Virtual spatial navigation tests based on animal research – spatial cognition deficit in first episodes of schizophrenia

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ABSTRACT

The impairment of cognitive functions represents a characteristic manifestation in schizophrenia. Animal models of schizophrenia demonstrated behavioural changes in several spatial tasks. In order to assess spatial abilities in schizophrenia using methods applicable in comparative research, we designed two virtual tasks inspired by animal research: the Morris water maze and the Carousel maze. The tested subject is required to navigate toward several hidden goal positions placed on the floor of an enclosed stable arena or a rotating arena. Data obtained in a group of schizophrenia patients show cognitive impairment in both newly-developed virtual tasks comparing to matched healthy volunteers.

1. INTRODUCTION

The cognitive deficit is considered to be a characteristic and permanent manifestation accompanying schizophrenia and related psychotic disorders, affecting several cognitive domains including visual learning and memory (Green et al, 2004). Spatial tasks have the potential to assess similar cognitive performance in humans and animals. Impairment of visuo-spatial abilities has been already demonstrated in animal models of schizophrenia (e.g. Lobellova et al, 2013) and also in schizophrenia patients using various virtual tasks developed on the basis of the original paradigm for animals (e.g. Hanlon et al, 2006; Spieker et al, 2012).

In order to assess complex spatial abilities in schizophrenia and compare our results with the data obtained in animal models, we designed two virtual reality tasks adopted from the animal research, the Morris water maze and the Carousel maze paradigm. Experiments have been conducted in virtual reality (VR) that allowed us to build large-space and/or moving environment.

Due to the potential of VR to easily modify the environmental stimuli, the newly-developed tests could be applied in longitudinal clinical studies, such as the non-pharmacological intervention provided by the Prague Psychiatric Center. This computer-based and individually oriented cognitive remediation for psychotic patients combines several cognitive rehabilitation methods for 8 weeks (Rodriguez, 2013) and could later proceed in a form of online training (neurokog.pcp.lf3.cuni.cz; in development). Retest variants of the presented tests could be applied to test the outcome of therapy by monitoring complex spatial behavior.

2. METHODS

2.1 Participants

A study group of 30 (17 males and 13 females, age 18-35) first-episode schizophrenia patients (SZ, diagnosed as acute psychotic episode or schizophrenia according to DSM-IV) and a control group of healthy volunteers (HC) were recruited and matched for age, sex, education level and gaming experience.

2.2 Apparatus and software

The game engine Unreal Tournament (UT2004; Epic Games) was used to visualize the virtual scene to the respondents presented in a first-person view on a 24" LCD monitor. The custom-made java software toolkit called “SpaNav” was connected to the game engine to control the experiment and collect online data. Subjects controlled their movements in virtual environment using only one joystick of the gamepad device.

2.3 Design and Procedure

Prior to the experiment all participants underwent a short pre-training of movement control in complex virtual maze. Consecutively all performed experiment in two virtual tasks, which required the subject to navigate towards one of the 4 hidden goal positions placed on the floor of an arena, stable or rotating. Each single trial started with pointing towards the goal and was followed by navigation towards the goal using three visible orientation cues.

2.3.1 Stable arena. The virtual task with the hidden goal paradigm was inspired by the Morris water maze (MWM; Morris, 1984) and was performed in a large-scale enclosed virtual arena (see Fig. 1B). This virtual Four Goals Navigation (vFGN, Fajnerova et al, 2014) task requires the participant to find and remember the hidden goal position on the floor of an enclosed virtual tent using three visible orientation cues. Four separate phases of the vFGN task represent the analogies of the MWM protocol variants: *1) Training* - reference memory protocol with stable goal position, *2) Acquisition* - reversal protocol with changing goal position, *3) Recall* - delayed matching-to-place protocol, *4) Probe* - trials with removed goal position (without feedback).

2.3.2 Rotating arena. The second virtual test was inspired by the Carousel maze - Active allothetic place avoidance (AAPA) task - performed on a rotating arena (Cimadevilla, 2000). However, the original avoidance task was modified to a preference version of the task, as a virtual arena called the Active Allocentric Place Preference task (AAPP, Vlček et al, unpublished). The same hidden goal principle as in the previous task was used to test spatial abilities in subjects standing on a rotating arena. The hidden goal positions are either connected: 1) to the ARENA frame and rotate together with the tested individual or 2) to the ROOM frame moving with respect to the subject/arena (see Fig. 1D). Time limit for each trial was 20 s. The task was divided to four separate phases: *1) Training* - searching for two goals, one in the arena frame and one in the room frame; *2) Arena frame* - navigation towards two stable goals in arena frame; *3) Room frame* - navigation towards two moving goals in room frame; *4) Frame switching* - alternated search between 4 goals placed either in arena frame or in room frame.

