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A Virtual Reality Investigation Of Spontaneous Navigation Strategies And Spatial Memory Performance In Schizophrenia

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A VIRTUAL REALITY INVESTIGATION OF SPONTANEOUS NAVIGATION STRATEGIES AND SPATIAL MEMORY PERFORMANCE IN SCHIZOPHRENIA

by

Leanne Karyn Wilkins, B.Sc. Hon., University of Toronto, May, 2005

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Abstract

There is strong evidence that schizophrenia (SCZ) patients perform poorly on spatial memory tasks. We investigated whether these deficits were associated with subdivisions of spatial memory (locale/cognitive map and taxon/response) or whether these deficits represented a general cognitive decline. This study investigated the types of spontaneous navigation strategies used by individuals living with SCZ to solve the 4 on 8 task. It was predicted that SCZ participants who spontaneously chose a spatial strategy would have the longest latencies and make the most errors. Four of five measures of latency and errors produced a medium magnitude effect size (*r*), providing evidence that the SCZ participants who chose the spatial strategy performed more poorly than the healthy control (HC) spatial participants. However, there was no significant difference between the SCZ and HC response landmark groups. This finding is important as it was able to isolate intact versus deficient domains of spatial memory.

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Dedication

To those who think there is no light at the end of the tunnel.

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Virtual Reality Investigation of Spontaneous Navigation Strategies and Spatial Memory Performance in Schizophrenia

Introduction

Schizophrenia (SCZ) is a devastating and chronic psychiatric disorder that affects approximately one percent of the general population. Although distortions of reality (e.g., delusions) are the most known symptoms of SCZ, it is also characterized by serious cognitive impairment. Despite a focus on research and treatment of psychotic symptoms, the level of functional disability remains high. There is evidence that cognitive deficits are an important part of SCZ, potentially preceding the emergence of the illness (Fletcher & Honey, 2006). In this regard, cognition has moved to the fore as a unique and important predictor of functional disability in SCZ (Gold, 2004; Bowie & Harvey, 2006; Heinrichs, 2005; Ranganath, Minzinberg & Ragland, 2008).

The hippocampi are bilateral structures located in the medial temporal lobe (MTL), and are critical structures involved in episodic memory and spatial cognition. There is evidence that individuals living with SCZ show abnormal hippocampal functioning relative to healthy comparison samples, which seems to be connected to deficits in spatial memory. Recent research has identified the importance of specifically considering whether these deficits are associated with specific subdivisions of spatial memory or whether they represent a general cognitive impairment. In this thesis, I first provide an overview of the connection between episodic/ spatial memory deficits and functional outcome in SCZ. I then discuss the neonatal ventral hippocampal lesion model of spatial memory impairments associated with SCZ. Then I present an overview of the two main subdivisions of spatial memory (locale/cognitive map and taxon/response) and the

two central brain structures associated with each subtype (hippocampus and striatum). Lastly, I review evidence of either intact or deficient recruitment of central brain structures associated with each subtype of spatial memory in SCZ. The main objective of my thesis is to investigate the specific nature of intact and impaired abilities in SCZ. Based on the framework of preferential hippocampal pathology I hypothesize that spatial memory deficits found in SCZ are specific to subdivisions that require intact recruitment of the hippocampus.

Episodic memory is a primary predictor of functional outcome

SCZ is associated with widespread cognitive deficits and memory performance is one of the strongest predictors of functional outcome even compared to clinical symptoms or a host of other cognitive and demographic variables (Ranganath et al., 2008). In particular, episodic memory impairments seem to be one of the primary predictors of social and vocational functioning in SCZ (Bowie & Harvey, 2006). Episodic memory impairments compromise daily living skills and show only modest improvement with current available therapies in SCZ (Ranganath et al., 2008).

Episodic memory and spatial cognition are thought to depend on an intact hippocampus. Episodic memory facilitates the acquisition and retrieval of information about specific personal experiences that occur at a particular time and place (Eichenbaum, 2007). Spatial cognition is an important component of episodic memory as it provides information about the relations among objects and oneself within a specific context.

Spatial navigation paradigms are an important tool to investigate impairment in spatial cognition and episodic memory. In order to successfully navigate one's environment one must learn to reach a target end goal by learning the location of a single landmark within an

environment or by learning the relation between multiple landmarks. One can continue to update this information while moving in space (Eichenbaum, 2007; Eichenbaum, Yonelinas & Ranganath, 2002). There is strong evidence that relational/associative binding (learning the relationship between landmarks) requires intact recruitment of the hippocampus. The hippocampus is disproportionately affected in SCZ (Heckers, 2001). In contrast, research shows that item memory, which is less dependent on the hippocampus, might be relatively spared (Boyer, Phillips, Rousseau & Ilivitsky; Ranganath et al., 2008). Despite spatial memory being an important component of episodic memory, there have only been a limited number of research studies investigating spatial memory and spatial navigation abilities in SCZ. Therefore, the goal of the current thesis is to investigate the specific nature of intact and impaired spatial memory and navigation abilities in SCZ. Based on the framework of preferential hippocampal pathology I hypothesize that spatial memory deficits found in SCZ are specific to forms of spatial memory that require intact recruitment of the hippocampus.

