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Hippocampal activation and memory in schizophrenia depend on spatial strategy use in a virtual maze

Leanne K. Wilkins^a, Todd A. Girard^{a*}, Katherine A. Herdman^b, Bruce K. Christensen^c, Jelena King^d, Michael Kiang^e, Veronique D. Bohbot^f

^aDepartment of Psychology, Ryerson University, Toronto, ON, Canada

^bDepartment of Psychology, York University, Toronto, ON, Canada

^cResearch School of Psychology, Australian National University, Canberra, ACT, Australia

^dSt. Joseph's Healthcare Hamilton, and Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada

^eCentre for Addiction and Mental Health, and Department of Psychiatry, University of Toronto, Toronto, ON, Canada

^fDouglas Institute, and Department of Psychiatry, McGill University, Montreal, QC, Canada

*Correspondence to: Todd A. Girard, Department of Psychology, Ryerson University, 350

Victoria St, Toronto, ON, M5B 2K3, Canada. Telephone: (001) 416-979-5000 ext. 2646. Fax:

(001) 416-979-5273. E-mail: tgirard@psych.ryerson.ca

Abstract

Different strategies may be spontaneously adopted to solve most navigation tasks. These strategies are associated with dissociable brain systems. Here, we use brain-imaging and cognitive tasks to test the hypothesis that individuals living with Schizophrenia Spectrum Disorders (SSD) have selective impairment using a hippocampal-dependent spatial navigation

strategy. Brain activation and memory performance were examined using functional magnetic resonance imaging (fMRI) during the 4-on-8 virtual maze (4/8VM) task, a human analog of the rodent radial-arm maze that is amenable to both response-based (egocentric or landmark-based) and spatial (allocentric, cognitive mapping) strategies to remember and navigate to target objects. SSD (schizophrenia and schizoaffective disorder) participants who adopted a spatial strategy performed more poorly on the 4/8VM task and had less hippocampal activation than healthy comparison participants using either strategy as well as SSD participants using a response strategy. This study highlights the importance of strategy use in relation to spatial cognitive functioning in SSD. Consistent with a selective-hippocampal dependent deficit in SSD, these results support the further development of protocols to train impaired hippocampal-dependent abilities or harness non-hippocampal dependent intact abilities.

Keywords (MeSH Terms): Schizophrenia Spectrum and Other Psychotic Disorders; Spatial Memory; Spatial Navigation; Magnetic Resonance Imaging, Functional; Hippocampus; User-Computer Interface

1. Introduction

Schizophrenia is a chronic mental illness, for which cognition has moved to the fore as a unique and important therapeutic target (Gold, 2004). In this context, deficits in memory and hippocampal abnormalities are particularly robust among persons with Schizophrenia (e.g., Boyer et al., 2007; Saykin et al., 1991; Weiss and Heckers, 2001). The hippocampi are central to several pathophysiological theories of Schizophrenia (e.g., Christensen and Bilder, 2000; Grace, 2000) and are reliably implicated across meta-analytic studies of regional brain volume (Nelson et al., 1998; Vita et al., 2006; Wright et al., 2000). Therefore, further characterizing the specificity

of hippocampal-dependent memory deficits is important for advancing our understanding of the neuropsychology of Schizophrenia Spectrum Disorders (SSD). In particular, characterizing precise cognitive and neural mechanisms of this illness is informative for development of effective interventions aimed at ameliorating cognitive deficits.

Spatial memory is impaired among persons with SSD and is associated with hippocampal dysfunction (Folley et al., 2010; Hanlon et al., 2006; Ledoux et al., 2013; Weniger and Irle, 2008). However, there are different types of navigation that are dependent to different degrees on hippocampal and other brain systems (Bohbot et al., 2007; Iaria et al., 2003). Research from our team (Ledoux et al., 2013; Girard et al., 2010; Wilkins et al., 2013a) and others (Folley et al., 2010; Hanlon et al., 2006; Weniger and Irle, 2008; Spieker et al., 2012) indicates that SSD participants are impaired in their ability to use a *spatial strategy* to learn and remember the spatial relations among targets and environmental cues. These findings contrast with relatively spared performance using a *response strategies* that involve learning target object locations in relation to their own bodies or in relation to a single landmark. Taken together, these findings support a selective deficit in hippocampal-dependent spatial memory in SSD. It is important to note that these studies defined strategy use behaviourally, by manipulating same and different viewpoint for to-be-remembered objects between study and test. That is, participants were placed in experiments with environmental demands that require either a fixed viewer-dependent egocentric approach (individual is located in the same location between study and test, requiring recall of target object-location pairings in relation to the one's body centered frame of reference) or a viewer-independent allocentric approach (individual is located in a different position between study and test, requiring recall of target object-location pairings in relation to landmarks in the environment). Importantly, however, under normal real-world circumstances individuals

can adopt different strategies to support navigation. Depending on environmental demands, either spatial or response-based strategies can be successful (Bohbot et al., 2004, 2007; Echemendy and Bohbot, 2007; Iaria et al., 2003).

