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Research report

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

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HIGHLIGHTS

- Behavioural flexibility is impaired in many schizophrenia patients.
- The study tested flexibility in a rat model of schizophrenia-like behaviours by MK-801.
- MK-801 impaired spatial reversal in an active place avoidance and the Morris water maze.
- The active place avoidance was more sensitive than the Morris water maze.
- Navigation towards visible platform was impaired by the highest dose (0.15 mg kg^{-1}).

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ABSTRACT

Schizophrenia is a chronic and devastating illness. Exact causes of the disease remain elusive; however, neurodevelopmental changes in the brain glutamate system are recognized to play an important role. Several animal models of the disease are induced by a systemic blockade of N-methyl-D-aspartate (NMDA) receptors. This study examined the animal model of schizophrenia-like behaviours induced by acute treatment with MK-801, a non-competitive NMDA-receptor antagonist. Behavioural flexibility is an ability to adapt to the changes in environment, and schizophrenia is often accompanied by its decrease. The study tested the effect of MK-801 on behavioural flexibility in an active place avoidance task and the Morris water maze (MWM). Flexibility was tested under reversal conditions, i.e., after changing the location of the target. Each spatial task addressed different functions; continuous coordinate-frame segregation was present in the active place avoidance and precise place representation in the MWM. Results showed that reversal was altered in both tasks by MK-801 at doses of 0.10–0.15 mg kg^{-1}. Some impairment was observed in the active place avoidance task at 0.08 mg kg^{-1}. Swimming towards a visible platform was impaired only by the highest dose (0.15 mg kg^{-1}). The results demonstrate that a significant impairment of behavioural flexibility accompanies this acute animal model of schizophrenia-like behaviours, and that active place avoidance had higher sensitivity for such deficits than the MWM. This suggests the usefulness of the reversal paradigm in both tasks for examining novel drugs with antipsychotic and procognitive actions.

1. Introduction

Schizophrenia is a chronic and devastating neuropsychiatric disease, affecting approximately 1% of the world's population and having serious consequences on the patient's quality of life including social and working abilities [1]. The exact aetiology of this disease is unknown, yet neurodevelopment-related changes in the glutamatergic system in the brain are suspected to play an important role [2]. Alterations of glutamate system of the brain were documented in schizophrenia patients in both *in vivo* and *post mortem* examinations [3–5] and the importance of the glutamate system was underlined by the finding that the application of non-competitive antagonists of NMDA subtype of glutamate receptors, such as phencyclidine (PCP) or ketamine, caused acute psychosis in humans [6,7].

Animal models of schizophrenia-like behaviours represent experimentally induced analogies of selected symptoms of the

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disease, and have proven useful in elucidating the mechanisms underlying this disease, its symptoms and designing new ways of treatment in preclinical research [8–11]. Animal models of schizophrenia-like behaviours do not; however, represent the full manifestation of this typically human disorder. It is due to the obvious difficulty in conceptualizing symptoms like hallucinations and delusions in animals. Instead, animal models do mimic observable manifestations of the disease, and scientists rely on observing the behavioural changes following specific experimental manipulations. Animal models are usually evaluated in terms of validities [9,12]. Construct validity reflects the agreement of the real disease and the animal model in terms of pathogenesis and (possible) causes. 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 [12]. This study used the animal model of schizophrenia-like behaviour induced by 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 [9,13], and importantly, the model exhibits a substantial face validity since it elicits numerous symptoms resembling symptoms observed in affected human subjects [8,14].

It has been shown that MK-801 produces hyperlocomotion (which was analogized to positive symptoms based on increased activity of mesolimbic dopamine circuits [15]), social flattening (at low doses [16]), and perhaps most importantly a deficit in various cognitive domains [14]. MK-801 has been described to fulfil the criteria of a "cognition impairer", and by carefully titrating the dose, researchers can induce behaviours resembling those present in schizophrenia patients [9,14]. MK-801 has been 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 [14,17]. At least some deficits resulting from the administration of NMDA antagonists (including MK-801) could be alleviated by pretraining [18]. Nevertheless, a deficit in the re-acquisition of the active place avoidance task induced by MK-801 (0.15 mg kg^{-1}) has been shown to be resistant to previous experience with the task under no influence of the drug [17].

Importantly, deficits in cognitive flexibility [19] and managing of multiple information streams and changed contingencies are documented in many schizophrenia patients [20], who often display general problems in distinguishing relevant information from irrelevant information [12]. Indeed, alterations of cognitive control, behavioural flexibility and adapting to changed conditions were detected in animal models of schizophrenia-like behaviours in various experiments [21–23]. 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 its animal models [24]. This study aimed at testing the hypothesis that MK-801 application would result in a deficit of flexibility in spatial reversal. Moreover, this study employed two established behavioural tests of spatial navigation, the active place avoidance task and Morris water maze, 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 Section 2).

2. Methods

2.1. Animals

179 adult male Long–Evans obtained from the breeding colony of the Institute of Physiology, ASCR were used in the study (250–300 g upon delivery).

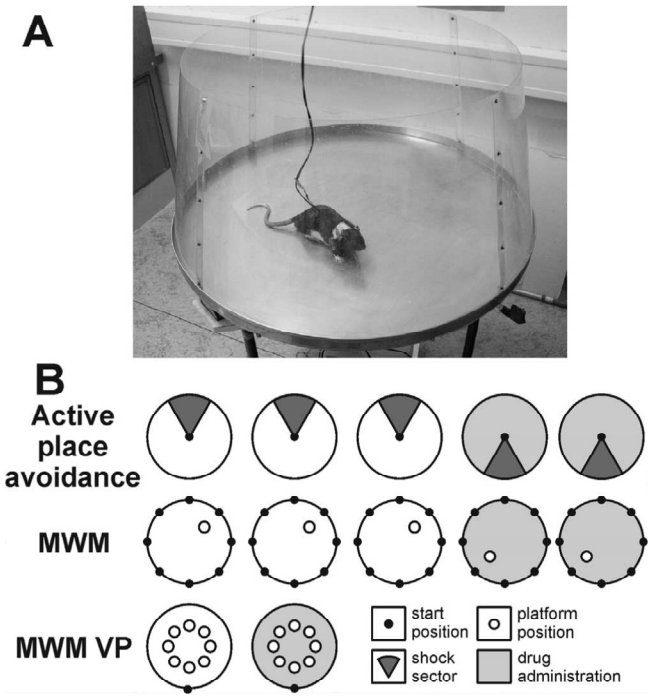

Fig. 1. (Panel A) A photograph of the experimental active place avoidance arena. The arena is elevated 1 m above the floor in a room containing multiple extra-maze landmarks (*not shown*). It is surrounded by a transparent Plexiglas wall. One light-emitting diode is placed between rats shoulders and another is mounted on arena circumference (*bottom right corner of photo*). (Panel B) 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).

Animals were housed in plastic translucent boxes (25 cm × 25 cm × 40 cm) in an air-conditioned animal room with constant temperature (21 °C), humidity (40%) and 12/12 h light/dark cycle. Water and food were freely available throughout the study. Before experiments in the active place avoidance task, animals were gently implanted with a subcutaneous needle connector, which pierced the skin between rat's shoulders. The needle had a blunted and swirled end, which provided purchase for an alligator clip connecting a shock-delivering wire (see Section 2.3). This procedure is analogous to hypodermic injection in humans and does not require anaesthesia. Separate groups of animals were used for the active place avoidance and the Morris water maze testing (see later). All animal manipulations were conducted in accordance with the Animal Protection Code of the Czech Republic and corresponding directives of the European Community Council (2010/63/EC).

2.2. Drugs

(+)-MK-801 (dizocilpine maleate) was purchased from Sigma–Aldrich, 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 intraperitoneally (i.p.) 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 i.p. 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.

2.3. Apparatuses and behavioural procedures

2.3.1. Active place avoidance

A photograph of the experimental apparatus is shown in Fig. 1A. The active place avoidance apparatus [25–28] was a smooth metallic arena (82 cm in diameter), enclosed with a 30-cm-high transparent Plexiglas wall and elevated 1 m above the floor (Fig. 1A). 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 centre of the arena, which rotated constantly at one revolution per minute. 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 [29]. This sector was defined by the computer-based tracking system (Tracker, Biosignal Group, USA), which recorded 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, indicated 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 footshocks (AC, 50 Hz, 200–600 μA) were delivered at 1200-ms intervals up to the moment the 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 [25–29]. 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. Each session lasted 20 min. The initial three sessions were designated as acquisition sessions which were followed by two reversal sessions (see below).

2.3.2. Morris water maze

The Morris water maze (MWM [30,31]) consisted of a grey circular pool (180 cm in diameter) filled with water at a temperature of 21 ± 2 °C to a depth of 35 cm. 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 centre of quadrants that were labelled based on compass directions.

In the visible platform sessions (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 centre 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 demonstrate the remembered platform position.

2.4. Design of the study, measured parameters and data analysis

The design of the study is shown schematically in Fig. 1B. Saline was applied to all animals (1 ml kg^{-1}) 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 30 min 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 travelled 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 total time spent in the target quadrant, which was defined as a 90-degree sector of the Morris water maze centred 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 × 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 × sessions × swims with repeated measures on sessions and swims). Groups again served as a between-subject factor. Time in the target quadrant in the probe trials were analyzed with a two-way ANOVA (groups × 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 × 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. 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 subsection). 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.

3.1. Reversal learning in the active place avoidance

There was a significant effect of MK-801 on the total distance in active place avoidance (Fig. 2A). A two-way ANOVA (groups × 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. 2B). A two-way ANOVA (groups × sessions) with repeated measures on sessions showed a significant main

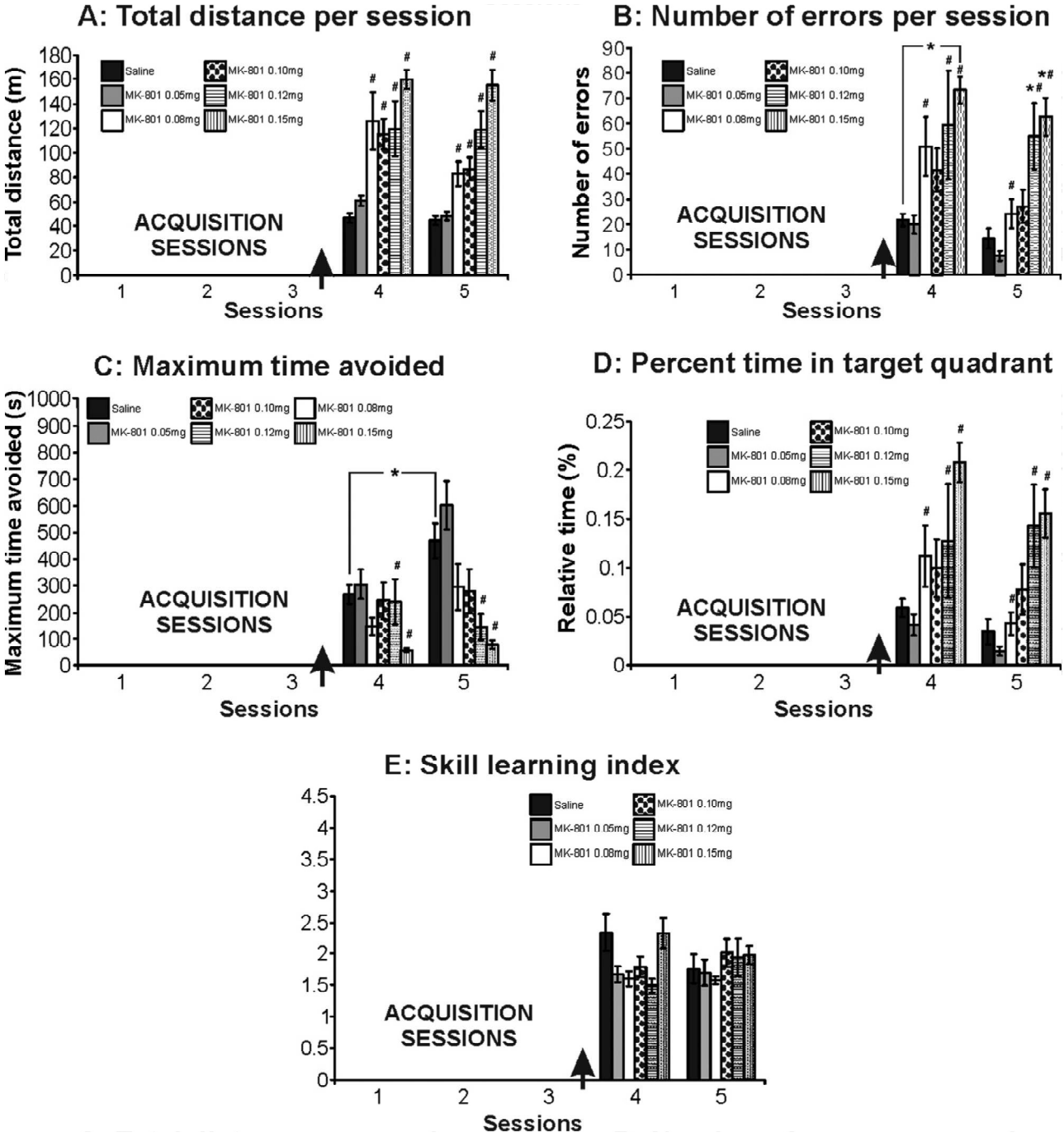

Fig. 2. (Panel A) Effect of MK-801 on the total distance in the active place avoidance task. Note that all doses of MK-801 (except the lowest one 0.05 mg kg^{-1}) increased locomotion. (Panel B) Effect of MK-801 on the number of errors. There was a worsening of this parameter after MK-801 at doses 0.08 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 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. Arrows demote relocation of the goal and start of MK-801 application. Annotation: $^{\#}P < 0.05$ in the main effects of the drug and $^{*}P < 0.05$ in the interaction term.

effect of groups ($F(5,55) = 9.71$; $P < 0.001$), 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 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 Ps > 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, although there was a trend in at some lower doses too (see Fig. 2B). 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 Ps < 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. 2C). A two-way ANOVA (groups × 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

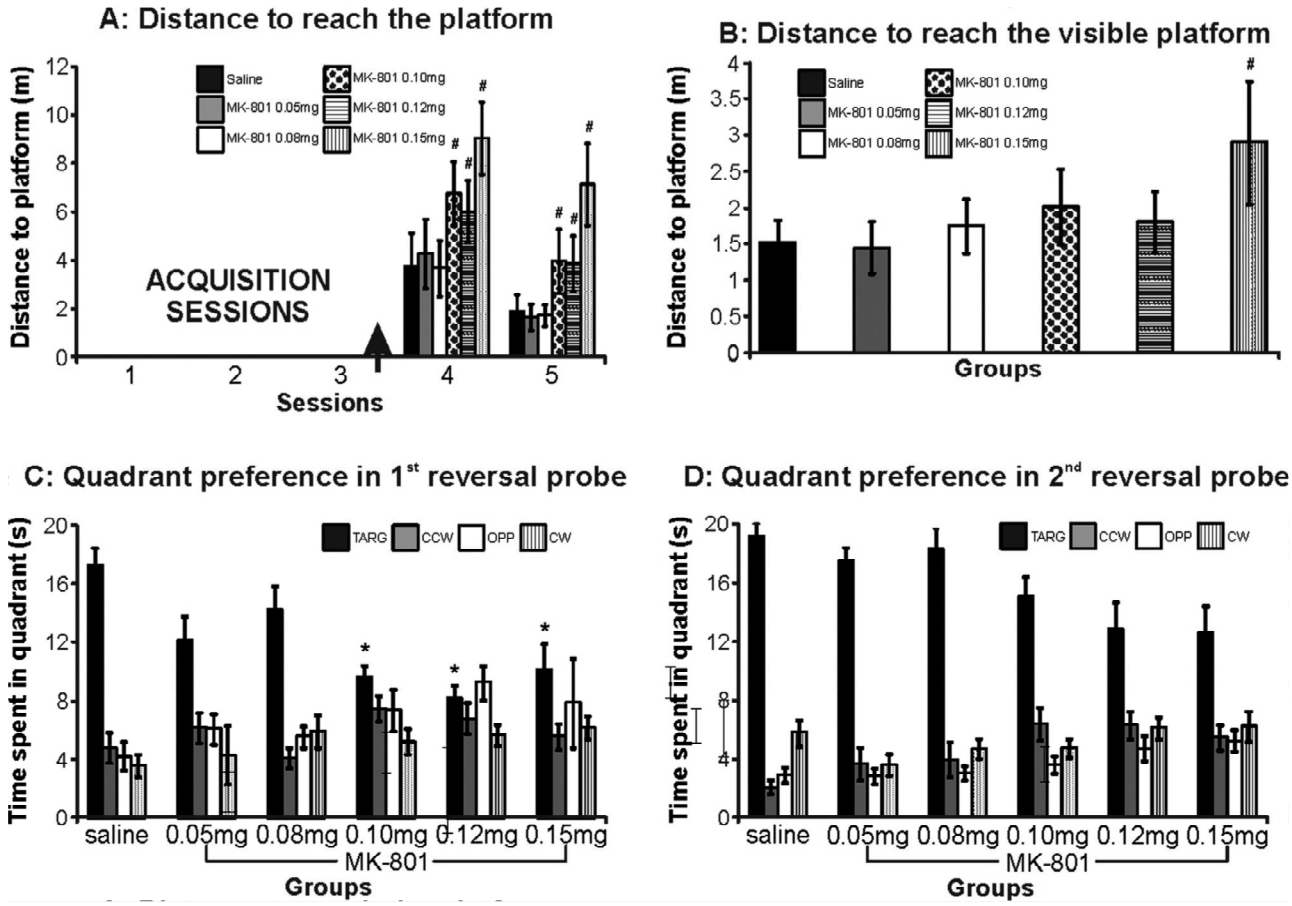

Fig. 3. (Panel A) Effect of MK-801 on the total distance to reach the platform in the reversed hidden platform experiments in the MWM. Doses 0.10–0.15 mg kg^{-1} impaired reversal learning measured by this parameter. (Panel B) Total distance to reach the visible platform in the second sessions of visible platform testing was only increased by 0.15 mg kg^{-1} MK-801. Arrows demote relocation of the goal and start of MK-801 application. Annotation: $^{\#}P < 0.05$ in the main effect and $^{*}P < 0.05$ in the interaction term. (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}. TARG, target quadrant; OPP, opposite quadrant; CCW, counter-clockwise adjacent quadrant; CW, clockwise adjacent quadrant. (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.

($F(5,55) = 2.18$; $P = 0.07$). 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. 2D). 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. 2E). 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. There were high variances in the skill learning index and this finding should be interpreted cautiously. However, in general there were no robust increases in the skill learning index due to application of MK-801.

3.2. Reversal learning in the Morris water maze

Reversal learning (cognitive flexibility) in the MWM was affected by treatment with MK-801 (Fig. 3A). Regarding the total distance to reach the platform, a general-linear-model three-way ANOVA (groups × sessions × 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 ($F(7,357) = 5.62$;

$P < 0.0001$) 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 × 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.

A two-way ANOVA conducted on the time in the target quadrant (groups × sessions) involving the first and second reversal sessions showed a significant main effect of groups ($F(5,52) = 12.46$; $P < 0.0001$), an effect of sessions ($F(1,58) = 19.23$; $P < 0.0001$) but no interaction between both factors ($F(5,52) = 0.66$; $P > 0.5$) (Fig. 3C). Post hoc analysis of the factors group showed that groups between 0.10 mg kg^{-1} and 0.15 mg kg^{-1} had lower preference for the target quadrant. In the second reversal session, however, the preferences of all groups were again generally high, tending to return to values obtained prior to treatment (Fig. 3D).

3.3. Visible platform testing in the Morris water maze

All animals adopted a strategy of swimming towards the platform in the first visible platform 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. 3B). A two-way ANOVA (groups × 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 ($Ps < 0.05$), suggesting that only highest dose caused significant impairment of navigation to the visible platform.

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*).

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 doses of 0.12–0.15 mg kg^{-1}, and some deficits (such as that in percentage of time in a target quadrant or number of errors in the place avoidance task) were seen even at the lower dose of 0.08 mg kg^{-1}. With the present data, it is impossible to explain why a dose 0.08 mg kg^{-1} affected active place avoidance reversal, but such deficit was not seen at the dose 0.10 mg kg^{-1}. MK-801-induced impairments were seen in both tasks. These data extend our knowledge of behavioural deficits in this animal model of schizophrenia-like behaviour in several aspects.

4.1. Active place avoidance with reversal

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 [17,26,32] For example, our previous study [32] 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 [17] 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 [10], more specifically, the level of final asymptotic performance.

4.2. Reversal experiment in the MWM

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 [32], 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 versus reversal configuration are equivalent. Interestingly, a recent study [14] and an older report [33] 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 colony may have lower sensitivity to MK-801 than other rat lines and this is also corroborated by a previous finding by our research group [26], which showed a lower sensitivity to MK-801 of Long–Evans compared to Wistar rats. Data from probe trial appear to confirm the general view that doses from 0.10 mg kg^{-1} impair memory trace in the MWM in reversal configuration. It is interesting that in the final reversal probe (day 5), all groups again tended to prefer the target quadrant over adjacent and opposite quadrants, despite they were still impaired in reversal testing.

4.3. Possible procedural deficits in the tasks

Furthermore, previous studies (e.g., [18]) 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., 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).

4.4. Comparison with other studies

The present results clearly demonstrate that MK-801 at relatively low doses affects behavioural flexibility tested by reversal configuration. Such results are consistent with previously published findings obtained in different paradigms and models. The study by Chadman et al. [34] 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 behavioural sensitization and state-dependent learning [34]. Moreover, the effect of MK-801 on this discrimination reversal learning was found to be mediated by NMDA-receptor blockade in the hippocampus [35], dorsomedial striatum [36] and medial prefrontal cortex [37] 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 [38]. A study by Beninger et al. [39] showed a deficit in the MWM reversal learning in MK-801-treated rats (however, at much higher dose of 0.50 mg kg^{-1}), and our results confirm this finding. Interestingly, Caramanos and Shapiro [40] 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 [26,41]). Additionally, another work [42] detected impairment in acquisition and reversal of a visuospatial task in marmoset monkeys.