Ventral hippocampal lesions as a pathophysiological model of SCZ

The hippocampus is a brain structure intimately related to spatial memory and is central to several pathophysiological theories of SCZ (Brady, Saul & Wiest, 2010; Boyer et al., 2007; Lipska, 2004; Tseng, Chambers & Lipska, 2009). One of the most thoroughly characterized neurodevelopmental models of SCZ is the neonatal ventral hippocampal lesion model. Seven-day old rat pups receive lesions to their ventral hippocampus during a critical phase of hippocampal development. The neonatal ventral hippocampal lesion triggers behavioural and cognitive features similar to those in persons living with SCZ. Although the lesion is administered during postnatal development, these animals do not exhibit deficits until at least

puberty, similar to the delayed onset of psychosis in humans. Lesions of the neonatal ventral hippocampus also impact the development of multiple surrounding brain regions similar to SCZ (Tseng et al., 2009). During early development damage to the hippocampus produces abnormalities in efferent targets such as the dorsal prefrontal cortex (dPC) and the dPC's ability to regulate the striatal dopamine function (Brady et al., 2010; Lipska, 2004). Spatial learning and memory are altered in rodents with lesions to the neonatal ventral hippocampus; these rodents are unable to learn the eight arm radial maze task or a spatial delayed win-shift task (Brady et al., 2010; Chambers, Moore, McEvoy & Levin, 1996).

These findings in the rodent literature are supported in the human literature as hippocampal volume reduction is a consistent structural abnormality found in SCZ (Heckers, 2001; Grace, 2010). Meta-analysis indicates the hippocampus to be four percent smaller bilaterally in SCZ compared in healthy controls (Nelson, Saykin, Flashman & Riordan, 1998). Evidence of reduced hippocampal volume is now considered to be a robust brain abnormality and individuals living with SCZ consistently show impaired recruitment of this brain region during performance on memory tasks (Heckers, 2001; McCarley et al., 1999). Episodic forms of memory are particularly affected in SCZ, which is consistent with findings of hippocampal dysfunction (Bowie & Harvey, 2006; Heinrichs, 2005). The pattern of memory impairment in SCZ has been found to be similar to performance of individuals with MTL lesions (Bartholomeusz et al., 2011; Ornstein, Sahakian & McKenna, 2008). The overlap in deficits between MTL and SCZ in contextual binding and episodic memory provides further evidence for the role of hippocampal dysfunction in SCZ (Bartholomeusz et al., 2011).

Overlap in behavioural performance between MTL patients and SCZ provides support that the hippocampus is involved in memory deficits found in individuals living with SCZ. However, proponents of the neonatal ventral hippocampal lesion model do not view cognitive impairment found in individuals living with SCZ being a result of isolated hippocampal dysfunction. That is, although the hippocampus is one of the regions most consistently impaired, SCZ is associated with widespread brain abnormalities. One advantage of the neonatal ventral hippocampal model is that it promotes investigation of the hippocampus in concert with other regions, such as the striatum, within a neurodevelopmental framework (Tseng et al., 2009). The objective of the current thesis is to investigate relative spatial memory abilities that are differentially dependent on the hippocampus and striatum in individuals living with SCZ. This investigation is of interest as different spatial strategies have been differentially associated with the hippocampus and striatum.

The role of strategies in spatial memory performance

As reviewed above, the hippocampus is integral to spatial memory. Remembering the spatial context of events and being able to navigate and form a cognitive map or use a locale approach allows one to remember and navigate a spatial environment (O'Keefe & Nadel, 1978). According to this view, the spatial arrangement of the environment is represented as a map and the hippocampus plays an important role in creating representations of these maps. This view is supported by the finding that place cells in the hippocampus of freely moving rats fire maximally when the rat visits certain locations. These neurons are thought to involve the encoding of specific spatial locations (O'Keefe & Dostrovsky, 1971). The hippocampus as a central structure

critical for formation of a flexible cognitive map of space has been supported by findings from imaging studies with healthy subjects and human lesion studies.

Individuals differ in spatial navigation abilities and these differences in performance seem to be correlated with measures of hippocampal integrity. Healthy individuals who report having spontaneously learned to navigate their environment by relying on the relations between landmarks have higher levels of gray matter in the hippocampus and show greater blood oxygenation activation in the hippocampus while navigating these environments (Bohbot, Lerch, Thorndycraft, Iaria & Zijdenbos, 2007; Etchamendy & Bohbot, 2007; Iaria, Petrides & Dagher, 2003). Also, individuals with a high fractional anisotropy in the hippocampus were found to be faster and more efficient in forming a cognitive map of their environment (Iaria, Lanyon, Fox, Giaschi & Barton, 2008). Human lesion studies have also found support for the hippocampus as the central structure involved in formation of a cognitive map. Individuals with lesions to their MTL were unable to efficiently utilize a spatial strategy and performed these spatial navigation tasks with longer latencies and more errors relative to healthy participants (Bohbot, Iaria & Petrides, 2004; Goodrich-Hunsaker & Hopkins, 2009; Holdstock, Cezayirli, Isaac, Aggleton, & Roberts, 2000; Iaria et al., 2008; King, Burgess, Hartley, Vargha-Khadem & O'Keefe, 2002; Parslow, Morris, Fleminger, Rahman, Abrahams & Michael, 2005).