The 4-on-8 virtual maze (4/8VM) is a human analog of a rodent eight-arm radial maze that allows individuals the freedom to spontaneously adopt either a spatial or a response strategy. Use of a spatial, cognitive-mapping strategy involves learning the relations between target locations relative to proximal (e.g., trees) and distal (e.g., mountain range) extra-maze environmental cues. Alternatively, use of a response strategy involves navigating using sequences of left and right turns based on a single landmark or start position. The 4/8VM has provided valuable insight regarding individual differences associated with spontaneous use of these strategies (Iaria et al., 2003). For instance, in previous studies with healthy participants, individuals who spontaneously adopted a spatial approach had higher hippocampal gray matter and demonstrated greater brain activity during the task (as measured with fMRI), whereas response strategy use was associated with higher gray matter and fMRI activity in the caudate nucleus (Bohbot et al., 2004; Iaria et al., 2003). These findings suggest that subtypes of navigation approaches are specifically associated with different memory systems. Moreover, the 4/8VM task provides a useful multiple-memory systems framework to investigate specificity of hippocampal-dependent spatial memory deficits in SSD.

In a recent behavioural study using the 4/8VM (Wilkins et al., 2013b), we observed that SSD and healthy participants using a response strategy performed comparably. In contrast, SSD participants using a spatial strategy were significantly impaired relative to their healthy counterparts. Specifically, the SSD-Spatial group took more trials to reach criterion (2 error-free trials), had longer latencies to locate target objects, and visited more incorrect pathways during

learning trials relative to the Healthy-Spatial group. These findings provide behavioural support for selective hippocampal-dependent memory dysfunction in SSD relative to intact response learning systems. Although studies have provided evidence of abnormal hippocampal function in relation to spatial memory performance in SSD (Folley et al., 2010; Hanlon et al., 2006), here we provide an important extension of this research investigating the patterns and locations of neural system activation associated with spontaneous navigational strategy use among persons with SSD.

2. Methods

2.1. Participants

SSD participants ($n = 16$) were recruited through a research registry at St. Joseph's Healthcare Hamilton (SJHH), as well as through referral from outpatient clinics/programs at SJHH and the Hamilton Program for Schizophrenia. Healthy participants ($n = 16$) were recruited from the community via newspaper, Craigslist, and poster advertisements. Participants were included if able to provide informed consent (assessed via the MacArthur Competency Assessment Tool), 18-60 years of age, spoke English as their primary language, and had normal or corrected-to-normal vision (ascertained via a Snellen Acuity Chart). SSD participants met criteria for a DSM-IV-TR psychotic disorder, ascertained using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Diagnostic interviews were conducted by trained senior research assistants and graduate students. All SSD participants were clinically and pharmacologically stable (i.e., no change in medication or clinical status in the past 6 weeks). Exclusion criteria consisted of a self-reported lifetime history of a neurological condition or a lifetime or current nonpsychotic Axis 1 psychiatric

disorder (including lifetime alcohol or substance dependence or current alcohol or substance abuse). Healthy individuals with first-degree relatives with a psychotic disorder were excluded.

Participant characteristics are summarized in Tables 1 and 2. Overall, the SSD group had fewer years of education ($M = 13.6$) than the Healthy group ($M = 17.0$), $\eta^2 = 0.34$, and scored lower ($M = 95.2$) than the Healthy group ($M = 109$) on the Wide Range Achievement Test-Reading subtest, $\eta^2 = 0.26$ (Table 1). The SSD group included participants with diagnoses of Schizophrenia ($n = 10$) and Schizoaffective Disorder ($n = 6$). There were no differences between these subgroups on the experimental, cognitive, or demographic variables ($ps > 0.05$; data not shown). There were also no significant differences between the SSD-Spatial and SSD-Response group on symptom measures (Table 2). The SSD-Spatial group were on higher dosages of antipsychotics based on CPZe (chlorpromazine equivalent) conversions (SSD-Spatial = 239.1; SSD-Response = 104.0) (Virani et al., 2011; Woods, 2003). As detailed in the Results, accounting for the variables showing group differences, including education and reading scores, in the analyses did not affect the pattern of findings.

All participants provided written, informed consent and were provided with a cash honorarium of \$10 per hour. The study was approved by the Research Ethics Boards at Ryerson University and SJHH, and by the Imaging Research Centre at SJHH.

2.2. The 4/8VM task

The 4/8VM is a computerized virtual environment (created using Unreal Tournament, Epic Games Inc., Raleigh, N.C.) comprising an eight-arm radial maze with a central starting position, surrounded by extra-maze landmarks (e.g., tree, rock, mountain, and valley; Figure 1). Participants navigate with forward, left turn, and right turn buttons on a keypad.

Testing consisted of two-part trials from a constant starting position. In the Study Phase, participants visited four open pathways to retrieve target objects hidden in a pit located at the end (the other four pathways were blocked). In the Test Phase, all eight pathways were open and participants were required to avoid paths previously visited during study and find the hidden objects down the unvisited pathways (that were previously closed). Before the fMRI scan, participants were given the opportunity to practice using keystrokes in a different virtual environment and receive any clarification regarding the task. Four trials were administered while in the fMRI scanner. The configuration of pathways that contained the target objects changed across these four trials. The first (trial A1) and second configuration (trial B1) differed, whereas the third and fourth trial (trial A2, trial A3) had the same configuration as the first (trial A1) (Figure 2). This sequence of A-B-A-A trials was conducted across four runs in the scanner. Prior to the beginning and end of each run, participants completed a Visuo-Motor Control condition during which they counted backwards by threes starting at 1000 and were informed that there was nothing to learn during this Control task (Etchamendy et al., 2012); they were presented with eight open arms, but just needed to visit any four arbitrary arms to obtain the objects at the end of the pathways.