4.5. Role of the hyperlocomotion

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 [8,10,15,32,39] but at considerably higher doses compared to the ones used in the present study (see also [26], 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 [17] and (ii) occurred in the task where pre-drug sensory and motor demands and behavioural 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 Section 3).

5. Conclusions

This study provides the 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 behaviour. Furthermore, the present data suggest higher sensitivity of active place avoidance task in reversal configuration (being sensitive to 0.08 mg kg^{-1}) than the MWM (being sensitive from the doses 0.10 mg kg^{-1}), which underlines the importance of the task in searching for novel treatments for cognitive deficits in schizophrenia.

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A virtual reality task based on animal research – spatial learning and memory in patients after the first episode of schizophrenia

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Objectives: Cognitive deficit is considered to be a characteristic feature of schizophrenia disorder. A similar cognitive dysfunction was demonstrated in animal models of schizophrenia. However, the poor comparability of methods used to assess cognition in animals and humans could be responsible for low predictive validity of current animal models. In order to assess spatial abilities in schizophrenia and compare our results with the data obtained in animal models, we designed a virtual analog of the Morris water maze (MWM), the *virtual Four Goals Navigation (vFGN) task.*

Methods: Twenty-nine patients after the first psychotic episode with schizophrenia symptoms and a matched group of healthy volunteers performed the *vFGN* task. They were required to find and remember four hidden goal positions in an enclosed virtual arena. The task consisted of two parts. The Reference memory (RM) session with a stable goal position was designed to test spatial learning. The Delayed-matching-to-place (DMP) session presented a modified working memory protocol designed to test the ability to remember a sequence of three hidden goal positions.

Results: Data obtained in the RM session show impaired spatial learning in schizophrenia patients compared to the healthy controls in pointing and navigation accuracy. The DMP session showed impaired spatial memory in schizophrenia during the recall of spatial sequence and a similar deficit in spatial bias in the probe trials. The pointing accuracy and the quadrant preference showed higher sensitivity toward the cognitive deficit than the navigation accuracy. Direct navigation to the goal was affected by sex and age of the tested subjects. The age affected spatial performance only in healthy controls.

Conclusions: Despite some limitations of the study, our results correspond well with the previous studies in animal models of schizophrenia and support the decline of spatial cognition in schizophrenia, indicating the usefulness of the vFGN task in comparative research.

Keywords: schizophrenia, spatial navigation, learning and memory, virtual reality environment, cognitive deficit, Morris Water Maze (MWM), psychotic disorders, spatial behavior

INTRODUCTION

The impairment of cognitive functions is considered to be a characteristic and permanent manifestation in patients with schizophrenia disorder (Andreasen, 1999; Elvevag and Goldberg, 2000). 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, problem solving, social cognition, and verbal and visuo-spatial learning (Green et al., 2004). 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). This deficit is demonstrated in 82–84% of the patients (Reichenberg et al., 2009).

Various "paper-and-pencil" or simple computer tests are traditionally used to assess cognitive deficit in schizophrenia. However, these methods 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 et al., 2012). Considerable attention is therefore devoted to the assessment of visuo-spatial 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. It was demonstrated that schizophrenia patients exhibit

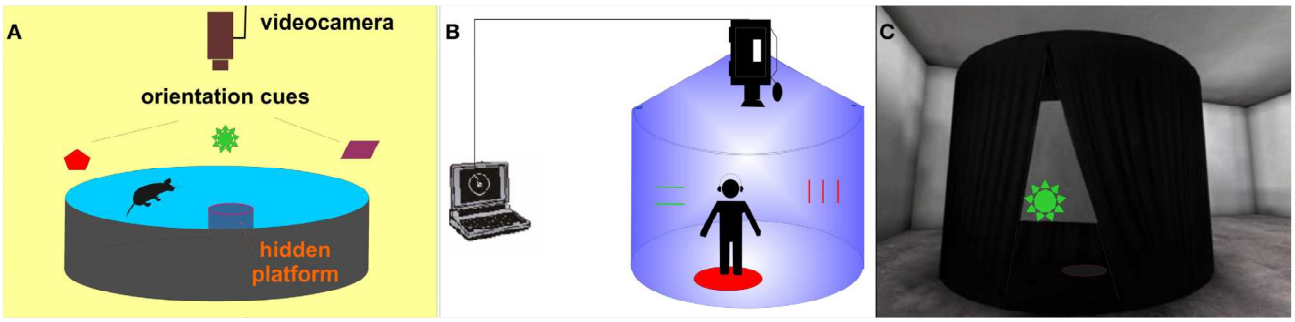

FIGURE 1 | Morris water maze—the hidden platform paradigm - and its human analogs. (A) Scheme of the original MWM apparatus for rats. **(B)** Schematic view of the real human analog called Blue Velvet Arena (BVA). **(C)** Virtual analog of BVA (view of the virtual tent from the outside).

impaired performance on all levels of spatial cognition, from the most basic level of mental rotations of letters and objects (de Vignemont et al., 2006) to more complex spatial navigation abilities (Weniger and Irle, 2008; Landgraf et al., 2010). Numerous studies demonstrated the deficit of the visuo-spatial working memory in schizophrenia (see review; Piskulic et al., 2007) using various tasks. These findings motivate the development of human analogs of animal spatial tasks for application in comparative clinical research.

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 (**Figure 1A**). The MWM apparatus is used in several basic versions (shortly described in Morris, 2008) or protocols (for further information see section Materials and Methods): (1) the *reference memory protocol*, with the hidden platform placed in a stable position; (2) the *reversal protocol*, with a changing platform position; (3) the *delayed-matching-to-place (DMP) protocol* often referred to as the "working memory protocol" which uses variable inter-trial intervals and 4) the *probe trial* with the platform removed. Measurable impairment of visuo-spatial abilities in MWM has already been demonstrated in several animal models of schizophrenia (see review; Bubenikova-Valesova et al., 2008). Several animal studies including the work of our group confirmed that the rodent model of schizophrenia based on administration of MK-801 (dizocilpine, a non-competitive NMDA glutamate receptor antagonist) leads to decreased cognitive functioning in rats, resulting in compromised performance in all variants (reference, reversal, and working memory protocol) of the MWM task (Stuchlik et al., 2004; Vales et al., 2006; van der Staay et al., 2011; Lobellova et al., 2013).

Several real space human MWM analogs have been developed to test the human spatial navigation, mostly in dry circular arenas (Overman et al., 1996; Skolimowska et al., 2011). A real analog of the MWM has also been developed in our laboratory as an apparatus named the "Blue Velvet Arena (BVA)" (Stepankova et al., 1999; Laczo et al., 2010; see **Figure 1B**). 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 (Bohbot et al., 1998; Jacobs et al., 1998; Moffat and Resnick, 2002; Astur et al., 2004; Mueller et al., 2008; Goodrich-Hunsaker et al., 2009) or working memory paradigm (Rodriguez, 2010). However, only the reference memory protocol has been applied to schizophrenia patients (Hanlon et al., 2006; Folley et al., 2010).

Thus, our aim 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 analog of the real BVA apparatus designed previously by our group (Stepankova et al., 1999; depicted in the **Figure 1C**). 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 the healthy controls in the vFGN task in terms of: (1) impaired spatial learning during the Reference memory (RM) session; and (2) decreased working memory performance in the Delayed-matching-to-place (DMP) session. Since several studies described sex differences in spatial abilities of rodents (see meta-analysis by Jonasson, 2005) and humans (e.g., Astur et al., 1998, 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 the same in both groups. Moreover, the effect of several clinical parameters, such as the duration of untreated psychosis (DUP), general functioning (GAF score), clinical symptoms (PANSS scores) and antipsychotic medication [dose calculated in chlorpromazine (CPZ) equivalents], was evaluated in the group of patients.

MATERIALS AND METHODS

EXPERIMENTAL SUBJECTS

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: (1) no history of neurological disease or loss of consciousness longer than 10 min; and (2) native in Czech/Slovak

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).

	Group mean (*SD*)		Group differences	
Demographic variable	**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	–		
Neurocognitive assessment	**Raw test scores—Mean (*SD*)**			
	SZ	**HC**	**Mann-Whitney U**	***p*-value**
TMT—*A*	38 ± 12.1	26.5 ± 8	131.5	0.0001
TMT—*B*	98 ± 44	50 ± 11.5	82	0.0001
RCFT—copy	31.6 ± 5	35.7 ± 0.9	98.5	0.0001
RCFT—3 min recall	17.2 ± 8	26.2 ± 5.5	108.510	0.0001
RCFT—30 min recall	17.7 ± 7	26 ± 4.9	4.5	0.0001
Digit Span (WAIS-III)—*forward*	9.3 ± 3.7	10 ± 2.3	254.5	0.09
Digit Span (WAIS-III)—backward	5.3 ± 2.1	7.4 ± 2.1	137.5	0.0001
Spatial Span (WMS-III)—*forward*	8.5 ± 1.8	9 ± 1.4	281.5	0.42
Spatial Span (WMS-III)—*backward*	7.5 ± 2.5	9 ± 1.4	218.5	0.046

SZ, first episodes schizophrenia patients; 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; TMT, Trial Making Test; RCFT, Rey-Osterrieth Complex Figure. WMS-III, Wechsler Memory Scale III edition; WAIS-III, Wechsler adult intelligence scale III edition.

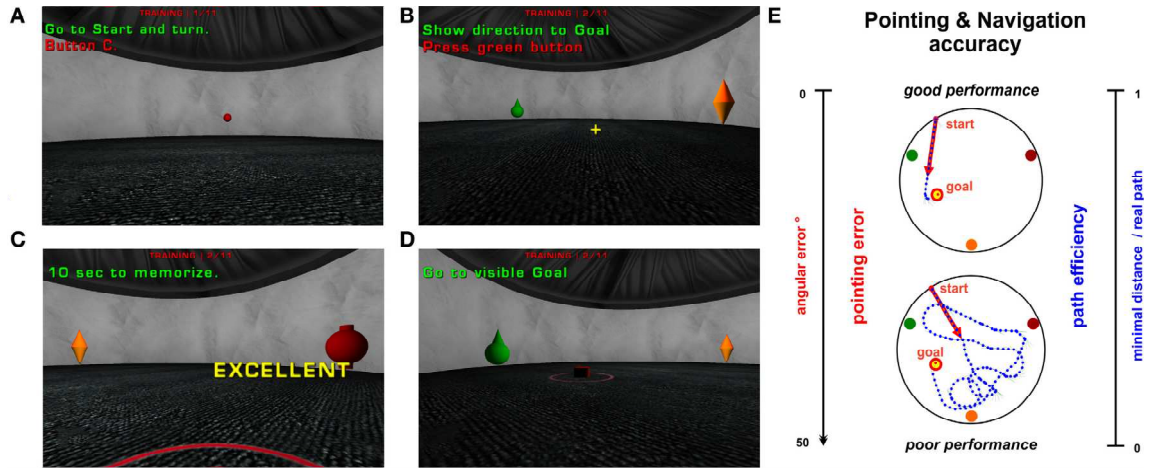

FIGURE 2 | Virtual version of the BVA apparatus from the inside—one trial procedure. (A–D) demonstrate individual phases of one trial using the first-person previews from the vFGN task. The short instructions used as a reminder for the participants were translated to English. **(A)** The starting position is presented as a red sphere. **(B)** Two visible orientation cues (from a set of three cues with various shapes and colors) and yellow cross in the middle of the screen used to point toward the hidden goal direction. **(C)** Goal position visualized after 60 s trial time limit. **(D)** Movement blocked after the entrance to the goal position enabling only rotational movement in 10 s memorizing. **(E)** Illustration of the two parameters measured in all trials (except the probe trial). 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 the 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 the path efficiency parameter.

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.

APPARATUS AND SOFTWARE

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 *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 2C**). 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.

CLINICAL AND NEUROPSYCHOLOGICAL ASSESSMENT

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 CPZ equivalents (according to Woods, 2003; Andreasen et al., 2010). For details on the clinical parameters see **Table 1**.

Overall cognitive performance was measured in both patients and healthy controls with several neuropsychological tests compatible with the MATRICS battery to assess psychomotor speed, mental flexibility, learning, and memory (see **Table 1**): *Trial Making Test* (A and B; Reitan and Wolfson, 1993 modified by Preiss, 1997); *Rey-Osterrieth Complex Figure* (Meyers and Meyers, 1995); *Digit span* of the WAIS-III (Wechsler, 1997a); *Spatial span* (computer version adapted from the Corsi block test in the PEBL battery (PEBL, 2012) and modified according to Spatial span of the WMS-III (Wechsler, 1997b).

PRE-TRAINING OF MOTOR CONTROL

Prior to the task, all of the participants underwent a short (5 min long) pre-training of movement control using the gamepad apparatus (see time schedule in **Figure 3**). Afterwards, the participants performed a simple task in a complex virtual labyrinth maze 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." After completing the pre-training, all of the tested subjects performed the vFGN task.

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 toward a pseudorandom starting position displayed as a red sphere near the arena wall (see **Figure 2A**). Then, three orientation cues were

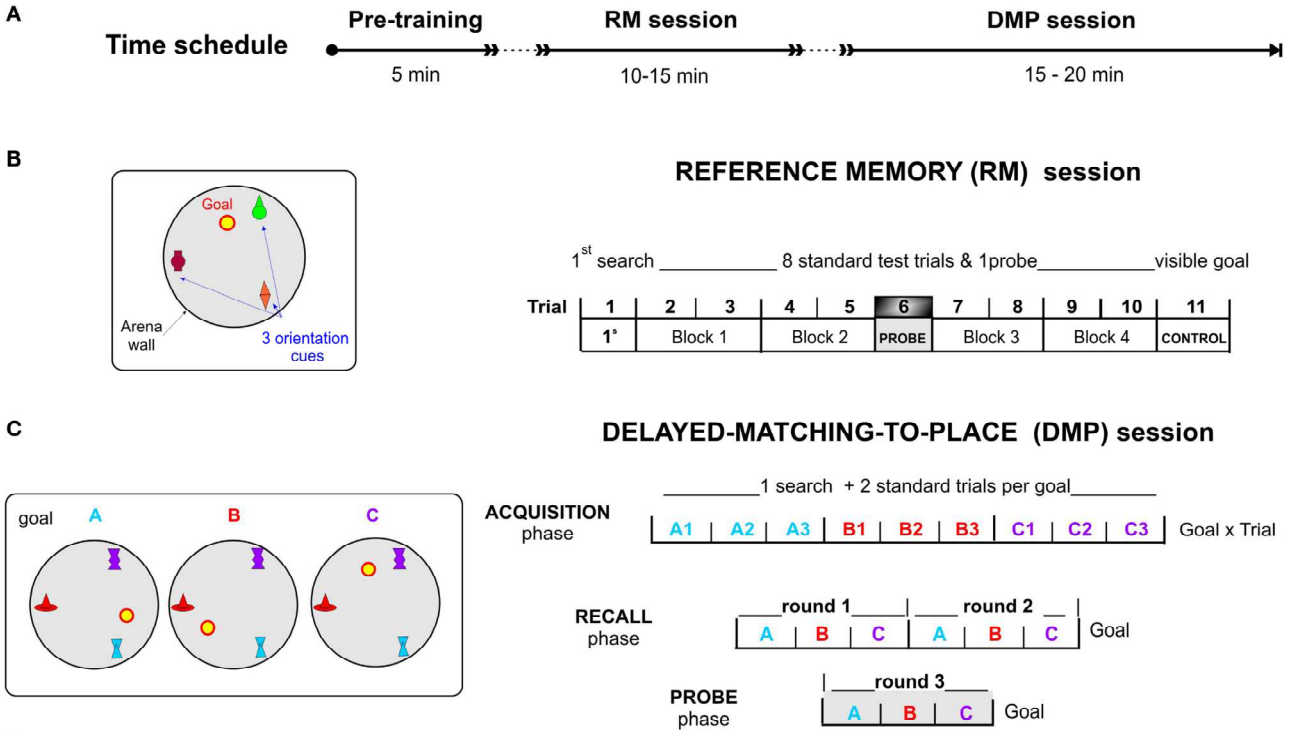

FIGURE 3 | The virtual Four Goals Navigation (vFGN) task. (A) upper panel presents the time schedule of the experiment. Spatial configurations with the goal positions used in individual sessions are presented on the left and the procedure of individual parts of the task on the right. **(B)** REFERENCE 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 toward a visible goal. **(C)** DELAYED-MATCHING-TO-PLACE session with goal in three 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 ABC (6 trials in total); PROBE phase, one spatial sequence ABC with inactivated goal positions (3 trials).

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 toward the hidden goal position using the yellow cross in the middle of the screen (see **Figure 2B**) 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 2C**) 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 2D**). This "learning time" represented the analogy of an animal standing on a platform for several seconds after each trial.

The vFGN task consisted of two parts: the RM and the DMP sessions; both administered successively in 1 day protocol (Time schedule in **Figure 3**).

Part I—Reference memory (RM) session

In the session completed at the beginning of the vFGN task, was designed according to the original reference memory protocol (Morris, 1981, 1984; Morris et al., 1982). Similar to other human MWM analogs (Jacobs et al., 1998; Astur et al., 2002) the task was shortened into 1 day protocol to test spatial learning and memory by monitoring the performance improvement in 11 consecutive trials (see **Figure 3B**). 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 2 trials in **Figures 3, 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 toward 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

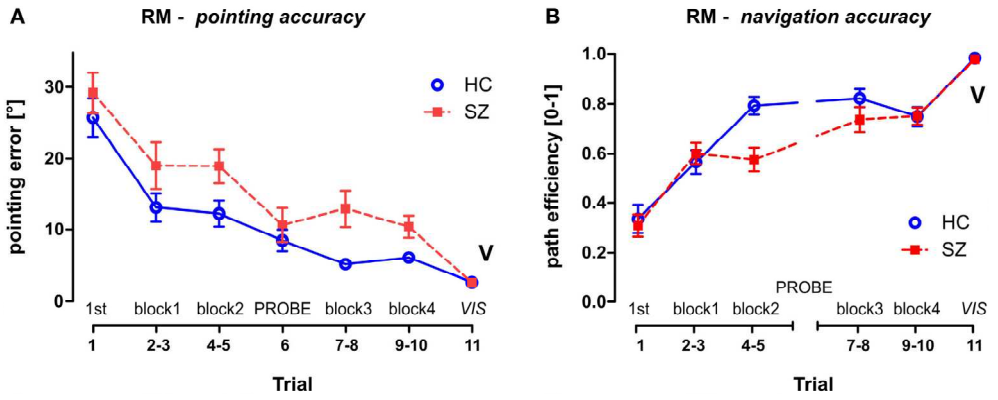

FIGURE 4 | Reference Memory (RM) session group performance. (A) The pointing error (mean ± s.e.m) and **(B)** the path efficiency (mean ± s.e.m) measured in individual trials and/or blocks of trials. The probe trial T6 is not depicted in the path efficiency parameter, the control trial T11 is marked by letter V (as displayed). HC—Healthy controls; SZ—first-episode schizophrenia patients.

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 3C**):

(1) The **ACQUISITION** phase involved 9 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 3 trials (see **Figure 3B**). 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 (Lipp et al., 1998; Vorhees and Williams, 2006; Garthe et al., 2009; Lobellova et al., 2013) 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.

(2) The **RECALL** phase together with the Acquisition phase represents a modified version of the DMP paradigm (for review see Dudchenko, 2004; also in Morris et al., 1986; Steele and Morris, 1999; O'Carroll et al., 2006) 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, 2001). 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 3B**).

(3) The **PROBE** phase, involving 3 trials with inactivated goal position, was conducted directly after the Recall phase as a final third round of the spatial sequenced recall (see **Figure 3B**). 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, 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 (Hanlon et al., 2006; Moffat, 2009; Folley et al., 2010). 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 toward the goal position and its value decreases with growing precision in pointing performance (see **Figure 2E**). The distance parameter expresses the *navigation accuracy* and it is referred to as **path efficiency** (abbr. **path eff**) with the range of 0–1. 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 2E**). 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 × 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.

RESULTS

The groups did not differ significantly in any of the demographic parameters, except the gaming experience, 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 1**). 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 **Figures 4–8**).

GROUP DIFFERENCES IN THE vFGN TASK

RM session

To analyze the group differences in the RM session a GLM analysis was performed with the group as one of the main factors (group × sex) and block (pairs of standard trials, see **Figure 3A**) as a repeated measure factor. This analysis showed impaired learning performance of the schizophrenia group in both measured parameters (see **Figure 4**). 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 × 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 ($p < 0.001$).

To compare the first search trial (T1) of the RM session with the remaining standard trials, another GLM analysis was performed on individual trials. The interaction identified between the group and repetition trials was tested by the *post-hoc* test and revealed that T1 differed significantly from all of the following standard trials in the RM session ($p < 0.05$) in both of the measured parameters. This demonstrates fast learning of the goal position after one learning episode.

One probe trial (T6) was inserted in the middle of the RM session (see **Figure 5**) 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 [$t_{(56)} = 1.4$, $p = 0.16$].

The visible goal trial (T11, marked as V in **Figure 4**) 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 [$t_{(56)} = 0.09$; $p = 0.93$].

DMP—ACQUISITION phase

The main effect of the trial as repeated measures factor was found in the Acquisition phase of the DMP session ($p < 0.001$)

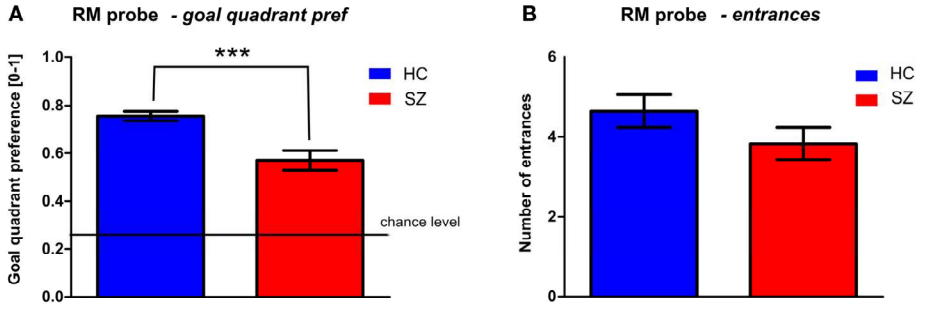

FIGURE 5 | Probe trial (trial T6) performance in the middle of RM session. (A) The goal quadrant preference (mean ± s.e.m) and **(B)** the number of entrances (mean ± s.e.m) into the inactivated goal position. Annotation: ***$p < 0.001$ group difference. HC, Healthy controls; SZ, first-episode schizophrenia patients.

tested using GLM analysis (group × sex) with repeated measures (goal × trial) (see **Figure 6**). The main group effect was found in the pointing accuracy for trials 2 and 3 [$F_{(1, 54)} = 7.8$; $p < 0.01$]. The 1st search trials—A1, B1, C1—representing the free exploration trials were excluded from the analysis as they represent random performance. However, no group differences were identified in the path efficiency parameter, even the interaction effect (trial × group) only approached the significance level [$F_{(2,108)} = 2.8$, $p = 0.068$]. No other significant interactions were obtained from the analysis.

