patients was only 57 ± 23 %. The goal quadrant preference of both groups differed from the chance level (25%). The t-test revealed a main group effect in the goal quadrant preference ($t (56) = 3.9$, $p < 0.001$) but not in the number of entrances to the inactivated goal ($t (56) = 1.4$, $p = 0.16$).

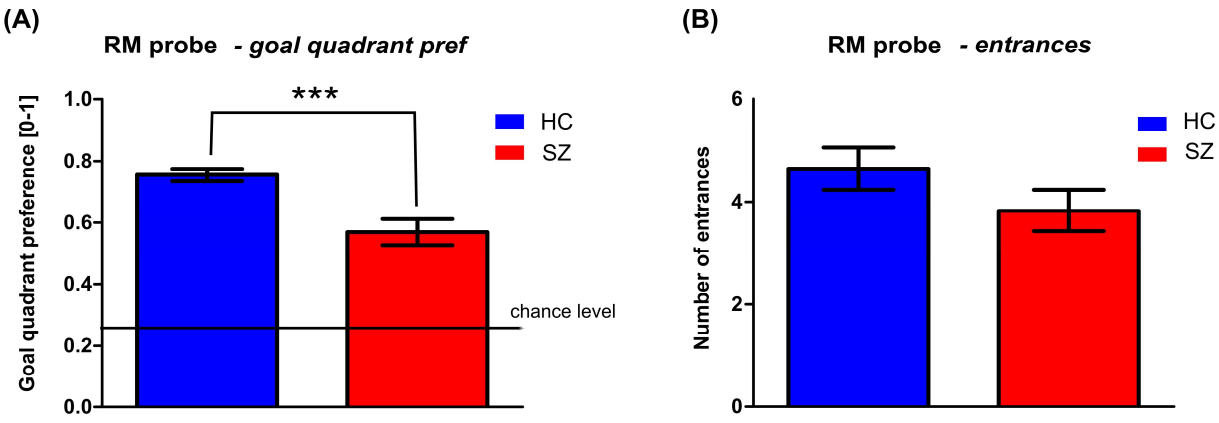

Figure 22. *Probe trial (trial T6) performance in the middle of RM session. (A) The goal quadrant preference (mean ±SEM) and (B) the number of entrances (mean ±SEM) to the inactivated goal position. Annotation: *** p < .001 group difference.*

DMP session 2

ACQUISITION phase. The main effect of the trial as repetition factor was found in the Acquisition phase of the DMP session ($p < 0.001$) tested using GLM analysis with repeated measures (goal x trial) (see Figure 23). The main group effect was found in the pointing accuracy if the 1st search trials (A1, B1, C1 - representing the free exploration trials) in the Acquisition phase were excluded from the analysis as they represent random performance ($F(1, 54) = 7.8$; $p < 0.01$). However, no group differences were identified in the path efficiency parameter, even the interaction effect (trial x group) approached the significance level ($F(2,108) = 2.8$, $p = 0.068$). No other interactions were obtained from the analysis.

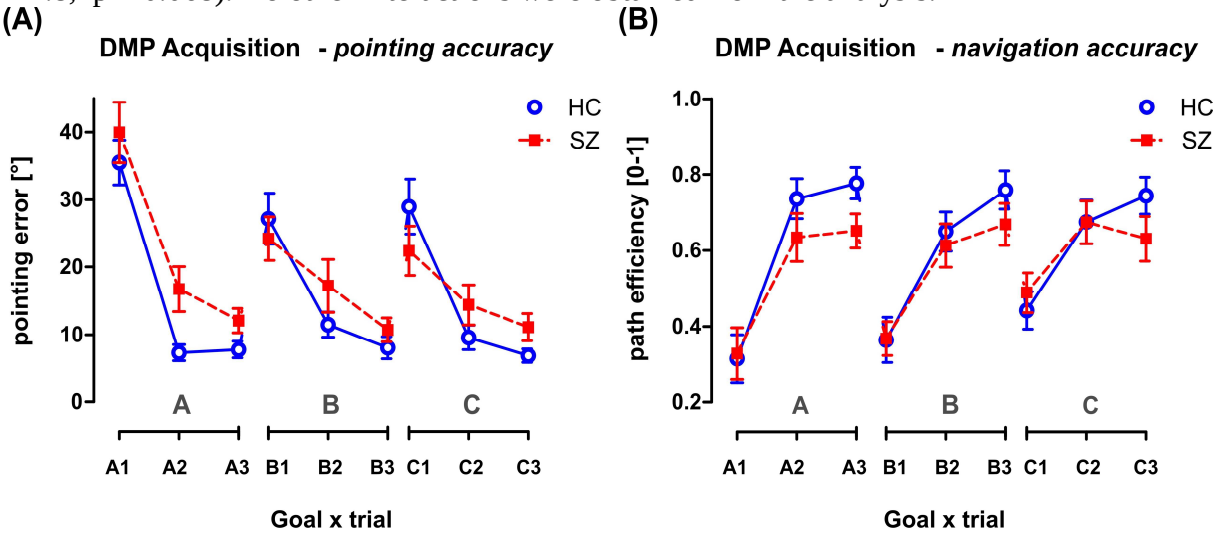

Figure 23. *The performance of both groups in the Acquisition phase of the DMP session. Three consecutive spatial changes, the hidden goal is placed in three possible goal positions (A, B and C) placed in different relationships to the orientation cues. Trials marked as A1, B1 and C1 required the subject to search for the hidden goal after announcement of the positional change. The next two trials required repeated search for the hidden goal. The behavior is shown in all nine trials presented in the order applied during the Acquisition phase using the two following parameters: (A) The pointing error (mean ±SEM) and (B) the path efficiency (mean ±SEM).*

RECALL phase. The GLM analysis with repeated measures (round x goal) was used to analyze the performance in the last Acquisition trials (A3, B3 and C3) and in the two Recall rounds (see Figure 24). The analysis performed on both recall rounds showed significant group differences in both measured parameters, as a main effect in pointing error ($F(1, 54) = 20.4$; $p < 0.001$) and in path eff ($F(1, 54) = 9.9$; $p < 0.01$). Interestingly, while the path eff parameter showed only main effect of round as repetition factor ($p < 0.001$), we identified an interaction effect (group x round) in the pointing error ($F(2, 108) = 4.4$; $p < 0.05$). The post-hoc test on this interaction revealed that healthy controls showed stable performance over the DMP session (individual rounds did not differ in the group of healthy controls), but the schizophrenia group showed significant drop of performance between the Acquisition phase and the first Recall round ($p < 0.001$), probably due to the time delay. No differences have been identified between

the two Recall rounds. Interestingly, no effect of goal position or any main or interaction effects of the goal position were identified.

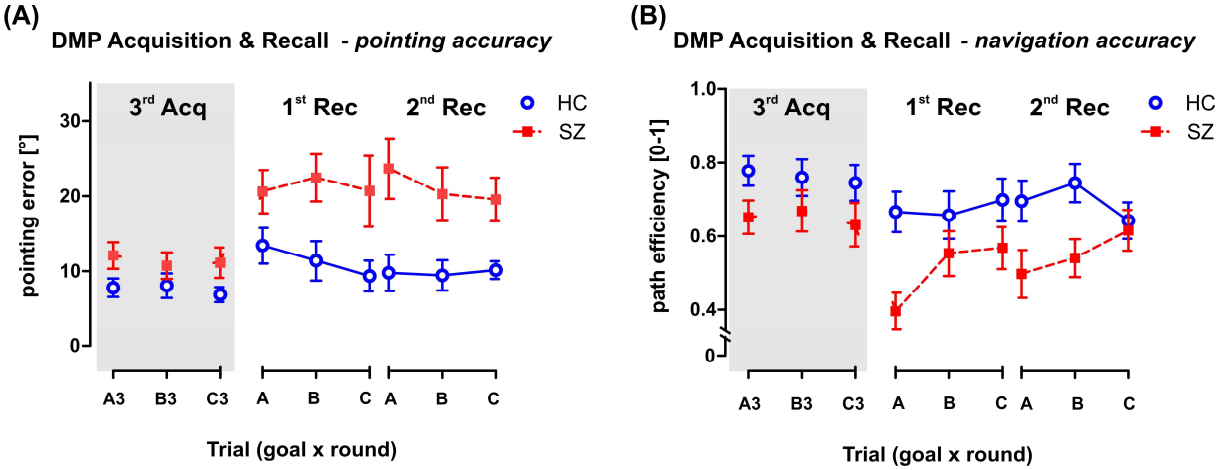

Figure 24. *Performance in the Recall phase vs. the 3rd trial of the Acquisition phase of the DMP session. (A) The pointing error (mean ± SEM) and (B) the path efficiency (mean ± SEM) in individual trials of the Recall phase. Panels on the right - 1st Rec, 2nd Rec - show the group performance in the two recall rounds. Each round requires recalling the previously learned goal positions in the correct sequence (ABC). Gray area on the left (3rd Acq) represents the performance in the last (3rd) repetition trials for each goal position in the Acquisition phase (A3, B3 and C3). It illustrates the drop in behavioral performance due to time delay between the Acquisition and Recall phase.*

PROBE phase. The performance of both groups in the PROBE phase (conducted as the last repetition of the spatial sequence after the Recall session) is shown in Figure 25. Despite the fact that the performance of both groups differed from the chance level (0.25), the GLM analysis with goal as repetition factor identified significant group differences in the goal quadrant preference ($F(1,54) = 16.9$; $p < 0.001$). However, we found no differences between the individual goal positions. The performance in healthy controls shows that well-trained subjects search for all three goal positions most of the time in the correct quadrant of the arena, as can be seen in their goal quadrant preference of around 73 ± 18 %. The averaged performance in the schizophrenia group is lower for all three goals, only around 50 ± 23 %. No significant group differences were identified in the number of entrances to the goal position.

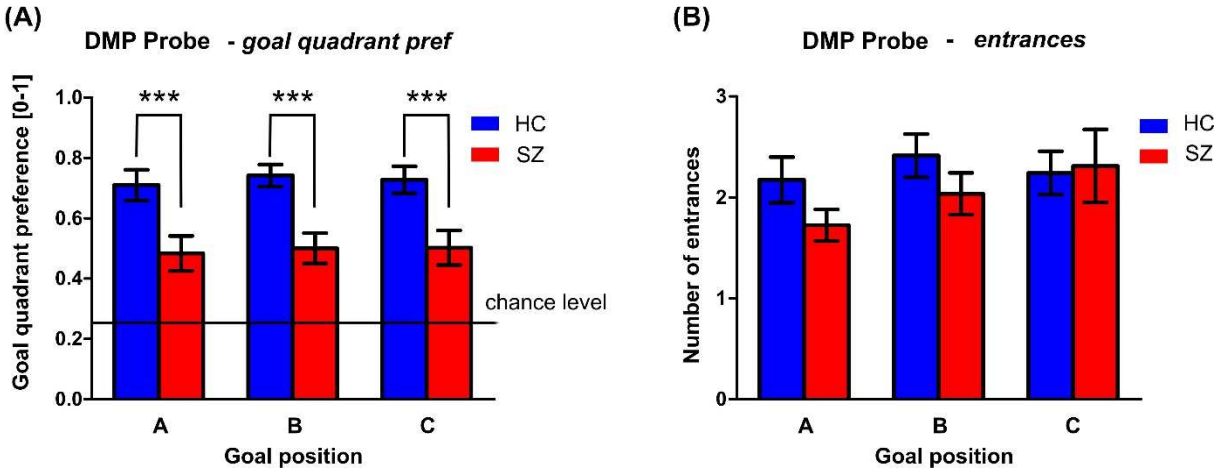

Figure 25. *PROBE phase of the DMP session. (A) The goal quadrant preference (mean ± SEM) and (B) the number of entrances (mean ± SEM) to the inactivated goal position presented separately for individual goal positions. Annotation: ** p < .01 group difference.*

Differences in spatial strategies

To understand the observed behavioral differences, we analyzed the ***strategies*** used by both groups to search for the goal position. Automated analysis (see Figure 26) was used to identify the strategies, according to performance values such as path efficiency, goal quadrant preference or heading direction angle.

We were able to identify the following strategies: direct search, mark strategy, focal search, and incorrect focal search (see Figure 27). All other strategies were evaluated as Unknown. Cochran-Mantel-Haenszel test for repeated 2x2 tests of independence was used to identify possible group differences. We identified the following group differences:

Direct strategies (direct swim and search) were used in the (2) Acquisition phase more frequently in healthy controls (51%) than in patients' group (43%) (Chi-square = 4.817, $p < 0.5$); and similarly in the (3) Recall phase in healthy controls (61%) and in patients' group (45%) (Chi-square = 8.347, $p < 0.01$).

Focal search strategy was used more frequently in healthy controls (83%) than in patients' group (53%) in the (4) Probe phase (Chi-square = 17.977, $p < 0.0001$).

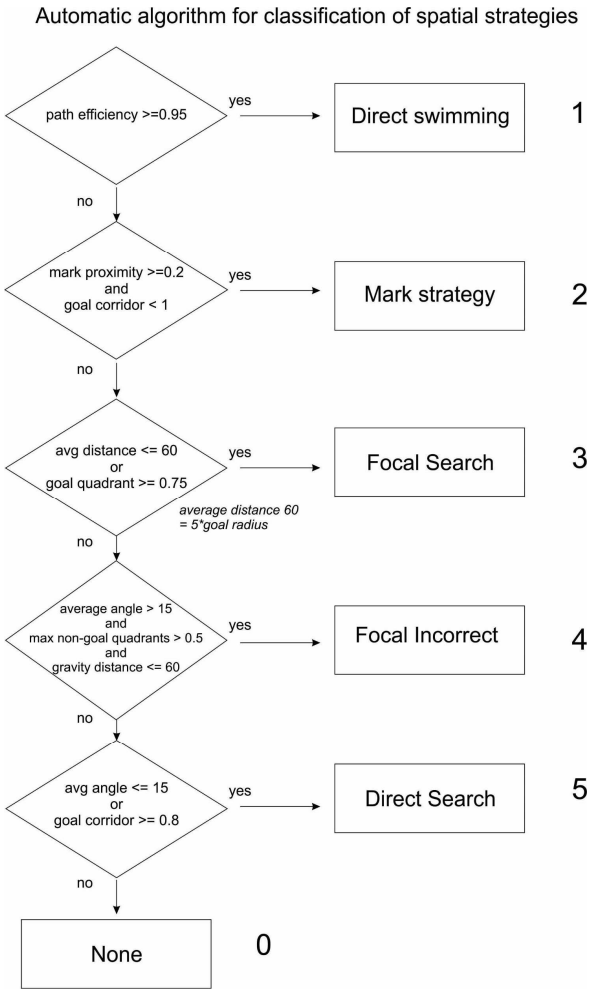

Figure 26. *Illustration of the automatic algorithm used for classification of spatial strategies in the vFGN task.*

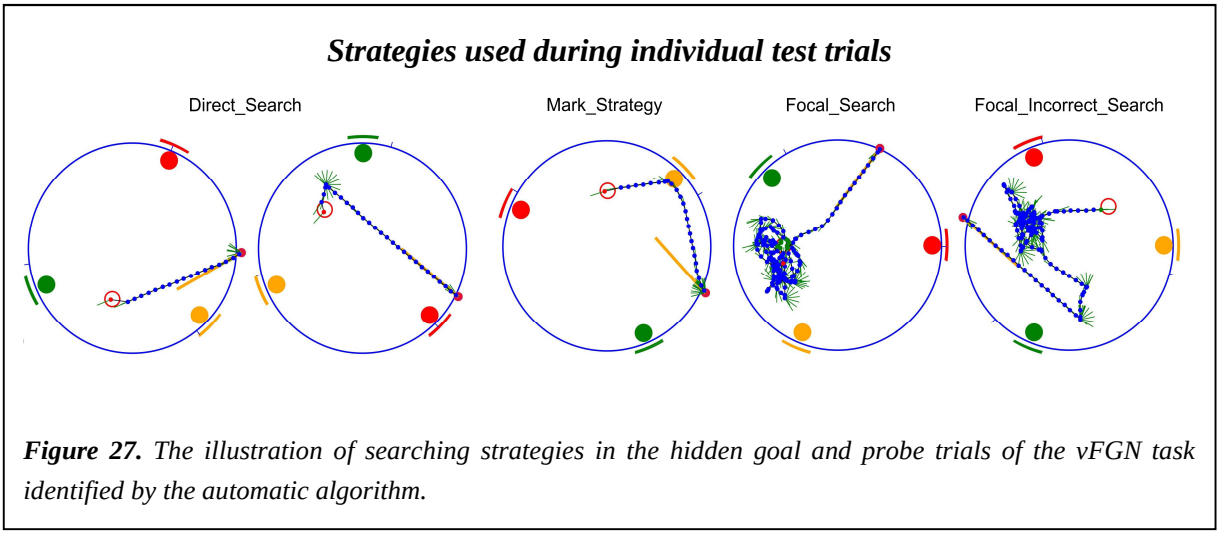

Figure 27. *The illustration of searching strategies in the hidden goal and probe trials of the vFGN task identified by the automatic algorithm.*

Sex and age differences

In order to show possible effects of sex on spatial performance in the vFGN task, sex has been used as additional main factor in the GLM analysis with repeated measures (group x sex) performed for individual phases of the task. Interestingly, some sex differences have been observed in almost all parts of the task but exlusively only for the parameter of path efficiency. Nevertheless, the main effect of sex was found significant only in the navigation accuracy measured during the RM session ($F(1,54) = 4.2$, $p < 0.05$). However, sex differences approached the significance level in path eff measured in the Acquisition ($F(1,54) = 3.6$, $p = 0.064$) and Recall phase ($F(1,54) = 3.7$, $p = 0.06$) of the DMP session. In all cases males showed superior performance in comparison to females. Any differences have been observed either in the pointing accuracy or in the quadrant preference measured in probe trials. No interaction of sex and group factor was observed.

In order to analyze how the age of our participants had affected their performance in the vFGN task, we performed a correlation analysis. The spatial performance of individual participants was averaged for all trials in individual parts of the vFGN task and correlated with the age variable, separately for group of patients and for healthy volunteers (see Table 4). The averaged navigation accuracy in the group of healthy volunteers negatively correlated with the age of individual subjects in all parts of the task. Similarly, the averaged pointing accuracy in Recall phase and number of entrances in the Probe phase was significantly affected by the age variable. However, no such correlation was identified for the group of schizophrenia patients.

Regression model of clinical variables effect on performance in the vFGN task

From the set of potential clinical and demographic factors that could contribute to the cognitive decline observed in the group of patients, the following predictors were added to the regression model (age, DUP, PANSS-P, PANSS-N, PANSS-G, GAF and CPZ level) analyzing their effect on performance measured in the vFGN task (performance averaged separately for individual parts of the vFGN task – the RM session and three parts of the DMP session). A stepwise forward multiple regression analysis employed using these predictors identified only the following significant effects - positive effect of GAF score on spatial learning ability expressed as the averaged pointing accuracy ($bGAF = -0.52$; $p < 0.05$) and navigation accurcy ($bGAF = 0.49$; $p < 0.05$) in the RM session. The full model was significant only for pointing accuracy ($R= 0.57$; $R2= 32\ \%$; $p = 0.045$), but not for the path efficiency ($R= 0.54$; $R2= 30\ \%$; $p = 0.06$), both with GAF and DUP predictors added in 2 steps (all other predictors were removed). In Recall phase of the DMP session measured by path efficiency we identified significant effect of PANSS-G ($bPANSS\text{-}G = 0.68$; $p < 0.05$) and CPZ level ($bGAF = 0.7$; $p < 0.05$), however the whole model, with non-significant DUP and PANSS-N predictors added in later steps, was not significant ($R= 0.67$; $R2= 44\ \%$; $p = 0.066$). No other significant effect of the applied model was found in any of the three parts (Acquisition, Recall or Probe phase) of the DMP session.