If participants did not reach criteria within the four scan trials, additional trials were completed outside of the scanner until participants met a criterion of two A-type trials without error. At the end of the experiment, spontaneous navigation strategies were assessed by interview as in previous studies (Bohbot et al., 2004, 2007; Iaria et al., 2003; Wilkins et al., 2013a, 2013b). Interviews were audio-taped and two independent raters confirmed agreement on the coding of participant strategies.

2.3. fMRI Acquisition and Preprocessing

Brain images were acquired with a 3T Signa MRI scanner (GE Medical Systems, Milwaukee, WI). T1-weighted anatomical images were acquired with a multiplanar rapidly acquired gradient echo (MP-RAGE) sequence with a spatial resolution of 1 mm^3 . Functional data were obtained using T2*-weighted high-resolution echo planar imaging (EPI) scans on an oblique angle perpendicular to the long axis of the hippocampi with 34 contiguous 3-mm thick slices covering the whole brain (TR=4000 ms, TE =30 ms, FA=90°, 128 x128 matrix, FOV=25.6). The first four functional frames prior to administration of the task were discarded to allow for scanner and tissue equilibrium and were not included in data processing. The 4/8 VM A-B-A-A trials were completed in four 15-minute fMRI runs separated by short breaks. B0 field maps were obtained to correct for inhomogeneity-induced image displacement in the functional scans.

Standard preprocessing of functional images was completed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). The fMRI data were resampled to 2-mm^3 voxels and B0 field maps were applied to correct for inhomogeneity. Processing included rigid-body motion correction and unwarping, coregistration of the anatomical image with functional images, tissue segmentation of the coregistered anatomical image, spatial normalization of the realigned and unwrapped functional images to the Montreal Neurological Institution (MNI) template based on the grey-matter segmentation of the anatomical image. Normalized images were smoothed with an 8-mm Gaussian filter.

2.4. Statistical Analyses

2.4.1. Behavioural Data Analyses

Given the current focus on imaging data, we applied the MANOVA approach used in our prior behavioural study to succinctly summarize the current 4/8VM performance data (Wilkins et al., 2013b; Grice and Iwasaki, 2007). The MANOVA was used to assess Group

(SSD, Healthy) $\times$ Strategy (Spatial, Response) effects using three key dependent variables (1) ABAA Latency = The summed duration (in minutes) of the initial ABAA sequence of test trials, (2) ABAA Errors = Errors of commission at test across the ABAA trials, including entries into a pathway without a target and repeat entries into a pathway within a trial, and (3) Trials to Criterion = Number of trials after the ABAA scan trials required to reach two error-free A trials (Wilkins et al., 2013b). The linear composite of these variables contributing to the Group $\times$ Strategy interaction provided a single index of performance for subsequent univariate and correlation analyses, thereby minimizing redundancy. The standardized discriminate function coefficients were Trials to Criterion, $ws = -1.22479$, ABAA Latency, $ws = -0.35467$, and ABAA errors, $ws = 0.7804$. In our previous study (Wilkins et al., 2013b), errors did not contribute substantial unique variance to the model, but in the current analyses all three measures contributed to the multivariate composite. Given the different measurement scales, the dependent measures were standardized prior to this analysis. Our data met the required assumptions of independence, multivariate normality, and homogeneity of variance-covariance matrices (Grice and Iwasaki, 2007).

2.4.2. fMRI Analyses

We focused our analyses on the Test Phase data for Trials 1 and 4 (i.e., A1 and A3). These were the trials in previous studies where healthy samples were distinguished by maximal hippocampal activation in A1 for those using a spatial strategy and caudate activation in A3 for those using a response strategy (Bohbot et al., 2004, 2007; Iaria et al., 2003). First-level (individual) analysis consisted of t-test contrasts of Test Phase > Visuo-Motor Control at Trial A1 and at A3.

Anatomically based ROI masks of the hippocampi and caudate nuclei were created using MARINA (Tzourio-Mazoyer et al., 2002), given their prior associations with spatial and

response strategies, respectively (Bohbot et al., 2004, 2007; Iaria et al., 2003). Within these ROIs, we applied a voxel-wise threshold of $p < 0.01$ (uncorrected) and extent threshold of 5 voxels, consistent with the literature (Achim and Lepage, 2005). More exploratory whole-brain data were conducted at a statistical threshold of $p < 0.005$ with a cluster extent threshold of 15 voxels.