DMP—RECALL phase

The GLM analysis with repeated measures (round × goal) was used to analyze the performance in the two Recall rounds in comparison to the performance observed in the last Acquisition trials—A3, B3, and C3 (see **Figure 7**). 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 efficiency parameter showed only main effect of round as repetition factor ($p < 0.001$), we identified an interaction effect (group × 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 after the time delay between the last trials of the Acquisition phase (trials 3) and the first Recall round ($p < 0.001$). No differences have been identified between the two Recall rounds. Interestingly, no main effects or interactions of the goal position were identified.

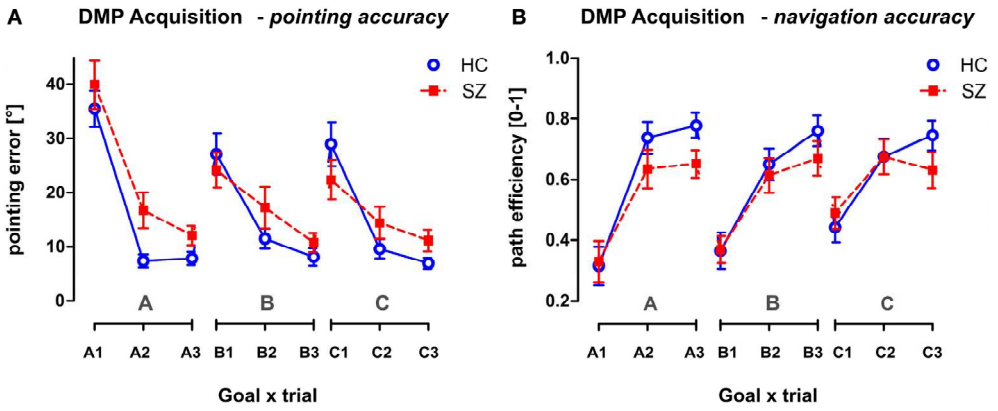

FIGURE 6 | The performance of both groups in the Acquisition phase of the DMP session. The behavior is measured after three consecutive spatial changes, the hidden goal is placed in three possible goal positions (A, B, C), in different relationships to the orientation cues. Trials marked as A1, B1, and C1 required the subject to search for the hidden goal after announcement of the positional change. The next 2 trials required repeated search for the hidden goal. The behavior is shown in all 9 trials presented in the order applied during the Acquisition phase using the two following parameters: **(A)** The pointing error (mean ± s.e.m) and **(B)** the path efficiency (mean ± s.e.m). HC, Healthy controls; SZ, first-episode schizophrenia patients.

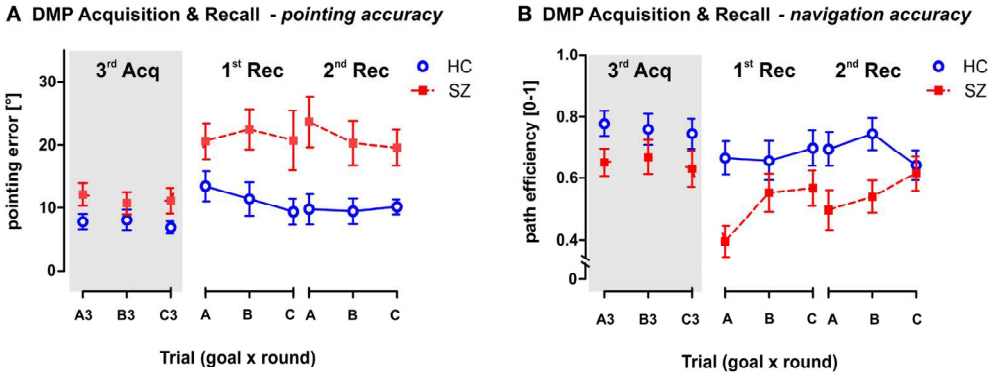

FIGURE 7 | Pointing and Navigation accuracy in the Recall phase of the DMP session in comparison to the performance in the 3rd trial of the Acquisition phase. (A) The pointing error (mean ± s.e.m) and **(B)** the path efficiency (mean ± s.e.m) measured in individual trials. Panels 1st Rec and 2nd Rec show the group performance in the two rounds of the Recall phase. Each round requires recalling the previously learned goal positions in the correct sequence (ABC). Gray area on the left (marked as 3rd Acq) represents the performance achieved in the last (3rd) repetitions of each goal position (A3, B3, and C3) in the Acquisition phase. It illustrates the drop in behavioral performance due to time delay between the last Acquisition trial and the Recall phase. HC, Healthy controls; SZ, first-episode schizophrenia patients.

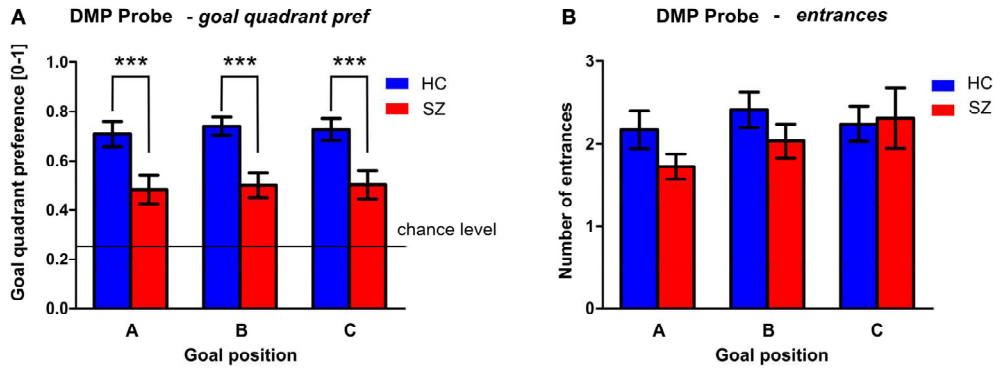

FIGURE 8 | PROBE phase of the DMP session. (A) The goal quadrant preference (mean ± s.e.m) and **(B)** the number of entrances (mean ± s.e.m) into the inactivated goal position presented separately for individual goal positions. Annotation: $***p < 0.01$ group difference. HC, Healthy controls; SZ, first-episode schizophrenia patients.

Table 2 | 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	Age correlations					
	Schizophrenia patients $N = 29$			Healthy Controls $N = 29$		
Averaged performance	$r(X,Y)$	t	p	$r(X,Y)$	t	p
avgPath-RM1	−0.48	−2.83	0.009	0.10	0.50	0.62
avgPoint-RM1	0.14	0.77	0.456	−0.20	−1.04	0.31
avgPath-AcqDMP	−0.38	−2.12	0.043	−0.06	−0.31	0.76
avgPoint-AcqDMP	0.33	1.82	0.079	0.10	0.55	0.59
avgPath-RecDMP	−0.49	−2.95	0.006	0.01	0.06	0.95
avgPoint-RecDMP	0.42	2.43	0.022	0.14	0.76	0.45
avgQuadrant- ProbeDMP	−0.36	−2.01	0.054	0.01	0.07	0.95
avgEntrances-ProbeDMP	−0.49	−2.92	0.007	−0.18	−0.96	0.35

avgPath, averaged path efficiency performance; avgPoint, averaged pointing error; avgQuadrant, averaged goal quadrant preference; avgEntrances, averaged number of entrances to the goal; RM1, first half of the RM session; AcqDMP, Acquisition phase of the DMP session; RecDMP, Recall phase of the DMP session; ProbeDMP, Probe phase of the DMP session; r (X,Y), correlation coefficient.

DMP—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 8**. 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 (50 ± 23%). No significant group differences were identified in the number of entrances to the goal position.

SEX AND AGE DIFFERENCES

In order to show the possible effects of sex on spatial performance in the vFGN task, sex has been used as additional main factor in the GLM analysis (group × sex) with repeated measures performed on individual phases of the task. Interestingly, some sex differences have been observed in almost all parts of the task but exclusively only for the parameter of path efficiency. The main effect of sex was found significant only in the path efficiency in the RM session [$F_{(1, 54)} = 4.2$, $p < 0.05$]. Sex differences approached the significance level in the path efficiency measured in the Acquisition [$F_{(1, 54)} = 3.6$, $p = 0.064$] and the 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. No differences have been observed either in the pointing accuracy or in the quadrant preference measured in the probe trials. Importantly, 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 2**). The averaged path efficiency in the group of healthy volunteers negatively correlated with the

age of individual subjects in all parts of the task. Similarly, the averaged pointing error in the Recall phase and the number of entrances in the Probe phase was significantly affected by the age variable. Importantly, 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 the 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 (averaged separately for individual vFGN parts—RM session and three parts of the DMP session). A stepwise forward multiple regression analysis employed using these predictors only identified the following significant effects—positive effect of GAF score on spatial learning ability expressed as the averaged pointing accuracy ($b_{GAF} = -0.52$; $p < 0.05$) and the navigation accuracy ($b_{GAF} = 0.49$; $p < 0.05$) in the RM session. The full model was significant only for pointing accuracy ($R = 0.57$; $R^2 = 32\%$; $p = 0.045$), but not for the path efficiency ($R = 0.54$; $R^2 = 30\%$; $p = 0.06$), both with GAF and DUP predictors added in 2 steps (all other predictors were removed). In the Recall DMP phase measured by the path efficiency, a significant effect of PANSS-G ($b_{PANSS-G} = 0.68$; $p < 0.05$) and CPZ level ($b_{GAF} = 0.7$; $p < 0.05$) was identified. The whole model, with non-significant DUP and PANSS-N as additional predictors added in the succeeding steps, was not significant ($R = 0.67$; $R^2 = 44\%$; $p = 0.066$). No other significant effects were found by applying this regression model.

DISCUSSION

Both parts of the newly developed virtual vFGN task demonstrated sufficient sensitivity toward 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 (Waller et al., 2001). This pointing error parameter showed higher sensitivity toward 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, 2008) calculated as percentage of time in the correct arena quadrant was more sensitive toward 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 (Hanlon et al., 2006; Folley et al., 2010) and animal models of schizophrenia (Gorter and de Bruin, 1992; 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 analogs (Nadel et al., 1998; Leplow et al., 2003). 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.

This assumption is supported by the fact that the navigation accuracy improved after the insertion of a single probe trial (in the middle of the RM session) that could facilitate their motivation to focus on important spatial information due to the previous unsuccessful search. This finding supports our assumption that the measured spatial performance is affected by attention deficit measured using standard neuropsychological tests (TMT and Digit span, see **Table 1**).

In addition, results obtained in the probe trial 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). Interestingly in animal studies only first half of the probe trial (first 30 s) shows group differences in rodent model of schizophrenia (e.g., Entlerova et al., 2013), as afterwards even the intact animals tend to leave the unrewarded position. However, due to the verbal instruction, our subjects tend to look for the goal during the whole trial. Despite these differences, the human analog 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. On the other hand, the number of entrances parameter failed to show significant group differences. This discrepancy indicates that most of the subjects (from both groups) identified the correct goal position, but only the healthy controls tend to stay in the goal area.

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 toward 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 was also observed in animal studies where only an 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 of individual goal positions, the goals were placed in identical positions (in the meaning of spatial relationship between the goal position and the orientation cues). Such settings could be a source of skill learning effect that could explain the lack of between-group differences observed in the navigation accuracy. Nevertheless, the low sensitivity of the reversal protocol toward the cognitive deficit in schizophrenia is in accordance with the animal studies that failed to find group differences after application of lower doses of MK-801 (Watson and Stanton, 2009; Lobellova et al., 2013). Interestingly, similar reversal protocol applied in the avoidance task on the rotating arena showed that the pre-training of animals in the task (as in our RM session) 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 the last repetition 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 analog of the DMP MWM protocol. 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. The strong performance decline in the group of patients (but not in healthy controls) demonstrates the working and/or 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. Nevertheless, 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 the studies describing sex differences in spatial abilities of both rodents (e.g., Roof and Stein, 1999; Cimadevilla et al., 2000) and humans (e.g., Astur et al., 1998, 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 exclusively for the navigation accuracy (path eff) parameter. This fact and the lack of significant sex differences in other parts of the task suggest the following: (1) the simple circular environment prevents the usage of abilities found to be affected by sex (environmental geometry); (2) the directional information was gained similarly in males and females, yet females tend to use less precise trajectories when navigating toward the goal. This could be due to sex differences in motor skill learning; (3) the animal experiments done with pre-training in MWM protocol showed to exhibit smaller sex differences (Jonasson, 2005), as all the three goal positions have been placed in geometrically identical positions. The lack of interaction between sex and group factor in the measured parameters shows that the presented group effects are independent of the sex differences.

According to the current literature describing negative effect of aging on spatial learning and memory processes (e.g., (Moffat and Resnick, 2002; Moffat, 2009)), 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 decline 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 SYMPTOMS AND ANTIPSYCHOTIC MEDICATION

One of the currently monitored clinical parameter is the *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.

Current literature describes a strong association of cognitive functions and negative symptoms, but the absence of a positive symptom 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 connection between the GAF score and spatial learning performance in the RM session and effect of generalized symptoms in the Recall phase of the DMP session. These results demonstrate that high-functioning patients perform better in the cognitive tasks than the low-functioning individuals in the group of schizophrenia patients (Green et al., 2004).

Older studies described negative effects of the first-generation antipsychotic treatment on the cognitive functioning in schizophrenia (Spohn and Strauss, 1989). On the contrary, the current studies addressing atypical antipsychotics reported slightly positive effects of some drugs on the 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 affected by the antipsychotic dosage calculated in CPZ equivalents in the navigation accuracy parameter. We did not find any other effect of the atypical antipsychotic treatment on the overall cognitive performance in the vFGN task. Nevertheless, 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 the 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 had been motivated as they all voluntarily 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 toward 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 1 day, the RM protocol could be considered too short to assess long-term memory processes. However, 1-day protocols are common in human studies testing learning abilities and long-term memory in standard tasks (such as verbal or non-verbal learning memory tasks) and in virtual MWMs that have been considered a valid human analogy of spatial RM in rats, and supported by both behavioral data (e.g., Jacobs et al., 1998) and dependence on hippocampal function (e.g., Astur et al., 2002; Goodrich-Hunsaker et al., 2009).

Also the DMP session in our study is not fully comparable to the animal DMP protocol 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 (3) trials, as an analog to a reversal protocol, and due to that the spatial information could be retained in the long-term and not the working memory. 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 the 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 analyzed 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 patient group observed in the vFGN task was not unitary and showed higher individual variability than the performance in the healthy control group. This variability could be partly produced by the early assessment of patients. Despite these limitations, our findings are supported by the results of studies describing variability of the cognitive deficit level measured in individual first-episode schizophrenia patients (Keefe et al., 2005). In order to understand how the spatial performance was affected by the present attention or memory deficits, further analysis of the spatial performance measured in the vFGN task and its association to standard measures of cognitive deficit is required. A separate paper will be devoted to tracking the possible effects of demographic variables, gaming experiences and cognitive functioning 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 toward 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 analog 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 and/or long-term 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 the first episodes of schizophrenia, confirmed by standard neuropsychological methods. We do believe that the vFGN task assessing complex visuospatial behavior could serve as an ecologically valid screening method more sensitive toward 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 1 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 due to potential relapse of the illness. Longitudinal data revealing the trajectory of vFGN performance during the course of schizophrenia are needed.

AUTHOR CONTRIBUTIONS

Mabel Rodriguez and Iveta Fajnerová designed the study and together with Kamil Vlček wrote the original protocol. Jiří Horáček refined the protocol. Iveta Fajnerová and Kamil Vlček prepared the VR experiment. Iveta Fajnerová, David Levčík and Lucie Konrádová recruited the participants, performed the behavioral and neuropsychological testing and Pavol Mikoláš collected the clinical data. Cyril Brom and his students provided all VR software used in the study. Iveta Fajnerová and Kamil Vlček processed the data and undertook the statistical analysis. Mabel Rodriguez, Kamil Vlček and Jiří Horáček supervised the study. Iveta Fajnerová wrote the first draft of the manuscript. Jiří Horáček, Aleš Stuchlík and Kamil Vlček contributed to data interpretation. All of the authors discussed the results and contributed to the final version of the paper and have approved it.

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Spatial navigation in virtual reality - from animal models towards schizophrenia

Spatial cognition tests based on animal research

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***Abstract*— Schizophrenia is manifested in positive, negative and cognitive symptoms. Especially, the cognitive symptoms offer useful methodological approach for comparative studies using spatial navigation tasks in both, schizophrenia patients and animal models of cognitive deficit in schizophrenia. In order to demonstrate the deficit of spatial cognition in schizophrenia and to test the validity of pharmacological model, we designed two virtual tasks inspired by previous animal research: the virtual Morris water maze and Carousel maze. The newly-designed tasks require the tested subject to navigate toward several hidden goal positions placed on the floor of an enclosed stable arena or on a rotating arena. Data obtained in a group of schizophrenia patients and matched group of healthy volunteers show cognitive impairment in first episodes of schizophrenia using both, standardized neurocognitive methods and newly-developed virtual tests. The virtual test batteries show different involvement of navigation strategies and different level of impairment in schizophrenia patients. These findings indicate usefulness of these virtual methods in future cognitive remediation. Despite the fact, that both virtual tasks test spatial navigation towards hidden goal, obtained results are divided into partly different clusters using PCA, while performance parameters measured in the stable arena form a cluster mostly with tests of memory and executive functions; the rotating arena seems to be more related to performance tests dependent on timing, psychomotor speed and mental flexibility.**

Keywords — cognitive functions; spatial navigation; schizophrenia; virtual reality environment, Morris water maze; Carousel maze; neurocognitive assessment; cognitive strategies

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I. INTRODUCTION

The impairment of cognitive functions is considered to be a characteristic and permanent manifestation in patients with schizophrenia disorder [1].

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 [2].

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 [3]. This deficit has been demonstrated in 82-84 % of the patients [4].

Tasks used to test spatial abilities have the potential to address similar cognitive performance in humans and animals. Impairment of visuo-spatial abilities has been already demonstrated in animal models of schizophrenia [5,6,7] and also in schizophrenia patients using various virtual tasks developed on the basis of the original paradigms for animals [8,9,10]

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 [11] and the Carousel maze paradigm (active place avoidance task developed by [12]). Both paradigms have been adjusted and transformed to single day protocols in order to test human subjects. Experiments have been conducted in virtual reality (VR) environments created using the Unreal Tournament game engine editor that allowed us to build large-space and/or moving environment.

Both groups of participants have been tested using standard neuropsychological methods in order to compare the performance in newly designed virtual tests with standardized performance.

II. METHODS

A. Participants

A study group of 29 (17 males and 12 females, age 18-35) first-episode schizophrenia patients (SZ, diagnosed as acute psychotic episodes with schizophrenia symptoms 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. Patients were recruited in the early remission phase during their first psychiatric hospitalization, therefore considered to be first-episode schizophrenia patients (FEP) with a variable duration of untreated psychosis (DUP, 6.4 ± 132.4 months) defined as the duration of untreated but clearly presented psychotic symptoms. All of the patients were tested prior to the end of their hospitalization

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: no history of neurological disease or loss of consciousness longer than 10 minutes; and native in Czech/Slovak language. The main exclusion criterion for control subjects was a personal history of any psychiatric disorder. All tested subjects signed a written informed consent approved by the Ethics Committee.

B. 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.

C. Design and procedure

Clinical and neuropsychological assessment. To confirm the cognitive deficit in our study subjects, all participants (SZ and HC) completed a battery of standard neurocognitive tests (for details on individual tests see Table I).

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;[13], averaged score 56 ± 16) and the Global Assessment of Functioning scale (GAF, [14], averaged score 64 ± 20.5). 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 equivalents (CPZ, avg = 426) according to [15].

TABLE I. LIST OF NEUROCOGNITIVE TEST BATTERY USED AS STANDARD MEASURES OF COGNITIVE FUNCTIONS

Neuro-cognitive battery	Tested function	Abbreviation
Trial making test	A - visual psychomotor speed B- mental flexibility and attention	TMT- A/B
Verbal Fluency Test	verbal psychomotor speed and fluency (phonological vs. categorical)	FAS CategFlu
Perceptual vigilance taks	lapses -reaction slower than 500 ms	PVT
Auditory Learning Test	verbal learning and memory	AVLT- I-V / VI / 30
Rey/Taylor Complex Figure	visual perception and memory	RCFT-copy / 3 / 30
Digit Span (WAIS-III)	verbal immediate attention (forward) working memory (back)	DigSpan-for; DigSpan- back
Spatial Span (Corsi block test)	visual immediate attention (forward) working memory (back)	COR-for COR- back
Block design (WAIS-III)	Spatial perception, visual abstract processing, problem solving	BLOCK
Similarities (WAIS-III)	Abstract verbal reasoning	SIM
Key Search test	executive functions - visual planning	KST
Money Road Map Test	left-right orientation, mental rotations, attention	RMT

Pre-training of motor control. Prior to the experiment, all of the participants underwent a short (5 min long) pre-training of movement control using the gamepad apparatus. Afterwards, the participants performed a simple task in a complex virtual labyrinth maze 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".

Consecutively all participants performed two virtual tasks, which required the subject to navigate towards 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.

Stable arena. The virtual task with the hidden goal paradigm was inspired by the Morris water maze [11] and was performed in a large-scale enclosed virtual arena (see Fig. 1), designed as a virtual analogy of real space apparatus called Blue Velvet Arena [16]. This virtual Four Goals Navigation (vFGN,[17]) 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.