TABLE 4. CORRELATION ANALYSIS BETWEEN THE AGE VARIABLE AND THE PERFORMANCES AVERAGED FOR INDIVIDUAL PARTS OF THE VFGN TASK, ANALYZED SEPARATELY FOR GROUP OF SCHIZOPHRENIA PATIENTS AND HEALTHY VOLUNTEERS.

Correlation analysis	**Correlations with AGE variable**					
	Schizophrenia patients N = 29			**Healthy Controls N = 29**		
Measured performance	**r (X,Y)**	**t**	**p**	**r (X,Y)**	**t**	**p**
Path-RM1	-0.48	-2.83	0.009	0.10	0.50	0.62
Point-RM1	0.14	0.77	0.456	-0.20	-1.04	0.31
Path-AcqDMP	-0.38	-2.12	0.043	-0.06	-0.31	0.76
Point-AcqDMP	0.33	1.82	0.079	0.10	0.55	0.59
Path-RecallDMP	-0.49	-2.95	0.006	0.01	0.06	0.95
Point-RecallDMP	0.42	2.43	0.022	0.14	0.76	0.45
Quadrant- ProbeDMP	-0.36	-2.01	0.054	0.01	0.07	0.95
Entrances-ProbeDMP	-0.49	-2.92	0.007	-0.18	-0.96	0.35

Legend: *Path – averaged path efficiency performance, Point – averaged pointing error, Quadrant – averaged goal quadrant preference, Entrances – averaged number of entrances to the goal, RM1 - first half of the RM session, Acq-DMP - the Acquisition phase of the DMP session, RecallDMP – Recall phase of the DMP session, ProbeDMP - Probe phase of the DMP session, r (X,Y) – correlation coefficient.*

3.2.1.4 Discussion

Both parts of the newly developed virtual vFGN task demonstrated sufficient sensitivity towards the impairment of visuo-spatial functions identified in our schizophrenia patients using standard neuropsychological methods.

First, it is important to discuss the sensitivity of the parameters measured in our study. The pointing error parameter has yet not been applied in similar studies, with the exception of the bearing error used to address spatial abilities in a virtual maze (Wall et al., 2001). This pointing error parameter showed higher sensitivity towards behavioral impairment in schizophrenia than the path efficiency parameter. This finding indicates that the simple pointing paradigm could be used to assess spatial abilities separately. Possible explanation of different sensitivity of measured parameters is that the navigation accuracy (expressed in path eff) could

be more affected by sex and age differences, connected to skill learning abilities. The common spatial bias parameter (Morris, 1984;Morris, 2008) calculated as percentage of time in the correct arena quadrant was more sensitive towards the impairment in schizophrenia than the other applied parameter, the number of entrances to the goal.

Spatial learning performance in the RM session

The spatial performance measured during the RM session in our participants strengthen the idea of spatial learning impairment in schizophrenia demonstrated in other human studies (Folley et al., 2010;Hanlon et al., 2006) and animal models of schizophrenia (Gorter and de Bruin, 1992a;Latysheva and Rayevsky, 2003;Sircar, 2003;Stuchlik et al., 2004). We found decreased performance in the schizophrenia patients in both pointing and navigation accuracy to the goal. However, the navigation accuracy was decreased only in the first half of the RM session.

We were able to demonstrate the continual improvement of performance in healthy controls during the whole RM session, expressed by the decreasing pointing error and path shortening (growing path efficiency). This is in agreement with the evidence that the latency is shortened in animals during consecutive RM sessions (D'Hooge and De Deyn, 2001;Mulder and Pritchett, 2003;Vorhees and Williams, 2006) and in RM blocks tested in human virtual analogues (Leplow et al., 2003;Nadel et al., 1998). Similar continual improvement was present in our group of schizophrenia patients, but interestingly only in the pointing accuracy. In agreement with another human study (Hanlon et al., 2006) the path efficiency of the schizophrenia group did not improve in the first half of the RM session (trial T2-T5). The discrepancy between these two measured parameters supports the idea that navigation performance could be divided into two distinct parts (directional vs. place navigation in Hamilton et al., 2008): 1) selection of direction to the goal at the beginning of the navigation process represented here by the pointing accuracy and 2) precise determination of goal position represented by the path efficiency. We assume that while the patients do improve in directional navigation by remembering the approximate position of the goal (near a particular cue), they do not improve in direct navigation to the goal due to imprecise perception and memorizing of spatial information. Interestingly, their navigation accuracy improved after the insertion of probe trial (in the middle of RM session) that could facilitate their motivation to focus on important spatial information due to the previous unsuccessful search.

In addition, a single probe trial inserted in the middle of the RM session (T6) showed impairment of spatial bias in schizophrenia, in accordance to animal studies (Norris and Foster, 1999;Stuchlik et al., 2004). In rats, the probe test is known to start extinction process; we expected human subjects to respond similarly. The probe trial was therefore applied in the middle of the RM session as a form of interference (often used in learning tasks (cit). Interestingly in animal studies only first half of the probe trial (first 30 from 60 s) shows group differences in rodent model of schizophrenia (e.g. Entlerova et al, 2013), as afterwards the intact animals tend to leave the unrewarded position. However, due to the verbal instruction, our subjects tended to look for the goal during the whole trial. Despite these differences, the human analogue of probe trial shows the same pattern as observed in the rodent model of the MWM; lower occupancy of the goal quadrant in the group of schizophrenia patients in comparison to the healthy controls.

Importantly, the final visible goal trial showed that the impaired performance observed in the group of schizophrenia patients was not produced by locomotor or sensory deficits. This one-trial finding is in accordance with other human (Hanlon et al., 2006) and animal studies (e.g.; Gorter and de Bruin, 1992;Vales et al., 2006), suggesting that the usual block (of several trials) procedure is not essential for demonstrating the control performance of navigation towards a visible goal. Taken together, our findings confirm the designed RM session as a useful tool for assessing visuo-spatial learning in schizophrenia.

Mental flexibility and working memory performance in the DMP session

The ACQUISITION phase**.** A major performance improvement in the Acquisition phase of the DMP session appeared immediately after the 1st search trial. Similar behavior has been observed also in animal studies, where only improvement between the first and the second trial is present in well-trained animals in the DMP or reversal protocol (Garthe et al., 2009;Saab et al., 2011). Despite the observed group differences in the pointing accuracy, the announcement of positional change to our participants was probably responsible for the low group differences in this part of vFGN task. In addition, in order to be able to compare the group performance in later recall of the spatial sequence regardless individual goal positions, the goals have been placed in identical positions (in the meaning of spatial relationship between the goal position and the nearest orientation cue). Such settings could be a source of skill learning effect that could explain the lack of between group differences observed in navigation accuracy. Nevertheless, the low sensitivity of the reversal protocol towards cognitive deficit in schizophrenia is in accordance with animal studies that failed to find significant group differences after application of lower doses of MK-801 (Lobellova et al., 2013; Watson and Stanton, 2009). Interestingly, similar reversal protocol applied in the avoidance task on rotating arena showed, that the pre-training of animals in the task can lead to lack of group differences after application of MK-801 (Zemanova et al., 2013).

Importantly, the performance of individual groups achieved in the Acquisition phase (in last repetitions of the goal positions A3, B3 and C3) did not differ between the three goal positions, enabling us to test the consecutive recall of this sequence after a time delay. .

The RECALL phase. Our study was the first to demonstrate impairment in schizophrenia patients using the analogue of the Delayed-matching-to-place protocol of MWM. Our results showed impaired recall of spatial sequence in schizophrenia patients in both pointing and navigation accuracy. The working memory performance was here expressed in the performance decrease observed after the time delay between the Acquisition phase and the first round of the Recall phase. Some small but not significant decrease in spatial performance could be seen in control subjects as well, due to delayed recall of spatial sequence. However, the strong performance decline in the group of patients demonstrates the working and long-term memory deficit in schizophrenia. These findings are in agreement with the data obtained in animal models of schizophrenia using the DMP protocol (van der Staay et al., 2011).

The PROBE phase. We demonstrated the schizophrenia specific disturbance of spatial bias expressed as decreased goal quadrant preference in the PROBE trials completed in the end of the task. The observed behavioral impairment is similar to the observations of rats injected with dizocilpine or scopolamine in pharmacological screening models of schizophrenia and dementia, respectively (Entlerova et al., 2013;Lobellova et al., 2013), which exhibit disturbed performance in probe trials. However, in most of the schizophrenia patients the observed probe

trial performance was better than in rats after lesion of the hippocampus (Morris et al., 1982;Sutherland et al., 1983) performing by random search patterns.

Effect of demographic variables

Based on studies describing sex differences in spatial abilities of both rodents and humans (e.g. Cimadevilla et al., 2004; Astur et al., 2004), we expected to find similar effects in spatial abilities measured by the vFGN task. However, we identified significant sex differences only in learning abilities assessed in the RM session. In addition, sex differences have been observed only in the navigation accuracy parameter. This fact and the lack of sex differences in the other parts of the task suggest the followings: 1) the simple circular environment prevents the usage of abilities found to be affected by sex; 2) the directional information for individual goals was gained similarly in men and women, yet women tend to use less precise trajectories when navigating towards the goal. This could be due to sex differences in motor skill learning (cit), as all the three goal positions have been placed in geometrically identical positions. The lack of interaction between sex and group factor in any of the measured parameters shows that the presented group differences are independent of the minor sex differences.

According to the current literature describing negative effect of aging on learning and memory processes (Moffat and Resnick, 2002; Moffat, 2009; Young et al, 2013) we expected to find significant correlation between the age and spatial performance in the vFGN task, both during learning and recall of the spatial information. We confirmed this hypothesis as we observed age effects in all parts of the vFGN task in our healthy volunteers. Interestingly, such effect was fully suppressed in schizophrenia patients. This finding supports the idea that the observed cognitive deficit is a characteristic pattern in schizophrenia disorder. This result is in contrary to the current meta-analysis (Rajji et al., 2009), which assumed a better prognosis and less expressed cognitive deficit in patients with a lower age of illness onset. However, our study describes the visuo-spatial deficit only in the early remission phase after the first psychotic episode; repeated assessment in the full remission could reveal a different pattern.

Effect of psychiatric symptomatology and antipsychotic medication

One of the currently monitored parameter is the duration of untreated psychosis (DUP) defined as the time from appearance of the first psychotic symptom to the initiation of suitable antipsychotic treatment (for review see; Marshall et al., 2005). In accordance to a recently published follow-up study (Barnes et al., 2008), we found no significant effect of DUP on spatial performance.

Current literature describes a strong association of cognitive functions and negative symptoms, but the absence of a positive symptoms effect on cognitive deficit in schizophrenia (e.g.; Addington et al., 1991;Rossi et al., 1997). Interestingly, we found no significant effect of negative or positive symptoms on the performance in the vFGN task. However, we observed a strong effect of GAF score on spatial learning performance in the RM session and effect of generalized symptoms in Recall phase of the DMP session. These results demonstrate that high functioning patients perform better in cognitive tasks than the low functioning individuals in the group of schizophrenia patients (Green et al, 2004).

Older studies described negative effects of first-generation antipsychotic treatment on cognitive functioning in schizophrenia (Spohn and Strauss, 1989). On the contrary, current studies addressing atypical antipsychotics reported slightly positive effects of some drugs on

cognitive functioning in schizophrenia patients (e.g; Meltzer and McGurk, 1999) and in an NMDA model of schizophrenia in rats (Bubenikova et al., 2005). Interestingly, only the memory deficit found in the Recall phase of the DMP session was partially affected by the CPZ level in the navigation accuracy parameter. We did not find any other significant effect of the atypical antipsychotic treatment (dosage calculated in CPZ equivalents) on the overall cognitive performance in the vFGN task. However, our study was not aimed at individual antipsychotic compounds and this could distort the analysis.

Limitations of the study

There are some limitations to the current study. Firstly, both animal protocols (RM and DMP) were modified in order to test human subjects, inducing possible behavioral changes.

The lack of a strong reward motivation present in animal studies (escape from water reaching the platform) could change the motivation to higher performance in the task. However, we assume that our subjects have been motivated enough as they all voluntary participated in the study. Moreover, in the group of patients the vFGN task was performed in the time of neuropsychological assessment aimed to support the diagnostic process. We do believe that during this time period our patients were motivated towards higher performance in general. In addition, both groups judged the level of entertainment during the task similarly as averaged (not reported). Nevertheless, some positive reward could be applied in order to prevent possible lack of motivation in future studies.

In order to enable fast assessment of our participants in only one day, the RM protocol could be considered too short to assess long-term memory processes. However, such short protocols are common in human studies testing learning abilities and long-term memory in standard virtual tasks (such as verbal or nonverbal learning memory tasks; cit) and virtual MWMs that have been considered a valid human analogy of spatial reference memory in rats, and supported by both behavioural data (e.g. Jacobs et al 1998) and dependence on hippocampal function (e.g. Astur et al 2002, Goodrich-Hunsaker et al 2010).

Also the DMP session in our study is not fully comparable to the DMP protocol of animal studies and was modified in the following three details: 1) The inter-trial interval was not controlled directly but was naturally formed by the number of trials included before the recall trial (6 trials for goal A, 4 for B and 2 for C); and 2) Positional changes applied in our study between acquisition and recall of the goal position are not usual in animal studies; 3) The acquisition of the goal position (spatial sequence) was repeated for several (three) trials, as an analogue to a reversal memory protocol. Despite these modifications we were able to demonstrate that the results obtained in the individual phases of the vFGN task could be compared to the performance patterns obtained in animal models.

Secondly, despite the smaller number of participants in our study we were able to demonstrate the deficit in spatial cognition in schizophrenia group. However, matching of the healthy controls to the patients produced an unbalanced distribution in demographic variables, such as the two-peak age distribution in analzyed groups and variable age distribution in males and females caused by the typical age of the early and late onset of schizophrenia.

Thirdly, it is important to note that the navigation performance of schizophrenia patients group observed in the vFGN task was not unitary and showed higher individual variability than the performance in the healthy control group. This supports the findings of other studies describing variability of the cognitive deficit level measured in individual first-episodes schizophrenia patients (Keefe et al., 2005). Therefore, further individual analysis of the spatial

performance measured in the vFGN task and its association to standard measures of cognitive deficit is required. A separate paper is devoted to tracking of possible effects of demographic variables and gaming experience in the group of healthy volunteers, in order to produce normative data for vFGN task performance (in preparation).

Concluding remarks

The novel vFGN task covered several MWM protocols in a single task and was sensitive towards the impairment of spatial navigation performance, which was observed in nearly all parts of the designed battery. Our results documented strong parallels between the real animal MWM and the presented virtual analogue for humans. Therefore, this novel computer task could serve as a useful method of preclinical trials for assessment of spatial behavior and complex cognitive processes in schizophrenia. According to the animal studies, we propose that the vFGN task could be used to assess spatial learning, attention, mental flexibility and spatial working memory processes in three-dimensional space. Future work should confirm the validity of the individual parts of the designed task using a simultaneous examination of the related cognitive functions by standardized neuropsychological methods.

Future directions

The data presented in this paper demonstrated the sensitivity of the vFGN task toward the cognitive deficit in first episodes of schizophrenia, confirmed by standard neuropsychological methods. We do believe that the vFGN task assessing complex visuo-spatial behavior could serve as an ecologically valid screening method more sensitive towards the future course of illness in individual patients than the standard methods measuring single cognitive functions. In order to test this sensitivity, a second assessment session takes place one year later in the same patients. This time delay is used to evaluate possible cognitive deficit persisting in our patients after the full remission of symptoms or potential relapse of the illness, their adherence towards treatment and their subjective quality of life. Longitudinal data revealing the trajectory of vFGN performance during the course of schizophrenia are needed.

3.2.2 EXPERIMENT III – ASSESSMENT OF SPATIAL MEMORY IN VIRTUAL ANALOGUE OF THE CAROUSEL MAZE (ROTATING ARENA)

3.2.2.1 Aims and hypothesis

The presented study explored the hypothesis that mental spatial representations of two dissociated RF are independent and not accessible simultaneously and focused also on separation of these representations in schizophrenia. This psychiatric disease has been associated with deficits in cognitive flexibility and in the ability to distinguish the relevant from irrelevant information. These deficits present also as impairment in reference frames switching. The aim of this study was therefore to create and test a human version of Carousel maze task previously demonstrating deficit in cognitive coordination in animal model of schizophrenia. We used a virtual environment with a rotating platform dissociating the reference frames (RFs) of the room and the arena platform to study the associated spatial cognitive maps in human and their impairment in schizophrenia patients.

The original active place avoidance task (AAPA, Bures et al., 1997) for animals was modified to a preference version of rotating arena for humans called the virtual **Active Allocentric Place Preference task** (vAAPP, Vlcek et al, in preparation; Fajnerova et al, 2015b). The same hidden goal principle as in the previous vFGN task (MWM analogue) was used here to test spatial navigation abilities in subjects moving on a rotating platform. Movement of one part of an environment relative to others (like on a carousel) dissociates them regarding orientation in space. Finding a goal in such environment requires that one selects the relevant frame of reference (RFs) (i.e. rotating or stable) and orients relative to it to estimate his/her own position and position of the goal.

The presented study describes the newly-developed virtual AAPP task and presents data obtained in a group of first episode schizophrenia (FES) patients in comparison to a group of healthy volunteers. In order to assess the usefulness of the vAAPP task in preclinical studies, we discuss the obtained data with the previously published animal studies.

On the basis of animal and human literature, we hypothesized that the FES patients would perform worse compared to healthy controls in the vAAPP task in terms of: a) impaired spatial learning and mental flexibility during alternation of two goal positions in the Arena and Room frame test sessions; and b) decreased cognitive coordination performance in the final test session requiring mental switching between the two previously acquired maps of reference frames.

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Fajnerova I, Rodriguez M, Spaniel F, Horacek J, Vlcek K, Levcik D, Stuchlik A, Brom C. Spatial navigation in virtual reality - from animal models towards schizophrenia: Spatial cognition tests based on animal research. Virtual Rehabilitation Proceedings (ICVR) 2015: 44- 50. IEEE Conference proceedings available at: http://ieeexplore.ieee.org/.

3.2.2.2 Methods

Subjects, Clinical and neurocognitive assessment and Pre-training of motor control

For details see section Methods for Experiment II.