Previous studies (Ledoux et al., 2013; Wilkins et al., 2013b) indicate a selective impairment in the SSD-Spatial group. A primary goal of the current study was to assess the extent to which this selective deficit relates to hippocampal activity. This question was best addressed with specific hypothesis-driven *a priori* contrasts comparing the SSD-Spatial group to the other three groups, as opposed to exploratory omnibus approaches (Rosnow and Rosenthal, 1989; Rosnow et al., 2000). More specifically, we contrasted the SSD-Spatial group against the Healthy-Spatial, Healthy-Response, and SSD-Response groups using “hypoactivation” $[-3 \ 1 \ 11]$ and “hyperactivation” $[3 \ -1 \ -1]$ contrasts. Follow-up pairwise contrasts using equal weights directly addressed differences between the Healthy and SSD Spatial groups using a hippocampal ROI, and between the Healthy and SSD Response groups using a caudate ROI.

Data were visualized and localized using SPM8, xjview (Ciu, X., <http://www.alivelearn.net>, Stanford, USA), and the WFU_PickAtlas (Department of Radiological Sciences, WakeForest University, Winston-Salem, USA) toolboxes via Matlab (version 2013A, The Mathworks Inc).

3. Results

3.1. Behavioural Results

3.1.1. 4/8VM Performance

A univariate ANOVA on the multivariate performance composite confirmed a Group x Strategy interaction, $F(1,28) = 8.80, p = 0.006, \eta^2 = 0.24$, and a main effect of Group, $F(1,28) = 9.21, p = 0.005, \eta^2 = 0.25$. As shown in Figure 3, the interaction indicated that the SSD-Spatial group ($n = 9$) was impaired relative to the other three groups. Most importantly, the SSD-Spatial group was impaired relative to the Healthy-Spatial, $t(14) = -3.24, p = 0.006, d = -1.73$, and SSD-Response groups ($n = 7$), $t(14) = -2.58, p = 0.022, d = -1.34$, whereas the SSD-Response group performed near-equivalently to the Healthy-Response group, $t(14) = -0.45, p = 0.965, d = -0.24$. Importantly, demographic and cognitive differences between groups did not interact with strategy.

3.1.2. Correlational Analyses

Relations between demographic, cognitive and clinical variables with the multivariate composite of 4/8VM performance were explored via bivariate correlations within groups. In the Healthy group, participants with higher scores on the WRAT-Reading subtest performed better on the 4/8VM composite score, $r = 0.72, p = 0.009$. Within the SSD group, higher scores on both WRAT-Reading and FSIQe were associated with better performance on the 4/8VM composite score, $r = 0.53, p = 0.036$, and $r = 0.55, p = 0.026$, respectively, whereas higher doses of antipsychotic medication (CPZe) related to worse performance, $r = -0.59, p = 0.017$.

In light of these correlations with WRAT-Reading and FSIQe, along with group differences in WRAT-Reading (Healthy>SSD), we explored the impact of these cognitive variables on the Group x Strategy interaction reported above using a covariate analysis. We acknowledge caution associated with potential correction of not just error, but overlapping true-score variance given the group differences on the WRAT (Miller and Chapman, 2001).

However, accounting for the noise variance associated with these covariates enhanced the relative variance accounted for by the Group $\times$ Strategy interaction by 15%, $F(1,22) = 14.01$, $p < 0.001$, $\eta^2 = 0.39$ (compare to $\eta^2 = 0.24$ from ANOVA).

Following up on the CPZe correlation, the SSD-Spatial group had higher CPZe values compared to the SSD-Response group, $t(13) = 2.95$, $p = 0.011$, $d = 1.58$ (Table 2). The difference in 4/8VM performance between the SSD-Spatial and SSD-Response groups remained a large effect, but did not reach statistical significance, when covarying for CPZe, $F(1,13) = 2.22$, $p = 0.160$, $d = 0.84$. This result suggests that correlation with CPZe at least partially reflects the differences between the SSD-Spatial and Response groups. However, inspection of the data also supported a continuous linear relation between antipsychotic dose and performance (i.e., not a basic heterogeneous subsampling issue). Moreover, a large negative correlation observed within the SSD-Spatial group alone, $r = -0.59$, indicates increased dosage relates to worse performance on the 4/8VM. Additional follow-up assessment regarding use of other medications (coding use of antidepressant, anxiolytic, neither or both) and type of antipsychotic (atypical, typical, both, none) did not reveal differential performance. This Medication Type $\times$ Strategy ANOVA maintained the main effect of Strategy, $F(1,9) = 7.91$, $p = 0.02$, $\eta^2 = 0.47$, but there was neither an effect of Medication, $F(3,9) = 1.44$, $p = 0.295$, $\eta^2 = 0.32$, nor Medication $\times$ Strategy interaction, $F(2,9) = 0.34$, $p = 0.723$, $\eta^2 = 0.07$.

3.2. fMRI Results

3.2.1. Hippocampal ROI

The SSD-Spatial group revealed lower activation, particularly in the right anterior hippocampus during both Trials A1 and A3 compared to all other groups combined

(‘hypoactivation’ contrast: Table 3; Figure 4). At Trial A3 only, the SSD-Spatial hyperactivation contrast revealed one left hippocampal cluster (Table 3). Direct comparison of the Healthy-Spatial > SSD-Spatial group supported a robust right anterior hippocampal cluster in the Healthy-Spatial group at Trials A1 ($xyz = 38, -14, -18, t = 3.43, p < 0.001, k = 61$) and A3 ($xyz: 32, -16, -16, t = 3.60, p < 0.001, k = 61$), but the reverse (hyperactivation) showed no significant peaks. The Healthy-Spatial group also evidenced greater hippocampal activation than the Healthy-Response group at trial A1, $t = 3.54, k = 123, p < 0.001$ ($xyz: 34, -28, 12$), thereby replicating previous results (Iaria et al., 2003).