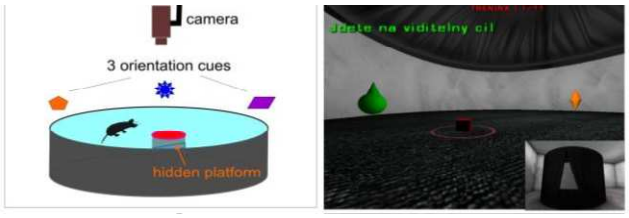

Fig. 1. MWM paradigm (adjusted from Fajnerova et al., 2014): (left) model of the original MWM apparatus for rats; (right) Virtual version, the vFGN task in an enclosed dry arena

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).

Rotating arena. The second virtual test was inspired by the Carousel maze - Active allothetic place avoidance (AAPA) task - performed on a rotating arena [12]. 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, Vlcek 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 connected to two reference frames either: 1) to the frame of the slowly rotating ARENA and rotate together with the tested individual or 2) to the static ROOM and move with respect to the subject and arena (see Fig. 2). 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 goals moving with the arena; *3) Room frame* - navigation towards two goals connected to the room frame (appearing as moving); *4) Frame switching* - alternated search between 4 goals placed either in arena frame or in room frame.

D. 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.

Principal components analysis (PCA) was used in both groups separately to analyze the relationship between the newly-developed virtual tests and standard neuropsychological test battery.

Fig. 2. [left] - The original AAPA task (carousel maze); [middle] - 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). [right] - Rotating arena from the first-person view.

III. 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.

A. Neuropsychological battery

Results obtained using the standard neurocognitive battery has 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 II).

TABLE II. 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*
Perceptual Vigilance task-lapses	9±9	2±4	111 ***
Verbal fluency	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 **

B. Hidden goal on the 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 [17]).

- The first Training phase demonstrates learning difficulties presented in lower accuracy in pointing (Fig. 3A) and navigation ($p < 0.01$) 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

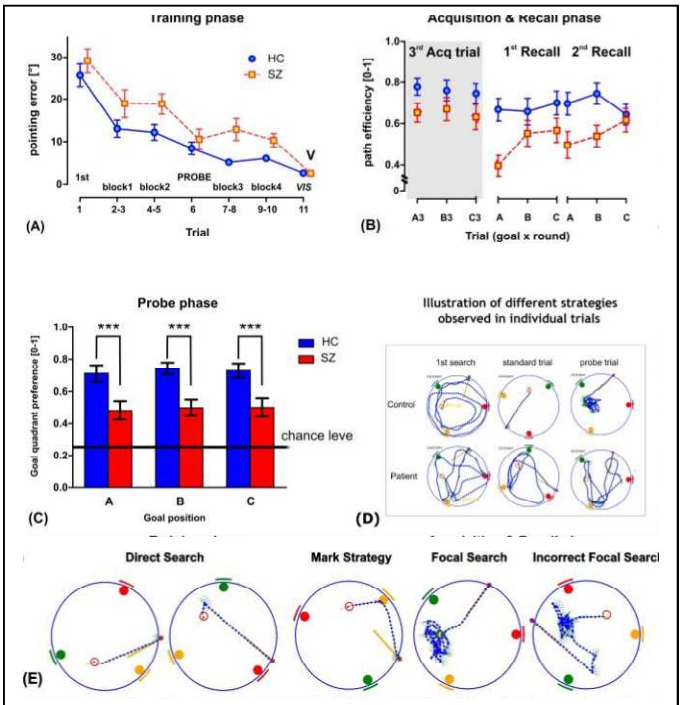

Fig. 3. Performance of both groups in the Stable arena - vFGN task (modified according to Fajnerova et al., 2014). (A) The Training session performance expressed using the pointing error parameter. (B) The path efficiency in Acquisition phase (last trial for each goal position) and in all Recall trials. (C) The time proportion spent in the correct arena quadrant in the last Probe phase. (D) Illustration of some differences observed in individual strategies used in individual trials of the Training session (during the first search, standard trial and probe trial). (E) Illustration of the navigation strategies identified in standard and probe trials during repeated search for the hidden goal position.

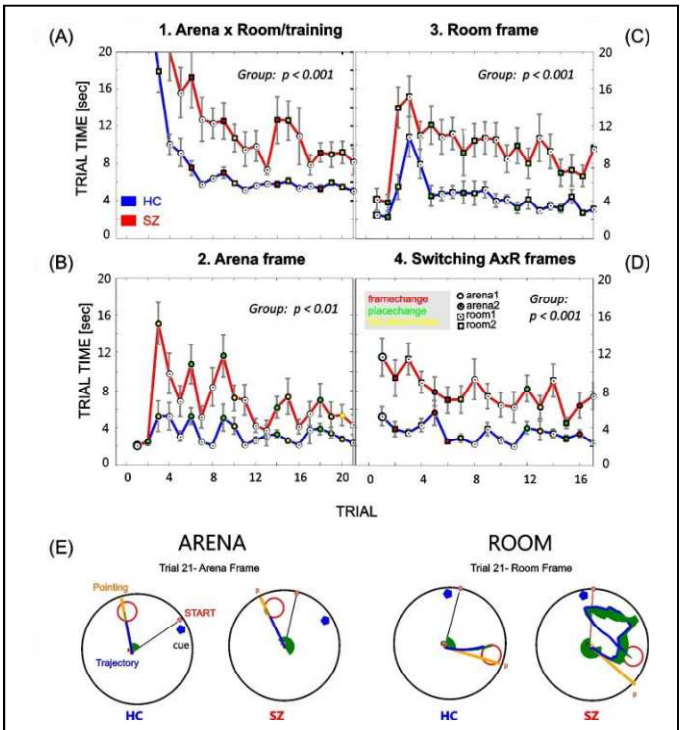

Fig. 4. Performance of both groups in four phases of the Rotating arena -AAPP task - expressed using the trial time parameter. (A) The Training phase with simple frame change (arena x room). (B) The Arena frame performance. (C) The Room frame performance. (D) Frame change -Alternation between all 4 previously acquired goal positions, placed in Arena or Room frame. (E) Illustration of SZ and HC in the last trial in Arena (left) and Room (right) phase: pointing accuracy (orange line) and search trajectory (blue line) towards the goal position (red circle).

navigation accuracy (Fig. 3B – 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. 3B).
- 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. 3C).

To understand the observed behavioral differences, we analyzed the strategies used by both groups to search for the goal position (see Fig. 3D and 3E). Automated analysis 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 Fig. 3E). All other strategies were evaluated as Unknown. We identified the following group differences using the Cochran-Mantel-Haenszel test for repeated 2x2 tests of independence:

Direct search strategies were used in the (2) Acquisition phase more frequently in healthy controls (51%) than in patients' group (43%) (Chi-square = 4.817, $p < 0.5$). Similar difference (even more pronounced) was observed in the (3) Recall phase in HC (61%) and in SZ 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 trials (Chi-square = 17.977, $p < 0.0001$).

C. Hidden goal on the Rotating arena

Similarly, all phases of the virtual AAPP task show decline of spatial performance in schizophrenia. All differences are presented using trial time (TT) parameter (pointing time (PT) and pointing error (PE) parameters are not presented.

- The first Training phase showed impaired learning abilities on the rotating arena (more pronounced in the room frame goal) ($p < 0.01$, Fig. 4A).
- The second phase performed in the Arena frame with 'stable' goals showed only mild decrease in measured

parameters ($p < 0.01$), less expressed in the second half (Fig. 4B).

- However, the third phase with navigation towards the goals connected to the Room frame, moving relative to the subjects (Fig. 4C) showed strongly profound decline of spatial abilities in schizophrenia ($p < 0.001$), probably due to the dissociation between reference frames of the subject and goals.
- 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. 4D).

We individually analyzed the behavior of schizophrenia subjects (see Fig. 4E) and we have identified two main reasons for more profound impairment in navigation abilities while 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 future position of the goal, while patients' own position is shifted by the arena rotation.

D. Virtual tests vs. Standard tests

In order to understand the relationship between the results obtained from the two newly-designed virtual tests (inspired by previous animal research) and the battery of standard neurocognitive methods, we analyzed the data obtained from all tests using a Principal Components Analysis and factor analysis. Prior to the analysis all data were transformed to the same direction (increasing value means larger impairment) and to standard Z-scores.

Performed factor analysis (rotated - Varimax normalized) revealed two main factors (presented on Fig 5 separately for the group of healthy controls and schizophrenia patients). Factor 1 explains 18% of variability in healthy controls and 37% of variability in the group of schizophrenia patients; Factor 2 explains another 12/14 %. Similarly the PCA analysis shows two main factors (see Fig.6): Factor 1 explaining 39% of variability in HC group and 48% in SZ group. Factor 2 explains 30% variability in HC and 12% in SZ group.

Results from individual test batteries (Stable and Rotating arena, Standard neuropsychological methods) are for better visualization presented in different colors (for abbreviations see also Table I). Interestingly, all three test batteries (see FA and PCA results, Fig. 5 and 6) show different distribution in healthy controls and schizophrenia patients. Moreover the Results from the Stable arena environment show more scattered distribution in HC group along with Factor 2, on the other hand results from the Rotating arena environment are more scattered along the Factor 1 in the SZ group. This indicates the following:

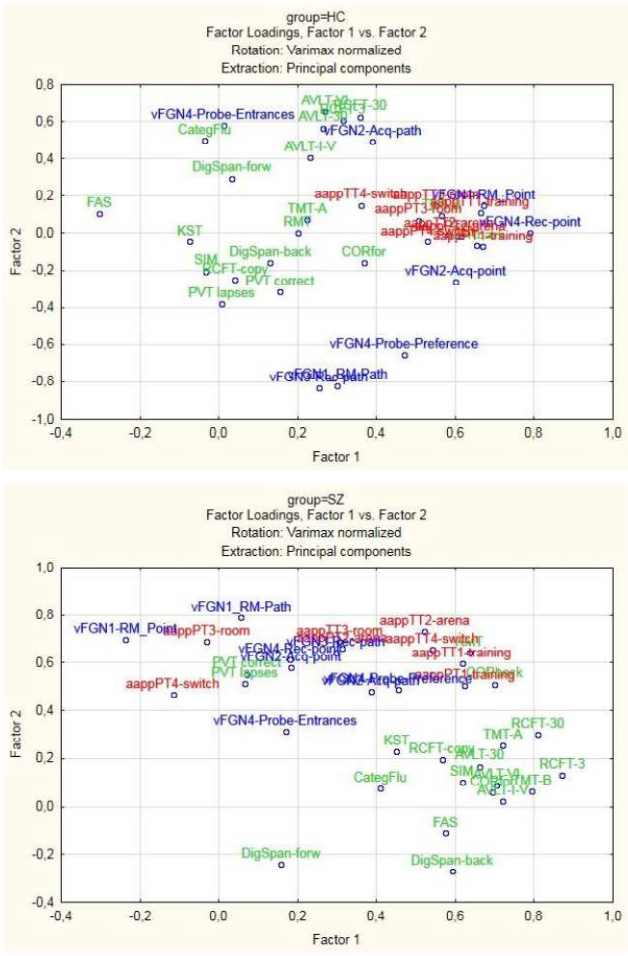

Fig. 5. Results of the factor analyses performed on both tested groups separately, showing the relationship of the two main factors obtained from the analysis. The upper image shows the results obtained from HC group and the lower image the results from the group of SZ patients. Results from individual batteries are presented in different colors (Stable arena – blue, Rotating arena – red, Standard neurocognitive tests – green). Data from virtual test batteries are marked by the number of the test phase order (vFGN 1-4, aapp1-4).

- In general, cognitive performance of SZ group shows decreased variability in comparison to HC group (patients tend to fail in most of the tests).
- The factor analysis in performance of HC group on Stable arena shows assessment of more variable abilities (probably due to more variable measures) in comparison to the uniform performance on the Rotating arena, where only time parameters are measured.
- On the other hand, the SZ group shows increased variability in Rotating arena performance, probably due to observed deficit in room frame and switching condition (not observed in HC group) in contrast to less demanding arena frame performance.
- According to PCA results in HC group, Factor 2 creates clusters of tests focused either on learning and

memory (together with Stable arena results) or on cognitive flexibility and psychomotor speed (together with Rotating arena results). This finding suggests that despite that both virtual batteries test spatial navigation towards hidden goal, they assess partly different abilities.

IV. CONCLUSION

Presented results show significant deficit of visuo-spatial functions in first episode schizophrenia patients, which is demonstrated in both tested paradigms (hidden goal search on stable and rotating arena). The deficit is present in all four phases of these two virtual test batteries. These findings are supported by our results obtained using the battery of standard neurocognitive measures and also data obtained previously in similar paradigms [8, 10]. Our results demonstrate the necessity for remediation of spatial learning and memory after the first psychotic episode.

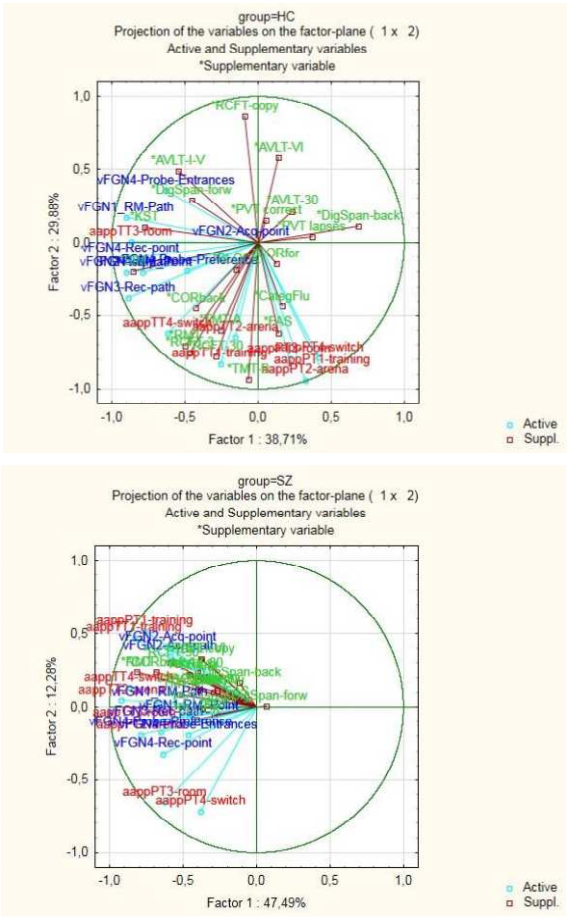

Fig. 6. Results of the PCA performed on the group of schizophrenia patients, showing the relationship of the two main factors. Results from individual batteries are presented in different colors (Stable arena – blue; Rotating arena – red; Standard neurocognitive tests – green). Standard tests results are presented using abbreviations explained in Table I. Data from both virtual batteries (Stable, Rotating arena) are marked by the tests name and order of the test phase (vFGN 1-4, aapp1-4). Individual type of variables are marked by abbreviations (TT-trial time; PT - pointing time; Point/PE – pointing error; Path – path efficiency; Preference – Time spent in the goal quadrant; Entrances- Number of entrances to the goal in Probe trial).

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.

Importantly, individual phases of both presented virtual tests demonstrate 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 and long-term memory, mental flexibility etc.). The first test battery on Stable arena showed that the performance in SZ group was more impaired in Recall and Probe phase than during the training and acquisition process. Similarly in the Rotating arena test battery the navigation towards goals fixed in the room frame, that are unstable relative to the subject's position, was more affected than the search for goal positions rotating together with the arena and the subject. These findings indicate that some parts of these virtual test batteries could form suitable tools for future virtual remediation of impaired visuo-spatial abilities in schizophrenia. Individual parts could be therefore used for remediation of specific functions with increasing level of difficulty.

Moreover we were able to identify some group differences in the strategies used to search for the hidden goal position on Stable and on the Rotating arena. These findings will be later applied in the cognitive remediation of schizophrenia patients, since the incorrect strategies and typically observed mistakes can be individually explained and discussed with the patient during training. This information can be also used to explain typical problems and manifestation of the disease (e.g. deficit in planning) and the way they can be managed.

Considering the fact that our results are in consistence with the behavioural deficit observed in animal models of schizophrenia using similar methods [5,6,7], we believe that both virtual test batteries could be used as tools for future comparative research, in order to identify cognitive changes in neuropsychiatric disorders. In addition, both tests will be useful in future translational research focused on development of new drugs for pharmacological treatment of schizophrenia patients. This can be achieved using similar comparative methods enabling comparison of possible effects of new treatment methods on cognitive functions in schizophrenia and animal model of the disease.

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 and can be easily modified to retest variants.

Currently we perform also repeated assessment one 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. The future analysis will therefore address the results obtained using this repeated measure and possible sensitivity of the developed methods to the future course of illness in individual patients.

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Comparison of Visuospatial and Verbal Abilities in First Psychotic Episode of Schizophrenia Spectrum Disorder: Impact on Global Functioning and Quality of Life

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Objectives: 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). The significance of clinical symptoms and antipsychotic medication was also studied.

Methods: Thirty-six FES patients and a matched group of healthy controls (HC group) were assessed with a neuropsychological battery focused on visuospatial (VIS) and verbal (VERB) functions. Using multiple regression analysis, we evaluated the cumulative effect of VERB and VIS functions, psychiatric symptoms (PANSS) and antipsychotic medication on global functioning (GAF) and quality of life (WHOQOL-BREF) in the FES group.

Results: The FES group demonstrated significant impairment both in VIS and VERB cognitive abilities compared to the HC group. Antipsychotic medication did not significantly affect either VIS or VERB functioning. PANSS was not related to cognitive functioning, apart from the Trail Making Test B. In the FES group, the GAF score was significantly affected by the severity of positive symptoms and VERB functioning, explaining together 60% of GAF variability. The severity of negative and positive symptoms affected only the Physical health domain of WHOQOL-BREF. The degree of VERB deficit was associated with both Physical and Psychological health. Although we did not find any relation between VIS functioning, GAF, and WHOQOL-BREF, a paradoxical finding emerged in the Environment quality domain, where a worse quality of the environment was associated with better VIS functioning.

Conclusions: Our results suggest that the deficit in VIS functions is an integral part of cognitive deficit in schizophrenia spectrum disorders, rather than a side effect of

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symptomatology or antipsychotic medication. Moreover, 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 in evaluating the impact of global cognitive deficit on everyday life in schizophrenia could be questioned.

Keywords: cognitive deficit, first psychotic episode, schizophrenia spectrum disorder, global functioning, quality of life, visuospatial functions, verbal functions, antipsychotic medication

INTRODUCTION

Abnormalities in cognitive functions are considered to be one of the key components in Schizophrenia (SZ). Neurocognitive deficit represents a reliable feature, with moderate to large effect size on global functioning across all cognitive domains (Milev et al., 2005). 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 Quality of life (QOL) (Heinrichs and Zakzanis, 1998; Bilder et al., 2000; Mesholam-Gately et al., 2009). However, studies focusing on specific relationships among cognitive domains or relationships inside the domains and their influence on daily functioning are limited (Harvey et al., 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 a comparative research on animal models of SZ (Fajnerová 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; Spohn and Strauss, 1989; Bilder et al., 1992; Meltzer and McGurk, 1999; Arana, 2000). 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., Peuskens et al., 2005; Houthoofd et al., 2008) and these findings were supported by results in an animal model of SZ (Bubeníková 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 (Jones et al., 2006; Keefe et al., 2007; 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 extent the visuospatial functions impact daily functioning and the quality of life requires more research.

Visuospatial 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., Stuve et al., 1997; Doniger et al., 2001; Butler et al., 2005; Hanlon et al., 2006; Piskulic et al., 2007; Weniger and Irle, 2008; Cocchi et al., 2009; Folley et al., 2010; Landgraf et al., 2010; Fajnerová et al., 2014). This decline in VIS performance is already present in the first episode of schizophrenia and performance further deteriorates over time, predicting poor outcome (Stirling et al., 2003). Cross-sectional studies in subjects with late-life schizophrenia report the impairment in visuospatial ability, alongside with the executive and verbal fluency deficit. Moreover, longitudinal studies suggest that the 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 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., 2005; Malla and Payne, 2005; Milev et al., 2005; Makara-Studziñska et al., 2011). Negative symptoms are more strongly related to poor QOL and psychosocial functioning in SZ outpatients (Eack and Newhill, 2007; Rocca et al., 2009), 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 toward negative and general symptomatology being more evident, varying only in the extent of impact (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 et al., 2004; Chaplin et al., 2006; Leeson et al., 2009), while other studies also point out the importance of specific neuropsychological domains. 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 the 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 (Ritsner, 2007; Fiszdon et al., 2008; Matsui et al., 2008). 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.

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

(1) Are visuospatial abilities impaired in the 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 the antipsychotic medication and the actual psychiatric symptomatology (measured with PANSS)? Is similar effect visible in the VERB functions?
(3) Is the global functioning and the 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?

MATERIALS AND METHODS

Subjects

Thirty-six subjects (22 males and 14 females, FES group) who met ICD-10 criteria for the 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 6-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 min; (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 1**). In each group there were 16 participants with a higher education level (university studies) and 20 with a 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

TABLE 1 | 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

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). All values are present as mean ± SD. 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.

was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 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 0–100) 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 et al., 2010) were used to evaluate the effect of medication dosage on cognitive functioning. For details on the clinical parameters see **Table 1**.

The quality of life was subjectively evaluated by FES subjects using the Quality of life questionnaire WHOQOL-BREF (WHO group, 1998), 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-Expósito et al., 2011). The questionnaire was translated and validated for a Czech population (Dragomirecká and Bartoňová, 2006b).

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 (Green et al., 2004; Nuechterlein et al., 2008). 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 the 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

TABLE 2 | Description of (A) Visuospatial and (B) Verbal neuropsychological tests.

Test	Monitored cognitive function	Test outputs	References	Test description
(A) VISUOSPATIAL NEUROPSYCHOLOGICAL TESTS				
Trail Making Test (TMT A and B)	Psychomotor speed (A); visuospatial working memory (B); mental flexibility (B/A)	Time A (s); Time B (s); Ratio B/A	Reitan and Wolfson, 1985; Preiss and 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 min (RCFT-30)	Osterrieth, 1944; Preiss et al., 2012	Copy and reconstruction of figure after 3 and 30 min
Key Search Test (KST)	Executive functions	Raw scores of strategy	BADS (Wilson et al., 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 et al., 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 to 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 [Reaction time (RT) over 500 ms], average RT speed	PEBL battery (PEBL, 2012; Dinges et al., 1985; Loh et al., 2004)	Response to stimulus appearing in the variable time interval (1–9 s) during 10 min
(B) VERBAL NEUROPSYCHOLOGICAL TESTS				
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	Rey, 1964; Preiss et al., 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 et al., 2012	Speaking aloud words beginning with letters N, K, P or naming category of animals during 1 min
Digit Span (DS)	Attention (forward), verbal working memory (backward)	Raw scores: total (forward + backward)	WAIS-III (Wechsler, 1997); Czech version (Černochová et al., 2010)	Repeating list of numbers forward and backward
Similarities (Sim)	Verbal conceptualization	Raw score–correct responses		Describe similarities between pair of words

performance in the FES subjects with the healthy population, the same test battery was administered to a HC subjects. Below is a description of the three visuospatial methods that have some specific characteristics.