Software and apparatus - Virtual Environment

The environment, created by UnrealEd editor under Unreal Tournament 2004 (Epic Games), consisted of a rectangle room with a circular arena in its center (see Fig. 28). The arena slowly rotated counter-clock-wise at a speed of 6.2 degrees/s. With its diameter of 1716 Unreal Units (UU, about 32 virtual meters) it could be traversed in 5 sec. Three objects (a coniferous tree, a bush and a flower) were positioned on the arena periphery and rotated with it, while three different objects (a pillar, a statue and a stone cup) were positioned in the room, around the arena and did not rotate. Both arena and room objects were positioned at 120° intervals relative to the arena center. In this environment, four goals were positioned on the arena, two rotating with the arena (circular shape) and two stable in the room (squared shape). The goals were in the same positions in the environment in all phases of the experiment except the pre-training phase and were positioned in the exact middle between the object pairs, in the same distance from the arena center as the arena objects. However, the subjects were not informed about these regularities. The diameter of the goals was 296 UU (5.6 meters). When visible, the goals appeared as discs or squares floating 12-24 UU (23-46 centimeters) above the arena. The goals stable in room were shown as blue or red squares, while the goals rotating with arena were shown as blue or red discs. The three rotating objects defined the position of the two rotating goals, while the three stable objects defined the position of the two stable goals. The center of the circular arena was marked by a green-yellow slab with the size of 116 UU (2.2 meters). To control the environment (arena rotation, goals activation, screen messages) and collect the data, custom software SpaNav written in Java was used (Supalova, 2009), connecting to the Unreal engine via the TCP/IP protocol.

Similarly as described in the previous Experiment II (in the virtual Four Goals Navigation task on stable arena) the subjects became accustomed with the Unreal Tournament environment and the game control in a short practice task in a complex maze (see Pre-training of motor control in Experiment II, Figure 17). The forward movement was controlled by the forward press of the left/right joystick of the gamepad device (a forward joystick press started the movement and a release stopped it), but the backward movement was blocked. The left/right turning of the view was controlled by the left and right press of the same joystick. No other

direction of movement (look up/down, move left/right, move backward) was possible. For marking the direction to the hidden goal, the green key of the gamepad devise was used.

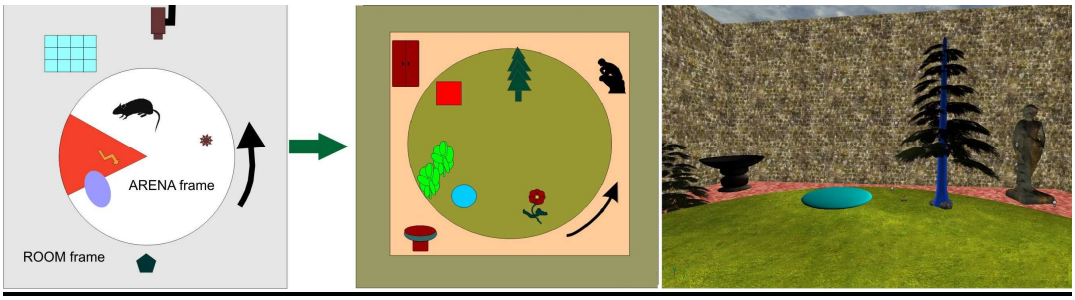

Figure 28. *The schematic picture of the original AAPA task (Carousel maze; (left)); Schematic view of the Virtual version of the AAPP task. - Training conditions in two possible reference frames: Room frame (square shape) and Arena frame (circular shape) (middle); Rotating arena from the first-person view (right).*

Procedure - Design of the Active Place Preference (AAPP) task

The same hidden goal principle as in the previous vFGN task was used to test spatial abilities in subjects standing on a rotating arena. The hidden goal positions were connected to one of the two reference frames: frame of the ARENA that slowly rotates together with the tested individual, or the static ROOM frame surrounding the arena.

The actual experiment consisted of one training phase; two learning (acquisition) phases and one test phase, with four goals or selection of two goals present (see description of the phases below). The training and the acquisition phases were similar in their design. At the beginning of each phase, the subject went to the center of the arena, marked by a green platform. The platform than disappeared and a notice on the screen, consisting of a goal identification (circle or square of a specific color) (Fig. 29), indicated one of the four goals to visit. The subjects were instructed first to point at the goal position and then to visit the indicated goal by the shortest path possible. To point at goal, the subject used left/right press to the joystick to turn left or right in the estimated direction to the goal and pressed the green key on the gamepad to save this direction. The pointing speed was preferred before precision. The subject translation movements were blocked during pointing, before the green (S) key press, so that s/he could only change the angle of view while standing in the center of the arena.

In two initial trials at the beginning of each re-training or learning phase, each of the goals was visible one after each other and it disappeared only after the subject entered it. After these initial trials the goals were hidden, but a to-be-visited goal appeared if the subject could not find it for limited time of 20 sec. After entering the goal, a sound was played as a confirmation of finding the goal, this was considered as the end of the trial. Then the subject should go again to the center of the arena and then to the next goal position according to the instructions. The goals were visited in a predefined complex sequence. In this sequence, each of the two or four goals occurred with same frequency and the same goal was repeated three times in a row at most. In addition, as the main effect of interest was the effect of the previous goal in sequence, four categories of goal change also occurred with the same frequency in each phase (see Data Analysis section for more details).

Training phase 1 – pre-training of the AAPP task

The experimental environment was shown and design of the experiment explained in detail to the subject, who was then allowed to ask for additional explanation. Then the pre-training phase started, where the subject visited two goals (one arena goal and one room goal) in a pseudorandom order, ten times each. Of these 21 trials, in the first two the goals were visible. The subjects were informed that the goal positions were different from the following training and test phases and they should forget their positions after the pre-training phase. In order to prevent transfer of information different colors were used for these pre-training goal positions.

Learning phases 2 and 3 – Arena and Room frame acquisition

Two consecutive phases were aimed for acquisition of two reference frames and goal positions attached to them. Set of two goals was connected either to the rotating arena platform (phase 2 - Arena frame) or to the stable room environment (phase 3 - Room frame). The subjects were instructed to find and remember the goal positions and their attachment to either room or arena. In the first training phase (Arena, A2) consisting of 21 trials, the subjects first pointed and then visited a pair of circularly shaped goals (red or blue disk) connected to the arena platform. In the second training phase (Room, R3) the subject pointed and visited two square shaped goals (red or blue square) in another 21 trials. The goals were visible in the first two trials of both sessions. In both phases the subjects learned the final positions of the four goals as used in the last test phase, but different from the training phase.

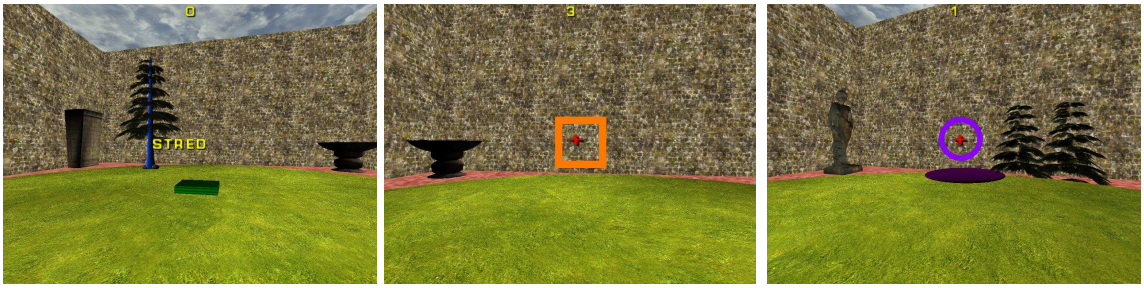

Figure 29. *Illustration of the first person view on the Start position placed in the center of arena (left), pointing condition with the visible goal in the first trial of the session 2 (middle), and pointing in the direction of invisible goal (right).*

Test phase 4 – Frame switching

Afterwards, there was one test phase (Frame switching) with 17 trials and all four goals. This session required alternated search of all four goal positions learned in the previous two learning phases, attached either to the arena or room frame. At the beginning of the test phase, the subject went to the center of the arena, marked by a green platform, but then the translation was blocked. The subject should first point at the goals as fast as possible, just by changing the angle of view, and then walk towards the goal position. The goals were never visible in the test phase.

Data Analysis

Using the recorded subject's positions and directions and the pressed keys, several measures of performance were calculated. (1) Time to point at goal was computed as the time

between appearance of the name of the next goal on the screen and pressing the green (S) key. (2) Time to reach goal in the learning phases was computed as the time between pointing at the goal and entering it. (3) Angular error in pointing was computed as the absolute value of the angle between a subject's heading when the green (S) key was pressed and the direction of the current goal from the current subject's position.

The main factor of interest, when calculating the pointing time, was the category of the change of goals in the predefined sequence. This factor in the analysis was called Place-Change with three possible levels: the previous goal could be either the same as the current goal (Place-Change=0) or different from the current one but in the same reference frame, attached to either rotating arena or room (Place-Change=1). In the other two categories of the goal change the reference frame of the previous frame was different than of the current one (rotating arena vs. room) (Place-Change=2). The predefined sequences of goals in the final test phase (see above) contained several trials in each of these three categories (plus one trial at the beginning of each phase, where this Place-Change category was undefined as there was no previous goal).
The analysis of the subjects' recorded position and direction was performed using custom functions in PHP 5.3.0 (the PHP Group) and Matlab 2010b (The MathWorks, Natick, MA). All statistical analyses were run using Statistica 8.0 for Windows (StatSoft, Inc.).

*3.2.2.3 **Results***

All test phases of the virtual AAPP task showed decline of spatial performance in first episode schizophrenia patients in comparison to matched healthy volunteers.

In contrast to the stable environment of the vFGN task both the **pointing time** and **pointing error** (angle error) parameter was evaluated as well. Schizophrenia (FES) patients showed impaired performance in both pointing time ($F(1,62) = 14.67$, $p < 0,001$) and pointing accuracy ($F(1,62) = 17.62$, $p < 0,001$) when compared with healthy controls using two-way ANOVA (group x phase). Despite the fact that both groups made larger pointing errors in the room frame condition (see Fig. 30), schizophrenia group showed significantly impaired pointing accuracy in all test phases regardless the reference frame ($F(3,186) = 2.28$, $p < 0.05$). While the pointing error in schizophrenia group increased in the Room frame and switching conditions (test phase 3 and 4) in comparison to A2 (Arena test phase 2), their pointing time was slower when pointing in the final test phase 4 with frame switching present. The additional **trial time** parameter showed impaired navigation abilities in schizophrenia when compared to healthy volunteers in all test phases ($F(1,62) = 23.63$, $p < 0,001$), see Fig. 30.

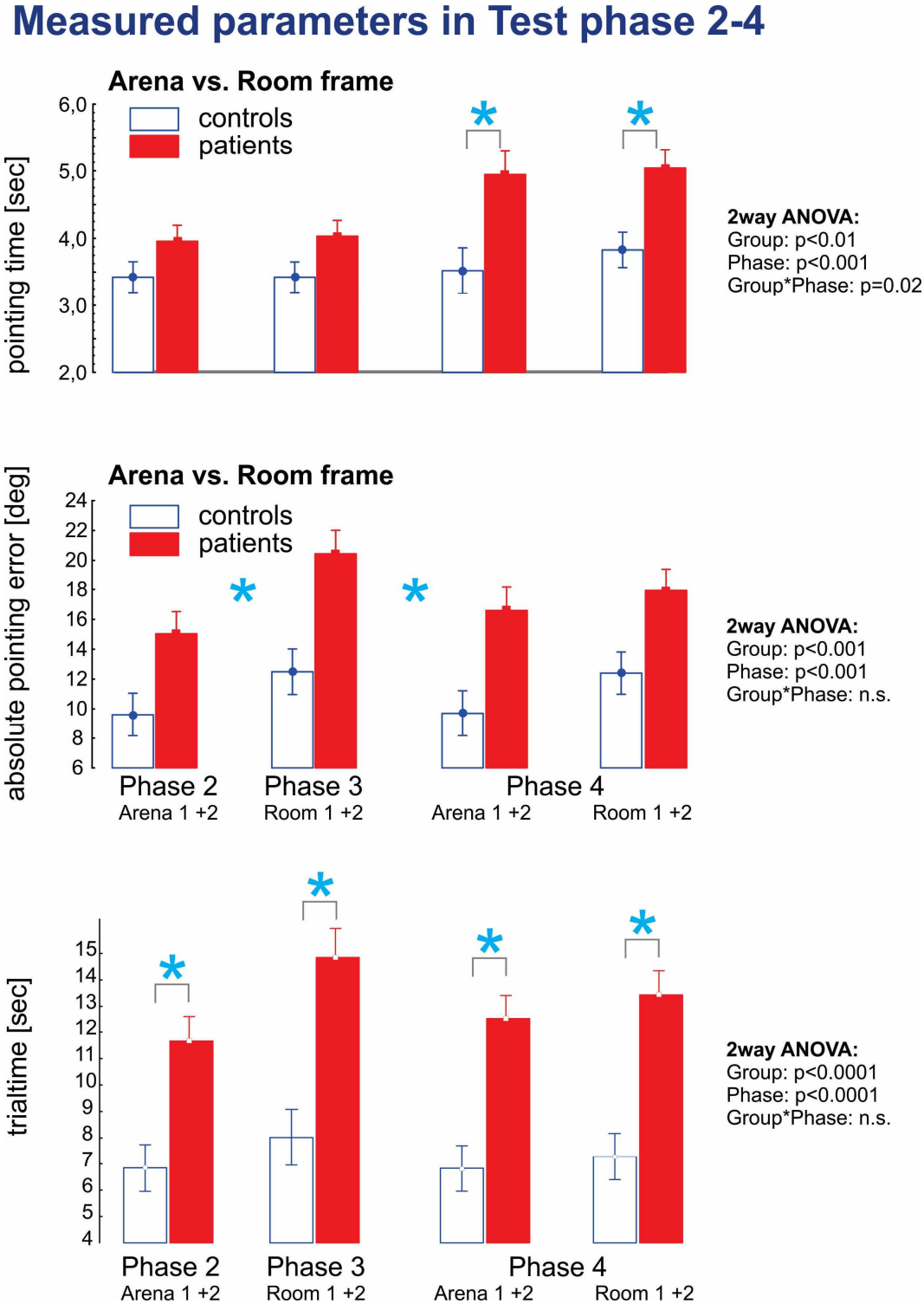

Figure 30. *Group performance in individual test phases measured using three different parameters (pointing time, pointing error and trialtime). Legend: Phase 2 (Arena frame); Phase 3 (Room frame); Phase 4 (Arena-Room frame switching).*

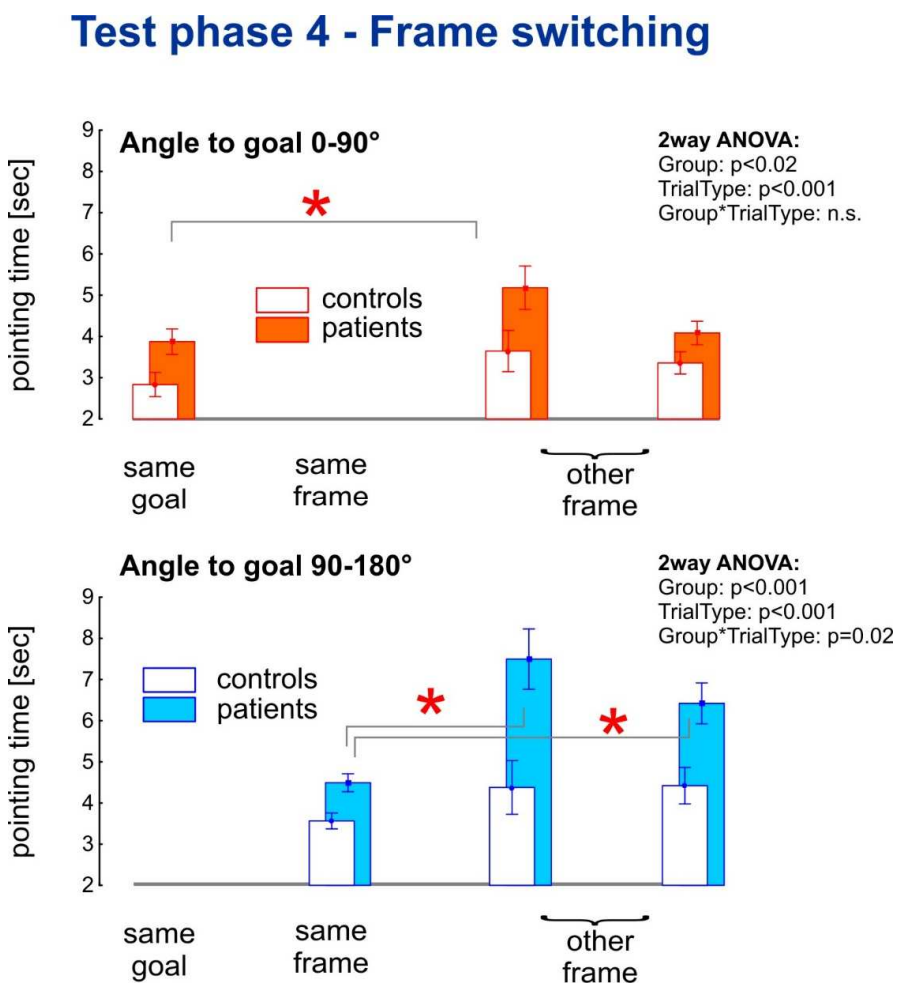

Figure 31. *Group performance presented in the context of place-change analysis (change of the goal position either in the same or different reference frame) separately for trials requiring rotation in the environment smaller or bigger than 90 degrees. Schizophrenia patients demonstrate similar impairment in all types of tasks, except the situation of the same goal repetition.*

With respect to the Place-Change (PCH) category schizophrenia patients were impaired in all types of trials (except the same frame trial, ($F(1,50) = 13.64$, $p < 0.001$), see Figure 31. Nevertheless, in general the point time increases in the switching PCH condition (test phase 4) in both groups (place-change effect, ($F(1,50) = 13.08$, $p < 0.001$).

ANOVA for repeated measures was used to analyze navigation performance in individual test phases using the trial time parameter, in order to test learning effect. The first Pre-training phase showed impaired learning abilities on the rotating arena ($p < 0.01$, Fig. 32A). The second tests phase with Arena frame (A2) (see Fig. 32B) showed only mild decrease in measured parameters ($p < 0.01$), even less expressed in the second half of trials (effect of trial repetition, $p < 0.001$). However, the third Room frame learning (R3) phase with navigation towards the goals connected to the Room frame, moving relative to the subjects (Fig. 32C) showed strongly profound decline of mental flexibility and spatial planning in schizophrenia ($p < 0.001$), probably due to the dissociation between reference frame of the subject and the

reference frame of goals and orientation cues. The last test phase requiring both goal alternation and switching of reference frames created to assess the cognitive coordination, as it required repeated switching between the two reference frames (switching between two mental maps, two sets of orientation cues for arena and room), shows substantial deficit in schizophrenia patients ($p < 0.001$, Fig. 32D).