3.2.2. Caudate ROI

The SSD-Spatial hyperactivation contrast revealed a left-caudate cluster at Trial A3 (Table 3). The hypoactivation contrast and pairwise comparisons failed to reach significance. The two Response groups failed to reveal any significant difference.

3.2.3. Whole Brain Analyses

At Trial A1, the SSD-Spatial group demonstrated lower activation relative to the two Healthy groups and SSD-Response group in the temporal lobe including clusters in the parahippocampus, inferior and middle temporal gyri, as well as in precentral, paracentral and cerebellar regions (Table 4). In contrast, the SSD-Spatial group revealed greater activation in the left inferior orbital prefrontal cortex (PFC) regions (Table 5).

At Trial A3, the SSD-Spatial hypoactivation contrast identified temporal regions including the hippocampus, as well as parietal, occipital, and frontal regions (Table 4);

whereas SSD-Spatial hyperactivation was observed in the insula, cingulate, pallidum, temporal lobe and inferior PFC regions (Table 5).

4. Discussion

This study highlights the relevance of strategy in understanding brain systems involved in navigation and memory in SSD. Behavioural results replicate our previous finding of a differential deficit among SSD participants who spontaneously adopted the Spatial strategy, whereas SSD participants using a Response strategy were not impaired (Wilkins et al., 2013b). Consistent with this memory impairment, the current fMRI results revealed lower right-hippocampal activation in the SSD-Spatial group during test trials. Importantly, the SSD and Healthy samples using Response strategies did not differ in terms of caudate activation, or 4/8VM task performance. This unique finding warrants future investigation into the mechanisms and reasons for their relatively intact performance and further characterizing their pattern of activity compared to the Healthy and SSD-Spatial group.

Lower hippocampal activation in the SSD-Spatial group was particularly robust in the right anterior hippocampus. Previous literature has associated the right and left hippocampi with different functions associated with spatial navigation. For instance, lesion studies support a central role of the right hippocampus visual-spatial and left-hippocampus in verbal memory task performance (Bohbot et al., 1998); Bohbot et al. (1998), however, observed right parahippocampal lesions to be more associated with impairment on a real-space human analog of the Morris water maze. The right hippocampus was deemed central for spatial navigation by Spiers et al. (2001), who reported that individuals with right temporal lobectomies were impaired on spatial navigation and memory in a virtual town, whereas those with left temporal lobectomies were impaired on episodic memory tasks that were more verbal in nature. More

recently, smaller right-hippocampal volume associated with pathological aging was also associated with poorer navigation abilities in both virtual and real-space human analogs of the Morris water maze (Nedelska et al., 2012). Interestingly, Igloi et al. (2010) demonstrated that the right hippocampus is involved during tasks requiring allocentric spatial representations, whereas the left hippocampus is involved in sequential egocentric representations (e.g., temporal sequence to find a target location). Overall, the poor navigation performance in our SSD-Spatial group is consistent with their deficient recruitment of the right hippocampus.

In contrast, it is interesting that the SSD-Spatial group revealed a cluster of greater activation in the left hippocampus, which exceeded even those of the Response groups. This greater left hippocampal activation may reflect compensation for deficient right activation or abnormal left-sided over-activation in SSD. Atypical lateralization of hippocampal structure and function in SSD has been noted in the literature (Achim and Lepage, 2005; Hanlon et al., 2011; Petty, 1999). In contrast to this pattern of greater left / lower right hippocampal activation on our visual-spatial memory task, a meta-analysis by Achim and Lepage (2005) highlighted greater right and lower left hippocampal activation in SSD compared to control samples during verbal episodic memory retrieval. These patterns support abnormal lateralization of hippocampal recruitment in SSD, modulated by stimulus type. However, in a direct comparison using MEG during verbal and non-verbal transverse patterning tasks by Hanlon et al. (2011), their SSD group failed to demonstrate the increased left and right hippocampal activation observed among healthy participants, respectively. Thus, relative group differences may also reflect failure of SSD participants to demonstrate lateralization of activation.

In addition to the left hippocampal cluster, greater activation was observed in the left caudate ROI among the SSD Spatial group; as noted above, both of these structures have been associated with sequence processing (Bohbot et al., 2004, 2007; Iaria et al., 2003; Igloi et al., 2010). Thus, although SSD Spatial participants reported attempting to use a spatial strategy, it is possible that their response memory system was over-activated. Similarly, our data showed greater left orbital PFC activation in the SSD-Spatial group compared to the other groups. These results suggest potential compensation in the left orbital PFC and left hippocampus in the face of dysfunctional right hippocampal involvement in the SSD-Spatial group when engaged in virtual navigation.