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

A computerized version of the Spatial Span (SS) 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 et al., 2000) applied in the PEBL battery (PEBL, 2012) to match individual positions and spatial sequences of the SS in the WMS-III (Wechsler, 1997; Černochová et al., 2010).

The Money Road-Map-Test (Money et al., 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 Marková et al., 2015) by the angle of the route before each turn relative to the subject's heading: (A) rotation of $<70°$ (9 turns), (B) rotation of 90° (13 turns), and (C) rotation of more than 110° (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 VERB and 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 the accuracy of 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) four individual domains of quality of life measured by WHOQOL-BREF (WHO group, 1998).

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 (**Figure 1** and **Table 1**). 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 **Tables 3A,B**).

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 ms). The FES subjects also made more errors on the Road Map Test (RMT). In addition, splitting of individual turns in the RMT (according to Marková 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 2**). 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 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 DS task. No

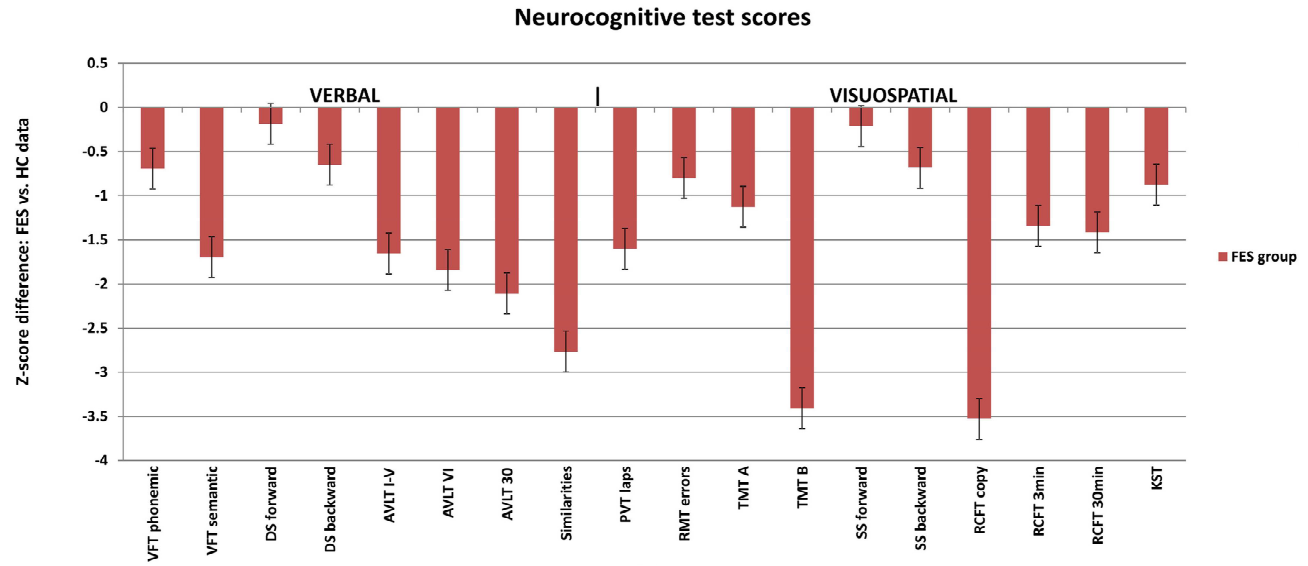

FIGURE 1 | Neuropsychological profile of FES subjects calculated in z-scores for individual test parameters relative to the healthy controls (average Z-score = 0). Selected test results are divided into verbal (left) and visuospatial (right) tests. FES, first psychotic episodes of schizophrenia spectrum 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.

difference was observed in the immediate recall and attention performance in DS forward.

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 the 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 4**). No effect of individual PANSS scores was identified on cumulative VERB and VIS scores.

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 5**). 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.

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 nearly 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 7**).

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

TABLE 3 | Group differences in (A) Visuospatial and (B) Verbal neurocognitive tests.

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***

SE, standard error of the mean; SD, standard deviation. For abbreviations of individual methods see ***Table 1****. TMT, Trail Making Test; RCFT, Rey-Osterrieth Complex Figure; KST, Key Search Test; RMT, Money Road-Map Test (A, B, C—type of errors); SS, Spatial Span; PVT, Perceptual Vigilance Test; AVLT, Auditory Verbal Learning Test; VFT, Verbal Fluency Test; DS, Digit Span. Significance level: *p < 0.05, **p < 0.01, ***p < 0.001.*

parameter, the cumulative VIS score performance. This factor explained together with CPZ level around 27% of the observed variability in domain 4 (see **Table 8**). However, worse Environment QOL was predicted by better VIS functioning and higher AP dosage.

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 the first episodes and chronic SZ subjects (e.g., Green et al., 2004; Fioravanti et al., 2005). First, we selected the 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

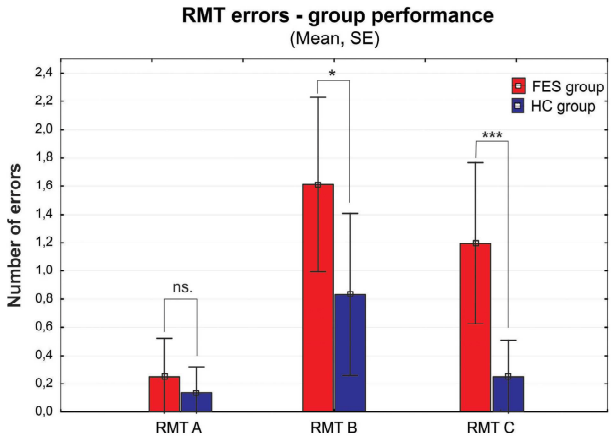

FIGURE 2 | Group performance presented as number of errors on the Money Road Map Test (RMT) (mean ± standard error). Errors are divided into three different types according to the rotation toward subjective perspective of the tested subject (A–less than 70° deviation from subject's heading; B–90°; C–more than 110°). FES group, first psychotic episodes of schizophrenia spectrum disorders; HC group, healthy controls. Significance; ns, non-significant; $^{*}p < 0.05$, $^{***}p < 0.001$.

Figure Test- RCFT) and in the 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 the omission of significant details and even whole sections of the figure (Golden et al., 2002).

Trail Making Test (TMT-A and B) also showed significantly slower 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 et al., 2012). The repeated finding of significantly impaired TMT A and B performance in SZ (Heinrichs and Zakzanis, 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 to our knowledge has not been previously used in FES patients. The higher number of total errors shows deficit in left/right direction sense, and additionally in perspective taking abilities (Schultz, 1991; Marková et al., 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–C), similarly to the mental rotation abilities described previously (e.g., de Vignemont et al., 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 et al., 1997; Ihara et al., 2003; Vargas et al., 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 five 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 (see Fiszdon et al., 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 the key in the retrieval process (Lezak et al., 2012).

The verbal and visuospatial measures (DS and SS) 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 (DS and SS forward). Even though the deficit in verbal WM (DS backward) was stronger than in the spatial WM, there was a trend of significance in SS 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

TABLE 4 | 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

*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.*

TABLE 5 | 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

*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.*

in SS 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 SS and its alternative, the Corsi block tapping test, are commonly used in clinical studies (e.g., Kessels et al., 2000; or studies reported in Lezak et al., 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 (Andreasen et al., 2005; Keefe and Fenton, 2007; Ventura et al., 2009), 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 et al., 2000), whereas positive symptoms and cognitive performance are usually independent in SZ (Addington et al., 1991; Rossi et al., 1997; Andreasen et al., 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 (Jones et al., 2006; Keefe et al., 2007; Lewis and Lieberman, 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

TABLE 6 | Regression model of clinical and neuropsychological variables (predictors) on perceived quality of Physical health (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

*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.*

TABLE 7 | Regression model of clinical and neuropsychological variables (predictors) on perceived quality of Psychological health (dependent variable).

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

*Stepwise multimodal linear regression (N = 27); Psychological health, domain 2 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.*

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 toward TMT-B performance described earlier (see Section Effect of Symptomatology on Cognitive Functioning in FES) 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 et al., 1995; Roy-Byrne et al., 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 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 FES 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 a scale of functioning recommended as a mandatory control assessment by EGOFORS (European Group On Functional Outcomes and Remission in Schizophrenia) initiative (Peuskens and Gorwood, 2012). However, in our opinion, a more ecologically valid scale to measure functioning in relationship to individual neurocognitive domains is needed.

[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 ($r = 0.36$, $p < 0.01$).

TABLE 8 | Regression model of clinical and neuropsychological variables (predictors) on perceived quality of Environment (dependent variable).

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); Environment, domain 4 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.*

Clinical Factors and Neurocognition, and their Effect on Quality of Life in Schizophrenia Spectrum Disorder

According to our results, the quality of life seems to be related more to verbal than visuospatial cognitive measures. Two of the 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 counterintuitive negative correlations (Prouteau et al., 2005; Fiszdon et al., 2008; Narvaez et al., 2008). This negative relation between QOL and neurocognition is often explained with a lack of insight (Prouteau et al., 2005; Narvaez et al., 2008) or with an overestimation of the level of disability due to present depressive symptoms (Bowie et al., 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 and Bartoňová, 2006a). WHOQOL-BREF might therefore not be a suitable tool for the 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 et al., 1997; Aksaray et al., 2002; Fiszdon et al., 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 toward 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 (e.g., Fiszdon et al., 2008; Matsui et al., 2008) 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: $r = -0.602$).

Concluding Remarks

The studies addressing effect of cognitive deficit on global functioning or QOL are common in current research of SZ. However, studies that address these findings in first psychotic episode of schizophrenia spectrum disorder and which include complex verbal and visuospatial cognitive assessment are quite rare. We addressed the need for such research in the present study.

The results of the present study confirmed a deficit of visuospatial functions in FES. This deficit is independent of antipsychotic medication and clinical symptoms. Both global functioning and quality of life were shown to be more related to verbal than to visuospatial functions. Given the findings of negative or missing effect of visuospatial 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. We suggest the need for further investigation of the association of QOL questionnaires and GAF scale to cognitive functioning. Finally, according to our findings, the deficit in executive and memory domains is the most pronounced in the FES group. We suggest that these two domains may contribute to the cumulative cognitive performance affecting QOL and GAF scores. Further research needs to clarify this assumption.

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 toward 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 vs. 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 1 year after their first hospitalization to measure the cognitive functioning in full remission state. Moreover, studies comparing FES 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.

AUTHOR CONTRIBUTIONS

MR, KV, and IF designed the study and together with KD, FS, and ZK wrote the original protocol. IF, DL, LK, and KS recruited the participants, and they performed the neuropsychological assessment. IF and KV pre-processed the data and JP undertook the statistical analysis. MR supervised the study. MR and IF wrote the first draft of the manuscript. FS, KV, and KD contributed to data interpretation. All of the authors discussed the results and contributed to the final version of the paper and have approved it.

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PROSTOROVÁ KOGNICE A SCHIZOFRENIE

SPATIAL COGNITION AND SCHIZOPHRENIA

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SOUHRN

Prostorové chování zvířat i člověka zahrnuje komplexní systém kognitivních schopností, které vykazují vysokou evoluční homogenitu. V navigaci rozlišujeme zejména egocentrické procesy (relativní k vlastní poloze) a allocentrické procesy (orientované vůči externím objektům). Ke studiu navigace často slouží úlohy původně vytvořené pro zvířata (zejména potkany). Dnes nejznámější prostorovou úlohou je navigace na skrytý cíl v Morrisově vodním bludišti. Méně známý je pak Test vyhýbání se místu na rotující aréně. Pro testování lidí byly vytvořeny zejména virtuální verze těchto prostorových úloh. Sledování aktivity nebo důsledku lokálních poškození mozkových oblastí během navigace v těchto úlohách pomohlo objasnit neuronální koreláty prostorové kognice. Tyto poznatky vedly také k testování prostorových úloh při stanovení kognitivního deficitu u schizofrenie i schizofrenii podobného chování u zvířat. Výsledky těchto studií naznačují, že budoucí klinické využití virtuálních prostorových testů může být velice slibné.

Klíčová slova: prostorová kognice, schizofrenie, kognitivní deficit, test hledání skrytého cíle, vyhýbání se místu na rotující aréně

SUMMARY

The spatial behavior of animals and humans involves a complex system of cognitive abilities, which show high evolutionary homogeneity. In particular, we distinguish egocentric navigation processes (relative to their own position) and allocentric processes (oriented towards external objects). To study the spatial cognition tasks originally created for animals (especially rats) are usually used. Today the most famous orientation task is the navigation to the hidden goal in Morris water maze. Less known is the avoidance test on the rotating arena. Virtual versions of these spatial tasks have been created to test the navigation in people. The neuronal activity observed using imaging methods or effects of local brain damage tested during navigation tasks have helped to clarify the neuronal correlates of spatial cognition. These findings also led to the usage of these spatial tasks in evaluation of cognitive deficits in schizophrenia and schizophrenia-like behavior in animals. Results of these studies suggest that future clinical use of virtual spatial tests could be very promising.

Key words: spatial cognition, schizophrenia, cognitive impairment, hidden goal task, place avoidance on rotating arena

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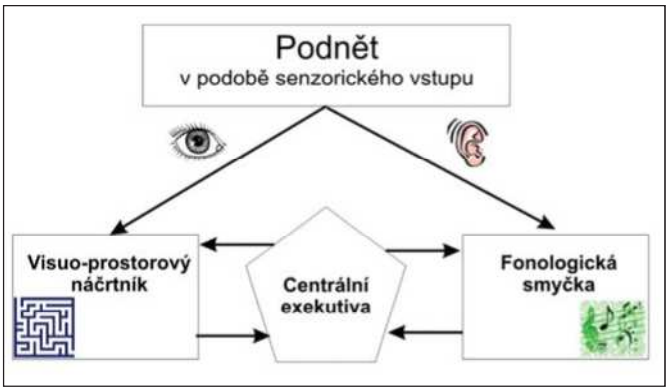
Úvod

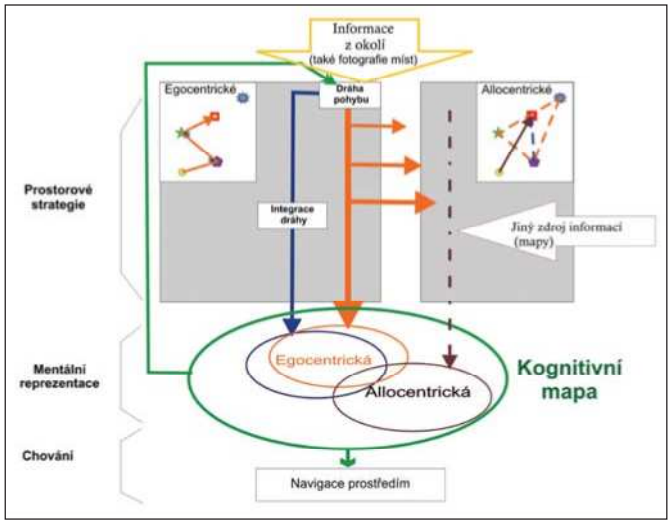
Prostorová kognice představuje složitý systém kognitivních schopností, které umožňují získávání, organizaci, využití a revizi poznatků o prostoru. Tyto procesy jsou pak využity pro orientaci ve dvoudimenzionálním prostoru (např. na ploše papíru nebo monitoru počítače) i během pohybu v jakémkoliv třídimenzionálním prostředí. Testy prostorové kognice dnes patří k častým metodám studia deficitu kognitivních schopností u zvířat i lidí (viz Bohbot et al., 1998; Morris 1984). Prostorové úlohy jsou užitečné ve srovnávacích studiích. Tyto studie sledují především evoluční vývoj kognitivních schopností živočichů různých skupin a umožňují srovnání jejich kognitivních schopností. Mohou se tak uplatnit i při testování účinku léčiv na zvířecí (farmakologické) modely lidských neuropsychiatrických onemocnění, které vedou k rozvoji kognitivního deficitu (např. Alzheimerova demence nebo schizofrenie). Vzhledem k tomu, že u schizofrenního okruhu onemocnění je dnes značná pozornost věnována právě kognitivnímu deficitu, je cílem animálních studií otestovat chování a kognici modelových zvířat. Nejčastějším prostředkem pro takové studie jsou pak prostorové úlohy.

Aby bylo možné srovnávat chování zvířecích modelů a lidí pomocí porovnatelných úloh, je potřebné vyvinout sadu kognitivních testů použitelných u obou skupin. Vzhledem k tomu, že není možné testovat kognitivní schopnosti zvířat pomocí běžných psychologických testů (spojených s verbální složkou), je naopak nutné aplikovat animální metody testující chování a kognici na lidskou populaci. Tyto úlohy vždy testují několik kognitivních funkcí současně, protože není možné je od sebe plně oddělit. Z tohoto důvodu představují prostorové testy komplexní metodu, která je tak často bližší reálným životním situacím, než mnohé stolní testy. Je ovšem náročné vytvořit dostatečně rozsáhlé experimentální prostředí v reálném světě, které by současně umožnilo zaznamenávat chování lidského jedince. Vzhledem k prostorovým omezením těchto úloh v reálném prostředí se dnes stále častěji přistupuje k tvorbě testů využívajících virtuální realitu.

Cílem tohoto sdělení je poskytnout přehled studií věnujících se problematice prostorových úloh u zvířat i u lidí a popsat mozkové



Obrázek 1: ***Schematické zobrazení modelu pracovní paměti tvořené vizuo-prostorovým náčrtníkem, fonologickou smyčkou a centrální exekutivní složkou*** *(Baddeley, 1992)*



Obrázek 2: ***Schematické zobrazení modelu tvorby kognitivní mapy, při kterém se postupně zapojují nejdříve egocentrické a pak i allocentrické procesy*** *(upraveno podle Roche et al., 2005)*

struktury, které se při řešení takových úloh uplatňují, a to s ohledem na možnosti studia schizofrenie.

Prostorová kognice

Prostorová kognice je procesem určování a pamatování si pozice (vlastního těla i okolních objektů), směru a vzdáleností vůči jiným objektům v jakémkoliv prostoru. Součástí prostorové kognice je i následný navigační proces, který využívá těchto informací při udržování určitého kurzu trajektorie směrem k naplánované cílové pozici (Jeffery, 2003). Jedná se o velice komplexní chování využívající do jisté míry všechny kognitivní funkce. Pokud se totiž chceme zorientovat v prostředí a najít v něm cestu k cíli, musíme v první řadě svému okolí věnovat náležitou pozornost a soustředit se na různé zdroje informací (převážně vizuální, sluchové nebo i vnitřní informace o vlastním pohybu). Aby bylo možné z velkého množství dostupných informací vybrat ty, které jsou důležité a vhodné k orientaci, musíme si je správně organizovat. Musíme nejdříve rozpoznat, na jaký objekt se díváme, zařadit ho do určité kategorie, např. na pohyblivé/proměnlivé versus stabilní prvky prostředí, abychom ke své orientaci využili jen ty informace, které jsou relevantní. Při našem pohybu prostředím dochází k neustálým změnám, neobejdeme se proto ani bez činnosti pracovní paměti, která nám umožňuje sledovat, neustále obnovovat a po určitou dobu si pamatovat důležité informace pro naši orientaci. Ve spojitosti s prostorovou kognicí lidí, kteří využívají jako primární zdroj informací vizuální podněty, nás bude zajímat především kapacita vizuo-prostorové složky pracovní paměti (VPP), nazvané vizuo-prostorový náčrtník (Baddeley, 1992). Nemůžeme však opomenout ani centrálně exekutivní složku pracovní paměti, která je odpovědná za vybavování informací, uložených v tomto náčrtníku (viz obr. 1). VPP je přitom definována jako proces zpracovávání a uchovávání informací o vizuální identitě objektů a jejích pozic v prostoru (McAfoose et al., 2009). Předpokládáme proto, že VPP a pozornost jsou pro proces prostorové navigace klíčovými funkcemi. Pro navigaci je samozřejmě důležitá i schopnost odhadu vzdáleností a úhlu vůči sledovanému objektu, založená na naší schopnosti vnímání hloubky pomocí binokulárních a monokulárních vodítek.

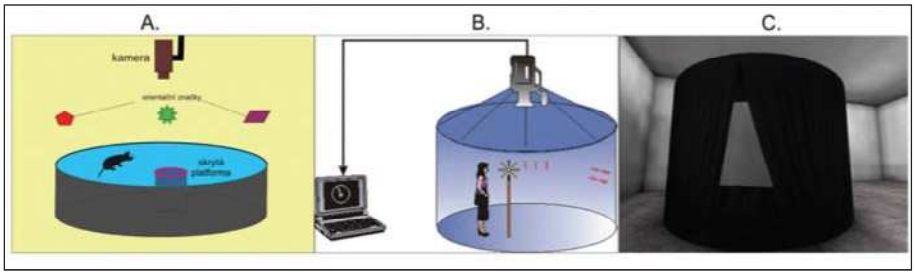
Typy prostorového chování

Ve snaze pochopit, jaké informace zvířata i lidé používají při své navigaci prostředím a jaké mozkové procesy se účastní jejich zpracovávání a následné odpovědi organismu, bylo prostorové chování roztříděno do několika kategorií. Jelikož existuje několik různých systémů třídění prostorového chování, zaměříme se jenom na nejběžnější taxonomii. Zjednodušeně tak můžeme rozlišit zejména egocentrické a allocentrické navigační procesy (Jeffery, 2003; O'Keefe et al., 1978; Roche et al., 2005).