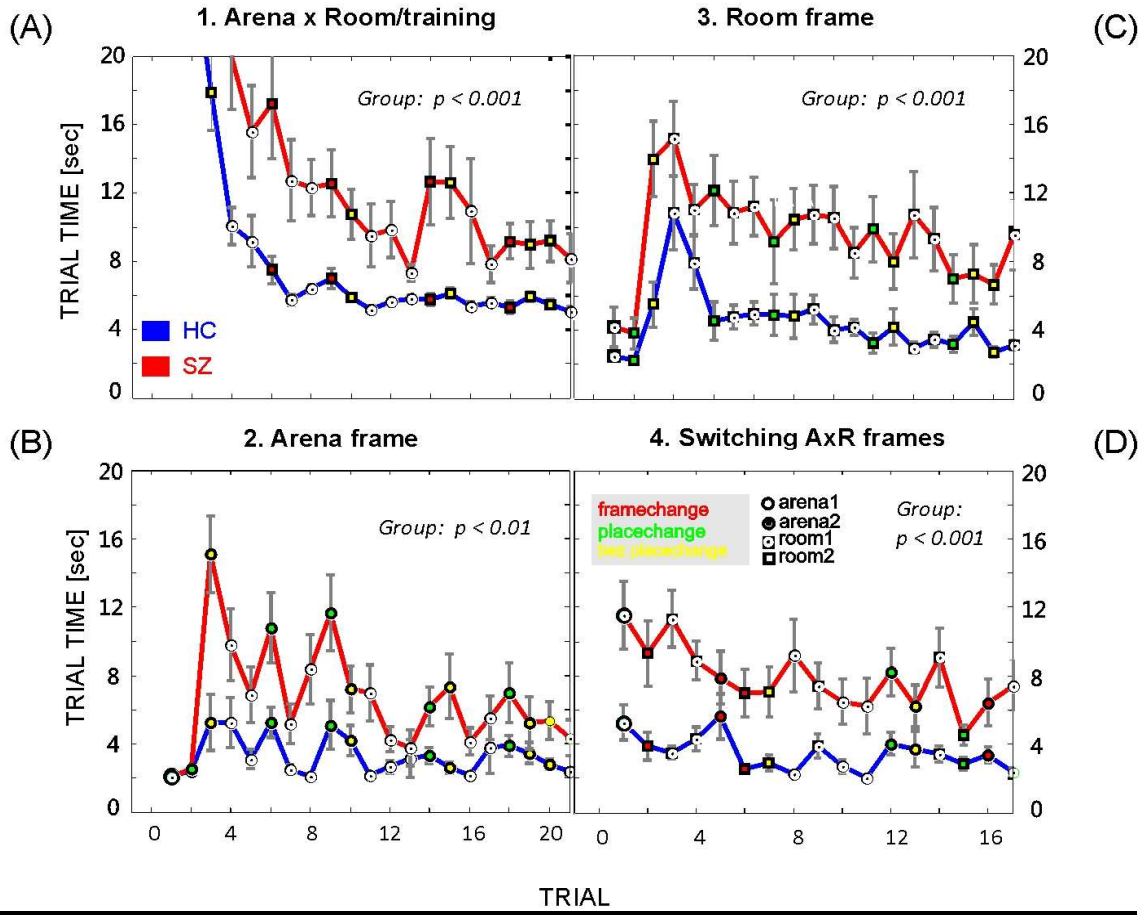

Figure 32. *Performance of both groups in four phases of the Rotating arena - vAAPP task - expressed using the trial time parameter. (A) The Training phase with simple frame change (arena x room). (B) The Arena frame performance. (C) The Room frame performance. (D) Frame change -Alternation between all 4 previously acquired goal positions, placed in arena or room frame.*

Strategies used in Arena and Room frame phases of the virtual Carousel maze

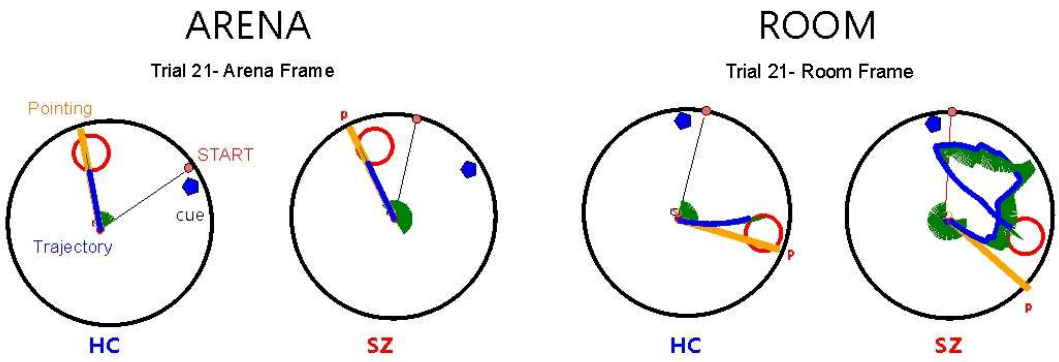

Figure 33. *Illustration of SZ and HC in the last Arena (left) and Room (right) frame: pointing accuracy (orange line) and search trajectory (blue line) towards the goal position (red circle).*

In order to understand the spatial behaviour during navigation towards stable or unstable goal position, we individually analysed the behaviour of schizophrenia subjects and we have identified two main reasons for more pronounced impairment in navigation abilities when navigating in Room frame: 1) the goal is identified in incorrect frame of reference and is therefore falsely linked to incorrect set of orientation cues in arena frame; 2) the navigation towards objects (cues, goals) in the Room frame is deficient due to impaired ability to plan trajectory and anticipate the position of the goal, while patients' own position is shifted by the arena rotation.

Sex and age differences

In order to show possible effects of sex on spatial performance in the vAAPP task, sex has been used as additional main factor in the GLM analysis with repeated measures (group x sex). Sex differences have been observed only in the pointing time parameter during the first training phase ($F(1,61) = 6{,}71$, $p < 0.05$). Any differences have been found in other test phases or other measured parameters (pointing error or trial time).

In order to analyze how the age of our participants had affected their performance in the vAAPP task, we performed a correlation analysis. The spatial performance of individual participants was averaged for all trials in individual phases of the vAAPP task (excluding the visible trials in the beginning of the phase) and correlated with the age variable, separately for group of patients and for healthy volunteers. Performance correlated with the performance of the healthy control group only in the trial time measured in the Arena ($r = 0.435$, $p < 0.05$) and Room frame ($r = 0.497$, $p < 0.05$) in the group of the control subjects. However, no such correlation was identified for the group of schizophrenia patients.

Regression model of clinical variables effect on performance in the vFGN task

From the set of potential clinical and demographic factors that could contribute to the cognitive decline observed in the group of patients, the following predictors were added to the

regression model (age, DUP, PANSS-P, PANSS-N, PANSS-G, GAF and CPZ level) analyzing their effect on performance measured in the vAAPP task (performance averaged separately for individual parts of the task – Training, Arena frame, Room frame and Frame switching paradigm). A stepwise forward multiple regression analysis employed using these predictors identified only the following significant effects in the Arena frame phase: a) positive effect of PANSS-P score on behavioral performance expressed as the averaged pointing (error) accuracy ($R= 0.64$; $R2= 41\ \%$; $p < 0.01$; $bPANSS = 0.63$; $p < 0.01$) and effect of age, PANSS-G and GAF on pointing time ($R= 0.72$; $R2= 53\ \%$; $p < 0.01$; $bAge = 0.45$; $p < 0.05$; $bPANSS\text{-}G = 0.47$; $p < 0.05$; $bGAF = 0.43$; $p < 0.05$). PANSS-G showed significant effect on trial time parameter in the Frame switching phase ($R= 0.59$; $R2= 35\ \%$; $p < 0.05$; $bPANSS\text{-}G = 0.52$; $p < 0.05$). No other significant effect of the applied model was found in any of the three parameters and/or test sessions.

3.2.2.4 Discussion

All parts of the AAPP task showed impaired performance in schizophrenia patients. The ability to orient and remember spatial positions in unstable environment with constantly changing information in this rotating environment could be explained as an ability to identify context using task-relevant information stored in a working memory, which impairment is well documented in SZ (Nuechterlein et al., 2004; Green et al., 2004). This function involves the dorsolateral prefrontal cortex (DLPFC), area described in context of hypofunction in SZ (Verébová and Horacek, 2010; Shenton et al, 2010).

The original AAPA task in animals (Carousel Maze, Bures et al., PNAS, 1997) is reported in the context of cognitive coordination (Stuchlik et al., Physiol. Res., 2013; Wesierska et al., 2005; Kubík et al., 2014). The fact that performance of schizophrenia patients decreases in the environment with goals in dissociated reference frames (in comparison to the vFGN task, or when arena and room condition are compared between each other) could be related to cognitive coordination impairment hypothesis (Philips and Silverstein, 2003). Impaired cognitive coordination (i.e. neural control of cell population activity in time and context) (Phillips and Silverstein, 2003) is considered the core or main cause for cognitive disorganization and complex cognitive deficit observed in schizophrenia. This impairment should include inappropriate perceptual associations and beliefs, deficits in an ability to integrate contextual information as well as impaired discrimination between relevant and irrelevant information (Hemsley, 2005). According to another but related model (Rolls, 2012), instability of neuronal cortical attractor states, due to general reduction of firing rates of glutamatergic neurons, contributes to cognitive as well as negative schizophrenia symptoms. This instability results in interfusion of working memory items and poor ability to allocate attention. Findings in animal models of schizophrenia support this suggestions.

The hypersynchrony theory claims that the cognitive deficit in psychosis results from increased coactivity specifically between neurons which normally do not fire together (Fenton, 2008). TTX-induced cognitive disorganization on rotating circular arena disrupted ability to segregate relevant associations in rats and led to coactivity (hypersynchrony) of hippocampal pyramidal cells discharge (Olypher et al., 2006). Such hypersynchrony could produce the excessive associations observed in schizophrenia by reduced separation between representations of unrelated events and contexts in the hippocampus. Later observations of MK-

801 (NMDA receptor blocker) induced impairment of spatial coordination in carousel maze (Stuchlik et al., 2004) and elimination of contextual specificity (increased similarity) of IEG expression in hippocampal CA1 ensembles (Kubik et al., 2014) also supported the hypersynchrony theory.

This is the first study to our knowledge that involved the processes of switching between spatial reference frames in dynamic environments applied to schizophrenia patients. In healthy controls, the time to point to a hidden goal seems to be strongly influenced by the RF of previous goal: changing the goal RF was associated with a longer pointing time. This switch cost results from the processes of activation of the spatial representation of relevant RF, followed by reorientation in this frame (Vlcek et al., in preparation). Nevertheless, schizophrenia patients are impaired generally in pointing time, but not specifically in reference frame switching. This results support the hypotheses of general impairment in mental flexibility and cognitive coordination reported by animal studies (Lobellova et al.,2013; Zemanova et al, 2013; Kubik et al, 2014). Similar observations have been done in all task-switching paradigms related to dysfunction of medial and lateral PFC areas (Jamadar et al., 2010; Monsell, 2003).

All test phases of the virtual AAPP task showed decline of spatial performance in first episode schizophrenia patients in comparison to matched healthy volunteers.

In contrast to the stable environment of the vFGN task the pointing time was one of the main parameter analysed in FES performance on the rotating arena compared with control group performance, due to the instruction to point towards the goal position as fast as possible (see Methods). Nevertheless, similarly to vFGN task the pointing error (angle error) parameter was evaluated as well. Schizophrenia (FES) patients showed impaired performance in both pointing time and pointing accuracy.

As expected, both groups made larger pointing errors in the room frame condition, where the direction towards “moving goal” has to be estimated, however, schizophrenia group showed significant impairement in pointing accuracy in all test phases regardless the reference frame, when compared to control group. In contrary, the pointing time in FES group was slower when pointing in the final test phase 4 with frame switching present. This suggests that in contrast to pointing error parameter that was affected mainly by movement of the goals (Room phase 2), the switching condition demands increased time needed to make the decision about the current goal position, that can be affected by both switching between reference frames and/or alternation between 4 choices of possible goal position. The pointing ability is not directly comparable with theresults obtained in animal studies. Some parallels could be however found in the human studies in schizophrenia, showing imprecise predictions when pointing in rotatin virtual environment (Synofzik et al., 2010) and impaired performance in the set-shifting (Wilsmeire et al., 2010) or response-switching (Franke et al., 2009) paradigms in schizophrenia.

The third trial time parameter was analysed in order to test the ability to navigate towards the hidden goal position in unstable environment of the rotating arena. First episode schizophrenia patients showed impaired navigation abilities in all test phases when compared to healthy volunteers, with more pronounced deficit in the Room frame phase 3 and the Frame switching phase 4. This is in agreement with the evidence from animal experiments showing in the real version of Carousel maze that place avoidance is more affected in moving than in stable environments both in intact animals (Cimadevilla, Fenton and Bures, 2001), after lesion to PPC

or hippocampus (Svoboda et al., 2015; Cimadevilla et al., 2001), and in animal model of schizophrenia (Kubik et al, 2014).

With respect to the Place-Change (PCH) cathegory schizophrenia patients were impaired in all types of trials (except the 'same frame' trials). Their impairment therefore seems to be independent of the changing reference frame and associated with a simple task-switching paradigm. These results support the hypotheses of general impairment in mental flexibility and cognitive coordination reported by both animal (Stoet and Snyder, 2006; Svovoda et al., 2015) and human studies applying task-switching paradigms (Jamadar et al., 2010; Wylie et al., 2010).

In conclusion, the above presented results suggest that the AAPP task presents sensitive measure of cognitive coordination impairment in schizophrenia and could serve as a useful tool in future comparative resarch.

Limitations of the study

There are some limitations to the current study. Firstly, in order to enable fast assessment of our participants in only one day, the original 5-day protocol was applied in one day session procedure and can be thus sensitive towards short-term changes in behavior of patients due to fatique, emotional state, etc. Secondly, the animal protocol of the active avoidance task was modified to a preference version for humans both in order to: 1) design task comparable to the hidden goal paradigm in stable arena environment (vFGN task presented above), 2) ensure sufficient motivation to complete the task. Original avoidance protocol would require the tested individuals to move on the virtual arena and avoid the to-be-avoided sector. The entrance to the sector could be announced by beeping, however, such feed-back is not very aversive (in comparison to the mild shock in animals) and would present too mild punishment for the entrance. Similar avoidance protocols were alredy tested in healthy human subjects (Vlcek et al., 2006; Cimadevilla et al, 2011). However, we believe that the lack of strong motivation by punishment present in animal studies could change the motivation of schizophrenia subjects to perform in the task, as in fact their motivation is already altered (Salamone et al, 2016).

3.2.3 EXPERIMENT IV – VERBAL AND VISUOSPATIAL COGNITIVE FUNCTIONING IN QUALITY OF LIFE AND GLOBAL FUNCTIONING

3.2.3.1 Aims

Deficit in visuospatial functions can influence both simple and complex daily life activities. Despite the fact that visuospatial deficit was reported in schizophrenia, research on visuospatial functions as an independent entity is limited. Our study aims to elucidate the impact of visuospatial deficit in comparison with verbal deficit on global functioning and quality of life in the first psychotic episode of schizophrenia spectrum disorder (FES).

To our knowledge, no study to date has described the extent to which visuospatial functions affect everyday life of schizophrenia patients, in contrast to the effect of verbal abilities. Our study therefore aimed to answer the following questions:

1) Are visuospatial abilities impaired in first-episode schizophrenia spectrum (FES) patients in comparison with the matched group of healthy controls? If that is the case, is the degree of the deficit the same as in verbal functions?

2) Are the VIS functions in FES patients affected by antipsychotic medication and the actual psychiatric symptomatology (measured with PANSS)? Is similar effect visible in the VERB functions?

3) Is the global functioning and quality of life in FES patients affected by VIS functioning when analyzed in the presence of VERB functions and clinical characteristics (symptoms and medication dose)? If so, is the effect of visuospatial and verbal functioning the same?

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3.2.3.2 Methods

Subjects

Thirty-six subjects (22 males and 14 females, FES group) who met ICD-10 criteria for first psychotic episode of schizophrenia spectrum disorder (F20.X (n=4) and F23.1/F23.2 (n=32)) were recruited at the National Institute of Mental Health (NIMH). Patients were evaluated once they were stabilized at the end of their first psychiatric hospitalization in partial symptomatic remission state, according to Andreasen´s remission criteria (2005). The group was considered in partial remission state rather than in complete remission, as they did not fulfill the criterion of asymptomatic six-month period. Study subjects were diagnosed in a routine clinical process by two experienced psychiatrists. In case of diagnostic disagreements (e.g. comorbidity) the specific case was excluded from the study.

In order to compare the cognitive performance in FES subjects with the healthy population, a group of healthy control subjects (N=36, group HC) was recruited from the same socio-demographic background via a local advertisement. The inclusion criteria for both groups were: a) 17 – 35 years of age; b) no history of neurological disease or loss of consciousness

longer than 10 minutes; c) native in Czech/Slovak language; and d) additionally for the FES group to meet ICD-10 diagnostic criteria (dg F20.X or F23.1, F23.2) and to be first admitted to psychiatric care. The main exclusion criterion for the control subjects was personal history of any psychiatric disorder; for the FES group it was the fulfilled diagnostic criterions for another psychiatric disorder. Both groups were carefully matched in terms of sex, age (max 2 years difference tolerance) and level of education (for details and statistical comparison of the matching parameters, see Table 5). In each group there were 16 participants with a higher education level (university studies) and 20 with lower level of education.

Prior to the study, all participants signed a written informed consent in accordance with the Declaration of Helsinki, approved by the Ethics Committee of NIMH.

Clinical and neuropsychological assessment

Two psychiatric scales were used to evaluate clinical characteristics in the FES subjects. Current symptomatology was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay, 1987). The Global Assessment of Functioning (GAF; Jones et al., 1995) was used in order to objectively evaluate general psychosocial functioning of the FES group. The GAF scale is used to address general functioning (score 0 to 100) in daily activities of individual FES subjects. All FES subjects were medicated by different dose and type of atypical antipsychotics or their combination (olanzapin, amisulpirid and risperidon), that is why chlorpromazine equivalents (CPZ; Woods, 2003;Andreasen, 2010) were used to evaluate the effect of medication dosage on cognitive functioning. For details on the clinical parameters see Table 5.

The quality of life was subjectively evaluated by FES subjects using the Quality of life questionnaire WHOQOL-BREF (WHO group, 1996), a short-form quality of life assessment that calculates four domain profiles (Physical health, Psychological health, Social relationships and Environment), and was validated for FES population (Mas-Exposito, 2011). The questionnaire was translated and validated for a Czech population (Dragomirecká, 2006).

Regarding the neuropsychological assessment, the used measures were chosen in accordance with the evidence of related articles (mentioned in introduction) and suggested also by the MATRICS initiative (Nuechterlein, 2008;Green, 2004). Some additional measures not commonly used and standardized in schizophrenia population were used in order to assess VIS functions in greater detail. The final neuropsychological battery consisted of 11 tests focused on both the visuospatial and verbal functions (see Table 2). All tests were assessed by trained clinicians, according to the cited administration protocols. Detailed information about all test methods is provided in Table 2. In order to compare cognitive performance in the FES subjects with the healthy population, the same test battery was administered to a group of healthy control (HC) subjects. Below is a description of three of the visuospatial methods that have some specific characteristics.

The PEBL (PEBL, 2012) version of the Perceptual Vigilance Task (PVT) was used in its 10-minute-long alternative (Loh, 2004) in order to test attention and vigilance. A simple circle stimulus appears in the PVT at intervals ranging between 2 and 12 sec, and the participant is required to press the spacebar as quickly as possible.

A computerized version of the Spatial Span test was used in order to test spatial attention and working memory without uncontrolled examiner effects (such as prolonged presentation of the longer spatial sequences). We adjusted the original protocol of the Corsi block-tapping test

(Kessels, 2000) applied in the PEBL battery (PEBL, 2012) to match individual positions and spatial sequences of the Spatial Span in the WMS-III (Cernochová, 2010;Wechsler, 1997).