O'Keefe & Nadel (1978) also proposed that rodents could learn to navigate their environment using a taxon learning strategy, which would require learning various sequences of left and right body turns independent of multiple cues within the environment, or relying on a single cue to guide a sequence of left and right body turns. In both rodent and human studies the taxon learning strategy requires intact recruitment of the caudate nucleus (the caudate nucleus

forms a part of the striatum) rather than the hippocampus. In sum, there appear to be at least two ways in which rodents and humans can learn to navigate their environment. In daily life either type of strategy will typically be used to navigate.

More recently, Bohbot et al. (2004) provided evidence that individual differences in hippocampal anatomy and function are preferentially associated with use of a cognitive mapping strategy, whereas differences in caudate/dorsal striatal anatomy and function are associated with use of a response learning strategy (Bohbot et al., 2004). Bohbot et al.'s (2004) use of the terminology of a cognitive map is similar to O'Keefe & Nadel (1978), meaning the ability to flexibly learn the relationship between landmarks within an environment to guide navigation. Bohbot et al.'s (2004) response strategy parallels O'Keefe and Nadel's (1978) definition of a taxon learning strategy. However, Bohbot et al. (2004) define a response strategy as consisting of two different subtypes. The first subtype is defined as a response-landmark strategy that involves using a single landmark and a sequence of responses (ie. left and right body turns) to aid navigation. The second subtype is defined as a response starting position strategy, which involves identifying a static starting position and learning a sequence of body turns (ie. left and right) independent of landmarks available in the environment (Bohbot et al., 2004; Bohbot et al., 2007). Based on the lesion and imaging literature both types of strategies (cognitive map and response strategy) are preferentially dependent on dissociable brain regions (hippocampus and caudate/dorsal striatum).

These behavioural findings of a double dissociation in healthy humans are in conjunction with rodent lesion studies. Rodents with damage to the hippocampus are impaired at learning a spatial version of the Morris water maze task, which requires using multiple cues in the

environment to successfully navigate to a submerged platform. However, these same rodents are not impaired on a cued version (stimulus response) of the water maze task. Rodents with lesions of the caudate nucleus and the fimbria-fornix revealed a double dissociation (Packard & McGaugh, 1992; Packard & McGaugh, 1996). The fimbria-fornix is a major subcortical output/input pathway to the hippocampus and thus provides evidence that intact recruitment of the hippocampal system is necessary to perform the cognitive map spatial learning task (spatial task), whereas intact recruitment of the caudate is necessary to perform the response learning task (cued visual discrimination task) (Miranda, Blanco, Begega & Rubio, 2006; White & McDonald, 2002).

These rodent findings are also consistent with the human imaging studies and human lesions studies using a virtual reality version of the 4 on 8 task (Bohbot et al., 2004; Bohbot et al., 2007; Etchamendy & Bohbot, 2007). This task presents a virtual environment composed of an eight-arm radial maze with a central starting position. The maze is surrounded by landmarks (a tree, rock, mountains and sunset). As the subject walks down a staircase at the end of the maze arm, there is an end target object. The goal is to remember the location of the pathways visited (i.e., from where goal objects were already retrieved) and avoid those pathways on the following trial. In this paradigm, individuals are interviewed about the type of navigation strategy used to solve the task. As mentioned above, there are two possible strategies that participants could use to navigate. A cognitive map strategy would be using multiple landmarks to remember which pathways have been previously visited. A response strategy would involve using a single landmark and/or a sequence of body turns.

MTL patients who reported using a response learning strategy (60%) to solve the 4 on 8 task made fewer errors (e.g., visiting an unrewarded arm or revisiting a pathway) as compared to those MTL patients who reported using a cognitive map strategy (Bohbot et al., 2004). Those MTL patients who persisted with a spatial strategy made the largest number of errors and had the longest latencies overall. Based on findings with MTL participants on the 4 on 8 task, the current hypotheses are that individuals living with SCZ will more often spontaneously choose and persist with a cognitive map strategy while making both maximal errors and latency overall.

Spatial memory impairment in individuals living with SCZ

Impairments in spatial abilities in SCZ have been identified and connected to hippocampal abnormalities (Girard, Christensen, & Rizvi, 2010). However, within the SCZ literature there are only a few spatial memory studies, and only fairly recently have researchers started to investigate spatial navigation in SCZ. There have been findings of individuals living with SCZ having spatial memory impairments on the virtual Morris water maze (Folley et al., 2010; Hanlon, Jagannathan, Calhoun & Pearlson, 2006). Importantly, however, there are multiple forms of memory in which persons with SCZ may show different levels of impairment. The current thesis is motivated by previous research that has shown that (a) different regions of the brain control different aspects of spatial memory and (b) specific forms of neuropathology target specific brain regions and should therefore result in discrete spatial memory impairment. For example, Girard et al. (2010) used a human analogue of a rodent maze paradigm to probe different aspects of visual-spatial memory abilities and found viewer-independent spatial memory to be particularly impaired among persons with SCZ. Viewer-independent memory

requires forming an observer-independent mental representation of the spatial relations among objects similar to a cognitive map.