Egocentrické procesy jsou zapojené během našeho pohybu prostředím a neustále reagují na změny polohy těla, a tak aktualizují jeho pozici vůči objektům v okolním prostoru (Jeffery, 2003). Do tohoto procesu vstupují jak informace z externích zdrojů (vizuální, sluchové, taktilní a olfaktorické), tak i vnitřní somatosenzorické informace. V nepřítomnosti externího zdroje informací nabývají značný význam právě vnitřní inerciální vstupy z vestibulárního systému a substrátové informace z proprioreceptorů (Mittelstaedt et al., 1991). Při navigaci za tmy proto mluvíme spíše o procesu integrace dráhy nebo idiothetické navigaci (Whishaw, 1998). Takový způsob navigace však vede k postupně narůstajícím chybám v odhadu vzdáleností, které pak musí být čas od času korigovány referenční informací z vnějších zdrojů (vizuální, auditivní, nebo taktilní), jinak dochází ke vzniku kumulativní chyby. Proces integrace dráhy je dnes z důvodu častého využití virtuálních navigačních testů často opomíjen.

Allocentrické procesy naopak představují komplexnější způsob zpracování prostorových informací, které jsou na vlastní pozici těla nezávislé. Informace jsou zde integrovány v podobě jakési souřadnicové soustavy, která charakterizuje vzájemné prostorové vztahy známých objektů v prostředí (Jeffery, 2003).

Oba popsané procesy během navigace vzájemně kooperují za tvorby jakési vnitřní reprezentace prostředí, která byla Tolmanem již v roce 1948 označena pojmem „kognitivní mapa". Současný model pravděpodobného procesu vzniku kognitivní mapy je zobrazen na obr. 2 (upraveno podle Roche et al., 2005). Již tradiční teorie „kognitivního mapování" (O'Keefe et al., 1978) předpokládá, že vznikající mentální mapa ukládá informace v podobě allocentrického souřadnicového systému pozic zapamatovaných objektů. Kromě této teorie se však objevují i navigační modely, které ukazují, že pamatování si cílových pozic může být ve skutečnosti založeno i na uložených lokálních pohledech (mentálních snímcích) z cílového místa (McNaughton et al., 1989). Prostorové vztahy mezi několika takovými místy jsou pak uloženy v podobě mentální reprezentace pohybů potřebných k přesunu od jednoho k druhému.



Obrázek 3: ***Morrisovo vodní bludiště: (A) původní verze pro hlodavce; (B) reálná analogie pro lidi nazvaná Blue Velvet Arena; (C) Virtuální analogie arény***

Metody studia prostorové kognice

Testy prostorové kognice bychom mohli rozdělit do dvou kategorií, na stolní testy („table-top tasks") a na navigační úlohy. Tyto dva typy testů se liší především velikostí testovacího prostředí a perspektivou, ze které musí testovaná osoba úlohu řešit.

Výzkum prostorové kognice je u lidí výrazně rozmanitější než u zvířat, ačkoliv používané testové úlohy často vychází právě ze zvířecích modelů. V literatuře najdeme mnoho úloh testujících prostorovou kognici na různé úrovni náročnosti. Mezi ty nejjednodušší můžeme zařadit i paradigma mentální rotace (Shepard et al., 1988). 2D nebo 3D objektů. V této úloze je využitý proces mentální transformace (rotace) vizuálních podnětů. Vzhledem k současné prezentaci podnětu v původní i rotované pozici je tento test závislý spíše na vizuo-prostorové představivosti než na paměťových procesech.

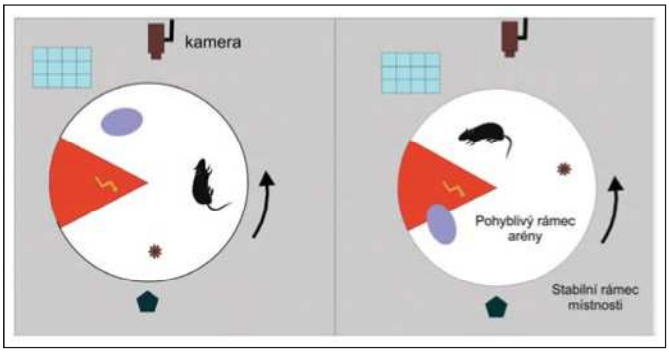
Velice často se využívají i testy vizuo-prostorové pracovní paměti (VPP). Cílem takových testů je vyšetřit schopnost jedince správně si zapamatovat pozice (nebo směry, orientace a vzdálenosti) určitých objektů v časovém sledu v ohraničeném 2D nebo 3D prostoru. Mezi typické úlohy testující VPP řadíme především prostorovou verzi testu oddáleného vybavení (sDRT, Spatial Delayed-Response Task; Piskulic et al., 2007) a jeho různorodé varianty. Pro testování VPP je tak možné použít např. i známou úlohu n-back, která při sledování série podnětů vyžaduje vybavit si např. prostorový podnět po několika (n) krocích. Naprostá většina těchto testů však využívá jenom dvojdimenzionální prostor (obrazovky počítače nebo papíru), a představují tak jednodušší formu prostorové orientace. Dalším známým prostorovým testem VPP je test prostorového rozsahu (Corsi block test), který je součástí testové sady WMS-III. (Wechsler, 1997). V jeho reálné i počítačové verzi je úkolem testované osoby zapamatovat si a zopakovat pořadí několika kostek (tvořících mřížku 2D pozic), a to ve správném (předvedeném a následně převráceném) pořadí.

Pro testování prostorové kognice však byly vytvořeny i výrazně složitější úkoly vyžadující navigaci v reálném nebo virtuálním 3D prostoru (např. radiální a komplexní bludiště, navigace ve městě nebo budově a navigace bez použití zraku).

K nejrozšířenějším testům prostorové kognice však jistě patří různé analogie Morrisova vodního bludiště (MWM; Morris, 1981). Toto paradigma bylo původně vytvořeno pro potkany jako test učení a paměti, který využívá přirozenou snahu zvířete uniknout z vody za pomocí platformy skryté pod hladinou vody (viz obr. 3A). Později se tento test stal užitečným prostředkem studia stárnutí, experimentálních lézí i sledování účinku farmakologických léčiv a toxických látek na kognici (především u potkanů). Od roku 1982 bylo publikováno více než 2500 článků využívajících tento model nebo jeho variace. MWM se využívá ve dvou základních modifikacích, a to jako test referenční nebo pracovní paměti (Morris, 1984). V referenční verzi zůstává pozice skryté platformy na stejném místě během několikadenního tréninku, naopak u verze zaměřené na pracovní paměť se pozice platformy mění každý den (Dudchenko, 2004). Skrytou cílovou pozici je možné najít jenom odvozením její relativní polohy vůči různorodým orientačním bodům v okolí arény. Tento test si tedy vyžaduje allocentrickou navigaci (orientaci podle vzdálených převážně zrakových vodítek). Protože startovní pozice se během experimentu neustále mění, je nezbytné před pohybem k cíli provést re-orientaci vlastní pozice vůči relevantním orientačním značkám v okolí bazénku (nebo arény). Později byly vytvořeny i lidské analogie MWM testující navigaci na cíl převážně v suchých kruhových arénách, a to jak v reálné podobě, tak i v mnoha virtuálních verzích. U nás je analogie této úlohy provozovaná v aparatuře nazvané Blue Velvet Aréna, která dnes existuje ve své reálné i virtuální podobě (viz obr. 3A a 3B). V posledních letech se analogie MWM úlohy začínají uplatňovat i jako prostředek vyšetření deficitu prostorové kognice u pacientů trpících neurodegenerativními změnami (Hort et al., 2007) nebo neuropsychiatrickou poruchou (Hanlon et al., 2006).

Dalším velmi slibným testem je i Test aktivního allocentrického vyhýbání se místu (AAPA; Cimadevilla et al., 2000), nazývaný také kolotočové bludiště (carousel maze). Tento test je prováděn na pohyblivé aréně, kde díky rotaci vznikají dva oddělené referenční rámce (viz obr. 4). Úkolem testovaného subjektu pak je aktivně se vyhýbat 60° výseči, která je skrytá a stabilní v rámci místnosti. Pro úspěšné vyhýbání se zakázané oblasti je nutné správně rozpoznat relevantní a nerelevantní informace (Cimadevilla et al., 2001). Oddělit tedy informace vázané na stabilní referenční rámec místnosti (převážně vizuální informace) od těch informací, které jsou vázané na rotující arénu (referenční rámec arény, viz obr. 4). Ukázalo se, že tento test (na rozdíl od MWM) je citlivý již na jednostranné poškození hippokampu u potkana.

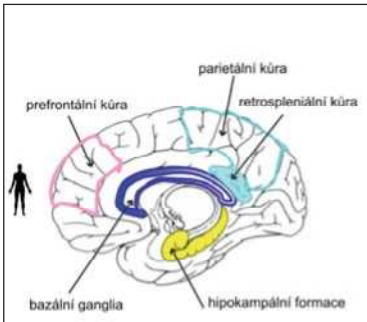
Reálné analogie obou testů byly vyvinuty i pro testování lidí a jsou zprovozněny v aparatuře nazvané „Blue Velvet Aréna" (BVA; Stepankova et al., 2003; viz obr. 2B), která má podobu uzavřeného kruhového stanu s možnou rotací podlahy. Analogie úlohy, MWM byla pojmenovaná Test hledání skrytého cíle (Hidden Goal Task, HGT; Kalova et al., 2005), analogii kolotočového bludiště nalezneme pod názvem Test disociovaných referenčních rámců (Dissociated reference



Obrázek 4: ***Úloha aktivního vyhýbání se místu (AAPA) na rotující aréně.*** *Úlohou testovaného zvířete je aktivně se vyhýbat 60° výseči (vyznačené červeně), která je stabilní v rámci místnosti (neotáčí se s arénou). Pokud tedy zvíře sedí, je rotací arény přivezeno do zakázané oblasti a potrestáno slabou elektrickou rankou. Zvíře tak musí odlišit podněty relevantní (stabilní) od irelevantních, které se točí spolu s ním a arénkou, a použít je při vyhýbání se zakázané oblasti.*

frames test, DRF; Vlcek et al., 2006). Oba testy jsou dnes úspěšně používány pro testování deficitu prostorové kognice u různých onemocnění, především ale u pacientů s Alzheimerovou demencí a mírnou kognitivní poruchou (Hort et al., 2007).

Významný metodický posun přineslo testování prostorové navigace v prostředí virtuální reality (VR), které bylo poprvé předvedeno v roce 1983 (Krueger et al., 1985). Navzdory určitým omezením, jako jsou užší zorné pole a absence skutečného pohybu, poskytuje VR mnoho výhod. Hlavní výhodou VR je především možnost podrobného záznamu chování a pohybu testované osoby spolu s využitím širokého spektra stimulů a jejich snadné manipulace. Díky automatické prezentaci podnětů dosahují počítačem řízené testy vyšší časové přesnosti, než tradiční neuropsychologické testy (tužka-papír) prezentované člověkem. Bylo také prokázáno, že kognitivní mapy vytvořené ve 3D VR jsou srovnatelné s těmi, které vznikají v reálném prostředí (Arthur et al., 1997). Pro tento účel byly srovnávány mapy zakreslené pokusnými osobami po aktivním pohybu v reálném nebo virtuálním prostředí, které obsahovalo několik běžných objektů v určitém prostorovém uspořádání. Virtuální prostor nám ve srovnání se standardními testy navíc poskytuje i jakýsi pocit „přítomnosti", což může vést k vyšší ekologické validitě.



Mozková oblast	Funkce
Hipokampální formace	visuo-prostorová paměť; místo vzniku kognitivní mapy a jejího vybavování
Prefrontální kůra	pracovní paměť, plánování a rozhodování; vybavování časového pořadí prostorových pozic; navigace integrací dráhy bez vizuálních podnětů
Parietální kůra	visuo-motorická koordinace pohybů a odhad vzdáleností
Retrospleniální kůra (posterior g. cinguli)	překlad referenčních rámců (mezi ego- a allo-centrickým)
Bazální ganglia	navigace naučenou trasou, procedurální učení

Obrázek 5: ***Oblasti mozku zapojené během zpracování prostorových informací a orientace v prostředí (obrázek vlevo) a jejich specifické funkce (tabulka)***

Vzhledem k nepřítomnosti informací, generovaných vlastním pohybem osoby ve virtuálním prostředí, jsou u VR experimentů často zanedbávané procesy integrace dráhy. Je však nutné poznamenat, že tyto procesy využívají mimo vnitřních somato-senzorických informací i část zrakových informací v podobě optického toku. Jde o vizuální změny vznikající při pohybu pozorovatele prostředím, které se projevují zjevným pohybem prvků vizuální scény a napovídají tak, kterým směrem se osoba pohybuje. Proto účast idiothetické složky na navigaci ve VR nemůžeme plně opomíjet.

Metodika VR je také významným prostředkem objasňování činnosti jednotlivých oblastí mozku zapojených v procesu navigace pomocí zobrazovacích metod (fMRI, PET, EEG). VR nám navíc umožňuje vytvořit srovnatelné testy pro zvířata i lidi.

Neuronální základy prostorové kognice

Funkce kognitivního systému prostorové navigace je zajišťována sítí mozkových oblastí, zahrnujících především mediální temporální lalok (MTL), prefrontální a parietální kůru, mozeček, části bazálních ganglií a také retrospleniální kůru (Maguire et al., 1998a). Vzhledem k tomu, že výsledná kognitivní mapa vzniká spolupůsobením několika navigačních procesů, které se vzájemně doplňují, není experimentálně jednoduché je od sebe plně oddělit. Během navigačních úloh tak často nalezneme aktivované oblasti sdílené všemi prostorovými procesy. Do jisté míry však můžeme kontrolovat, které informace budou k navigaci použity, a tím ovlivnit výslednou aktivitu mozku.

Pokud budou k navigaci použité jenom zrakové podněty, nalezneme zřejmě aktivitu zrakové kůry v okcipitálním laloku. Pokud však využijeme i sluchových nebo čichových podnětů, objeví se i aktivita senzorických a asociačních oblastí, která je s těmito smysly spojena. Vzhledem k tomu, že u člověka se při testování navigace využívá především vizuálních podnětů, nemůžeme opomenout ani oblasti odpovědné za rozpoznávání objektů a prostorových scén. Pro rozpoznávání objektů byla identifikována oblast laterálního okcipitálního komplexu (LOC) a fusiformní kůry a pro pozorování prostorových scén posteriórní část parahipokampálního závitu (Hasson et al., 2003).

Pokud se subjekt během navigace pohybuje (aktivně či pasivně), a tedy využívá procesu integrace dráhy, nalezneme i aktivitu parietální somato-senzorické oblasti (Aguirre et al., 1998). Parietální kůra se ale účastní i běžného odhadu vzdáleností pomocí zrakových informací. Důležitá je i funkce retrospleniální kůry (mediálně uložená parietální kůra cingulárního gyru, viz obr. 5), která spolupracuje se strukturou hipokampu. Předpokládá se, že oblast retrospleniální kůry je odpovědná za překlad informací mezi referenčními rámci, a podílí se tak na přesunu pozornosti z egocentrického na allocentrický rámec a naopak (Iaria et al., 2007).

Za významnou strukturu účastnící se tvorby allocentrické kognitivní mapy však považujeme oblast mediálního spánkového laloku (dále jen MTL), a to především struktury hipokampální formace (HF, dále jen hipokampus, viz obr. 5). Aktivita hipokampu byla již prokázaná v mnoha navigačních úlohách (viz Roche et al., 2005). O'Keefe a Nadel publikovali v roce (1978) knihu, ve které popsali, že u savců může být výsledná allocentrická kognitivní mapa kódována právě ve struktuře hipokampu. Tato teorie je založená mimo jiného i na pozorování tzv. místových buněk („place cells"), excitačních pyramidálních neuronů v oblastech Cornus Ammonis (CA1-CA3) hippokampu potkana, které vykazují prostorově selektivní aktivitu.

Bylo potvrzeno, že bilaterální léze struktur MTL, konkrétně hipokampu, u potkana značně narušuje prostorové schopnosti. Jde však především o deficit v allocentrické navigaci, např. při hledání skryté platformy v MWM (Morris et al., 1982). Testování potkanů v kolotočovém bludišti prokázalo narušení kognice již po jednostranné lézi hipokampu (Cimadevilla et al., 2001). Na druhé straně, základní prostorové procedurální schopnosti jsou i po lézi hipokampu zachovány. Nebyla např. narušena egocentrická navigace ke skryté platformě při vypouštění ze stejné startovní pozice (Eichenbaum et al., 1990). Na hipokampu závislá je ale taky idiothetická navigace, čili integrace dráhy za nepřítomnosti zrakové informace (Whishaw 1998). Nesporná úloha HF v prostorové kognici byla potvrzena i vyšetřením pacientů s hipokampální lézí. Již unilaterální (pravostranná) léze HF vedla k závažnému narušení vizuo-prostorové paměti, jak při 2D lokalizaci objektů, tak i v navigaci na skrytý cíl v lidské analogii MWM (Bohbot et al., 1998).

Tato zjištění potvrzují i zobrazovací studie u zdravých lidí, které prokázaly aktivitu MTL v různých prostorových úlohách (např. Gron et al., 2000; Maguire et al., 1998b). Několik studií však později ukázalo, že při řešení určitých prostorových úloh nemusí být oblast MTL aktivní. Tato aktivace se objevuje převážně u studií vyžadujících allocentrickou navigaci a flexibilitu, např. při hledání trasy novým prostředím. Naopak v úlohách sledování již dobře naučené trasy nebývá aktivita hipokampu a přilehlé MTL nalezena.

V takovém případě se aktivuje spíše neuronální síť zahrnující corpus nuclei caudati (bazální ganglia), insulární kůru a rozsáhlé oblasti parietální kůry (Hartley et al., 2003). Tyto oblasti jsou pravděpodobně odpovědné za udržování, vybavování a vykonávání určitého sledu činností (pohybů), vedoucích k cíli pomocí jakési „reprezentace naučenou trasou" (‚action-based navigation', Hartley et al., 2003). Takový typ navigace naučenou trasou tedy můžeme chápat jako automatizovaný proces podobný procedurálnímu učení, které je na aktivitě MTL nezávislé. Důkazem tohoto tvrzení byl výkon pacienta H. M. trpícího oboustrannou hipokampální lézí, která vedla k nevratnému narušení jeho deklarativní paměti, navzdory zachovalé schopnosti procedurálního učení (Milner, 1972). Pacient H. M. tak byl nadále schopen zlepšovat se, tedy učit se různým postupům a činnostem (byl např. schopen zlepšování v testu, kde měl pomocí zrcadla překreslovat obraz hvězdy na papír). Pokud by ale během navigace naučenou trasou došlo k zablokování známé trasy překážkou, opět by se objevila aktivita hipokampu a prefrontální kůry, potřebná pro plánování nové trasy již známým prostředím (Maguire et al., 1998a).

Významnou úlohu v prostorové kognici hraje i prefrontální kůra (viz obr. 5), která je zapojena jak v prostorové pracovní paměti (Goldman-Rakic, 1996), tak v exekutivních funkcích, jako jsou plánování a flexibilita chování, rozhodování a strategické volby. U potkanů byla ve spojitosti s prostorovou kognicí sledována především mediální prefrontální kůra (mPFC; Uylings et al., 2003), která je do prostorových procesů zapojena i díky husté komunikaci s HF. Výkon zvířat s lézí prefrontální kůry však není v úloze MWM narušen, výjimku představuje jen situace odebrání orientačních bodů (Jo et al., 2007). Naopak, léze mPFC úplně naruší idiotetickou navigaci (de Bruin et al., 2001) a také vede k oslabení výkonu v úlohách, které vyžadují zapamatování časového pořadí prostorových lokací (Kesner et al., 1987). Předpokládá se, že mPFC participuje v prostorové kognici při plánování navigace na cíl. Výsledky těchto studií dále naznačují, že mPFC a hipokampus pracují paralelně, a léze mPFC tak nemusí nutně vést k deficitu prostorové kognice v úlohách, které nejsou silně závislé na vizuo-prostorové složce pracovní paměti, protože hipokampus dále pracuje. Vzhledem k tomu, že právě prefrontální kůra hraje důležitou úlohu v neuropatologii schizofrenie, je velice užitečné využití prostorových úloh (se zaměřením na pracovní paměť) i při testování kognitivního deficitu u tohoto onemocnění.

Prostorová kognice a její testování u schizofrenie

Důležitou a klinicky vysoce relevantní součástí klinického obrazu schizofrenie je dnes stále více zmiňován kognitivní deficit. Ten byl již dobře vymezen iniciativou MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia; Kern et al., 2004). MATRICS uvádí sedm kognitivních oblastí, jejichž deficit je pro schizofrenii specifický: pozornost, rychlost zpracování informací, pracovní paměť, verbální a vizuo-prostorové učení, logické myšlení, řešení problémů a sociální kognice. Zdá se však, že pro schizofrenii je typická především porucha organizace a zpracování informací na úrovni centrálně exekutivní složky pracovní paměti. (Longevialle-Henin et al., 2005). To je důvodem, proč se negativní symptomy projevují na úrovni zpracování jak verbální, tak i vizuo-prostorové informace, s následnými chybami v zapamatování. Narušené zpracování vizuo-prostorové informace tak vede ke vzniku mentální reprezentace prostoru, tedy kognitivní mapy, která obsahuje chyby a nepřesnosti. Vybavování informací z kognitivní mapy pak může narušit prostorovou orientaci na různé úrovni. Důkazy narušené prostorové kognice byly popsány u schizofrenního onemocnění, a také u animálního modelu schizofrenie (viz níže).

Při testování poruch popisovaných kognitivních domén byly použité různorodé metody, zaměřené často jen na některou z nich. Taková frakcionace ale vede k obrovské variabilitě výsledků, které jsou tak často nejednoznačné a rozporuplné. Využití mnoha tradičních testů metodou tužka-papír navíc snižuje ekologickou validitu, tedy využitelnost výsledků v reálném životě. Bylo by tedy užitečné sledovat kognitivní funkce u schizofrenie testem, který by vyšetřil více modalit současně v co nejvíce přirozených podmínkách. Takový komplexní přístup představují právě testy prostorové kognice, které mohou být využité jak v animálních modelech schizofrenie, tak i v klinickém výzkumu. Tyto úlohy testují soubor kognitivních schopností, které využíváme během své orientace v prostředí.