The Money Road-Map-Test (Money, 1965) is not traditionally used in standard test batteries such as MATRICS; this test was selected in order to test specific visuospatial functions, such as mental rotation and perspective taking strategy. For this reason, the total number of errors (out of a total of 32 turns) was divided into three categories (according to Markova, 2015) by the angle of the route before each turn relative to the subject's heading: A) rotation of less than 70 degrees (9 turns), B) rotation of 90 degrees (13 turns), and C) rotation of more than 110 degrees (10 turns). Another specifically selected test, the Key Search Test, was chosen as a sensitive method testing dysexecutive syndrome in schizophrenia (Evans et al., 1997), using spatial planning abilities.

Data analysis

Statistical analysis was performed using the SPSS software (version 15.0). The significance level of all statistical analysis was set to 0.05. The group differences in demographic variables (age, education) were analyzed using non-parametric Mann-Whitney U test. Identical method was used to compare the raw scores obtained in the visuospatial tests. Non-parametric Spearman Rank Order Correlations were used in order to detect correlations between variables.

The raw scores of neurocognitive tests were used to compare performance between the FES subjects and the HC. Raw scores were transformed to z-scores in order to calculate cumulative scores of Verbal (VERB) and Visuospatial (VIS) scores. Z-scores were calculated as the difference among raw scores of the individual FES subjects and the HC group mean, divided by the HC standard deviation. The cumulative scores (VERB and VIS) were computed as a sum of the standardized z-scores divided by the number of applied measures from the relevant variables list as follows (for explanation of individual abbreviations see Table 2): VERB score (AVLT_I-V, AVLT-VI, AVLT-30, VFT-semantic, VFT-phonemic, DS-backward, Similarities) and VIS score (RCFT-copy, RCFT-3, RCFT-30, TMT-A, TMT-B, SS-backward, RMT-total errors). PVT test results were not included in calculation of the cumulative scores, as performance on this test is purely attentional. In addition, to assure accuracy of the input variables to the cumulative scores and their consistency, reliability analysis and factor analysis were performed (Cronbach´s Alpha for VERB = 0.73; Cronbach´s Alpha for VIS = 0.75). Multiple linear regression analysis (stepwise method criteria as follows: probability-of-F-to-enter <= 0.05; probability-of-F-to-remove >= 0.10) was used to assess the effect of performance in individual visuospatial and verbal tests (dependent variables) of A) the clinical characteristics (independent variables): PANSS (scores divided into three sub-scores: general symptoms - G, positive symptoms – P, negative symptoms - N), and B) the antipsychotic medication calculated in CPZ. In additional stepwise multiple linear regression analysis an overall effect of PANSS scores, CPZ level, and cumulative VERB and VIS scores was assessed on A) global functioning measured by GAF and B) individual four domains of quality of life (WHO group, 1998) measured by WHOQOL-BREF.

TABLE 5. DEMOGRAPHIC DATA, CLINICAL ASSESSMENT AND QOL QUESTIONNAIRE

Demographic variables	Group mean ± SD		Group differences	
	FES	HC	Mann–Whitney *U*	*p*-value
N	36	36		
Sex (M:F)	22:14	22:14		
Age	26.3 ± 5.6	25.7 ± 5.2	614	0.697
Education level (1–6)	3.7 ± 1.3	4.0 ± 1.2	556	0.261

Clinical assessment	FES subjects (mean ± SD)
PANSS total score	50.8 ± 17
PANSS-positive	12.5 ± 5.2
PANSS-negative	16.0 ± 7.3
PANSS-general	26.4 ± 6
AP medication—CPZ equivalents (mg)	391.2 ± 122
GAF	64.5 ± 18.3

WHOQOL-BREF	FES subjects (mean ± SD)	Normative data (mean ± SD) (Dragomirecká and Bartoňová, 2006b)
Physical health (domain 1)	14.4 ± 2.4	15.5 ± 2.6
Psychological health (domain 2)	14.1 ± 2.5	14.8 ± 2.4
Social (domain 3)	13.2 ± 3.1	15.0 ± 2.9
Environmental (domain 4)	14.3 ± 2.1	13.3 ± 2.1

Legend: First psychotic episodes of schizophrenia spectrum disorder subjects (FES) and healthy controls (HC) individually matched by sex, age (within 2 years) and education level (see demographic variables). Clinical scales PANSS (Positive and Negative Symptoms Scale) and GAF (Global Assessment of Functioning), antipsychotic medication level in CPZ (chlorpromazine) equivalents, and Quality of life questionnaire WHOQOL-BREF assessed in FES subjects. Education level: 1 = less than high school, 2 = started high school, 3 = completed high school, 4 = started university, 5 = completed university, 6 = started postgraduate studies.

*3.2.3.3 **Results***

Differences in cognitive performance between FES and HC group

As a result of matching the participants on an individual basis, no significant group differences in age and education were observed (Table 5). In each group, there were 16 participants with a higher education level (university studies) and 20 with lower level of education.

Group differences in the results of neuropsychological tests were significant in most of the applied VIS and VERB measures, when analyzed from raw scores using the non-parametric Mann-Whitney U test (for more details see Table 6. A,B, Fig.34).

Neurocognitive assessment	FES raw scores ($N = 36$)				HC raw scores ($N = 36$)				Mann–Whitney *U*	*p*-value
	mean	SE	median	SD	mean	SE	median	SD		
(A) VISUOSPATIAL PERFORMANCE										
TMT–*A*	38.3	2.1	35.5	12.5	27.8	1.6	26.5	9.4	306.5	<0.001***
TMT–*B*	93.5	7.6	84.5	45.4	50.6	2.1	49.5	12.8	181	<0.001***
Ratio B/A	2.5	0.1	2.3	0.8	1.9	0.1	1.9	0.5	417	<0.01**
RCFT–copy	32.5	0.5	33.5	3.0	35.6	0.1	36	0.9	201	<0.001***
RCFT–3 min	18.8	1.1	22.0	6.5	25.7	0.9	26	5.2	234	<0.001***
RCFT–30 min	19.3	1.1	19.8	6.4	25.8	0.8	26	4.6	237	<0.001***
Recognition (errors)	4.6	0.4	4.5	2.1	3.6	3.0	0.3	1.9	360	0.073
KST	11.9	0.6	12.5	3.4	13.2	0.2	13	1.5	532.5	0.188
RMT–number of errors/32	3.1	0.6	2	3.6	1.2	0.4	0	2.4	394	0.003**
RMT A	0.3	0.1	0	0.8	0.1	0.1	0	0.5	628	0.661
RMT B	1.6	0.3	1	1.8	0.8	0.3	0	1.7	457.5	0.021*
RMT C	1.2	0.3	1	1.7	0.3	0.1	0	0.8	385	<0.001***
SS total	16.3	0.5	17	3.1	17.6	0.4	18	2.3	460	0.147
SS forward	8.6	0.3	9	1.6	8.9	0.2	9	1.4	535	0.592
SS backward	7.8	0.4	8	2.1	8.7	0.2	9	1.5	429	0.063
PVT–average response speed	337.3	8.7	321	44.5	305.5	8.0	294.5	40.8	189.5	0.007**
PVT–correct	66.3	1.8	70	10.0	70.7	0.8	72	4.9	415	0.068
PVT–comissions	1.3	0.4	0	2.5	0.9	0.2	0	1.3	541	0.791
PVT–lapses	7.9	1.6	4	9.1	2.1	0.6	1	3.6	279.5	<0.001***
(B) VERBAL PERFORMANCE										
AVLT—I-V	47.8	1.8	48.0	10.8	59.9	1.2	61.5	7.5	231.5	<0.001***
AVLT—3 min	9.3	0.4	9.0	2.5	13.1	0.3	14.0	2.1	157.5	<0.001***
AVLT—30 min	8.6	0.5	8.0	3.0	13.1	0.4	14.0	2.2	137.5	<0.001***
AVLT–repetitions	6.0	0.8	4.5	5.0	1.9	0.4	1.0	2.2	302.5	<0.001***
AVLT–confabulations	2.0	0.4	1.0	2.5	1.1	0.3	1.0	1.6	543.5	0.214
VFT phonemic	41.8	2.2	41	12.9	48.9	1.7	48.5	10.4	395.5	0.004**
VFT semantic	19.7	1.0	18.5	5.6	28.9	0.9	28.0	5.5	120	<0.001***
DS total	14.8	0.7	14.5	4.5	17.0	0.7	17.0	3.9	450	0.025*
DS forward	9.3	0.4	8.5	2.2	9.7	0.4	9	2.3	573	0.392
DS backward	5.2	0.4	6	2.1	7.4	0.4	7.5	2.3	397	0.004**
Similarities	22.9	0.8	23	4.9	28.8	0.4	29	2.2	165	<0.001***

TABLE 6. GROUP DIFFERENCES IN (A) VISUOSPATIAL AND (B) VERBAL NEUROCOGNITIVE TESTS.

Legend: SE – standard error; SD – standard deviation. Abbrevations: TMT – Trail Making Test; RCFT – Rey-Osterrieth Complex Figure; KST – Key Search Test; RMT – Money Road-Map Test (A, B, C – type of errors); WMS-III - Wechsler Memory Scale III edition; PVT – Perceptual Vigilance Test (-com – commissions); AVLT – Auditory Verbal Learning Test; VFT – Verbal Fluency Test

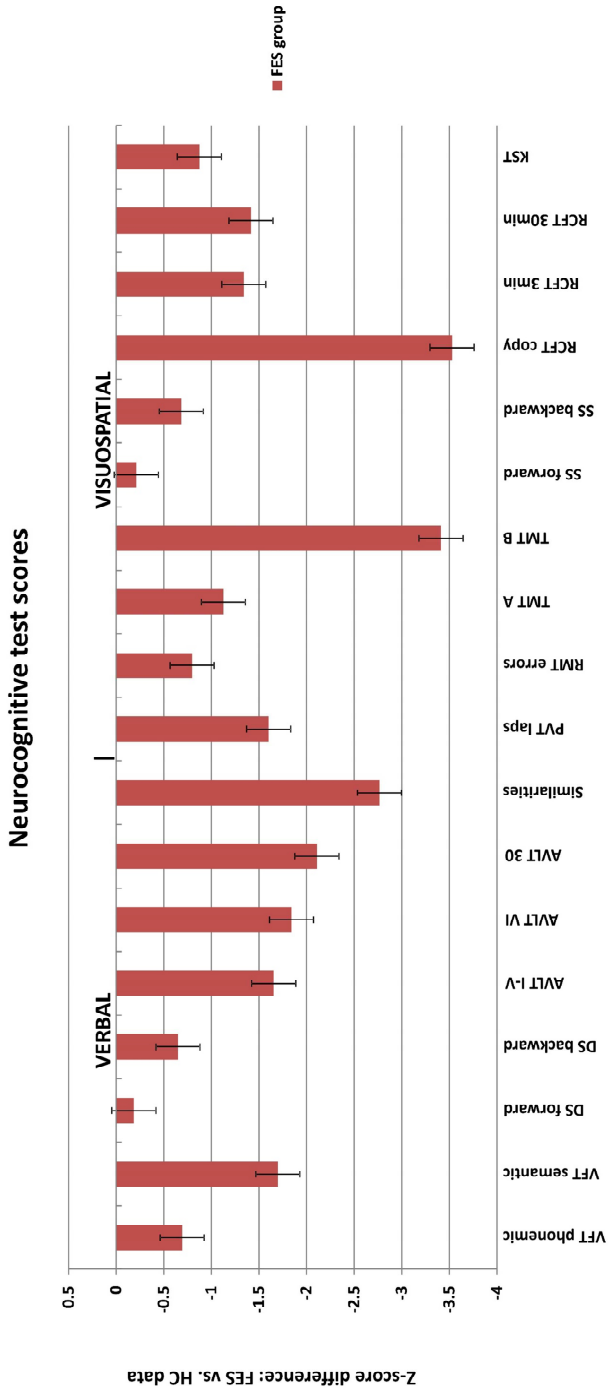

Figure 34. *Neuropsychological profile of FES subjects calculated in z-scores for individual test parameters relative to the healthy controls (level 0). Selected test results are divided into verbal (left) and visuospatial (right) tests. Legend: FES – first psychotic episodes of schizophrenia spectrum disorder; HC - healthy controls; VFT – Verbal Fluency Test; AVLT – Auditory Verbal Learning Test; DS – Digit span; PVT – Perceptual Vigilance Test; TMT – Trail Making Test; RMT – Money Road-Map Test; RCFT – Rey-Osterrieth Complex Figure; SS – Spatial span; KST – Key Search Test.*

The group of FES subjects showed significantly lower VIS performance on all three parts of the Rey-Osterrieth Complex Figure Test (RCFT-copy, RCFT-3, RCFT-30). The FES group was also slower in the Trail Making Test part A and part B. The average speed of FES subject responses in the PVT was lower and they also had a higher number of lapses (with reaction times above 500 milliseconds). The FES subjects also made more errors on the Road Map Test. In addition, splitting of individual turns in the RMT (according to Markova et al., 2015) to three possible error types showed that schizophrenia subjects tend to fail more in the turns demanding mental rotation of the spatial scene (turns B and C) compared to the turns that demand no or very small mental rotation (see Figure 35). We found no significant differences in the raw scores of the KST from the BADS battery. In contrast to the Digit Span (DS) test, the Spatial Span (SS) test did not show any significant group differences. However, the difference observed in the backward score was approaching the significance level ($p = 0.063$).

VERB performance was significantly impaired in most of the VERB measures as follows: verbal learning and delayed recall in the Verbal Learning Test (AVLT); the phonemic and semantic Verbal Fluency (VFT), abstract executive functions in the Similarities (Sim) and working memory in the Digit Span (DS) task. No difference was observed in the immediate recall and attention performance in DS forward.

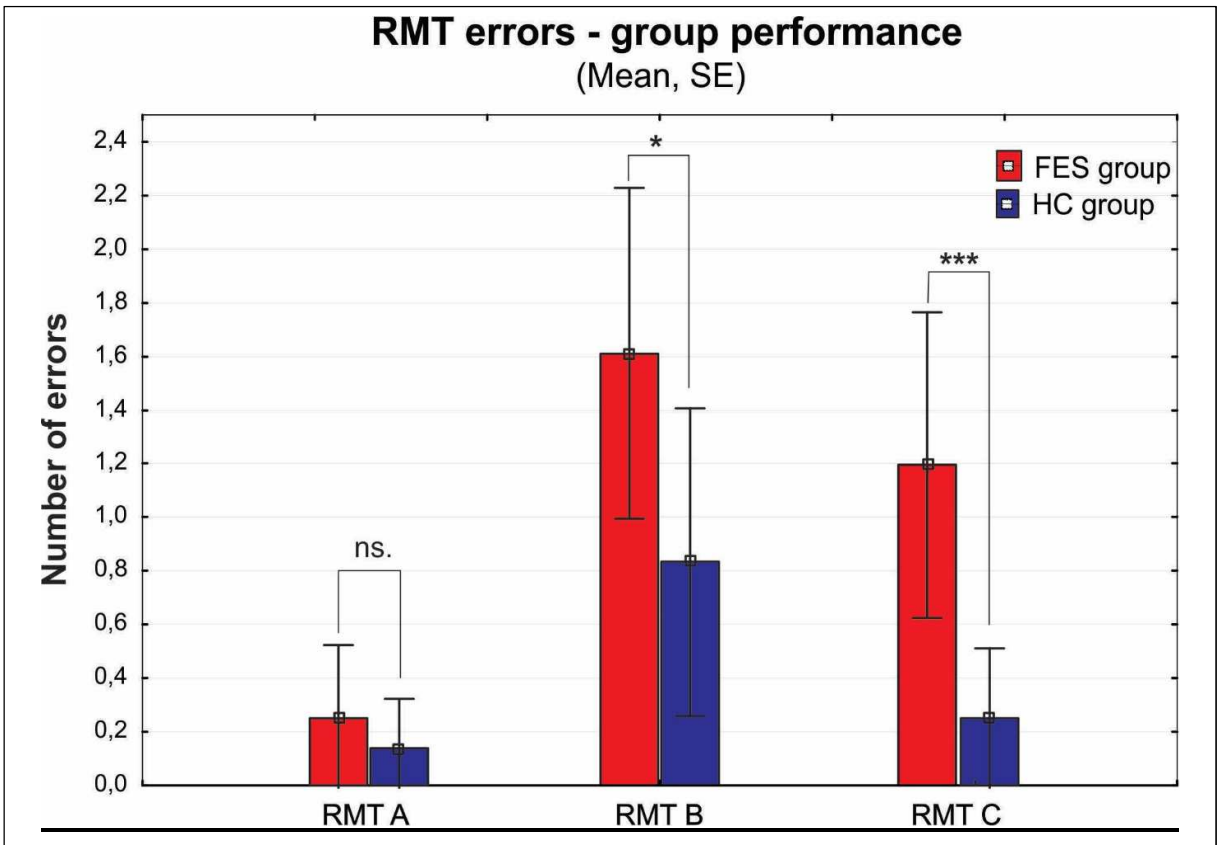

Figure 35. *Group performance presented as number of errors on the Money Road Map Test (RMT) presented in mean and standard error (SE). Errors are divided into three different types according to the rotation towards subjective perspective of the tested subject (A - less than 70 degree deviation from subject's heading; B – 90 degrees, C – more than 110 degrees). FES group – first psychotic episodes of schizophrenia spectrum disorders; HC group – healthy controls. Significance: ns – nonsignificant, * $p < 0.05$, *** $p < 0.001$.*

Regression model of PANSS effect on performance in visuospatial and verbal tests in FES

First set of stepwise multiple regression analysis models of psychiatric symptomatology measured using PANSS (predictors: PANSS-P, PANSS-N, PANSS-G) showed no effect of symptomatology on the performance in individual visuospatial and verbal tests (dependent variables), except for the performance in one single test – the Trail Making Test part B. Two of three predictors from the regression model performed by stepwise method were significant: PANSS-N and PANSS-G. They explained more than 40% of performance variability in the TMT-B test (see Table 7). No effect of individual PANSS scores was identified on cumulative VERB and VIS scores.

TABLE 7. REGRESSION MODEL OF PANSS EFFECT (PREDICTOR) ON PERFORMANCE IN TMT B (DEPENDENT VARIABLE).

Dependent variable *TMT–B*	Adjusted R^2	SE of the estimate	Durbin-Watson	*B*	*SE*	*Beta*	*F*	*p*
Predictor variable (Model):	**0.409**	**35.1850**	**1.850**				**12.4**	**<0.001**
(Constant)				112,244	29,361			0.001
PANSS-N				3.766***	0.850	0.599		<0.001
PANSS-G				−2.968**	1.034	−0.388		0.007
Excluded:								
PANSS-P						0.006		0.968

*Legend: Stepwise multimodal linear regression in FES subjects (N = 34); PANSS – Positive and Negative Symptoms Scale (N – negative, G – general, P - positive), TMT-B – Trail Making Test –part 2. Adjusted R^2 – explained variability; B - Unstandardized Coefficients beta; SE – Standard error; Beta – Standardized beta coefficient; Significance: ** p < 0.01, *** p < 0.001.*

Regression model of CPZ level effect on performance in visuospatial and verbal tests in FES

We did not observe any significant influence of medication (CPZ) on the performance in any of the visuospatial tests using the linear regression analysis. We identified negative effect of medication dosage (B = -0.040, SE = 0.017, Beta = -0.373) only in one verbal test – the phonemic Verbal Fluency Test (N = 35). CPZ explained 11% of performance variability (SE = 12.253, Durbin-Watson = 2.247; F = 5.338, p < 0.05). This observation would not survive Bonferroni adjustments (p = 0.027). No effect of CPZ level was identified on cumulative VERB and VIS scores.

