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

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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.

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

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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; Echamendy 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, 2. Overall, the SSD group had fewer years of education (M = 13.6) than the Healthy group (M = 17.0), η^2 = 0.34, and scored lower (M = 95.2) than the Healthy group (M = 109) on the Wide Range Achievement

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

Group	Healthy		SSD	
Strategy	Spatial	Response	Spatial	Response[d]
Demographics				
Sex (*n* 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 (0.9)	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(*n*)[c]	4	8	3	5
Cognition				
FSIQe[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*).
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).
[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 theVideo 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.

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] $p < 0.05$.