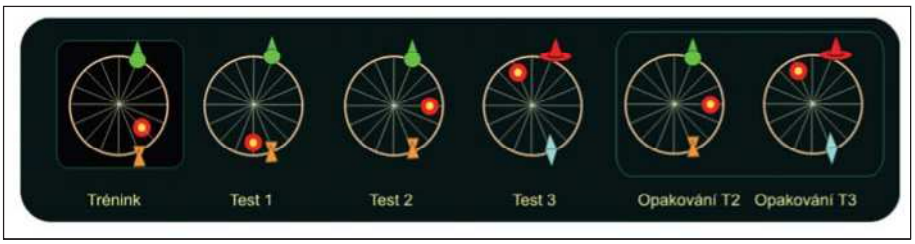
Animální model schizofrenie a prostorová kognice

Prostorové úlohy se ukázaly být velmi užitečným prostředkem pro testování kognitivního deficitu u farmakologického modelu schizofrenie. Nejčastějším modelovým zvířetem je hlodavec. Objevují se však i studie u opic, např. u makaků. Do jisté míry je u opic možné využívat i typicky lidské testy, např. již popsanou úlohu oddáleného vybavení (Cahusac et al., 1989). V takovém případě je poměrně jednoduché srovnat jejich výsledky s výkonností lidí. Nicméně farmakologické studie u opic jsou eticky problematické, velice nákladné finančně a náročné na prostor. Proto je nejčastějším modelovým zvířetem potkan. V případě hlodavců však není možné využít prostorové úlohy používané u lidí. Bylo sice prokázáno, že potkan je schopný reagovat i na prostorové podněty na monitoru počítače (Nekovarova et al., 2006), ale takové úlohy jsou pro farmakologické studie u hlodavců nevhodné, protože jsou velice zdlouhavé (vyžadují trénink mnohem delší než 1 týden). Je proto nutné využít již známých prostorových úloh vytvořených speciálně pro tato zvířata (např. MWM a kolotočové bludiště) a vytvořit naopak jejich lidské analogie.

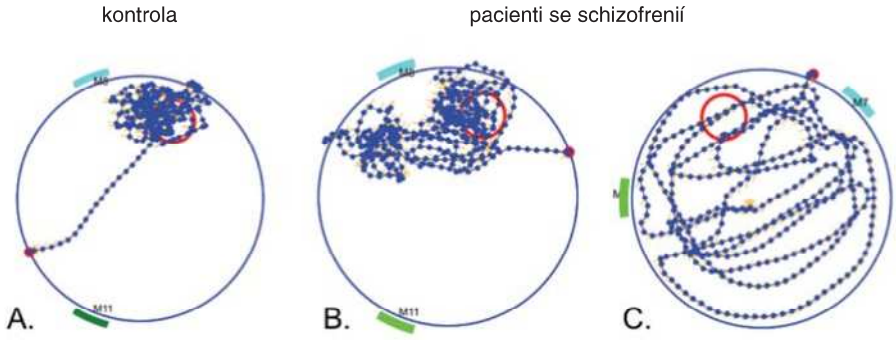
Deficit prostorové kognice byl v modelech schizofrenie prokázán u opic i u potkanů. Dnes nejznámějším modelem schizofrenie je aplikace antagonistů NMDA receptorů (ketamin, MK-801 nebo fencyklidin), která vyvolává psychóze podobné symptomy nejen u lidí, ale i u opic a potkanů (Bubenikova-Valesova et al., 2008). Ketamin podávaný zdravým dobrovolníkům prokazatelně vede k indukci schizofrenii podobných symptomů, k pozměněnému vnímání a kognitivnímu deficitu (Krystal et al., 1994). Podání ketaminu u potkanů také prokazatelně zhoršilo kognitivní funkce, v důsledku čeho byl narušen výkon v obou verzích MWM, jak v testu referenční, tak i pracovní paměti (Sircar et al., 1998; Vales et al., 2006). Deficit prostorové kognice u zvířecích modelů byl prokázán i v úloze s rotující arénou (AAPA; Stuchlik et al., 2004). Vzhledem k tomu, že tento test kolotočové arény využívá změny referenčních rámců, může být užitečným prostředkem i pro vyšetření pracovní paměti u schizofrenie. Aby bylo možné srovnat tyto výsledky pozměněného chování zvířecího modelu s kognitivním deficitem u schizofrenie, je ale nutné otestovat srovnatelným testem i pacienty schizofrenního okruhu.

Prostorová kognice u pacientů se schizofrenií

Pacienti se schizofrenií vykazují narušený výkon na všech úrovních prostorové kognice. Jsou pomalejší a méně přesní již na nejzákladnější úrovni, a to v mentální rotaci písmen a objektů (de Vignemont et al., 2006). Delší reakční čas může být vysvětlen celkovým zpomalením mentálních procesů u schizofrenie a také narušenou



Obrázek 6: ***Ukázka virtuální verze HGT pomocí 2 orientačních značek s postupně se měnící pozicí cíle.*** *Každý kruh představuje náhled na arénu v jedné fázi testu s několika pokusy. V prvních 3 fázích se testovaná osoba pohybuje v aréně se stejnou konfigurací značek, mezi fázemi se ale přesouvá pozice cíle (červené kolečko), což vyžaduje potlačení jedné zapamatované pozice druhou. Ve 4. fázi (Test 3) se testuje schopnost jedince si zapamatovat zcela novou konfiguraci. Dvě fáze opakování pak ověří, jak dobře si osoba zapamatovala pozici cíle po časové prodlevě v již naučených konfiguracích.*



Obrázek 7: ***Ukázka navigace na skrytý cíl (jeho pozice je označena červeným kolečkem) v „probe" pokusu HGT s neaktivním cílem.*** *(A) Pohyb kontrolního subjektu. (B-C) Ukázka pohybu dvou pacientů se schizofrenií, jejichž pohyb ukazuje nejistotu v naučené pozici cíle a jeho vztahu vůči nejbližší orientační značce. Tato nejistota vede k hledání cíle na obou stranách značky (B) nebo náhodnému hledání na celé ploše arény (C).*

funkcí vizuo-prostorového náčrtníku a centrálně exekutivní složky pracovní paměti zapojeného při imaginaci motorických pohybů (Baddeley, 1992).

Jednou z nejlépe sledovaných kognitivních domén u schizofrenního onemocnění je právě pracovní paměť (PP). Pokud se zaměříme výlučně na vizuo-prostorovou komponentu PP, stále najdeme nespočet prací, které prokázaly deficit VPP u onemocnění schizofrenního okruhu (Piskulic et al., 2007). Tyto studie využívají jednoduché podněty s prostorovou komponentou. Jejich ekologická validita, tedy využitelnost výsledků v reálném životě, je ale nízká. V posledních letech se ale objevují i studie vyšetřující deficit prostorové paměti u schizofrenie za použití rozsáhlých virtuálních prostředí. Jedna z takových studií (Weniger et al., 2008) prokázala deficit ve složitější allocentrické navigaci, s využitím orientačních značek, navzdory zachovalé egocentrické navigaci zapamatovanou trasou. V jiné studii byla testována i schopnost pacientů přepínat mezi egocentrickým a allocentrickým referenčním rámcem při hodnocení prostorových vztahů na zámeckém náměstí (Landgraf et al., 2010). Studie ukázala, že pacienti se schizofrenií mají schopnost vidět prostor v egocentrickém rámci zachovanou, ale ve srovnání s kontrolami jsou jejich allocentrické odpovědi nepřesné a přepínání mezi ego- a allo- referenčním rámcem je výrazně zpomaleno. To naznačuje, že úloha kolotočového bludiště, která vyžaduje právě takové přepínání referenčních rámců, může být velmi užitečná při testování kognitivního deficitu u schizofrenie.

U schizofrenie byl již testován i klasický model virtuální verze MWM, a to ve standardní referenční úloze hledání skrytého cíle i v navigaci na viditelný cíl (Hanlon et al., 2006). Tato studie prokázala významný behaviorální deficit u schizofrenie, projevující se delším časem a delší trajektorií v úloze hledání skrytého cíle. V případě označení cíle blízkou značkou však byl výkon pacientů srovnatelný s kontrolami.

Ve spolupráci Fyziologického ústavu AVČR a Psychiatrického centra Praha byla u pacientů se schizofrenií testována i virtuální verze HGT (analogie MWM), se zaměřením na pracovní paměť díky měnící se pozici cíle (viz obr. 6). Předběžné výsledky naZnačují, že pacienti s onemocněními schizofrenního okruhu jsou ve srovnání s kontrolami signifikantně pomalejší v hledání skrytého cíle (především v prvních částech úlohy) a jejich trajektorie vedoucí k cíli je signifikantně delší, tedy není přímá. Použití „probe" pokusu (bez zpětné vazby o vstupu do cíle) navíc prokázalo nejistotu v zapamatované pozici cíle, což vede k signifikantně nižšímu času stráveného ve správném kvadrantu arény, tedy v oblasti cíle (viz obr. 7).

Je zajímavé, že navzdory uvedeným nálezům popisujícím deficit prostorové kognice u schizofrenie, pacienti trpící tímto onemocněním nepopisují těžkosti s prostorovou orientací v reálném životě. Možným vysvětlením tohoto jevu je předpoklad, že pokud je schopnost egocentrické navigace v prostoru zachována, kompenzuje nedostatky či nepřesnosti narušených allocentrických procesů. Vznikající kognitivní mapa je tak pravděpodobně více egocentrická a vede spíše k navigaci zapamatovanou trasou. Tato jednoduchá strategie tak umožní orientaci na každém již navštíveném místě. Naopak navigace v novém prostředí nebo s použitím překážky může být narušena. Příkladem neznámého prostředí tak může být i experimentální prostředí. Určitý vliv můžeme připsat i časovým omezením stanoveným v průběhu klinického testování, které je v reálných situacích neomezuje. Jak již bylo řečeno, u schizofrenie dochází i k celkovému zpomalení mentálních procesů. Časový limit tak působí nejen jako motivační, ale i stresový faktor.

Závěr

Výsledky mnoha animálních i klinických studií prokázaly, že kognitivní deficit u schizofrenie se projevuje narušením výkonu v různorodých prostorových úlohách. V současnosti nejpoužívanější prostorovou úlohou je nepochybně Morrisovo vodní bludiště. Různorodé analogie této úlohy hledání skrytého cíle jsou již řadu let využívány při testování kognitivního deficitu hlodavců a lidí. Navzdory tomu, že tato úloha patří k běžným metodám výzkumu u animálního modelu schizofrenii podobného chování, bylo jeho využití v klinickém výzkumu zatím omezené. Velice slibnou úlohou se ukazuje být i tzv. kolotočové bludiště, které využívá segregace měnících se orientačních rámců na rotující aréně. Tato úloha tak vyžaduje mnohem složitější výběr navigačních strategií a relevantních podnětů, než je tomu při hledání skrytého cíle v MWM.

Dlouhodobý výzkum využívající obou těchto metod (Morrisova vodního bludiště i kolotočového bludiště) naznačuje, že jsou vhodným prostředkem pro vyšetření kognitivních funkcí jak u animálního modelu schizofrenie, tak i u pacientů trpících tímto onemocněním.

Velice slibným se proto jeví využití analogií těchto úloh pro klinické testování u lidí. K tomu je však potřeba vytvořit verze obou testů ve virtuálním prostředí, které by byly srovnatelné s výsledky z reálných testů u animálního modelu schizofrenie. Díky vzájemné spolupráci odborníků z neurofyziologických a výpočetních oborů dnes proto vznikají virtuální analogie těchto dvou prostorových úloh i u nás. Předběžné výsledky virtuální verze MWM (HGT-Test hledání skrytého cíle) jsou slibné a potvrzují narušení prostorové kognice u pacientů schizofrenního okruhu. Vzhledem k tomu, že navigace v pohyblivém prostředí (DRF-Test oddělených referenčních rámců) představuje náročnější test prostorové kognice, předpokládáme, že jeho použití prokáže i mírnější kognitivní deficit u pacientů s nenarušeným výkonem v úloze HGT.

Vzhledem k tomu, že obě úlohy testují prostorovou kognici ve 3D prostředí, je jejich ekologická validita vyšší v porovnání s tradičními metodami využívajícími tužku a papír. Domníváme se, že testování prostorové kognice během navigace v třírozměrném prostředí nám poskytne komplexní pohled na kognitivní deficit spojený s tímto onemocněním.

Objasnění toho, jakým způsobem se kognitivní mapa schizofrenních pacientů liší, nám může prozradit mnoho nejen o jejich kognitivním deficitu, ale i pozitivních příznacích. Bludy a halucinace totiž mohou do jisté míry představovat určitou obdobu chybných mentálních reprezentací, vznikajících během orientace ve vnitřním psychickém prostředí nemocného.

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Bridging disparate symptoms of schizophrenia: a triple network dysfunction theory

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Schizophrenia is a complex neuropsychiatric disorder with variable symptomatology, traditionally divided into positive and negative symptoms, and cognitive deficits. However, the etiology of this disorder has yet to be fully understood. Recent findings suggest that alteration of the basic sense of self-awareness may be an essential distortion of schizophrenia spectrum disorders. In addition, extensive research of social and mentalizing abilities has stressed the role of distortion of social skills in schizophrenia. This article aims to propose and support a concept of a triple brain network model of the dysfunctional switching between default mode and central executive network (CEN) related to the aberrant activity of the salience network. This model could represent a unitary mechanism of a wide array of symptom domains present in schizophrenia including the deficit of self (self-awareness and self-representation) and theory of mind (ToM) dysfunctions along with the traditional positive, negative and cognitive domains. We review previous studies which document the dysfunctions of self and ToM in schizophrenia together with neuroimaging data that support the triple brain network model as a common neuronal substrate of this dysfunction.

Keywords: schizophrenia, self, theory of mind, forward model, default mode network, salience network, central executive network

INTRODUCTION: PHENOMENOLOGICAL DOMAINS OF SCHIZOPHRENIA

Schizophrenia is a severe neuropsychiatric disorder with complex manifestations expressed in a wide variety of symptoms traditionally divided into positive and negative symptoms, and cognitive deficits (Crow, 1985; Andreasen, 1999; Sass and Parnas, 2003). Positive symptoms refer to phenomena exceeding normal mental functions, such as conceptual disorganization, abnormal thought contents and hallucinations. Negative symptoms are characterized by a decline in normal functioning, flattened emotions, decrease of social behavior and anhedonia. Cognition is affected in several domains such as attention/vigilance, psychomotor speed, cognitive coordination, visual and verbal learning and memory, working memory, executive functions and social cognition (Green et al., 2004). However, the common etiology of these disparate symptoms remains elusive.

Recent phenomenological research indicates that disturbance of the basic sense of self-awareness (core self) may be a core phenotypic marker of schizophrenia spectrum disorders (Nelson et al., 2013, 2014). Self-awareness is an essential component of more complex self-referential systems (self-representation). The term "self" refers traditionally to the human phenomenon of one's own experience including perceptions, thoughts, and emotions (Vogeley and Fink, 2003). This intrinsic representation (or meta-representation) of mental states as one's own mental states is paralleled by the representation of others, again in terms of cognitive content (perceptions and thoughts) and emotions (Vogeley et al., 2001). These cognitive and emotional representations of others are linked to two domains of social cognition, cognitively targeted "theory of mind" (ToM) and empathy. To capture more clearly the dynamic features of a complex self-concept, a two dimensional model of a human mind's representation could be delineated. The first dimension of this model refers to the self-other distinction, and the second represents the cognitive and emotional distinction (**Figure 1**). In this context, we use the term "cognitive" for all processes related to monitoring the perceptions, thoughts, planning and action performance of ourselves or others. The term "emotional" refers to the monitoring of motivational, positive and negative (aversive) hedonic values automatically assigned to a current situation or mental content. This model groups together four domains (self, ToM, empathy and hedonic evaluation) with one common denominator: meta-representation of the mind (**Figure 1**).

Interestingly, all of these four categories have been identified as dysfunctional in schizophrenia and represent an alternative approach to schizophrenia phenomenology. It is tentative to speculate that a common denominator could be a candidate

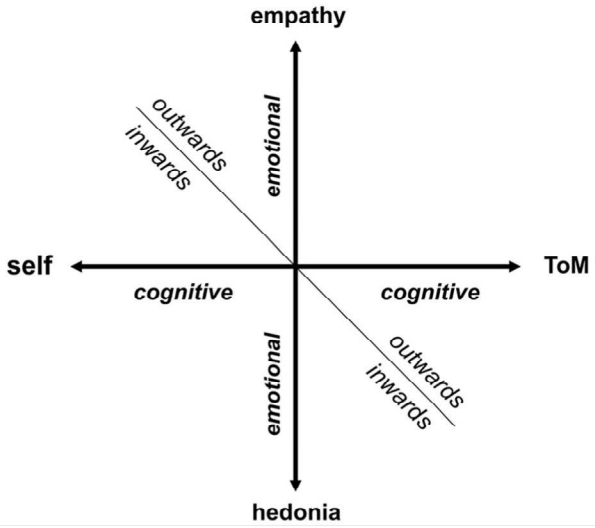

FIGURE 1 | Model of a human mind's representation (inwards/outwards). The horizontal axis refers to "cognitive" dimension, whereas the vertical axis refers to "emotional" dimension with stronger motivational accent. We assume that these two axes can create a mental representation of human mind, that can be focused outwards or inwards, forming four domains: self, ToM, empathy and hedonic evaluation.

for a unified neurobiological mechanism underlying the wide range of schizophrenia symptom manifestations. As we show further in this paper, recent advances in neuroimaging have proven that the array of bizarre perceptual experiences inherent to schizophrenia, i.e., pathological beliefs and cognitive deficits are part of the same core abnormality—prominent disturbance in the orchestration of large-scale brain networks that are conversely related to social cognition and emotional valence evaluation (ToM and empathy) and self-attribution. In order to explain co-occurrence of disparate symptoms of schizophrenia, encompassing broad range phenomenological domains, we have further elaborated the previously postulated theory of the triple network dysfunctional theory (Menon, 2011).

In this article we focus on the disturbance of the cognitive capability to represent ourselves/others as an unifying "super-domain" in schizophrenia (**Figure 1**). The emotional domain will be elaborated in a separate article. However, it is necessary to stress that the disturbances of the poles of the emotional axis belong to emotional flattening, a core negative symptom of schizophrenia differing in an inward (anhedonia) and outward (poor rapport or lack of empathy) perspective of reference.

This article aims to propose and advocate a concept of a common neurobiological substrate for self and ToM and to document its disturbance in schizophrenia. In the first two sections we review previous studies which refer to the dysfunction of self and ToM in schizophrenia together with neuroimaging data elucidating the neuronal substrate of this dysfunction. Secondly, we propose a triple network dysfunction as a candidate mechanism for the deficit of self-awareness, autobiographical self and ToM dysfunctions. Then, from this neurobiological perspective, we provide support for the assumption that the disruption in the orchestration of the triple network may underlie other prominent domains of schizophrenia phenomonology as well.

SELF: SELF-MONITORING AND SELF-DISTURBANCE

In general, self is defined as an essential human phenomenon—an intrinsic meta-representation of bodily and mental states (perceptions, sensations, emotions and thoughts) that are experienced as one's own (Newen and Vogeley, 2003). Literature offers various concepts of self, suggesting a plurality of this phenomenon. Gallagher (2013) proposed a "pattern theory of self", an approach allowing different aspects of self to coexist in parallel, in a "pattern", not exclusively. We use the term "self" as a denomination of the phenomenon itself. It is the most general term, linking and including all other aspects of self.

For the purpose of this article we recognize self-awareness, called "minimal" or "core self" (also called "ipseity" from Latin word ipse for "self" or "itself"), which refers to the fundamental sense of self-presence, to the "center of existence as an independent self-aware being", to the ability to separate oneself from others and to take a first person perspective (Sass and Parnas, 2003; Vogeley and Fink, 2003). Such perception of oneself as an active agent of one's own action is a central part of self-consciousness (David et al., 2008).

In contrast, we use term "autobiographical self" (Damasio, 1999) for a more complex phenomenon, based on autobiographical memory and on anticipation of a future, developing and maturing gradually throughout a lifetime. It also underlies representations of one's own mental states, a process parallel to the representation of the mental states of others (ToM). Newen and Vogeley (2003) propose five different levels of complexity of self-consciousness and emphasize the involvement of the minimal self in each of them. Accordingly, we consider self-awareness (minimal self) to be an intrinsic and essential component (prerequisite) of autobiographical self, allowing the first-person perspective to be taken in the representational processes.

The self-disorder or so-called ipseity-disturbance or ego-disturbance is hypothesized to be a core impairment in schizophrenia (Sass and Parnas, 2003; Sass, 2014). Self-awareness disturbances (passivity phenomena), one of the hallmarks of schizophrenia, are accompanied by a feeling of loss of one's own control and of being controlled by an external agent. This is common in patients suffering from false perception (hallucinations) or from false beliefs (delusions).

Nevertheless, it has been suggested that a deficit in self-monitoring could underlie abnormal perceptions and beliefs behind other positive symptoms in schizophrenia, beyond the scope of Schneider's symptoms (Fletcher and Frith, 2009). Recent evidence at a meta-analytical level has shown that a deficit in self-monitoring is associated with auditory hallucinations *per se* (Waters et al., 2012). Congruently, the impairment in the sense of agency is present in schizophrenia patients even without first-rank symptoms (Franck et al., 2001). Anomalous self-related experiences frequently precede the onset of psychosis by many years (Schultze-Lutter, 2009). In addition, self-monitoring deficit is detectable also in unaffected siblings of patients with schizophrenia (Hommes et al., 2012). Those findings indicate that the

deficit in this domain would belong to the endophenotype of schizophrenia.

It has previously been proposed that self-disturbance phenomena—delusions of alien control and thought insertion—can be caused by a distraction of the so called "forward model" (Frith et al., 2000; Frith, 2005; Leube et al., 2008). The forward circuit is a mechanism that allows us to distinguish between our own actions and actions initiated by an external source. The concept has been initially documented in motor-system control, in which two complementary elements were identified. The inverse model ("controller") provides motor commands to perform a sequence of actions determined by an intended goal. The forward model ("predictor") allows us to represent predicted consequences of actions. It creates an "efference copy" processed in parallel with the motor action (Wolpert and Kawato, 1998; Blakemore et al., 2000; Frith et al., 2000; Leube et al., 2008). In healthy subjects, self-monitoring could be based on a comparatory system computing the deviation between the predicted and the perceived consequences of both physical and mental actions. If there is no deviation between predicted and perceived, the action is experienced as self-initiated. Patients with self-awareness-disturbances have problems to correctly comparing predicted and perceived consequences and therefore they misidentify their own acts as external intervention (Leube et al., 2008).