Regression model of clinical and neuropsychological factors on global functioning in FES

In order to analyze the possible effect of verbal and nonverbal cognitive performance on global functioning (measured on the GAF scale), we performed a multiple regression analysis with the following predictors: PANSS-P, PANSS-N, PANSS-G, CPZ level, and cumulative VIS and VERB scores (see Table 8). Only two of the independent variables, the severity of positive symptoms (PANSS-P score) and verbal functioning (cumulative VERB

score), showed a significant effect on global functioning. Together, these variables explained more than 60% of GAF variability.

TABLE 8. REGRESSION MODEL OF CLINICAL AND NEUROPSYCHOLOGICAL VARIABLES (PREDICTORS) ON GLOBAL FUNCTIONING MEASURED BY GAF (DEPENDENT VARIABLE).

Dependent variable: *GAF*	Adjusted R^2	SE of the estimate	Durbin-Watson	*B*	*SE*	*Beta*	*F*	*p*
Predictor variable (Model):	**0.587**	**11.407**	**1.954**				**18.775**	**<0.001**
(Constant)				104.853	6.971			<0.001
PANSS–P				−2.153***	0.389	−0.712		<0.001
VERB				0.898*	0.388	0.298		0.030
Excluded:								
PANSS–N						−0.168		0.248
PANSS–G						−0.105		0.461
CPZ						0.044		0.754
VIS						0.093		0.603

*Legend: Stepwise multimodal linear regression in FES subjects (N = 26); GAF – Global Assessment of Functioning, PANSS - Positive and Negative Syndrome Scale (P – positive, N – negative, G – general), CPZ – chlorpromazine equivalents,), VERB – cumulative score for verbal tests, VIS– cumulative score for visuospatial tests; Adjusted R^2 – explained variability; B - Unstandardized Coefficients beta; SE – Standard error; Beta – Standardized beta coefficient; Significance: * p < 0.05, *** p < 0.001*

Regression model of clinical and neuropsychological factors on quality of life (QOL) in FES

The same model of clinical and neuropsychological parameters was applied in the stepwise multiple regression analysis that identified significant effect of severity of negative symptoms (PANSS-N score), verbal functioning (cumulative VERB score) and positive symptoms (PANSS-P score) on perceived quality of Physical health (domain 1) in FES. These predictors together explained more than 50% of the observed variability (for details see Table 6). The QOL domain Psychological health (domain 2) was found to be affected by the overall VERB functioning (see Table 9).

No significant effect of clinical and neuropsychological parameters was observed in the evaluated quality of Social relationships (domain 3). In contrast, the Environment quality (domain 4) appeared to be affected mostly by one significant parameter, the cumulative VIS score performance. This factor explained together with CPZ level around 27% of the observed variability in domain 4 (see Table 9). However, worse Environment QOL was predicted by better VIS functioning and higher AP dosage.

TABLE 9. REGRESSION MODEL OF CLINICAL AND NEUROPSYCHOLOGICAL VARIABLES (PREDICTORS) ON PERCEIVED QUALITY OF PHYSICAL HEALTH/PSYCHOLOGICAL HEALTH/ENVIRONMENT (AS A DEPENDENT VARIABLE).

Dependent variable: *Physical health*	Adjusted R^2	SE of the estimate	Durbin-Watson	*B*	*SE*	*Beta*	*F*	*p*
Predictor variable (Model):	**0.485**	**1.8198**	**1.753**				**8.234**	**0.001**
(Constant)				17.064	1.202			<0.001
PANSS–N				−0.162**	0.050	−0.520		0.004
VERB				0.173*	0.067	0.405		0.017
PANSS–P				0.150*	0.066	0.353		0.033
Excluded:								
PANSS–G						−0.079		0.628
CPZ						−0.172		0.354
VIS						−0.206		0.385

Dependent variable: *Psychological health*	Adjusted R^2	SE of the estimate	Durbin-Watson	*B*	*SE*	*Beta*	*F*	*p*
Predictor variable (Model):	**0.144**	**2.235**	**1.803**				**4.859**	**0.038**
(Constant)				16.214	1.013			<0.001
VERB				0.173*	0.079	0.425		0.038
Excluded:								
PANSS–P						0.031		0.879
PANSS–N						−0.235		0.250
PANSS–G						0.016		0.934
CPZ						−0.087		0.691
VIS						−0.107		0.728

Dependent variable: *Environment*	Adjusted R^2	SE of the estimate	Durbin-Watson	*B*	*SE*	*Beta*	*F*	*p*
Predictor variable (Model):	**0.278**	**1.9072**	**1.986**				**5.425**	**0.013**
(Constant)				15.946	1.404			<0.001
VIS				−0.107**	0.037	−0.533		0.008
CPZ				−0.008*	0.004	−0.392		0.043
Excluded:								
PANSS—P						−0.068		0.711
PANSS—N						−0.141		0.495
PANSS—G						0.224		0.251
VERB						−0.109		0.720

Stepwise multimodal linear regression (N = 24); **Physical health –** domain 1 in WHOQOL-BREF, **PANSS** - Positive and Negative Syndrome Scale (**P** – positive, **N** – negative, **G** – general), **CPZ** – chlorpromazine equivalents,), **VERB** – cumulative score for verbal tests, **VIS** – cumulative score for visuospatial tests; **Adjusted R^2** – explained variability; **B** - Unstandardized Coefficients beta; **SE** – Standard error; **Beta** – Standardized beta coefficient; Significance: ***** $p < 0.05$, ****** $p < 0.01$.

3.2.3.4 DISCUSSION

Differences in cognitive performance between FES and control group

Our study confirmed the presence of a deficit in visuospatial cognitive abilities in a sample of first psychotic episode of schizophrenia spectrum disorder subjects, when compared with matched group of healthy controls. Similar pattern of deficit was also observed in verbal functions. This result is in accordance with previous studies, both in first episodes (Bora and Pantelis, 2015) and chronic SZ subjects (e.g. Green et all, 2004a,b; Fioravanti et al., 2005).

First, we selected the Perceptual Vigilance Task (PVT) as an indicator of vigilance and response speed, as deficits in these abilities could affect performance in other applied measures. Our sample of FES subjects demonstrated deficit in vigilance and response speed on the PVT task. However, this deficit ranged between none and moderate (SD 0-1.5), with more severe deficits observed in other cognitive measures. Nevertheless, we suggest future visuospatial studies apply such attentional measure as a covariate factor in order to clarify how vigilance and response speed may affect tested visuospatial abilities.

Deficit on visuospatial functions was manifested in perceptual organization abilities (copy in the Rey-Osterrieth Complex Figure Test- RCFT) and in delayed recall of visuospatial information (RCFT after 3 and 30 min), while the recognition (RCFT recognition) of visuospatial material was comparable with the performance of HC. This finding was characterized by a reduced number of recalled details but not by an increased rate of forgetting. This is consistent with a disturbance in encoding or retrieval from memory but no deficit in information storage (Rodriguez, 2012). The problems in recall might be further compounded by a primary deficit in visual scanning abilities or limited analysis of the visual fields, leading to omission of significant details and even whole sections of the figure (Golden, 2002).

Trail Making Test (TMT-A and B) also showed significantly slowed processing speed, impaired visuomotor tracking and switching ability. Although the performance on the TMT might be perceived as partly language dependent, since the sequence of numbers or numbers and letters has a verbal component, participants' visuospatial tracking ability is the main cognitive domain assessed by this task. The higher ratio of TMT B/A also pointed out a deficit in executive control function (Lezak, 2012). The repeated finding of significantly impaired TMT A and B performance in SZ (Heinrichs, 1998), complemented by the TMT ratio B/A deficit, suggests an independent deficit in both processing speed and switching ability. Similar to the RCFT, the problems on both these functions might be further compounded by a primary deficit in visual scanning abilities. Future research in this area is needed.

Interesting results were found in the Money Road Map Test (RMT), which has to our knowledge not been previously used in FE schizophrenia. The higher number of total errors shows deficit in left/right direction sense, and additionally in perspective taking abilities (Schultz, 1991;Markova, 2015). These abilities are suggested as the main solution strategy in RMT. The lower RMT performance in FES group is therefore even more apparent if the individual intersections are divided into three types according to their perspective taking demands, which is essential in order to respond in the left/right condition. While the number of errors in condition A (no change in perspective) is not significantly disrupted in FES, both conditions B and C (90 and more degrees deviations requiring perspective taking) showed significant impairment. On top of that, the number of errors increased with the growing degree of deviation (from condition A to C), similarly to the mental rotation abilities described previously (de Vignemont, 2006). This finding deserves further investigation and standardization of the method that could lead to a wider usage of this test in SZ clinical research. Moreover, due to its spatial characteristic the test could also be very useful in comparative studies of SZ.

The visuospatial executive planning ability, measured with the Key Search Test (KST), failed to show a deficit in FES subjects. Impairment in KST was previously demonstrated in studies of chronic SZ (Evans, 1997;Ihara, 2003;Vargas, 2009). The fact that we evaluated first psychotic episode of schizophrenia spectrum patients in early remission could explain this

contradictory finding. Ihara et al (2003) showed connection between the KST performance and the severity of negative symptoms in chronic SZ subjects. The mild severity of negative symptoms in our FES group could be responsible for the lack of significance found in KST. The lack of information about the symptomatology in the other two cited studies does not allow us to properly compare our findings. In addition, the fact that the differences were analyzed using the raw scores (0-16) could cause smaller sensitivity of the KST measure, as the recalculated profile scores (range 0-4) separate the performance more strictly into 5 categories. To test this presumption, we did an ex post facto analysis with raw scores transposed to profile scores, which indeed led to significant disadvantage of the FES group ($U = 445$; $p = 0.023$).

Verbal abilities showed a deficit in conceptualization and executive functions (semantic Verbal Fluency Test and Similarities), and in verbal learning and delayed recall (AVLT). It would be interesting to also analyze the verbal recognition pattern and compare it to the results of visuospatial recognition. Studies addressing this topic in SZ showed that the verbal recognition is preserved (Fiszdon, 2008). However, because of some missing data in verbal recognition of HC group we were unable to complete this comparison. We are aware that this is a limitation of the present study. The significant increase in the number of repetitions suggests that SZ subjects have difficulties in self-monitoring and tracking abilities that are key in the retrieval process (Lezak, 2012).

The verbal and visuospatial measures (Digit Span and Spatial Span) of immediate recall and working memory (WM) showed similar patterns in FES (see Figure 1). No deficit was observed on either the verbal or visuospatial tasks assessing immediate recall and attention (Digit Span and Spatial Span forward). Even though the deficit in verbal WM (DS backward) was stronger than in the spatial WM, there was a trend of significance in Spatial Span backward ($p = 0.06$). Moreover, the pattern of deviation in both tests was similar (see Figure 1). One of the reasons for the lack of significance in Spatial Span backward could be the smaller size of the study sample producing reduced power size. Other reason might be the use of a computerized version of the task. Because the computerized version has not been validated, its sensitivity can be questioned. However, computerized version of Spatial Span and its alternative, the Corsi block tapping test, are commonly used in clinical studies (Kessels, 2000;Lezak, 2012), and they bring the advantage of administration reliability independent of examiner bias. Despite the lack of significance in the SS backward, the finding of impaired TMT-B (switching) supports the assumption of visuospatial WM deficit in SZ.

Effect of symptomatology on cognitive functioning in FES

In agreement with more recent reviews and empirical reports (Ventura, 2009;Andreasen, 2005;Keefe, 2007), we confirm the absence of relations between the symptoms severity and standard cognitive measures, except for performance on the Trail Making Test (TMT-B). TMT-B performance was negatively affected by negative symptoms and positively affected by general symptomatology. No effect of positive symptoms was identified. Current literature describes a strong to moderate association of cognitive functioning and negative symptoms (O'Leary, 2000), whereas positive symptoms and cognitive performance are usually independent in SZ (Addington, 1991;Rossi, 1997;Andreasen, 2005). The finding that better TMT-B performance was predicted by worse general symptomatology could be explained by the fact that the PANSS scale had higher inter-rater variability, particularly in the negative and general symptomatology, which could generate distortion in our findings. Indeed, our FES group showed higher scores especially in some general symptoms

(not reported in detail), such as the item G4 (tension), which was previously identified as more difficult for some raters (Khan et al, 2013). Despite the single observation in TMT-B, in general, the cognitive performance showed to be independent of clinical symptoms.

Effect of pharmacological treatment on cognitive functioning in FES

In agreement with other studies (Keefe, 2007;Jones, 2006;Lewis, 2008), we found no effect of atypical antipsychotic medication (antipsychotic dosage calculated in CPZ equivalents) on visuospatial or verbal performance, except the phonemic verbal fluency performance. There was a negative effect of CPZ on phonemic Verbal Fluency Test; however, this result became non-significant after Bonferroni correction. Our study implies that the impairment in visuospatial functions is independent of the dosage of neuroleptic medication.

Clinical factors and neurocognition, and their effect on global functioning in schizophrenia spectrum disorder

In our FES group we did not find any associations between GAF and VIS functions. The fact that the only visuospatial measure that correlated with the GAF score was the Trail Making Test B[1] could be responsible for this negative finding. Moreover, the strong association between the negative and general symptoms towards TMT-B performance described earlier (see section 4.2) suggests that VIS performance, moderated by the symptomatology, might not survive the regression analysis as an independent predictor. Another possible explanation for this finding is the fact that GAF scale was constructed as a measure of psychosocial disability in relation to symptomatology, rather than neurocognition (Jones, 1995;Roy-Byrne, 1996). Thus, more specific neurocognitive functions, such as VIS, might not be captured. On the other hand, GAF was positively affected by VERB functions (cumulative VERB score). However, VERB functioning was only an accompanying factor of the main negative effect produced by positive symptoms. The effect of negative symptoms reported in previous studies (Gaite, 2005) was not identified as significant in our FES sample. We assume that positive symptoms might have a more pronounced negative effect on the functioning of individuals' in our FE sample than negative and general symptoms, due to the early remission state.

In order to compare our results with previous studies, we used the GAF as scale of functioning recommended as a mandatory control assessment by EGOFORS initiative (Peuskens, 2012). However, in our opinion, a more ecologically valid scale to measure functioning in relationship to individual neurocognitive domains is needed.

Clinical factors and neurocognition, and their effect on quality of life in schizophrenia spectrum disorder

According to our results, quality of life seems to be related more to verbal than visuospatial cognitive measures. Two of four domains of WHOQOL-BREF (Physical and Psychological health) were positively associated with overall VERB performance, whereas only one domain (Environment) was related to overall VIS functioning and this association was negative. Better cumulative VIS score was associated with worse environment quality (health services, leisure time activities, etc.). Some previous studies have reported similar

[1] Ex post facto analysis revealed that the GAF scale is significantly correlated only with two neurocognitive measures. Negative correlation was found in visual Trail Making Test B ($r = -0,43$, $p < 0.001$) and positive correlation in the semantic Verbal Fluency Test ($r = 0,36$, $p < 0.01$)

counterintuitive negative correlations (Fiszdon, 2008;Narvaez, 2008;Prouteau, 2005). This negative relation between QOL and neurocognition is often explained with a lack of insight (Prouteau, 2005;Narvaez, 2008) or with an overestimation of the level of disability due to present depressive symptoms (Bowie, 2007). We do not attempt to interpret this negative relation in terms of insight, as some other possible moderators might attenuate the relationship between neurocognition and QOL. However, we are aware of this discrepancy and we suggest that future research is needed in order to clarify the character of such puzzling results.

The WHOQOL-BREF domain of Social relationships was not associated with any of the clinical or neurocognitive measures. We believe that this domain might not fully reflect quality of social relationships. This domain includes only three questions that report on the quality of social relations, sexual life, and social support. These items do not cover all aspects of interpersonal relationships. Moreover, the item friend's support was reported to be less relevant for the younger population assessed also in our study (Dragomirecká, 2006). WHOQOL-BREF might therefore not be a suitable tool for measurement of social QOL in such a specific population.

Our choice of QOL measure, the WHOQOL-BREF, likely also played a role in the obtained results. In general, research findings on the relationship of neurocognition and QOL are very heterogeneous and often report weak associations between these two constructs (Heslegrave, 1997;Aksaray, 2002;Fiszdon, 2008). One issue that has to be considered is how other QOL questionnaires address cognition in individual items. For example, only one question of the WHOQOL-BREF specifically concentrates on the cognitive functioning. When we ex post facto analyzed the correlation between this item (Q7, quality of concentration in Psychological health domain) and individual cognitive measures, we found a strong relationship towards several cognitive tests, both VIS and VERB (mostly related to processing speed, memory and executive functions).[2] This is in agreement with previous studies that highlighted the role of executive functions (Matsui, 2008;Fiszdon) and memory domains as the most representative measures related to QOL. If QOL questionnaires were more focused on cognitive functioning, we believe that the contradictory findings could be reduced.

In terms of clinical symptomatology, out of the four WHOQOL-BREF domains only Physical health appeared to be significantly affected by psychiatric symptoms. As expected, cognitive performance was not the only factor affecting subjective quality of physical health; the severity of the negative and positive symptoms obviously had some impact as well. Meta-analysis by Eack and Newhill (2007) described the strongest, but still small, association of Physical health QOL to general symptoms. However, our study found no such association. An explanation for the differences between our results and the previous findings can be the fact that we assessed first psychotic episode in schizophrenia spectrum patients and that the length of illness might moderate the relationship between symptoms and QOL (Eack and Newhill, 2007).

[2] Ex post facto analyzed relationship of Psychological health item Q7 (concentration) with individual test methods, showed positive correlation with the AVLT test in terms of learning ($r = 0.572$) and delayed memory ($r = 0.508$), Verbal Fluency (phonemic: $r = 0.519$; semantic: $r = 0.457$) and Spatial Span performance (total score: $r = 0.479$; backwards: $r = 0.445$), and similarly negative correlation with TMT processing time (part A: $r = -0.432$; B: $r = -0.602$).

Limitations of the study and future directions

There are several limitations of the present study that warrant discussion. First, the results of the study could be tempered by the small size of the sample and consequent reduction in power size. Despite the smaller number of participants, we were able to demonstrate the deficit in both visuospatial and verbal cognitive functioning in schizophrenia, and the relationship of these abilities towards global functioning and quality of life. In order to reveal possible effects of other variables on these relationships (such as demography and subtypes of schizophrenia) and to identify individual cognitive domains affecting QOL and GAF, a larger sample size is needed.

Second, the issue of cross-sectional versus longitudinal studies in this area is important. The present study, although cross-sectional, has identified some specific effects that can be examined over a longer time period. The next step in this research is, therefore, to track the longitudinal effect of visuospatial functions on global functioning and QOL in schizophrenia. We are currently conducting a follow-up assessment in our study group one year after their first hospitalization to measure the cognitive functioning in full remission state. Moreover, studies comparing FE with chronic schizophrenia patients are limited. To address this limitation we are assessing a chronic SZ sample in order to analyze the influence of the illness duration on relations between neurocognition, QOL and GAF.

Third, the fact that the verbal and visuospatial neuropsychological tests were not always matched in terms of the measured cognitive domain, and for psychometric parameters, might be another possible limiting factor. In addition, not all test methods are validated in schizophrenia and some of them are not standardized for Czech population either. Measures validated in schizophrenia population might be expected to be more sensitive when capturing a degree of deficit. We are also aware of the fact that we don't cover all the functions of each cognitive domain. For example we did not include verbal recognition in our analysis; therefore the encoding ability could not be assessed as clearly as in the visuospatial domain. More specific and detailed visuospatial assessment is necessary in order to cover all domains that can be related to functional outcome and QOL in schizophrenia spectrum disorders.