Weniger and Irle (2008) used a simulated first person environment to compare performance between SCZ participants and healthy controls on a virtual park (cognitive map task) and a virtual maze (response task). SCZ participants were significantly impaired at learning the virtual park, but showed intact performance on the virtual maze relative to controls. However, there are no SCZ studies that have directly compared the ability to form a cognitive map with the ability to learn a response-landmark strategy to solve a navigation task within a single paradigm. Furthermore, and no studies have investigated spontaneous navigation strategies used by individuals living with SCZ. Given that different brain regions control different aspects of spatial memory, and neuropathology in SCZ targets specific brain regions than further investigation of cognitive mapping and response strategies remains necessary to more explicitly identify intact or impaired abilities. Understanding the specific nature of intact and impaired abilities is important in SCZ for the development and refinement of intervention strategies that can harness intact abilities and/or target remediation of impaired abilities.

Evidence of intact stimulus response performance in SCZ

Keri, Nagy, Keleman, Myers and Gluck (2005), conducted one of the first studies that revealed that patients with SCZ showed a selective deficit on a MTL-dependent task, whereas stimulus-response learning was spared (basal ganglia dependent) within a single task (the caudate/striatum being part of the basal ganglia). Therefore, I expect performance on the 4 on 8 task to be relatively more intact among individuals living with SCZ using a response-landmark strategy relative to those using a spatial strategy.

Summary

SCZ is a devastating and chronic psychiatric disorder that affects approximately one percent of the general population. The hippocampus, is a brain structure intimately involved in memory and is the focus of numerous theories and research studies on SCZ. Importantly, there are multiple forms of memory in which persons with SCZ may show different degrees of impaired and spared abilities. Investigations of performance between SCZ patients and controls indicate that persons with SCZ are impaired on spatial-memory tasks that require the ability to form a flexible cognitive map (more dependent on hippocampal functioning), but may show intact performance on response learning tasks (dependent on caudate/dorsal striatum). Spatial memory is an important component of navigation. Therefore, it is important to investigate differential performance on tasks that measure specific forms of spatial navigation such as cognitive map and response-landmark spatial learning. The current thesis is motivated by previous research showing that different regions of the brain control different aspects of spatial memory and that specific forms of neuropathology target precise brain regions and, therefore, result in discrete spatial memory impairment. The current thesis will extend previous research by Weniger and Irle (2008) using a virtual reality spatial navigation task, the 4 on 8 task. There are three main novel aspects of this thesis:

1) This is the first study to investigate spontaneous navigation strategies that individuals living with SCZ use to solve a virtual navigation task.

2) The 4 on 8 task is a stronger design as compared to the virtual park and virtual maze utilized by Weniger and Irle (2008). The 4 on 8 task has construct validity based on findings with healthy controls and lesion patients which have identified double dissociations between the use of a

cognitive map strategy (intact hippocampal recruitment) and a response-landmark strategy (intact caudate recruitment) (Bohbot et al., 2004). This paradigm will aid in determining whether the spatial memory deficit in SCZ represents a specific or a general cognitive deficit.

3) This the first study to directly compare spatial memory performance of SCZ participants and controls following use of either a cognitive map or response learning strategy.

Main thesis objective and hypotheses

The first objective of the present protocol is to identify the types of spontaneous navigation strategies individuals living with SCZ use to solve the 4 on 8 task. The second objective is to identify whether these different types of strategies correspond to differences in the number of errors and latency between individuals living with SCZ and healthy controls. If response-landmark memory is spared in SCZ patients then this may indicate that the ability to form a cognitive map of one's environment may be a specific cognitive deficit. It is important to identify specific memory deficits associated with SCZ in order to program specific cognitive rehabilitation programs. Understanding the specific nature of intact and impaired abilities is important for the development and refinement of intervention strategies that can harness intact abilities and/or target remediation of impaired abilities.

Therefore, based on the evidence reviewed above, the current thesis predicts that individuals living with SCZ that spontaneously choose a response strategy to solve the 4 on 8 task will make fewer errors and require less time to solve the task as compared to those individuals living with SCZ who spontaneously choose to use a spatial strategy.

Method

Participants

Data were collected from 17 participants living with SCZ and 15 healthy controls (HC) (see Table 1 for demographics). HC were recruited from the Hamilton, Ontario community via newspaper, Craigslist and poster advertisements. Individuals living with SCZ were recruited through a research database at St. Joseph's Healthcare, Hamilton (SJHH) and through a referral from Services at SJHH and the Hamilton Program for Schizophrenia. All participants were compensated with a cash honorarium of $10 dollars per hour. Participants in the SCZ group were included if they were able to provide informed consent, were 18-60 years of age, spoke English as their primary language, and had normal or corrected-to-normal vision and were clinically and pharmacologically stabilized. Exclusion criteria consisted of a lifetime history of neurological injury or disease, or current nonpsychotic Axis I psychiatric disorder, including alcohol or substance dependence or abuse, first- degree relative with a psychotic disorder, recent use of psychotropic drugs or change in use of antipsychotic medications within two weeks of participation in the study (SCZ). There were no group differences with regard to age, education and SES, but there were proportionally more males and fewer females in the SCZ group. One SCZ participant was excluded from analysis because of nausea experienced during the 4 on 8 task. This study was approved by Ryerson University's Research Ethics Board and the SJHH Research Ethics Board.