In this context, it is important to acknowledge recent challenges regarding the reliability of hippocampal activation differences in schizophrenia and proposals that episodic memory deficits may depend particularly on PFC mechanisms (Ragland et al., 2009; Salgado-Pineda et al., 2016). However, the literature also indicates that the ability to detect differences in hippocampal activation in SSD depends on the specific contrasts analyzed, task conditions, and associated neurocognitive processes involved (Achim et al., 2007; Ledoux et al., 2013; Ragland et al., 2009, 2015). The current study demonstrates the importance of also considering potential differences in neurocognitive strategies used by participants that may rely to different degrees on hippocampal and non-hippocampal systems. Indeed, post-hoc exploration of an overall main effect of Group revealed only a small cluster in the hippocampal ROI at Trial 1, which was most explained by the two Spatial Groups (Healthy > SSD Spatial); whole-brain analyses also reflected that main-effects analyses masked differential patterns across strategy subgroups (data not shown). The role of PFC systems in regulating strategy use (e.g., Christensen et al., 2013) warrants further attention in this context.

Consistent with the ROI results, whole-brain analyses revealed lower activation in the SSD-Spatial group than the other groups in the right medial-temporal lobe, including the hippocampus. During the first trial, this hypoactivation was also seen across temporal and sensorimotor cortical regions, and cerebellum; by Trial A3 lower activation was observed across temporal, frontal, parietal, and occipital clusters. Many of these regions have been associated with spatial navigation performance (Hartley et al., 2003; Ohnishi et al., 2006; Spreng et al., 2009; Viard et al., 2011) as well as episodic memory deficits in SSD more generally (Achim and Lepage, 2005; Ragland et al., 2009). Interestingly, the SSD-Spatial group had greater activation than others in inferior PFC regions, with the addition of clusters in the insula, cingulate, pallidum, and temporal regions by Trial A3. The differential patterns of frontal-insular hyperactivation and temporal hypoactivation associated with navigation in the SSD-Spatial group may point to disconnection between PFC and medial-temporal regions (Ledoux et al., 2013, 2015). For example, it is possible that any spatial representation formed in medial-temporal areas is not being adequately transferred to PFC regions to support appropriate adoption and continued use of a successful spatial strategy.

Disconnection in SSD between PFC and temporal regions may be due to an initial impairment in the hippocampi (Friston, 1998; Zhou et al., 2007). Lower anterior hippocampal activation in the SSD-Spatial group is consistent with a neurodevelopment model of neonatal ventral hippocampal damage in rats that causes a cascade of impairments across efferent targets and leads to poor spatial memory performance (Brady et al., 2010; Lipska, 2004). Therefore, spatial memory impairments may be due to deficient recruitment of the hippocampi, but investigation of the impact on other regions involved in spatial navigation across the brain is also required (Bullmore et al., 1997).

With respect to between-group comparisons on the 4/8VM, deficient hippocampal recruitment among SSD individuals who spontaneously adopted a spatial strategy is supported. However, there is no direct evidence to speak to whether they have an intact or impaired caudate-dependent response system. Likewise, the ability of spontaneous Response learners to adequately use an allocentric spatial strategies is not addressed in these studies. These limitations are important because, for example, the impairment observed in the Spatial-SSD group may reflect a general impairment of both spatial and response learning specific to this subgroup of patients, whereas, it is possible that those in the Response group may have intact spatial learning. Alternatively, the SSD group may be more homogenous in terms of deficient spatial and relatively intact response learning, and such that the differences observed merely reflect individual differences in strategy use. Addressing this limitation is informative about the extent to which these types of learning are coordinated when one is intact and the other is impaired. Of note, the SSD-Spatial group was found to be on a higher mean dose of antipsychotics than the SSD-Response group and a linear relation was observed between CPZe dose and performance. These findings may reflect relations to severity of illness or more direct neurochemical relations to medication effects that may influence spontaneous strategy use. Understanding the underlying mechanisms associated with individual differences in spontaneous strategy selection and application in SSD and healthy samples warrants further investigation. Spatial memory paradigms that are able to provide convergence of evidence on within-subject performance differences are thus important to solidify and strengthen our understanding of multiple spatial memory abilities.

Another limitation of this study is that our SSD and healthy samples were not matched with respect to education and WRAT-reading levels. However, whereas matched samples

may address sources of confound, they can also limit generalizability. Even so, the findings of preferential impairment in SSD using hippocampal-dependent, viewpoint-independent forms of spatial memory are supported by prior work in which samples or subsamples were matched on demographic and general cognitive attributes (Girard et al., 2010; Wilkins et al., 2013a, 2013b). Moreover, the main findings of differential impairment and hippocampal activation particular to the SSD-Spatial participants are not explained by these differences; these variables did not interact with strategy use. Nonetheless, future investigation of potential contributions of demographic and cognitive factors on task performance may further refine understanding of spatial memory abilities and neurocognitive mechanisms underlying spontaneous strategy use in SSD. Larger samples will also be important to assess the reliability and generalizability of the findings. Further research may also explore relations to functional outcome and amenability to cognitive training.