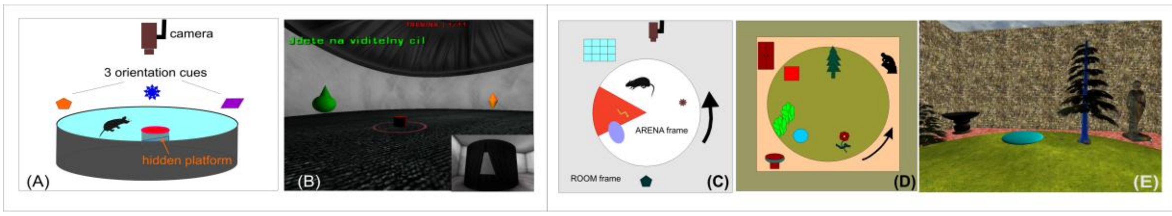

Figure 1. *MWM paradigm (adjusted from Fajnerova et al, 2014): (A) model of the original MWM apparatus for rats; (B) Virtual version, the vFGN task in an enclosed dry arena. (C) The AAPA task. (D-E) Virtual version - the AAPP task. (D) Schematic view of the Training conditions in two possible reference frames - Room frame (square shape) and Arena frame (circular shape).(E) Rotating arena from the first-person view.*

2.3.3 Clinical assessment. To confirm the cognitive deficit in our study subjects, all participants (SZ and HC) completed a battery of standard cognitive tests (Trial making test; Spatial Span (WMS-III); Rey-O/Taylor Complex Figure; Block Test (WAIS-III); Perceptual vigilance task, Money-road map test, Key-search test). In addition, all patients were evaluated using the PANSS and GAF psychiatric scales to address the presence of clinical symptoms.

2.4 Measured parameters and data analysis

The spatial performance measured in the *Stable arena* was in all except probe trials evaluated using two parameters, the *pointing error* (absolute angular difference between the pointed and linear direction towards the goal position) and the *path efficiency* (range 0 to 1, calculated as a ratio between the minimal path length and the real distance travelled by the subject). In probe trials the *goal quadrant preference* (proportion of the trial time spent in the correct arena quadrant) was evaluated. The performance in the *Rotating arena* was measured using the previously described *pointing error* parameter. The second applied *trial time* parameter represents the time needed to enter the goal position. Only selected parameters are presented in this paper. To analyze the data a custom-made PHP program called drf2track was used to produce primary data tables and trajectory pictures; further statistical analysis was performed in Statistica 11. The group differences were calculated using the repeated measures ANOVA and overall level of significance was set to 0.05.

3. RESULTS

The results of both virtual tests confirmed the deficit of cognitive abilities observed earlier using the battery of standard tests (not presented) in the group of first episode schizophrenia patients.

3.1 Stable arena

All phases of the vFGN task show decline in spatial abilities of schizophrenia patients in comparison to healthy volunteers (published in full extend in Fajnerova et al, 2014). The first Training phase demonstrates learning difficulties presented in lower pointing (Fig. 2A) and navigation accuracy ($p < 0.01$) in schizophrenia patients. The subsequent Acquisition phase with changing goal position as a measure of mental flexibility, showed only mild group differences in pointing ($p < 0.01$) but not in navigation accuracy (Fig. 2B – gray area), probably due to the skill learning effect (as all three goal positions were spatially identical). The recall of the three previously learned goal position sequence (ABC) in the later Recall phase showed deficit of spatial working/long-term memory demonstrated in significantly decreased navigation performance ($p < 0.001$) more expressed in the first repetition round (Fig. 2C). The last Probe phase without feedback about the correct position, showed significantly disturbed spatial bias in schizophrenia patients ($p < 0.001$), demonstrated in lower proportion of time spent in the correct arena quadrant (Fig. 2C).