Table 1

Demographic Characteristics of Healthy Control (HC) and Schizophrenia (SCZ) Groups

Characteristics	HC	SCZ	*p*
Demographic			
Sex (*n* males/ females)	6/9	14/3	.009
Age (Years) [a]	33.73±12.91	42.29±8.11	.131
Education [a]	15.54±2.37	12.82±1.29	.322
Socioeconomic Status (SES) [a]	42.12±11.68	41.30±8.01	.166
Video Game Experience			
Years of Experience [a]	9.40±7.73	11.53±10.97	.312
Hours Played Per Week [a]	4.87±22.01	4.63±9.72	.338
3D, *n*	12	6	.141

Note. SES = socioeconomic status calculations are based on parental occupations and calculated according to the method of Blishen, Carroll & Moore (1987); 3D, *n* = number of participants with first person immersive video-game; Sex and 3D were evaluated with a χ^2 statistic and all other variables were evaluated with *t* tests. [a] Use of (a) means ± standard deviation (M ± SD)

Procedure

Participants were tested individually in two separate 3-4 hour sessions. On day one participants gave informed consent to participate in the study, and conducted a standard lab interview to gather basic demographic information. The following tests were also administered

on day one: Wechsler Adult Intelligence Scale (WAIS-III Information and Matrix Reasoning Subtests; Wechsler, 1997), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), Mental Rotation Test (Peters, , Laeng, Latham, Jackson, Zaiyouna & Richardson , 1978), Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein & Opfer, 1987), Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and The Wide Range Achievement Test (WRAT-IV; Robertson & Wilkinson, 2006). On day two the video game questionnaire, 4 on 8 task and strategy assessment questionnaire were administered (Bohbot et al., 2004).

Cognitive Assessment

Measures of general cognition, memory abilities, and visual-spatial processes were obtained to characterize the samples' neuropsychological functioning (see Table 2 for descriptive statistics for cognitive measures):

WAIS-III. The WAIS – III (Wechsler, 1997) test was administered to measure an intelligence quotient (IQ). Two subtests from the WAIS-III were used to estimate full-scale IQ (global intelligence) as in previous studies (Girard et al., 2010). The Information test was a verbal subtest and consisted of questions that assess the degree of general knowledge that is acquired from a culture (e.g., "Who is Cleopatra?" or "At what temperature does water boil?"). Participants received a score of 1 for each correct answer. The scores on this test range from 0 – 26. The raw scores (0-26) attained on the test were converted to scaled scores. The scaled score was based on normative scores found in individuals of a similar age range as the participant and predetermined in the WAIS-III scoring booklet (Wechsler, 1997).

Table 2

Cognitive Characteristics of the Healthy Control (HC) and Schizophrenia (SCZ) Group as Expressed as M±SD

Characteristics	HC	SCZ	*p*
WAIS-III FSIQ	115.08±7.97	96.36±18.71	.003
WRAT-4	104.85 ±10.76	93.21±11.73	.013
Mental Rotation	13.53 ±7.29	7.00±5.40	.008
RBANS			
Immediate Memory Index	98.46±17.03	76.35±16.62	.002
Visuospatial Index	105.15±12.56	94.29±24.17	.639
Language Index	102.23 ±7.71	83.29 ±10.45	.001
Attention Index	98.23 ±17.68	26.78± 20.73	.008
Delayed Memory	101.46 ±11.73	78.86 19.63	.001

Note. WAIS-III FSIQ = Estimated full-scale intelligence quotient derived from the Matrix Reasoning and Information subtests of the Wechsler Adult Intelligence Scale – Third Edition (Sattler & Ryan, 1998; Wechsler, 1997); WRAT-4 = Wide Range Achievement Test- Fourth Edition (Robertson & Wilkinson, 2008); Mental Rotation (Peters et al., 1995); RBANS = Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, 1998)

The Matrix Reasoning test consisted of questions that assess nonverbal abstract problem solving, inductive reasoning and spatial reasoning. Participants view a grid of squares (two x four). Each square represents a pattern that is consistent across the two x four grid display (e.g.

all squares are yellow). Three fourths of the display demonstrate a pattern that needs completion by a fourth (i.e., three yellow squares would require the yellow option to complete the blank). The patterns are initially simple and progressively become more complex. Participants receive a score of one on the test for each correct answer. The total scores range from 0-26. The raw scores (0-26) attained on the test were converted to scaled scores. The scaled scores on both of these measures (Information and Matrix Reasoning) were to derive an estimate of Full-Scale IQ scores (FSIQ; Sattler & Ryan, 1999).

WRAT-4. The Wide Range Achievement Test (WRAT-IV; Robertson & Wilkinson, 2006) is a standardized measure of reading levels and academic skills. The Word Reading subtest was administered which includes the letter recognition (15 items) and word reading (55 words) which combined for a total score of 70. The Word Reading subtest was used to measure performance in linguistic achievement to ensure cognitive abilities were relatively matched between controls and individuals living with SCZ and also that all participants were of a sufficient grade level to understand the task instructions.

RBANS. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998) was administered as a neuropsychological screening battery. The battery produces scaled scores for 5 cognitive domains. The 5 domains: 1) Immediate Memory Index (list learning and story memory), 2) Visuospatial Index (figure copy and line orientation), 3) Language Index (picture naming and semantic fluency), 4) Attention Index (digit span and symbol coding) and 5) Delayed Memory (list recognition, story recognition and figure recall). Raw scores for each subscale within an index were converted into *T* scores that were standardized to a scale with a mean of 50 and SD of 10.