In sum, we provide evidence of impaired spatial memory and right hippocampal under-activation specifically among those SSD participants who spontaneously adopted a spatial-learning strategy. These findings replicate previous behavioural findings of selective hippocampal-dependent spatial memory deficits in SSD (Girard et al., 2010; Weniger and Irle, 2008; Wilkins et al., 2013a, 2013b). Moreover, fMRI data confirmed deficient recruitment of the right hippocampus in the SSD-Spatial group relative to all other groups during both the early and later trials. In contrast, the SSD-Response group performed in an equivalent fashion to its healthy counterpart and did not differ in terms of hippocampal or overall caudate activation. These findings provide direct evidence of a hippocampal-dependent dissociation in SSD that is moderated by strategy use. Additionally, the SSD-Spatial group recruited more PFC regions and fewer temporal-lobe regions than the other

groups while navigating the 4/8VM. Further investigation of the relations among these regions and the hippocampi are important for understanding the strategy-related deficits observed in the SSD group. It is imperative to answer these questions to better inform development of cognitive rehabilitation paradigms. The current results raise the importance of considering cognitive strategy use when evaluating and understanding memory abilities in SSD.

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Conflict of Interest

All authors reported no financial, personal, or other potential conflicts of interest.

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Figure Captions

Figure 1. Image of the 4-on-8 virtual maze (4/8VM) environment containing a tree, mountain and rock as landmarks surrounding the eight open pathways.

Figure 2. 4/8VM fMRI block design for Trial A1 in the scanner. Study Phase block is the configuration of pathways closed by barriers with a dark line through the arm. The circles at the end of the pathway indicate target arms. The Test Phase is the configuration of eight open pathways and the circles at the end reflect the target arms that were previously blocked by barriers in the Study Phase.

Figure 3. Differential deficit among schizophrenia spectrum disorder (SSD) participants reporting spontaneous use of a Spatial strategy. The multivariate composite score reflects a weighted combination of performance measured by Trials to Criterion, ABAA Latency and ABAA Errors based on a Group $\times$ Strategy interaction. Data represent standardized means and standard errors. Scores with a negative value indicate poorer performance.

Figure 4. The SSD sample using a Spatial strategy yielded lower activation during 4/8VM test trials than the other three groups (Healthy-Spatial, Healthy-Response, and SSD-Response). The scale bar represents colour-coded t values. Shown are data for Trial A3, peak voxel: $xyz = 32, -14, -16$, $t = 3.69$, $p < 0.001$, $k = 344$. Additional areas of hypoactivation in the SSD-Spatial group are visible (see Tables 3 and 4 for more details).

Table 1. Sample characteristics of healthy and schizophrenia spectrum disorder (SSD) groups by strategy (Spatial, Response).

Group	Healthy	SSD
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Strategy	Spatial	Response	Spatial	Response ^d
Demographics				
Sex (<i>n</i> males/ females)	2/5	4/5	5/4	6/1
Age(Years)	27.7(11.1)	33.9 (15.3)	44.4 (6.1)	34.6 (6.4)
Education (Years) ^a	17.6 (.9)	16.5 (4.1)	13.4 (1.7)	13.7 (2.0)
SES ^{b,e}	42.2 (11.9)	47.1 (11.4)	44.3 (9.3)	39.6 (8.6)
Video Game Experience				
Years of Playing	11.9 (9.0)	10.2 (9.2)	9.7 (9.9)	10.6 (9.6)
Hours Played / Week	3.7 (3.6)	1.9 (2.5)	2.1 (2.7)	1.9 (2.2)
3D Gamers(<i>n</i>) ^c	4	8	3	5
Cognition				
FSIQ ^e	114.0 (18.2)	115.1 (19.6)	104.4 (15.1)	105.3 (17.7)
WRAT-Reading ^{a,e}	107.3 (9.2)	110.3 (13.8)	93.0 (10.7)	98.4 (12.5)
MRT	9.4 (6.9)	9.5 (3.4)	7.8 (6.7)	8.0 (5.3)

Continuous data are presented as means (standard deviation), $M(SD)$; sex and experience with first-person immersive three-dimensional video-game experience (3D Gamers) are reported as frequency data (*n*).

^a Significant ($p < 0.05$) main effect of Group. There were no Group x Strategy interactions.

^b Socioeconomic status (SES) calculations were based on parental occupations.

^c 3D Gamer frequency was determined based on the Video Game Questionnaire (Bohbot et al., 2004).

^d The SSD-Response group consisted of one participant who used a sequence without awareness of a central starting location.

^e Appropriate data were unavailable for one Healthy participant for SES; data were missing for two Healthy-Spatial participants on WRAT-Reading and FSIQe.

Abbreviations: FSIQe= Estimated Full-Scale Intelligence Quotient derived from the Matrix Reasoning and Information subtests of the Wechsler Adult Intelligence Scale–Third Edition (Wechsler, 1997) as per Sattler and Ryan (1998); MRT=Mental Rotation Test (Peters et al., 1995); WRAT-Reading=Reading subtest from the Wide Range Achievement Test-Fourth Edition (Wilkinson and Robertson, 2006).