Fourth, measures of QOL and global functioning applied in this study could be limited in terms of their association with cognitive functioning in SZ. It would be very helpful to compare them to other methods that might be more related to neurocognition. For example, the Social and Occupational Functional Assessment Scale (SOFAS) could provide a better measurement of functional outcome that is not tied to symptomatology. In addition, only subjective QOL was measured in this study. Objective measures of QOL are needed in order to understand the complex relationships of psychosocial functioning and neurocognition in SZ. According to our results about relation of specific domains of QOL and GAF obtained in the ex post facto measures, we suggest that these associations should be further investigated in future research.

Finally, several neurotransmitter functions are affected by atypical antipsychotics and our study applied only the CPZ equivalent. Future study should also address other factors in order to analyze the effects of medication on cognitive abilities in greater detail.

4 General Discussion

This thesis presents two complex cognitive tasks designed in virtual reality environment, inspired by the original behavioral tasks used in animal research, the Morris water maze and the Carousel maze. Both tasks have been previously used in various animal models of neuropsychiatric disorders, such as schizophrenia, in order to test the face validity of the model, the ability to mimic symptoms similar to the modeled disease (for review see Bubenikova-Valesova et al., 2008; Jones 2011). Animal models provide valuable information for the development of novel therapeutic options that may help patients with specific neuropsychiatric disorders. Comparative behavioral methods, such as that presented in this thesis, are extremely important for preclinical research of cognitive deficit in neuropsychiatric diseases, since the presence of impaired cognitive functioning was demonstrated in a whole range of neuropsychiatric disorders. Neuropsychiatric disorders, ranging from that present from childhood (ADHD, autism) or later in adulthood (schizophrenia, depression) to that occurring in older age (such as Alzheimer disease), indeed provide evidence of disturbances of cognitive functioning (Sanchez, Lumbreras, 1999; Ewijk et al., 2014; Dowson et al, 2004; Steele et al., 2014; Jiang t al., 2014; Pan et al, 2011; Piskulic et al., 2007; Bora and Pantelis, 2015; Gold, 2004). Furthermore, in many disorders the cognitive symptoms are largely untreated by current medication and have significant impact on functional abilities of the threated patients (Milan et al, 2012). Neuropsychiatric disorders thus produce huge medicinal and socioeconomic burden for both patients and society, representing significant challenges to both clinical and preclinical researchers.

The fact that different assessment methods are used in humans and animals to evaluate cognitive impairment (paper-pencil test vs. spatial tasks), led to a huge gap between preclinical and clinical trials, mainly due to the low predictive validity of pharmacological animal models of schizophrenia. This low predictive validity of animal models of some neuropsychiatric disorders, especially schizophrenia (Pratt, Winchester, Dawson, and Morris, 2012), is highlighting the important role of comparative research, applying similar methods both in humans and animals. Comparative methods have to be established in order to overcome this gap and allow for more direct comparison of results emerging from animal and human studies. This dissertation thesis therefore aimed to demonstrate the usefulness of the comparative research enabling to build a bridge between animal models and neuropsychiatric patients.

Both the Morris water maze and the Carousel maze tasks were originally designed in order to test spatial memory and/or executive functioning in animals (Morris et al, 1982; Fenton et al, 2000). In schizophrenia, deficit in these very cognitive domains (memory and executive functioning), are believed to be a core symptoms of the disease (Aleman et al, 1999). This impairment has been shown to negatively affect daily functioning, sociability, and long-term outcome of the patients with the schizophrenia spectrum disorder (Green et al., 2004). Thus it is crucial to demonstrate the validity of behavioral symptoms in pharmacological animal models of schizophrenia that would enable the development of new antipsychotic drugs, effectively treating also cognitive symptoms of this devastating multifactorial disorder.

In *Experiment I* we presented the well-established model of schizophrenia induced by application of MK-801 (dizocilpine). In general, glutamatergic models of schizophrenia

represent valuable methods that already demonstrated that cognitive and behavioral deficit is present in the threated animals (Vales et al, 2006) and can be affected by pharmacological agents (Bubenikova et al, 2005). The MK-801 model was previously tested in several variants of the two above mentioned behavioral tasks (e.g. Kubik et al., 2014; Lobellova et al, 2015; Stuchlik et al, 2004; Vales et al., 2006) and successfully demonstrated the spatial memory impairment after acute, chronic or early development application of the MK-801 substance (for the review see Bubenikova-Valesova et al, 2008). In order to demonstrate the impairment of executive functioning, specifically working memory and mental flexibility, in this glutamatergic model of schizophrenia, we present the reversal variants of both tasks Morris water maze and Carousel maze (Lobellova et al, 2013). While reversal learning protocol of MWM witch platform relocated to another quadrant (usually the opposite one) after one week and 5 additional days of training is well documented (Vorhees and Williams, 2006), the reversal avoidance task on the rotating arena was not used in this model of schizophrenia before.

Reversal variant of the Morris water maze task showed impaired performance in rats already after the low dosage of MK-801, administered in the same sessions as spatial relations were changed. This finding is consistent with previous experiments using the reference memory protocol of the task (e.g. Stuchlik et al., 2004). Importantly, only high dosage impaired the swimming towards a visible platform (control task), allowing us to distinguish navigational and procedural impairment in this task, suggested as a problematic point in previous studies (Saucier et al., 1996). The presented reversal protocol of the active place avoidance task showed disruption of spatial performance after lower dosage of MK-801, than that shown to impair acquisition in the standard protocol (Stuchlik et al., 2004; Stuchlik and Vales, 2005, Vales et al., 2006), suggesting a preferential sensitivity of the reversal configuration to MK-801. Results of this study demonstrate that the behavioral flexibility of rats tested by reversal configuration in the Carousel maze and the Morris water maze is sensitive to systemic treatment with relatively low doses of MK-801, a non-competitive blocker of NMDA receptors. Such results are consistent with previously published findings obtained in different paradigms and models (Chadman et al, 2006; Caramanos and Shapiro et al, 1994; Bischoff and Tiedtke,1992). Based on the reported findings, we propose application of lower doses of MK-801 for future studies on cognitive performance in MK-801 model of schizophrenia. Moreover, based on previous findings showing that the effect of MK-801 on the discrimination reversal learning is mediated by NMDA-receptor blockade in the hippocampus (Watson and Stanton, 2009a), dorsomedial striatum (Watson and Stanton, 2009b) and medial pre-frontal cortex (Watson and Stanton, 2009c), we assume that the observed behavioral deficit seen in our study might have been mediated by a blockade of glutamate receptors in these structures.

Moreover, even that MK-801-induced impairments were seen in both tasks, the present data suggest higher sensitivity of active place avoidance task in the reversal configuration than the MWM task. This finding is in agreement to previous studies (Vales et al, 2006) and underlines the importance of the carousel maze task in searching for novel treatments for cognitive deficits in schizophrenia. Moreover, the *Experiment I* provides the clear evidence for disrupted cognitive flexibility in the active place avoidance task and Morris water maze in an MK-801 induced animal model of schizophrenia-like behavior.

In *Experiment II* and *Experiment III*, we applied the two comparative methods (virtual variants of the above presented animal tasks), in order to provide evidence of disrupted spatial

memory and executive functioning in schizophrenia patients. We decided to assess the patients of schizophrenia spectrum disorder after the first psychotic episode (first episode of schizophrenia – FES) instead of chronic schizophrenia patients for the following reasons: 1) cognitive deficit was repeatedly reported already after the first episode of schizophrenia (e.g. Green et al., 2004; Bora and Pantelis, 2015; Vidailhet 2013; Zaytseva et al., 2013); 2) neurocognitive changes in brain structure and connectivity accompanying the progressing disease due to neurodevelopment/neurodegeneration and possible long-term influence of antipsychotic medication, that could negatively affect cognitive functioning of schizophrenia individuals (Ho et al, 2011), are yet not clearly manifested (in contrary to chronic schizophrenia patients); 3) the above presented acute application of MK-801, preferred in preclinical studies due to the lower temporal demands (in comparison to chronic or early application), induces only short-term changes in the behavioral performance, and thus we believe it represents a model more appropriate for comparison towards first occurrence of the cognitive symptoms after the first acute episode, than the chronic state of the disease. This setting, however, does not allow us to analyze possible cognitive effects of repeating relapses occurring in the chronic state.

In all presented studies (Fajnerova et al, 2014; Fajnerova et al, 2015a,b) we first demonstrate the presence of cognitive deficit in the tested group of first episode schizophrenia (FES) patients using a battery of standard neuropsychological measures, both verbal and visuospatial. Our neurocognitive results are in agreement with previous studies showing that several cognitive domains are affected in schizophrenia spectrum disorder both after the first psychotic episode and in chronic state (for review see Bora and Pantelis; Green et al 2004).

In *Experiment II* we demonstrated that both parts of the novel virtual Four Goal Navigation (vFGN) task (composed of reference and working memory protocol) have a sufficient sensitivity towards the impairment of spatial abilities. The first Reference memory (RM) session was aimed both 1) to train all tested subjects in order to prepare them for the later reversal/DMP session and thus to produce stable performance in the following test session, and 2) to test spatial learning and memory in stable environment in FES individuals (Fajnerova et al, 2014). This phase confirmed impairment of spatial learning and memory performance of the FES group (when compared to healthy controls). The observed results are comparable to similar MWM protocols applied in chronic schizophrenia patients (Folley et al., 2010;Hanlon et al., 2006) and in animal models of schizophrenia (Gorter and de Bruin, 1992a;Latysheva and Rayevsky, 2003;Sircar, 2003;Stuchlik et al., 2004). In agreement with the evidence that the latency is shortened in animals during consecutive RM sessions (D'Hooge and De Deyn, 2001;Mulder and Pritchett, 2003;Vorhees and Williams, 2006) and in RM blocks tested in the human virtual analogues (Leplow et al., 2003;Nadel et al., 1998), we were able to demonstrate the continual improvement of both pointing and navigation performance in healthy controls during the whole RM session. Even that we found impaired performance in the group of FES patients in both reported parameters, the pointing accuracy showed continual improvement also in schizophrenia patients, in contrast to the navigation accuracy (path efficiency) that was less affected by the repeated training trials (similar to previous observations by Hanlon et al., 2006). This discrepancy between the measured parameters supports the idea of separate directional and place navigation reported previously by Hamilton et al. (2008), suggesting that the planning of the trajectory towards the hidden position in schizophrenia is less affected than the precise

determination of goal position represented by the path efficiency. Proximity of one of the orientation cues to the goal position could be responsible for this effect, as it enables the tested subjects to point towards this cue instead of the specific position of the goal. In addition, the navigation accuracy of patients significantly improved after the insertion of one probe trial (in the middle of RM session) that could facilitate their motivation to pay increased attention to spatial cues.

Importantly, no study yet addressed the reversal learning and/or working memory protocols in schizophrenia using human MWM analogues. The vFGN task therefore tested this effect in a consecutive delayed-matching-to-place (DMP) test session. The re-learning of the goal position after the reference memory phase could be used as analogue of the reversal learning protocol. In contrast to the above presented animal study (Lobellova et al., 2013), this reversal of the goal position showed only slight effect on the measured FES group performance. The missing group effect could be explained either by the fact that unlike in animals, tested participants have been instructed about the changing goal position, or by skill learning effect. Nevertheless, the low sensitivity of the reversal protocol towards cognitive deficit in schizophrenia is in accordance with some other animal studies that failed to find significant group differences after application of lower doses of MK-801 (Watson and Stanton, 2009). Since the major improvement appeared immediately after the 1st search trial in both groups and similar effect has been observed in animal studies in the DMP protocols (Garthe et al., 2009;Saab et al., 2011), we can argue that this part of the vFGN task represents mixed reversal and working memory protocol. In contrast, the delayed-matching-to-place recall of the spatial sequence (of the three previously learned goal positions) was impaired in FES patients both in pointing and navigation accuracy. The one-trial switching between individual goal positions in the sequence thus produced the working memory and mental flexibility impairment responsible for maintaining individual positions in short-term memory and attentional switching between them. These findings are in agreement with the data obtained in animal models of schizophrenia using the DMP or reversal protocols (van der Staay et al., 2011; Lobellova et al, 2013).

The spatial memory and mental flexibility deficits in FES group were confirmed by two specific types of control trials tested during various phases of the vFGN task: 1) probe trials inserted in the middle of the RM session and at the end of the DMP session showed lower occupancy of the goal quadrant (measure of spatial bias; see Morris, 1984;Morris, 2008) with pattern similar to that reported in animal studies of intact animals (Norris and Foster, 1999;Stuchlik et al., 2004) and in animal models of schizophrenia (Lobellova et al., 2013); 2) final visible goal trial showed in accordance with other human (Hanlon et al., 2006) and animal studies (e.g.; Gorter and de Bruin, 1992;Vales et al., 2006) no group effect, and thus confirmed that the above reported impaired learning and memory performance was not produced by locomotor or sensory deficits.

In *Experiment III* we presented the results of the novel virtual Carousel maze task, human analogue of the active allothetic (allocentric) place avoidance task (AAPA), designed in order to assess the ability to orient and remember spatial positions in unstable environment of the rotating arena. Decreased behavioral performance was observed in all four phases of the test battery. On top of that, individual parts (test sessions) of the virtual carousel maze, aimed to test spatial performance covering above mentioned clusters of memory and executive functioning, showed variable sensitivity towards cognitive impairment in FES patients. They

thus may represent potentially different and partially independent cognitive skills. Two separate reference frames created by the arena rotation enable us to focus on spatial skills of different level of difficulty and more importantly associated with different contexts (spatial maps).

Performance tested in the ARENA reference frame demonstrated the simple navigation towards egocentrically stable goal positions, similar to that assessed in the vFGN task. This test condition indeed showed similar pattern of behavioral performance in both tested groups. Schizophrenia patients manifested decreased pointing and navigation performance only in the first half of the trials, showing partially preserved learning abilities in FES patients (Fajnerova et al, 2015). However, a slight decrement in comparison to the control group was present in the asymptotic level of the FES group performance in the 2nd half of arena associated trials, showing some discrepancies when compared to the vFGN reference protocol. This difference could be related to the fact that the vFGN task assessed spatial skills in a stable environment of simple circular arena walls, with simple geometric shapes representing the orientation cues. In contrast the AAPP task is performed in more complex virtual room with rotating arena producing two reference frames associated with a set of objects/plants. Despite the fact, that the subject moves with the arena, thus in egocentrically stable environment, and should concentrate only on the reference map of the arena, he/she could be affected by the misleading presence of other cues (e.g. objects). Such cognitive test could represent a spatial learning and memory test with higher cognitive load than that tested in the vFGN task. In addition, the switching between the two different goal positions (even that placed in the same frame of reference) has to be maintained in the working memory. Our findings are in agreement with the previous animal studies reporting that the acquisition and reversal learning in the carousel maze task is more sensitive towards the impairment induced by application of MK-801, than the MWM task (Vales et al, 2006, Lobellova et al, 2013).

Despite some slight improvement the performance of the FES group tested in the ROOM frame condition was strongly impaired throughout the whole test session. In this task, tested individuals have to focus on relevant spatial information located around the rotating arena. In order to do so, they have to ignore (from their point of view stable but irrelevant) arena cues (Bures and Fenton, 1997). This process of separation of information associated with one of the spatial contexts, so called cognitive coordination, plays an important role in the etiology o schizophrenia. Deficit in cognitive coordination in the real carousel maze task was reported both in animal models of schizophrenia in rats (e.g. Kubik et al, 2014), and using standard task switching and working memory paradigms in schizophrenia patients (for review see Pisculic et al, 2007).

In summary, arena and room frame conditions showed different pattern of impaired performance in SZ (group effect), both in pointing and navigation performance. Moreover, we believe that individual parameters tested in the task can be related to different behavioral effects for several reasons. Pointing towards the correct goal position requires the attention focused towards the correct reference frame (while ignoring the irrelevant interfering orientation cues) and identification (recall) of the correct spatial location of the goal. However, the navigation accuracy may be affected both by maintenance (continuous updating) of the current spatial information in the working memory and, in case of moving goals, also by the ability to effectively plan and maintain the trajectory towards the moving target/object. This is possible both by flexible reaction to its current position as well as by anticipating its position in the next time point. Analogous animal task on the rotating arena (Telensky et al, 2011) suggest

hippocampal involvement in such flexible navigation (avoidance of a moving object - robot). As the training session (pre-training consisting of two goal positions hidden either in the arena or room frame) preceded both arena and room frame sessions, the above mentioned discrepancies cannot be easily explained by the effect of missing pre-training. Nevertheless, the asymptotic performance of the FES group during the pre-training was impaired in comparison to healthy controls suggesting additional role of the higher cognitive demands of the frame switching paradigm.

This results are further supported by the findings of the fourth vAAPP test session that required switching between both mental representations (reference frames/ sets of orientation cues) learned in the two previous sessions, in order to correctly identify the location of one of the 4 hidden goal positions. This task thus enabled us to test cognitive coordination and working memory in spatial environment. As in fact, the tested individual alternately recalls information related to one of the two spatial contexts, this task could be argued to test some processes involved also in contextual episodic memory (Boyer er al, 2007) and/or episodic buffer of the working memory (Baddley et al, 2000).

Importantly, while no substantial goal switching effect (changing goal position in the same reference frame - arena or room) could be observed in the pointing error parameter, in contrary this effect is evident in the pointing error and latency (trial time) parameter. Inverse effects were observed in the last frame switching paradigm of the task, where the pointing time visibly increased in comparison to previous two sessions, showing a tendency towards slower pointing in the trials with frame change (in contrast to trials without the change in the frame of reference). We suggest this task switching paradigm requires the subjects to identify context (reference frame) using task-relevant information stored in working memory, which impairment is well documented in SZ (Nuechterlein et al., 2004; Green et al., 2004). In general, executive processes of cognitive coordination and mental flexibility tested in set-shifting paradigms are traditionally associated with the hypofunction of the prefrontal cortices (PFC), specifically the dorsolateral prefrontal cortex (DLPFC) in schizophrenia (Verébová and Horacek, 2010; Shenton et al, 2010). However recently some studies reported also hippocampal involvement in higher cognitive control necessary for successful navigation in changing environments (Wesierska et al, 2005; Kubike and Fenton, 2005; Morellini et al, 2010; Brady, 2009; Malá et al, 2015).

Moreover, the original AAPA task in animals (Bures et al., PNAS, 1997) is often reported in the context of cognitive coordination in dynamic environments hypothesized to be affected in schizophrenia (Philips and Silverstein, 2003), which impairment is associated both with PFC and hippocampal dysfunction (Stuchlik et al., 2013; Wesierska et al., 2005; Kubík et al., 2014), resulting in an inability to integrate contextual information as well as in impaired discrimination between relevant and irrelevant information (Hemsley, 2005). This behavioral changes could be associated with various changes in the brain activity, such as general reduction of firing rates of glutamatergic neurons (Rolls et al, 2012) and increased coactivity of separate neuronal populations (hypersynchrony theory) in hippocampal pyramidal cells (Fenton, 2008; Olypher et al., 2006) resulting in elimination of contextual specificity (increased similarity) of immediate-early genes expression in hippocampal CA1 ensembles (Kubik et al., 2014) and/or retrosplenial cortex (Kubik, Buchtova, Fajnerova et al, in preparation).