Mental rotation. The Mental rotation test (MRT-A; Peters et al., 1995) was a paper and pencil task that tests spatial visualization of figures. Participants were asked to identify two correct target objects from among four test stimuli. The two correct target objects were two-dimensional cuboid shapes rotated from a primary target off of either the vertical or horizontal axis. Participants were given five minutes for each section. There were two sections that contain twelve questions each. Participants were given a score of 1 if they correctly identified the two target objects, but were given a score of 0 if at least one of the target objects was incorrect. The scores on this task range from 0 – 24.

In summary the SCZ participants were impaired on all of the cognitive measure except for the RBANS Visuospatial Index. However, the WAIS and the WRAT indicate that the SCZ group was within the average (normal) range for IQ. However, the HC were above average on the WAIS and the WRAT.

Clinical Assessment

The following standardized instruments were used to confirm diagnosis for the SCZ participants and HC for the comparison group, as well as to characterize schizophrenia and medication-related symptoms:

MINI. The Mini International Neuropsychiatric Interview was a short structured clinical interview used to confirm diagnoses and accompanying symptomology (MINI; Sheehan et al., 1998). The MINI contained 120 questions and screened 17Axis I Diagnostic and Statistical Manual-III-R disorders for current and lifetime diagnoses. Additional symptom questions within each disorder section were asked only if the screen questions were endorsed. The suicide and antisocial sections were not included in the assessment for ethical reasons. Participants that

endorsed criteria for a current Axis I disorder were excluded from participation in the study for the HC group. The MINI was also used to confirm diagnoses of either schizophrenia or schizoaffective disorder in the SCZ group.

PANSS. The Positive and Negative Syndrome Scale was administered only to the SCZ group (PANSS; Kay et al., 1987). The PANSS was a standardized measure developed to assess positive (e.g., hallucinations and delusions), negative and overall symptom severity (e.g., apathy and withdrawal). There were 30 items on the PANSS and ratings were based on information provided about experiences in the past week and were recorded on a seven-point rating scale. The questions probe pathological themes (e.g., Do you consider yourself to be famous?) and probe for experiences of hallucinations, delusional ideation, suspiciousness and grandiosity. There was also a section of questions aimed to gain information about mood states, anxiety, orientation and abstract reasoning ability. Lastly, the experimenter subjectively rated items about the participants' physical manifestations (e.g., Tension), interpersonal behaviour (e.g., Rapport), cognitive-verbal processes (e.g., Conceptual Disorganization), thought content (e.g., Grandiosity), and response to structured questions (e.g., Difficulty with Abstract Thinking). The PANSS were scored by summation of ratings that range from 7-49 for the Positive and Negative Scales and 16-112 for the General Psychopathology Scale and were converted to T scores (see Table 3 for descriptive statistics for clinical measures).

Main Experimental Task Material

A computer game (Unreal Tournament, Epic Games Inc., Raleigh, N.C.) was used by Dr. Veronique Bohbot at McGill University to create a navigation task that immersed individuals within a virtual environment called the 4 on 8 Radial Arm Maze. I trained with Dr. Bohbot during a month stay at McGill University to learn task design, administration and scoring.

Table 3

Characteristics of the Schizophrenia Patient Sample

Variable	Statistic
Diagnoses, *n*	8 schizophrenia, 9 schizoaffective
Antipsychotic medication, *n*	
CPZ [a]	374.44±536.40
Atypicals	14
Typicals	6
Antidepressant	13
Anxiolytics	13
PANSS-General T score [a]	33.06±3.93
PANSS- Negative T score [a]	32.47± 6.87
PANSS- Positive T-Score [a]	34.35±10.19

Note. PANSS = Positive and Negative Symptom Scale (Kay, Fiszbein & Opler, 1987); CPZ = chlorpromazine equivalents (Wood, 2003). [a] Use of (a) means ± standard deviation (M ± SD)

Participants performed the task using a personal laptop. The 4 on 8 task presented a virtual environment composed of an eight-arm radial maze with a central starting position. The maze was surrounded by landmarks (tree, rock, mountain and sunset). There was a boundary wall located between the landscape and the tree and rock. At the centre of the platform there were eight arms that extended from this central starting location. At the end of each arm there was a staircase that participants walked down that led to a small pit where an object (golden Buddha) was located. The participant started each trial on the central platform facing the same direction.

Participants were not able to see the location of the object until they walked down the staircase at the end of the arm. Prior to testing, participants were placed in a practice environment called the habituation room which is a similar environment to the 4 on 8 task, but without the landmarks.

There were two types of trials (trial A and B), each composed of a study phase and a test phase. In the study phase of trial type A, participants were free to visit the arms in any order. The order of correct path locations was Arm 1, 3, 5 and 8. Participants were forced to visit the four arms to be learned during the study phase by blocking off the other four arms of the maze. In the study phase of trial type B, the order of correct path locations was Arm 3, 4, 6 and 8.