Table 2. Clinical characteristics of the SSD sample by strategy (Spatial, Response)

	Spatial	Response
Diagnoses (Schizophrenia, Schizoaffective)	5, 4	5, 2
Medication		
CPZe ^a	239.1 (103.4)	104.0 (70.7)
Atypical, typical, neither, or both antipsychotics	8, 0, 0, 1	4, 2, 1, 0
Antidepressants	3	2
Anxiolytics	6	4
PANSS T-scores		
General	35.9 (5.2)	33.6 (2.2)
Negative	35.1 (4.3)	35.8 (7.5)

Positive 35.9 (5.2) 33.6 (2.2)

Continuous data are reported as $M(SD)$; frequency data reflect numbers of participants(n).

Abbreviations: CPZe = chlorpromazine equivalents (Virani et al., 2011; Woods, 2003); PANSS

= Positive and Negative Symptom Scale (Kay et al., 1987) ^a $p < 0.05$.

Table 3. ROI Analyses: Hippocampal and caudate activation in the SSD-Spatial group relative to other groups^a at Trials A1 and A3

Contrast/Trial	ROI	Hemisphere	x	y	z	t	k
Hypoactivation							
A1	Hippocampus	R	34	-14	-26	2.61 ^b	85
		R	32	-40	-2	2.43 ^b	11
A3	Hippocampus	R	32	-14	-16	3.69 ^c	344
Hyperactivation							
A3	Hippocampus	L	-34	-18	-12	2.65 ^b	29
	Caudate	L	-16	26	-2	2.97 ^b	235

^aHypoactivation contrasts reflect clusters of lower activity in the SSD-Spatial group (SSD-Spatial < Others). Hyperactivation contrasts reflect clusters of activity in the SSD-Spatial group greater (SSD-Spatial > Others). Others include the Healthy-Spatial, Healthy-Response, and SSD-Response groups.

^b $p < 0.01$, ^c $p < 0.001$.

Abbreviations/symbols: k =number of 8-mm³ voxels in the respective cluster; L = left; R = right; t = t test statistic; $x y z$ = MNI coordinates.

Table 4. Whole-brain clusters of hypoactivation^a in the SSD-Spatial group at Trials A1 and A3

Trial	Brain Region	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>	<i>k</i>
A1	Frontal					
	L Precentral	-28	-36	-6	3.76	374
	R Precentral	42	-12	62	3.32	50
	Temporal					
	R Parahippocampal Gyrus ^b	22	-16	-32	3.68	179
	R Middle Temporal Gyrus	56	-8	-24	3.43	28
	R Inferior Temporal Gyrus	38	2	-38	3.07	25
	Parietal					
	L Paracentral	-20	-26	68	3.75	89
	Cerebellum	26	-36	-34	3.48	17
A3	Frontal					
	L Precentral	-58	12	38	4.2	104
	R Precentral	62	8	34	3.73	85
	L Paracentral	-62	-10	38	3.73	130
	Temporal					
	R Hippocampus	32	-14	-16	3.69	27
		26	-42	0	2.94	39
	R Superior Temporal Gyrus	74	-18	-4	3.56	122
		48	-34	14	2.99	25
	Parietal (L Inferior)	-60	-28	50	3.49	111

Occipital (R Inferior) 54 -78 -6 3.46 54

^a $p < 0.005$, $k > 15$; hypoactivation reflects clusters of lower (SSD-Spatial < Others) activation in the SSD-Spatial group compared to the Healthy-Spatial, Healthy-Response, and SSD-Response groups.

^b Parahippocampal cluster extended into right hippocampus.

Abbreviations/symbols: k =number of 8-mm³ voxels in the respective cluster; L = left; R = right; t = t test statistic; x y z = MNI coordinates.

Table 5. Whole-brain clusters of hyperactivation^a in the SSD-Spatial group at Trials A1 and A3

Trial	Brain Region	x	y	z	t	k
A1	Frontal					
	L Inferior Orbital	-52	32	-10	4.79	406
A3	Frontal-Insular					
	R Inferior Opercularis	52	18	2	3.37	61
	L Inferior Orbitalis	-42	38	-6	3.31	37
	L Cingulate	-14	38	-4	3.73	161
	R Cingulate	14	46	4	3.27	50
	R Insula	38	16	-14	4.43	132
	L Insula	-14	8	-8	3.68	190
		-26	22	-4	3.30	82
	Temporal					
	L Fusiform	-26	-12	-32	3.90	81
	R Middle Temporal Gyrus	54	-4	-24	3.90	108

L Inferior Temporal Gyrus	-56	-38	-16	3.60	35
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L Pallidum	-12	-6	-8	3.10	31
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^a $p < 0.005$, $k > 15$; hyperactivation reflects clusters of greater (SSD-Spatial > Others) activation in the SSD-Spatial group compared to the Healthy-Spatial, Healthy-Response, and SSD-Response groups.

Abbreviations/symbols: k = number of 8-mm³ voxels in the respective cluster; L = left; R = right; t = t test statistic; xyz = MNI coordinates.

Figure 1.

Figure 2.

Figure 3.

Figure 4. **Highlights**

- We used a virtual maze to assess navigation strategy use and memory systems.
- Persons with schizophrenia were impaired when using a spatial learning strategy.
- Schizophrenia spatial learners also had lower brain activation in the hippocampus.
- Deficits were not observed among patients using a response strategy.
- Results highlight the importance of cognitive strategy use in schizophrenia.