In overall, our findings reported in individual experiments are in line with previous animal and human studies showing impaired spatial memory both in MWM and AAPA task after the inactivation/lesion of hippocampus in rats (Morris et al., 1982; Sutherland et al., 1983), and after unilateral HPC lesion in human subjects (Bohbot et al., 1998, 2004; Goodrich-Hunsaker et al., 2009).

To our knowledge this is the first study in schizophrenia patients that demonstrated impaired spatial memory and cognitive control in a task/context switching paradigm in both stable and dynamic environments. Contextual binding of information plays an important role in both memory formation and cognitive coordination of memory processes, crucial features of cognitive impairment in SZ (Chen et al, 1999; Penn et al, 2002). A study by Rizo et al (1996) indicated that memory for target or spatial information alone is quite intact in SZ relatively to binding the target and spatial information together, and thus that the contextual binding is impaired in SZ, a process in which the medial temporal lobe structures play a critical role (Eichenbaum et al., 2004). In agreement with this assumption, the above presented results suggest that the AAPP task presents sensitive measure of cognitive coordination and contextual spatial memory impairment in schizophrenia, and could serve as a useful tool in future comparative research addressing the role of hippocampal and prefrontal dysfunction involvement in schizophrenia. Beside well-established PFC dysfunction and associated executive deficits in SZ (Abruzzese and Scarone, 1993; Goldberg et al, 1989), alterations of the HPC on molecular and cellular level have been documented as well (Tamminga et al, 2010; Boyer et al, 2007); reporting neuroanatomical abnormalities in the hippocampal volume and HPC atrophy (Bogarts et al., 1990; Weiss et al, 2005; Wright et al, 2000), hippocampal shape abnormalities (Connor et al, 2004), smaller pyramidal neurons in CA subfields and reduced neural size in the entorhinal cortex and subiculum (Arnold et al, 1995; Zaidel et al, 1997); and biochemical abnormalities mainly in proteins involved in presynaptic function (Sawada et al, 2005), such as decreased levels of presynaptic proteins including synapsins and synaptic vesicle fusion proteins essential for neurotransmitter release (Browning et al, 1993) affecting hippocampal circuitry through the reduction of presynaptic and dendritic indices (Harrisson and Eastwood, 2001). (For more details on hippocampal abnormalities see review by Boyer et al, 2007). Synaptic disorganization in SZ is compatible with hypotheses related to the NMDA receptor-mediated synaptogenesis deficit (Harrison et al, 2004), affecting HPC regions crucial for encoding and contextual binding memory processes (dentate gyrus and CA subfields), and resulting in impaired retrieval of some event, due to its inadequate binding to the relevant context (O'Reilly and Rudy, 2001). Patients are thus able to remember isolated facts, but not their meaning within larger context, resulting in impaired long-term memory processing that could be partially responsible also for the development of delusions in SZ due to the impaired self-reference and the failure to integrate current contextual information with information previously stored in this context (Gray et al, 1991; Boyer et al, 2007).

Moreover, abnormal HPC-PFC connectivity in SZ was reported in several imaging and EEG studies (Hutcheson et al., 2015; Meyer-Lindenberg et al, 2011; Garrity et al, 2007; Samudra et al., 2015; Sigurdsson et al, 2010; Yoon et al, 2015). Animal glutamatergic models of schizophrenia disease also confirmed dysfunction in functional HPC-PFC connectivity, however, they mostly report increased connectivity with induction of pathological activity-independent synaptic potentiation (Kubik et al, 2014). This dissertation thesis provided new

evidence supporting the glutamatergic model of schizophrenia and an important role of hippocampal-prefrontal (frontotemporal) connectivity dysfunction in schizophrenia, both in preclinical and clinical part of the study. Our results in schizophrenia demonstrate presence of deficit in spatial memory associated with medial temporal lobe (hippocampal) function, and impaired executive functioning (mental flexibility and working memory) associated with the activity of prefrontal cortex. The observation of higher sensitivity of the carousel maze task (both in animals and humans) suggest a crucial role of cognitive coordination deficit in schizophrenia, reported in previous studies as a function of PFC-HPC interactions.

In summary, the group of FES patients and a group of healthy volunteers was assessed using virtual analogues of two spatial tasks mentioned above, addressing reversal learning and spatial memory, and/or cognitive coordination. Despite the fact that both virtual paradigms used the same hidden goal principle and the same amount of orientation cues (3 objects), the rotating arena shows more pronounced decline of the spatial performance in schizophrenia than the stable one. This is not surprising, as due to the arena rotation the task demands attention shifts and navigation in two frames of reference, in contrast to the stable arena. Considering the fact that our results support the visuo-spatial deficit observed in animal model of schizophrenia (Lobellova te al, 2013; Vales, 2006, Stuchlik 2004, etc.) both tasks (test batteries) could be used as tools for future comparative research aimed to identify cognitive changes in neuropsychiatric disorders. In addition, we do believe that both virtual tasks could be useful in measurement of cognitive enhancement as an outcome of pharmacological or non-pharmacological treatment in neuropsychiatric disorders, as they address complex cognitive functioning relevant for every-day life activities. Future imaging studies will address the HPC-PFC connectivity hypothesis by application of virtual carousel maze (vAAPP task) in the fMRI paradigm.

Interestingly, our results are also in line with the observations made in pharmacological model of dementia (Entlerova et al., 2013), and in the real human analogues of the spatial tasks tested in Alzheimer dementia patients (Hort et al, 2007, see also the DRF task in Vlcek et al, 2006), suggesting the possible application of the two novel virtual methods in the future preclinical and clinical research of Alzheimer disease. Moreover, in agreement with memory decline observed during healthy aging in human and animal studies (e.g. Moffat and Resnick, 2002; Moffat, 2009; Young et al, 2013) we observed age related effect on spatial performance in all phases of the vFGN and AAPP task in healthy volunteers. Interestingly, such effect was fully suppressed in schizophrenia patients, in contrary to the current meta-analysis (Rajji et al., 2009), which assumed a better prognosis and less expressed cognitive deficit in patients with a lower age of illness onset. However, assessment of chronic and late-onset schizophrenia patients could reveal a different pattern.

Interestingly, the results of similar reversal protocols applied in the avoidance task on rotating arena in rats showed that the pre-training in the task can lead to lack of group differences after application of MK-801 (Zemanova et al., 2013; Lobellova et al, 2013). This suggests possible application of the virtual carousel maze variants in the remediation of cognitive deficit in schizophrenia (Fajnerova et al, 2016, in submission process).

We further analyzed also the relationship of the performance measured in FES patients in the virtual tasks, and/or standard neurocognitive measures, with the monitored parameters of the illness, such as the duration of untreated psychosis (DUP, defined as the time from

appearance of the first psychotic symptom to the initiation of suitable antipsychotic treatment (for review see; Marshall et al., 2005)), severity of positive and negative symptoms (measured by PANS scale), global functioning (measured by GAF scale) and antipsychotic medication (CPZ dosage).

In accordance to a recently published follow-up study (Barnes et al., 2008), we found no significant effect of DUP on spatial performance. In respect to symptomatology, we found neither negative nor positive symptoms effect on the performance in the vFGN task. This finding is in contrast to current literature describing a strong association of cognitive functions and negative symptoms, and the absence of a positive symptoms effect on cognitive deficit in schizophrenia (e.g.; Addington et al., 1991;Rossi et al., 1997).

While older studies described negative effects of first-generation antipsychotic treatment on cognitive functioning in schizophrenia (Spohn and Strauss, 1989), current studies addressing atypical antipsychotics reported slightly positive effects of some drugs on cognitive functioning in SZ patients (e.g; Meltzer and McGurk, 1999) and in an NMDA model of schizophrenia in rats (Bubenikova et al., 2005). In agreement with more recent studies (Keefe et al. 2007;Jones et al. 2006;Lewis and Lieberman 2008), we found no effect of atypical antipsychotic medication (antipsychotic dosage calculated in CPZ equivalents) on visuospatial or verbal performance, when measured by standard neuropsychological test battery, except of the verbal fluency performance, a measure of mental flexibility. Interestingly, comparable results were obtained from the virtual task performance, showing that only the working memory deficit found in the DMP session of the vFGN task was slightly affected by the CPZ level, when measured by the navigation accuracy parameter; no other effects on the behavioral performance were observed.

With respect to the global functioning and quality of life in FES patients, we did not find any associations between GAF and VIS functions measured by standard cognitive methods. The fact that the only visuospatial measure that correlated with the GAF score was the Trail Making Test B could be responsible for this negative finding. On the other hand, GAF was positively affected by VERB functions (cumulative VERB score) as an accompanying factor of the main negative effect produced by positive symptoms. The effect of negative symptoms reported in previous studies (Gaite et al., 2005) was not identified as significant in our FES sample. We assume that positive symptoms might have a more pronounced negative effect on the functioning of individuals' in our FE sample than negative and general symptoms, due to the early remission state. Another possible explanation is the fact that GAF scale was constructed as a measure of psychosocial disability in relation to symptomatology, rather than neurocognition (Jones et al., 1995; Roy-Byrne et al., 1996); thus, more specific neurocognitive functions, such as VIS, might not be captured. However, we observed a strong effect of GAF score on spatial learning performance in the vFGN task and effect of generalized symptoms (evaluated by PANS-G scale) in the working memory performance in the DMP session. These results demonstrate that high functioning patients perform better in complex cognitive tasks than the low functioning individuals (Green et al, 2004).

According to our results, quality of life, measured using the WHOQOL-BREF questionnaire (Dragomirecká and Bartonová 2006a), seems to be more related to verbal than visuospatial cognitive measures. Two of four domains of WHOQOL-BREF (Physical and Psychological health) were positively associated with overall VERB performance, whereas only one domain (Environment) was related to overall VIS functioning and this association was

negative. Some previous studies have reported similar counterintuitive negative correlations (Fiszdon et al. 2008;Narvaez et al. 2008;Prouteau et al. 2005). Future research is needed in order to clarify the character of such puzzling results. In general, research findings on the relationship of neurocognition and QOL are very heterogeneous and often report weak associations between these two constructs (Heslegrave, Awad, and Voruganti 1997;Aksaray et al. 2002;Fiszdon et al. 2008). However, by addressing individual items of QOL measure in terms of cognition, we found a strong relationship towards several neurocognitive tests, both VIS and VERB (mostly related to processing speed, memory and executive functions). This is in agreement with previous studies that highlighted the role of executive functions (e.g. Matsui et al. 2008;Fiszdon et al. 2008) and memory domains as the most representative measures related to QOL.

In summary, the importance of assessment of visuospatial abilities in neuropsychiatric disorders was demonstrated using comparative methods both in humans and animals, motivated both by importance of comparative preclinical research to increase validity of animal models, and by the increasing number of bilingual patients due to bilingualism (BL) spreading around the world (Grosjean, 1994; Bialystok, Craik, Green, and Gollan, 2009), including Czech Republic. BL has been shown to have a broad impact—both positive and negative — on language and cognitive functioning (for details see Bialystok, Craik and Luk, 2012; De Bruin, Treccani, and Della Sala, 2015). In this context, if we take the cognitive functioning of monolingual neuropsychiatric patients (Stefanopoulou et al., 2009) as a standard, then the findings of cognitive deficits in bilingual neuropsychiatric patients can be distorted, especially because cognitive deficits are most evident in the executive and semantic features mostly assessed in the standard neurocognitive assessment (Paradis, 2008). A disorder-specific deficit may have different manifestations, depending on the person's language and/or culture, and because each language plays an independent role in the language/psychopathology relation (Toppelberg et al., 2002). It is thus not surprising that diagnostic mistakes have been described in earlier studies on BL (Kester and Peña, 2002; Toppelberg et al., 2006). It is therefore necessary to distinguish between an underlying deficit and the nature and form of its manifestations in each language separately, with the awareness that BL can alter normal performance expectations (Ardila, 2000), and that bilinguals are often disadvantaged relative to monolinguals on a variety of language measures, even when they are tested in their primary language (Gasquoine et al., 2007). Thus, in the whole range of neurological and neuropsychiatric disorders (depression, psychosis, dementia etc.), it will be essential to evaluate a patient's mental state in both languages (Paradis, 2008; Rodriguez et al, 2015), and/or to more extensively asses non-verbal visuospatial abilities that are not affected by the language of assessment.

5 Conclusion

Experiment I provided clear evidence for a deficient visuospatial working memory and disrupted cognitive flexibility in the allothetic place avoidance alternation task and reversal protocol of Morris water maze task in MK801 induced animal model of schizophrenia-like behavior. Furthermore, the present data suggest higher sensitivity of active place avoidance task in reversal configuration than the MWM, which underlines the importance of the task in searching for novel treatments for cognitive deficits in schizophrenia.

In Experiment II, we present the results of the newly-developed virtual Four Goal Navigation task, which represents the virtual analogue of the Morris water maze task, tested in FES patients and healthy control group. Mixed reference and delayed-matching-to-place protocol allowed us both to confirm the impaired performance in the reference memory in schizophrenia, and to demonstrate the presence of impaired working memory and cognitive flexibility during reversal learning and delayed matching to place paradigm.

In Experiment III, we present the results of the newly-developed Active Place Preference task, the virtual version of the Carousel maze task. Our findings showed disrupted cognitive flexibility and coordination in the mean of the reference frame switching paradigm on a rotating arena. Furthermore, this impairment is more pronounced in comparison to the MWM task analogue, which is in agreement with the previous findings and also results of the animal study presented above. In addition, our results show impaired executive functioning during planning of spatial trajectory towards the moving goal position.

In Experiment IV, we showed that deficit in visuospatial (VIS) functioning (tested using standard methods) is an integral part of cognitive deficit in schizophrenia spectrum disorders, rather than a side effect of symptomatology or antipsychotic medication. Verbal (VERB) functioning was a better predictor of GAF and WHOQOL-BREF than VIS functioning. Given the findings of negative or missing effect of VIS deficit on WHOQOL-BREF and GAF, the accuracy of these measures to evaluate the impact of global cognitive deficit on everyday life in schizophrenia could be questioned.

Finally, this dissertation thesis provided new evidence supporting the glutamatergic model of schizophrenia and an important role of hippocampal-prefrontal (frontotemporal) connectivity dysfunction in schizophrenia, both in preclinical and clinical part of the study. Our results in schizophrenia demonstrate presence of deficit in spatial memory associated with medial temporal lobe (hippocampal) function, and impaired mental flexibility and working memory associated with prefrontal cortex. The observation of higher sensitivity of the carousel maze task (both in animals and humans) suggests a crucial role of cognitive coordination deficit in schizophrenia, reported in previous studies as a function of PFC-HPC interactions.

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7 LIST OF PUBLICATIONS

7.1.1.1 Impacted journals:

a) Publications directly relevant to the thesis

Fajnerová I, Rodriguez M, Levčík D, Konrádová L, Mikoláš P, Brom C, Stuchlík A, Vlček K and Horáček J (2014a) A virtual reality task based on animal research – spatial learning and memory in patients after the first episode of schizophrenia. ***Front. Behav. Neurosci***. **8**:157. doi: 10.3389/fnbeh.2014.00157 (**IF 4,2**)

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Nekovarova T, **Fajnerova I,** Horacek J and Spaniel F (2014) Bridging disparate symptoms of schizophrenia: a triple network dysfunction theory. ***Front. Behav. Neurosci***. **8**:171. doi: 10.3389/fnbeh.2014.00171. (**IF 4,2**)

Lobellova V, Entlerova M, Svojanovska B, Hatalova H, Prokopova I, Petrasek T, Vales K, Kubik S, **Fajnerova I,** Stuchlik A. (2013). Two learning tasks provide evidence for disrupted behavioural flexibility in an animal model of schizophrenia-like behaviour induced by acute MK-801: a dose-response study. **Behav Brain Res.** 2013;246:55-62. (**IF 3,4**)

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b) Publications not directly relevant to the thesis

Fajnerova I, Kenney J, Lobellova V, Okrouhlicova S, Stuchlik A, Klement D. (2014b). Can rats solve the active place avoidance task without the room-bound cues? ***Behav Brain Res*.** 2014 Jul 1;267:126-32. doi: 10.1016/j.bbr.2014.03.028. (**IF 3,028**)

7.1.1.2 Peer-reviewed journals:

Rodriguez M, Kratochvilova Z, Kuniss R, Vorackova V, Dorazilova A, **Fajnerová I** (2015b). Case Report: Is verbal cognitive performance in bilingual neuropsychiatric patients test-language dependent? ***Psych Journal***.2015. 4(4): 208–217.

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8 Appendix

List of Abbreviations

2/3D – Two/three-dimensional
AAPA – Active allothetic place avoidance task
AAPP –Active allocentric place preference task
AD – Alzheimer disease (dementia)
ADHD- Attention deficit hyperactivity disorder
ASD - Autism spectrum disorders
AVLT - Auditory Verbal Learning Test
BADS - Behavioural Assessment of the Dysexecutive Syndrome
BVA – Blue Velvet Arena
CA – Cornus ammonis
CEN – Central executive network
CPZ – Chlorpromazine
CT – Computer tomography
DES - Dysexecutive syndrome
DLPFC – Dorsolateral prefrontal cortex
DMN – Default mode network
DMP – Delayed-matching-to-place
DS - Digit Span
DSM - Diagnostic and Statistical Manual
DTD – Developmental topographical disorientation
DUP – Duration of untreated illness
ECT - Electroconvulsive therapy
EPS - Extrapyramidal symptoms
FES – First episode schizophrenia
FOV – Field of view
GABA - γ-amino-butyric acid
GAF - Global Assessment of Functioning scale
HC – Healthy controls
HF - Hippocampal formation
HMD – Head-mounted display
HPC – Hippocampus
ICD - International Classification of Diseases
IEG – Immediate early genes
KST - Key Search Test
LSD - Lysergic acid diethylamide
MCI – Mild cognitive impairment
MPFC – Medial prefrontal cortex
(f)MRI – (functional) Magnetic resonance imaging
MRS - Magnetic resonance spectroscopy
MTL – Medial temporal cortex
MWM – Morris water maze
NMDA - N-metyl-D-aspartate
NVHL – neonatal ventral hippocampal lesion
OCD - Obsessive-compulsive disorder
PANSS – Positive and Negative Symptoms Scale
PCP – Phencyclidine
PEBL – The Psychology Experiment Building Language
PET – Positron emission tomography
PFC – Prefrontal cortex
PPI – Prepulse inhibition
PTSD - Post-traumatic stress disorder
PVT - Perceptual Vigilance Task
RAM – Radial arm maze
RF – Reference frame
RMT – Road map test
RCFT - Rey–Osterrieth complex figure test
RSC – Retrosplenial cortex
SDRT - Spatial Delayed-Response Task
SN – Salience network
SPECT – Single photon emission tomography
SS - Spatial Span
SZ – Schizophrenia
RM- Reference memory protocol
RT – Reaction time
TD – Topographical disorientation
TMT – Trail making test
TTX – Tetrodotoxin
UU – Unreal unit
vFGN – virtual Four-Goals Navigation task
VFT - Verbal Fluency Test
VIS – Visuospatial
VERB - verbal
VR – Virtual reality
VSWM - Visuo-spatial working memory
WAIS-III - Wechsler Adult Intelligence Scale 3rd edition
WM – Working memory
WMS-III - Wechsler Memory Scale 3rd ed.