In the test phase of trial type A, the correct path locations was Arm 2, 4, 6 and 7. In Part 2 of trial type B, the correct path locations was Arm 1, 2, 5 and 7. The correct paths to visit during the testing phase were the arms that were not previously visited during the study phase. There was a third type of trial (trial C) which was also composed of two parts and was called the probe trial. In the study phase of trial type Probe C the sequence of correct path locations was the same as Part 1 (study trial type A; Arms 1, 3, 5 and 8 and test trial type A; Arms 2, 4, 6 and 7), however, in Part 2 of Probe C the walls around the radial maze were raised to conceal the landscape and the tree and rock were removed so there were no landmarks available in the environment (see Appendix C). At the end of the experiment participants were interviewed about the types of strategies they used to solve the task (see Appendix D). The verbal report interview was recorded on a hand held audio recorder for each participant. Participants were also given a questionnaire to assess experience with video/computer games (see Appendix B).

Task Administration

To move within the environment, the participant used a keypad with forward, backward, left turn and right turn buttons. Prior to testing, participants were placed in a practice environment called the habituation room that consisted of eight radial arms and no landmarks. Participants were asked to spend time practicing moving in the habituation room to become familiar with the motor aspects and layout of the maze. When participants felt comfortable navigating the practice environment (habituation room) they informed the experimenter and were moved into the testing environment.

There are two types of trials (trial A and B), which were composed of two parts. In Part 1, four of the eight arms are accessible with objects at the end of each arm, the other four of the eight arms were blocked by a barricade and could not be accessed by the participant. When participants were immersed in the environment they were given the following instructions (see Appendix A for complete administration instructions):

"You are at the center of a platform from which branch out several pathways. At the end of these pathways are stairs that lead to a small pit. You will notice that there are 4 pathways closed by barriers, as you can see, and 4 pathways that are accessible. You must visit the 4 accessible pathways and pick up the objects located at the end of the stairs. Look carefully because you have to remember in which pathways the objects are located. You must remember which pathways you have taken, because in the next step, all 8 pathways will be accessible, there will not be any barriers to block your way and you will have to avoid the paths you had initially gone into to find objects. You have to go in the pathways and try to make as few errors as possible. If you enter the same pathway twice, this will be counted as an error; if you go into a

pathway that does not contain an object, it also counts as an error. This task is not a race, it is important you understand that the goal is to find the objects in the right pathway during the stage when the 4 arms are open and avoid these pathways during the second stage when all 8 arms are open."

When the fourth correct object was picked up, participants were made aware that they could take their time and look around to try and remember the paths where the objects were located. In Part 2, all arms were accessible and objects were present in the four arms that had been blocked in Part 1 (trial type A). Participants were again located at the same starting position at the centre of the platform in the arena and facing the same orientation towards the tree (as in Part 1) and were given the following verbal instructions (see Appendix A):

"All 8 pathways are now available and you have to remember where you have been and avoid these pathways in order to retrieve the objects. If you go down a pathway and there is no object located at the end, this indicates that you have taken an incorrect pathway and that you have already visited this pathway in the last part or it was a correct pathway that you have already visited during this part."

During each part of the task participants were permitted a maximum of 10 path visits (e.g., going down an incorrect path, re-entering a correct/incorrect path or visiting a correct pathway). After the 10^{th} visit participants were moved to the next part of the trial. All participants completed the following sequence A, B and A. The number of errors the participant made across the three trials was recorded. In order for the participant to move to the Probe C, they must have met a cut-off criterion. In order to meet criteria participants had to locate the four correct objects without visiting an unrewarded arm or revisiting either a correct or incorrect arm

on Part 2 of trial A. The participants were required to perform two type A trials without errors before they were moved to the probe. The number of trials given to participants was determined by how long it took to meet this criterion. If participants did not meet criterion after an initial sequence of ABA and fourteen extra trials, the experiment was discontinued and the participant was not given the Probe C trial.

Trial C was the probe trial. Part 1 of Probe C was identical to Part 1 of trial type A. However, in Part 2 of the Probe C the walls were removed so that no landmarks were visible. The purpose of the probe trial was to gather a second index other than verbal report to identify the types of strategies participants used to solve the task. If a participant used a cognitive map strategy based on their memory for the relations between landmarks, then removal of these landmarks during the probe trial should have resulted in an increase in errors. Participants that rely on a response learning strategy rely less on landmarks available in the environment, therefore, removal of the landmarks should have less effect on their performance. In Part 2 of Probe C only the first four pathways visited were recorded. After Probe trial C all participants receive an additional trial type A. The additional trial was provided after the probe trial to investigate whether individuals decided to shift their strategy. The optimal strategy to solve the Probe C is to learn the task without learning the relationship between the goal locations and the environment. Individuals who originally used a spatial strategy may choose to switch to a response strategy after the probe trial because it is advantageous. These individuals are more variable in their selection of navigation strategies and are termed shifters and are removed from subsequent analysis.

At the end of the experiment the participants were asked to report how they solved the task from beginning to the end during a brief interview (see Appendix D). Participants were categorized as having used a response landmark strategy if they associated the arms with numbers or letters or if they counted the arms (clockwise or counterclockwise) from a single landmark. Participants were categorized as having used a response starting position strategy if they associated the arms with numbers or letters or if they counted the arms (clockwise or counterclockwise) from a single starting position without reference to landmarks. Lastly, participants were categorized as having used a cognitive map strategy if they used the relationship between two or more landmarks to solve the task. Participants finished the experiment with an interview assessing previous experience with video/computer games (see Appendix B).