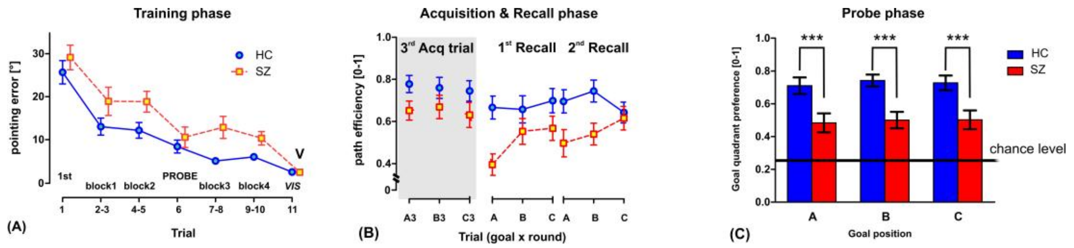

Figure 2. *Performance of both groups in the vFGN task (modified according to Fajnerova et al.,2014). (A) The Training session performance expressed using the pointing error parameter. (B) The path efficiency in Acquisition phase (last trial for each goal position) and in all Recall trials. (C) The time proportion spent in the correct arena quadrant in the last Probe phase.*

3.2 Rotating arena

Similarly, all phases of the virtual AAPP task show decline of spatial performance in schizophrenia. The first Training phase showed impaired learning abilities on the rotating arena ($p < 0.01$, Fig. 3A). The second phase performed in the 'stable' Arena frame showed only mild decrease in measured parameters ($p < 0.01$), less expressed in the second half (Fig. 3B). However, the third phase with navigation towards the moving goals connected to the Room frame (Fig. 3C) showed strongly profound decline of spatial abilities in schizophrenia ($p < 0.001$). The last phase created to assess the cognitive flexibility and 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. 3D).

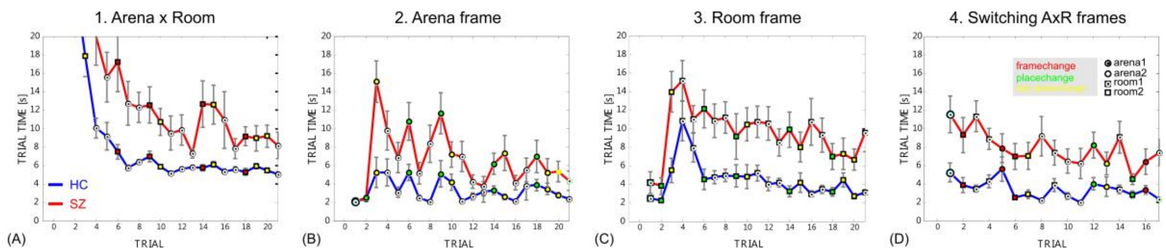

Figure 3. *(A-D) Performance of both groups in four phases of the AAPP task expressed using the trial time parameter. (A) The Training phase with simple frame switching (arena x room). (B) The Arena frame performance. (C) The Room frame performance. (D) Alternation between all 4 previously acquired goal positions, placed in one of the two reference frames.*

4. CONCLUSIONS

Presented results show significant deficit of visuo-spatial functions in first episode schizophrenia patients, which are demonstrated in both tested paradigms (hidden goal search on stable/ rotating arena) and in all four phases of the two virtual tasks. This finding supports our results obtained using the battery of standard cognitive tests (not reported here) and also results of other studies (e.g. Hanlon et al, 2006; Kern et al, 2011), showing the necessity for remediation of spatial learning and memory after the first psychotic episode.

Despite the fact that both methods used the same hidden goal paradigm 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 et al, 2013), both tasks could be used as tools for future comparative research, in order 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 functions.

Importantly, individual phases of both presented tests demonstrated variable extent of sensitivity towards the cognitive deficit in schizophrenia, supporting our assumption that particular parts of each test examine distinct visuo-spatial functions (e.g. learning, working memory, flexibility etc.). The first test with Stable arena showed that the performance in recall and probe phase was more impaired than during the acquisition process. Similarly in the experiment on Rotating arena the navigation towards moving goals was more affected than the search for stable goal positions. These findings indicate that some parts of these virtual tasks could form suitable tools for future virtual remediation of impaired visuo-spatial abilities in schizophrenia.

The future analysis will be aimed on clarifying the relationship between the two newly-developed virtual tasks and the standardized test battery used in this study. In addition, we currently perform repeated assessment 1 year after the first hospitalization to test the persistence of the cognitive deficit, either after the full remission of symptoms or due to potential relapse of the illness. This measurement also addresses possible sensitivity of the developed methods toward the future course of illness in individual patients.

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