Several brain regions have been assigned a role in this automatic self-referencing mechanism. Functional brain imaging studies confirmed that self-related processing may be specifically mediated by cortical midline structures (CMS) and insula. Several meta-analyses have demonstrated a predominant involvement of the anterior and posterior CMS (anterior and posterior cingulate, precuneus, the hubs of the default mode network (DMN)) in the processing of self-specific stimuli that occur across various functional domains in healthy subjects (Vogeley et al., 2001; Northoff et al., 2006; van der Meer et al., 2010; Qin and Northoff, 2011; Murray et al., 2012).

Although neuroimaging data of self-processing in schizophrenia are sparse, Farrer et al. (2004) demonstrated clear functional differences between schizophrenia patients with positive symptoms and healthy subjects in the action-attribution test. In this task the level of the subject's control of a virtual hand on a computer screen could be modulated by the experimenter. Positron emission tomography showed that the activity of the insular cortex along with right angular gyrus in healthy subjects correlated with the individual's control of a movement of the virtual hand. In contrast, schizophrenia patients did not show such a pattern of activity (Farrer et al., 2004).

In addition to forward system theory, some authors proposed an alternative explanation of the self-disturbance in schizophrenia. Three complementary aspects that manifest differently in the disease have been suggested (Sass and Parnas, 2003; Sass, 2014): (a) "Hyper-reflexivity" relates to an exaggerated form of self-consciousness. The subject can project some aspects of self-awareness onto external objects. (b) "Diminished self-affection" in the sense of a decreased experience of existing as an independent subject of awareness. This could be a source of disruption of the first-person perspective in some cases of schizophrenia disorder. (c) "Disturbed hold of the world" refers to the "disturbance of the spatiotemporal pattern of the world". This disturbance could affect the organization and structure of the field of awareness and a discrepancy between the perceived, remembered and imagined (Sass and Parnas, 2003; Sass, 2014).

Sass and Parnas (2003) assume that the sense of self is a deeply implicit phenomenon of the human mind and that there is no need for a "separate channel of self-monitoring or a second self-directed act of reflection", as was proposed by Frith (1992). Therefore, explicitly focused attention on an implicit experience could paradoxically lead to a sense of "alienation" that is often present in schizophrenia.

THEORY OF MIND

Humans have adopted the strategy to represent, anticipate and think about the mental states of others. This ability, referred to as the ToM or mentalizing, allows us to attribute and model the mental states (perceptions, motivations, knowledge, beliefs, emotions) of others and to predict their behavior. The term "theory of mind" was first introduced by Premack and Woodruff (1978). Initially, this term comprised the representation of the mental states of both ourselves and others. However, there is still an on-going and widespread discussion about the relation between self, a meta-representation of our own mental states (Vogeley et al., 2001), and ToM; and to what extent self is involved in the modeling of the mental states of others and vice versa (Brüne and Brüne-Cohrs, 2006).

Despite the variability in studies of ToM related neuronal activation and its abnormalities in schizophrenia, the most frequently replicated findings of these studies involve regions of the prefrontal area, the temporo-parietal junction and the middle brain structures (for review see Bosia et al., 2012).

In addition, Vogeley et al. (2001) demonstrated that ToM (representation of other's mental states) and SELF (representation of one's own mental states, a process parallel to ToM) capacities rely on both different and common neuronal mechanisms. While the ToM capacity predominantly activates mPFC along with the anterior cingulate cortex (ACC), the SELF capacity particularly activates the precuneus, bilaterally. In addition, an area within the right prefrontal cortex is particularly activated during conditions when an integration of ToM and SELF is demanded. Although ToM and SELF tasks also partly activate different brain regions, common brain areas are involved in both tasks.

It was demonstrated that the CMS including the medial prefrontal cortex (mPFC) and ACC are mainly activated in both processes, i.e., during self-referential processing (evaluation of one's personality traits) as well as during third-person perspective taking or meta-cognitive representations ("thinking about thinking") (Amodio and Frith, 2006; D'Argembeau et al., 2007). Interestingly, the degree to which the rostral part of mPFC was activated while processing others' personality traits correlated with the degree of similarity perceived between one's own and others' characteristics (Benoit et al., 2010). Mars et al. demonstrated in their meta-analysis that the brain regions involved in higher-order social tasks overlapped partly with the DMN, which is connected with self-referential processes.

These findings support the concept that self-referential (self-reflection) processes are employed also while thinking about other persons, where own person is used as a model for the evaluation of others. Mitchell et al. (2005) suggest that self-reflection is used to infer the mental states of others when they are sufficiently similar to one's own. This "social loop" is closed with the second level of self-referencing, when thinking about our reputation, which requires us to produce a representation of attributes that others apply to us (Amodio and Frith, 2006).

Essentially, regardless of the mechanism involved, available evidence suggests the importance of self-awareness processes in the representation of one's own mind (self) as well as in the representation of the minds of others (ToM). This concept parallels the fact that self-awareness, as a main component of self and also self-recognition (Irani et al., 2006), together with ToM are comparably affected in schizophrenia (horizontal axis of **Figure 1**).

ToM abnormalities were monitored in schizophrenia over the last few decades based on the difficulties in evaluating the mental states of others involved in the communication process, observed in some schizophrenia patients. Today, nobody argues the presence of the mentalizing deficit in schizophrenia, which was confirmed using various methodological approaches that can be divided into three categories: (a) verbal paradigms—indirect speech utterances (Corcoran et al., 1995), verbal jokes (Corcoran et al., 1997) and storytelling tasks involving false beliefs or deception (Andreasen et al., 2008); (b) nonverbal paradigms—comics strips or cartoon tasks (Sarfati et al., 1997), Mind in the Eyes test (Irani et al., 2006; Pentaraki et al., 2012) and false-belief picture sequencing task (Langdon and Coltheart, 1999; Brüne, 2003); or (c) combined methods—movies with actors for the assessment of social cognition (Montag et al., 2011), moving shapes paradigm, where the visual observations of actions are described verbally (Koelkebeck et al., 2010; Das et al., 2012; Pedersen et al., 2012) or verbal ToM stories presented simultaneously with cartoons that display the action occurring in the stories (Mazza et al., 2001).

Nevertheless, apparent variability in the applied methods has led to high heterogeneity in the obtained findings, making the investigation of the complex ToM deficit very problematic. The large degree of heterogeneity of ToM findings could be explained by the state variables and task differences, as was shown in a meta-analysis (Bora and Pantelis, 2013). In addition, it was demonstrated that the ToM deficit is not uniform in individual patients and is distributed varyingly among different components of ToM (Bosco et al., 2009). This opens the question of possible associations between the ToM impairment and psychopathology and/or cognitive functioning in schizophrenia. Nevertheless, the persistence of the ToM deficits in remitted patients (even less pronounced than in non-remitted ones) suggests that there are traits related to mentalizing impairments in schizophrenia as well as some potential effects of residual symptoms (Bora and Pantelis, 2013).

Several studies reported symptom specific ToM deficits by dividing the symptomatology into three subgroups according to the triadic domains model of schizophrenia (psychomotor poverty/negative symptoms, disorganization and reality distortion symptoms) (e.g., Mazza et al., 2001). Most studies observed a more prominent ToM deficit in patients with severe negative symptomatology or disorganization of thought and speech (Sarfati et al., 1997; Sarfati and Hardy-Bayle, 1999; Mazza et al., 2001). It was also demonstrated that some reality distortions, especially persecutory delusions, could be related to the ToM deficit (Corcoran et al., 1995; Mazza et al., 2001; Pousa et al., 2008). A current study showed that while negative symptoms are associated with a lack of mentalizing, positive symptoms such as delusions were associated with another type of error, overmentalizing (Montag et al., 2011). Importantly, patients without symptoms present at the time of testing showed normal ToM performance levels (Corcoran et al., 1997).

Interestingly, some studies focusing on schizotypal traits in clinical and non-clinical populations found the ToM deficit in a healthy population with higher schizotypy (Langdon and Coltheart, 1999). In addition, high levels of schizotypal traits (such as social anxiety, constricted affect and no close friends) have been shown to be important for the ToM performance in schizophrenia patients (Irani et al., 2007) which is more prominent than in their first-degree relatives (Irani et al., 2006).

Since mentalizing abilities demand some level of intact cognitive processes, several studies are focused on clarification of the relationship between the ToM deficit and a deficit in cognitive functioning present in schizophrenia. The poor ToM performance was demonstrated to be strongly associated with Intelligence Quotient (IQ) and measured cognitive performance, especially executive abilities (Abdel-Hamid et al., 2009) or working memory load (Brüne, 2003). However, importantly, some studies controlled for cognitive performance and IQ levels showed that the ToM deficit cannot be completely explained by the impairment of cognitive functioning in schizophrenia itself (Brüne, 2003; Bozikas et al., 2011; Montag et al., 2011; Pentaraki et al., 2012). A systematic review of the relationship between ToM and executive functions confirms the idea that the impairments in ToM and executive functions are independent of one another (Pickup, 2008).

TRIPLE NETWORK DYSFUNCTION: A CORE OF SCHIZOPHRENIA?

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. A wealth 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; **Figure 2**). It is widely accepted that coordination of these networks plays a key regulatory role in organizing neural responses underlying fundamental brain functions.

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 CMS, i.e., 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

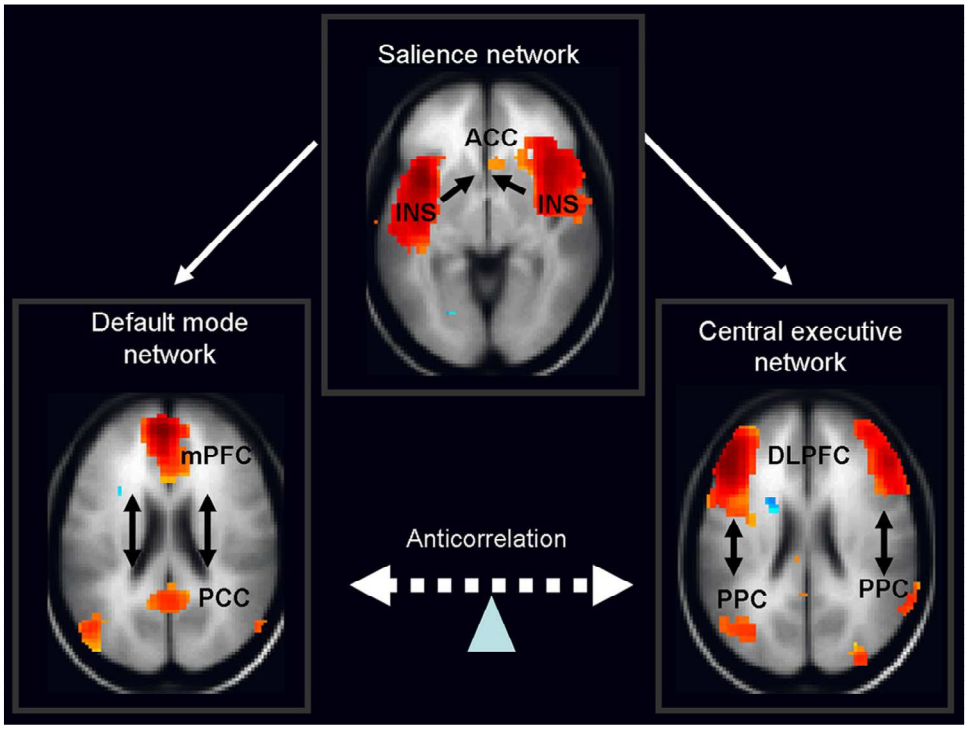

FIGURE 2 | Schematic figure of the triple network model consisting of the default mode network (DMN), salience network (SN) and central executive network (CEN). According to this model, the anterior insula (belonging to the salience network) activates the CEN and deactivates the DMN in response to the salient stimuli. Legend: ACC: anterior cingulated cortex, DPLFC: dorsolateral prefrontal cortex, PPC: posterior parietal cortex, mPFC: medial prefrontal cortex, PPC: posterior cingulate cortex, INS: anterior insula. Adapted from Menon and Uddin (2010); Sridharan et al. (2008), the images of networks derived from our in house resting fMRI sample, $n = 20$.

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 SN, composed of the anterior cingulate and the anterior insula, mediates selection of salient external and interoceptive signals (Sridharan et al., 2008; Menon and Uddin, 2010).

Accumulating evidence from neuroimaging studies in healthy individuals indicates that SN causally influences anticorrelated activation of DMN and CEN. The existing evidence supports a general role for the SN 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).

In this section, we examine how large-scale brain networks provide integrative albeit rather mechanistic models of schizophrenia psychopathology, traditionally clustered into positive, negative and cognitive domains. Furthermore, we emphasize a great deal of evidence accumulated over the last decade suggesting that insula/ACC i.e., SN dysfunction is a unified cause of brain-network disturbances observed in schizophrenia. Finally, we propose that deficits in coordination of these neurocognitive networks in schizophrenia may underlie a disruption in self-related functions that causes and also antecedes a disparate assortment of signs and symptoms encompassing such distant phenomena as first rank symptoms and impaired social cognition.

As a starting point, we take into consideration numerous resting-state and stimulus-evoked fMRI measurements in patients with schizophrenia compared to healthy controls that repeatedly showed aberrant functional connectivity within and between DMN, SN and CEN (White et al., 2010; Camchong et al., 2011; Kasparek et al., 2013; Moran et al., 2013; Orliac et al., 2013; Palaniyappan et al., 2013; Guo et al., 2014a; 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., 2012b). Indeed, based on non-psychiatric 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; Bonnelle et al., 2012). 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. Firstly, the existing data provide an explanation of a fundamental representation of positive symptoms: auditory verbal hallucinations (AVH). Data obtained from a resting state fMRI in schizophrenia patients suggest aberrant functional connectivity between the DMN and CEN as a denominator of AVH severity (Manoliu et al., 2014). Additionally, one recent fMRI study showed aberrant down-regulation of the DMN during a resting state that was concomitant with spontaneous hallucinations in schizophrenia, whereas overall spatial and temporal instabilities of the DMN correlated with the severity of hallucinatory experience (Jardri et al., 2013). This is of particular importance, since, as noted above, a large number of studies using both resting-state and task-related fMRI studies in healthy human subjects implicate the main hubs of DMN as being key structures for "self" as opposed to "other" discrimination (van der Meer et al., 2010; Qin and Northoff, 2011).

Therefore, keeping in line with this, the phasic hallucinations may emerge from a spontaneous switching off of the dysregulated and unstable DMN, secondary to SN dysfunction (Northoff and Qin, 2011). This may result in a malfunction of this self-attributional tagging system with a consequent misattribution of internal mental states to an external source. Along a somewhat different line, both structural and functional changes within the SN key node, the insular region, correlate with the occurrence of AVH in schizophrenia (Jardri et al., 2011; Palaniyappan et al., 2012a) and positive symptoms in general (Moran et al., 2014).

Correspondingly, a putative consequence of SN dysfunction, i.e., instability of DMN hub, correlates with overall positive symptom severity in schizophrenic patients (Rotarska-Jagiela et al., 2010). Correlation between illness duration, positive and negative symptom severity and an altered DMN cortical midline system has been further confirmed by combined resting-state fMRI and voxel-based morphometry (Guo et al., 2014b).

That is to say that a precise interlink between a triple network dysfunction and occurrence of positive symptoms, namely those beyond boundaries of first-rank symptoms, remains unclear. However, preliminary evidence suggests that the theoretical account presented herein may be complementary with the previously postulated alteration of the dopamine-dependent process of salience attribution in a psychotic state (Howes and Kapur, 2009).

Dopamine-mediated salience dysfunction hypothesis in a psychotic state has been suggested as an underlying cause for highly prevalent non-ego-disorder delusions, such as persecutory delusions and delusions of reference, whereas the theory appears at first sight less applicable to ego-disturbances inherent to first-rank symptoms in schizophrenia. Nevertheless, those disparate delusional phenomena may share the same mechanism. In a fMRI study, heightened self-relevance to ambiguous stimuli in patients with schizophrenia with delusions of reference compared to controls was associated with an increased blood-oxygen-level dependent (BOLD) contrast imaging response in DMN hubs as well as insula (SN) and midbrain dopaminergic regions (Menon et al., 2011). This finding suggests a direct link between dopamine-dependent aberrant salience and recruitment of main DMN cortical midline regions in heightened self-relevance that is thought to underlie delusions of reference. On top of that, the activity in insula and ventral striatum correlated with the strength of this particular type of delusions in patients.

It is tempting to conclude that following a continuum model approach, the same neural dysregulation within large scale brain networks may, on the one hand, underlie the sensation of delusions of reference and, on the other hand, lead—on its extreme end delusional alienation—to mental processes resulting in first rank symptoms of schizophrenia. This assumption is in accordance with the recent shift from a categorical to a dimensional concept of schizophrenia. It is in a general agreement with a factor analysis carried out in a large cohort of psychotic patients (Peralta and Cuesta, 2005). Based on this study, schizophrenia may be viewed as the "end-stage" disease or the extreme pole of the psychotic continuum. This and other evidence underline a dimensional construct of schizophrenia and support the continuum hypothesis of the psychotic illness.

Although the triple network theory provides a conceptual framework for an integrative psychophysiological approach for the study of a wide scope of positive symptoms, in the time being it is unable to provide significant additional explanatory power to the broadest context of schizophrenia-related variables, e.g., formal thought disorder, disorganized or catatonic behavior. On the other hand it is capable of providing a theoretical ground for a 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.

In line with the proposed role of SN structures in pathophysiological processes related to cognitive dysfunction in schizophrenia, there is a direct interlink between morphology of insula and inferior frontal gyrus (IFG) and a dysfunctional pattern of CEN activation and DMN deactivation during working memory in patients (Pujol et al., 2013). This is also in accordance with our findings (Horacek et al., 2005) which suggest that the medial forebrain pathways and cingulum bundle underlie the activity of cortical structures required for Stroop test processing.

Thirdly, deficits in social cognition (including ToM abilities) have been well documented in schizophrenia using a wide variety of tasks. Numerous studies suggested that brain areas associated with the DMN, namely mPFC, are involved in this cognitive faculty that includes also ToM (Amodio and Frith, 2006; Schilbach et al., 2006). This has been recently confirmed by an extensive study that compared resting-state networks in healthy participants with brain areas showing consistent co-activation during various task-based neuroimaging experiments archived in the BrainMap database. The DMN was heavily tasked exclusively with ToM and social cognition tasks (Laird et al., 2011). Concurrently, the reverse approach has been applied in additional meta-analyses of fMRI studies using the BrainMap database and likelihood estimations of functional brain activity associated with either rest or social cognition. Again, it has been shown that there is an overlap between the "social brain network" activated during ToM tasks and the DMN, both at the network level and at the level of individual brain regions (Mars et al., 2012).

Further direct evidence of the crucial involvement of DMN in theory of mind comes from a review performing a quantitative meta-analysis of neuroimaging studies of ToM, using the activation-likelihood estimation (ALE) approach (Mars, 2011).

Fourthly, an aberrant synchronization of large-scale networks may underlie even a negative symptom dimension. Both functional connectivity within and between distinct subsystems of the DMN, SN and CEN were calculated and correlated in a resting-state fMRI study. Internal functional connectivity between the SN and CEN correlated with the severity of negative symptoms in patients with schizophrenia (Bosia et al., 2012; Manoliu et al., 2013).

To sum up, meta-analyses targeting consistent activations across studies exploring the neural correlates of self (self-awareness and self-representation) and social cognition, namely ToM revealed shared activations within CMS. This finding parallels the simulation theory of social cognition based on the assumption that the same neural networks support thinking about self and other people.

Additionally, a recent large meta-analysis aimed at the identification of brain regions, which consistently show activations during social cognition, emotional processing and resting state showed a close convergence within CMS as well (Schilbach et al., 2012).

This study provides robust evidence for a shared neural network consisting of mPFC and precuneus that underlies activations during various emotional and social cognition tasks along with deactivations across different types of experimental paradigms. Identification of a common neural denominator of those seemingly disparate faculties brings some support to the above-mentioned two dimensional model of a human mind's representation.

In cognitive terms a commonality may exist between all three types of states, which could be termed "introspective processing". This specific mental faculty may represent a prerequisite for the processing either of one's own or other people's states on both a cognitive and an emotional level.

In schizophrenia, dynamic dysregulation of the CMS, which is considered the strongest part of the DMN, may substantially impair translation of cognitive processes from an internal to an external focus. This might explain schizophrenia symptoms related to defective self-monitoring, such as AVH or other ego-disturbances represented by thought insertion or thought withdrawal.

Nevertheless, an out of control increase in DMN activity or a failure of DMN deactivation may underlie a wide array of other schizophrenia symptoms, including non-ego-disorder positive symptoms, overall cognitive dysfunction and negative symptoms. Taken together, available evidence suggests a testable hypothesis that on the neural level, impaired self-monitoring, social and affective processing in schizophrenia converge and rely upon an aberrant recruitment of large scale brain networks. Principal causes may plausibly include impaired regulating machinery underlying the fine-tuned orchestration of those neural networks.

CONCLUSIONS AND FUTURE DIRECTIONS

This article aims to emphasize the concept of common self and ToM mechanisms and their disturbances as a marker of schizophrenia. We recognize the speculative nature of our hypotheses. Our goal is to provide future directions for neurobiological research in schizophrenia that extend beyond traditionally studied phenomenological dimensions and regional specific functional deviations. We propose an experimental approach addressing behavioral and neuronal features in both self and ToM paradigms in schizophrenia. This perspective provides us a novel direction to study not only brain and behavioral alternations in schizophrenia but also mutual relations between self and theory of mind, e.g., the possible role of the forward system in more complex processes. This approach reflects cumulating evidence of a disordered integration of large-scale brain networks as a critical pathophysiological mechanism underlying heterogeneous symptomatology in schizophrenia.

AUTHOR CONTRIBUTIONS

The main idea behind this work was courtesy of Filip Spaniel. All of the authors contributed to the final version of the paper equally and have approved it.

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