Data Analysis

A Pearson's Chi-square test (χ^2) was run to investigate the strength of the association between groups and spontaneous navigation strategy types that were chosen. Experimental data were analyzed using 2 (Group: SCZ and HC) X 2 (Strategy: Spatial and Response Landmark) between-subjects analyses of variance (ANOVAs). The results were evaluated at an alpha level of .05. Seperate ANOVAs were run for six different dependent variables:

1) Overall Latency was the total amount of time it took participants across all trials to locate the four correct objects during the study and phases.

2) Overall Test Phase Errors was the total number of errors across all test phase trials.

3) ABA Latency was the total amount of time it took participants across the first three trials (ABA) to locate the correct objects during the study and test phase.

4) ABA Errors was the total number of errors across the first three trials (ABA).

5) Extra Trials to Criteria was the total number of extra trials to meet criteria without making an error and did not include scores from the first three trials (ABA) or Probe C and the trial after Probe C (A).

6) Probe C Errors was the number of incorrect paths visited during the probe trial, where participants have four visits in total and a maximum score of four errors across all types.

Errors consisted of three different types, which were classified and scored based on the following: 1) reference memory (RM) errors were defined as when a participant visited a pathway that is not rewarded, 2) working memory correct (WMc) error was defined as when a participant revisited a rewarded pathway that had already been correctly visited within the same trial and 3) working memory incorrect (WMi) was defined as when a participant revisited a pathway that was not rewarded and had already been incorrectly visited within the same trial. An independent analysis was run for each error type that produced similar findings as to when all three were combined. Therefore, to reduce reporting of redundant statistics, only the sum of the three types of errors was used to calculate the ABA Errors and Overall Test Phase Error.

In addition, due to the small sample size I placed emphasis on effect size for each Group X Strategy interaction. In particular, I highlighted a medium (r>.20) or large (r>.30) magnitude according to the empirical guidelines provided by Hemphill (2003). I followed-up with additional analyses of each ANOVA with an independent sample *t* test. A priori hypotheses

guided testing of these contrasts, which consisted of *t* tests between groups and within strategy type (SCZ spatial v. HC spatial and SCZ response landmark v. HC response landmark). The direct *t* tests, particularly of SCZ vs. HC spatial groups, were conducted to test the a priori hypothesis of a differential impairment in the SCZ-spatial group. For comparison, direct *t* tests comparing SCZ vs. HC response landmark groups was also included to bolster support that the effect is due particularly to the spatial group. Independent sample *t* tests used a one-tailed alpha value of .05, predicting that the SCZ participants would perform poorly compared to the HC participants. There were four tests with a significant Levene's Test for Equality of Variance, therefore, I reported the modified degrees of freedom and *p*-values for these four tests.

Due to a small sample size and lack of normality, the non-parametric counterparts of these ANOVAs were also analyzed. The non-parametric tests did not result in a change from the results analyzed with the independent *t* tests, and were not reported. Age, gender, SES and 3D video game experience are variables that previous research suggests might influence spatial cognition and memory performance. We re-ran analyses using these variables as covariates and this did not result in a meaningful change to the results, therefore, the analyses with covariates were not reported.

4 on 8 Task Experimental Results

Strategy Assessment

In addition to spatial and response landmark strategies, individuals could also be characterized as having used a response starting position strategy if they reported learning the maze by counting the open and closed arms without the aid of any landmarks provided in their

environment. These individuals also had to be aware that they were starting in the same position in the arena and facing the same direction across test trials, otherwise this strategy was not useful. Two SCZ individuals reported using a counting strategy to solve the task, however, they also reported that they did not believe that they were starting in the same position and facing the same direction across the trials. Based on their report, these individuals did not meet the criteria to be characterized for being characterized as response static starting position learners and were removed from the main analysis. On average these two participants took 1818 seconds to complete trials ABA and made 11 errors, both took eight extra trials to meet criteria, 89 minutes to perform the task and committed 31.5 errors across all test phase trials.

There were also two HC participants who reported using a counting strategy, but were not included in the overall analysis due to the removal of the SCZ participants and low sample size. On average these two individuals took 711 seconds to complete trial ABA and made one error, both took one extra trial to meet criteria, 20.5 minutes to perform the entire task and committed only one error across all test phase trials.

Some individuals choose to switch from a spatial strategy to a response strategy. Given that the spontaneous use of strategies for these individual remains flexible, these individuals were characterized as shifters and were removed from the analysis because they did not fit into either the spatial or response landmark group. One HC participant and two SCZ participants reported a strategy shift during the experiment and were removed from the overall analysis.

In total there were 25 participants remaining in the analyses who reported a navigation strategy of either a spatial or response landmark strategy (SCZ = 13, HC = 12). Of those participants who were not removed from the data analyses, 33.3% of HC participants reported using a spatial strategy to solve the task (n = 4) and 66.7% of HC participants reported using a

response landmark strategy to solve the task (*n* = 8). 76.9% of SCZ participants reported using a spatial strategy (*n*=10) and 23.1% of SCZ participants reported using a response landmark strategy (*n* =3) (see Figure 1.).

The Pearson's Chi-Square Statistic was analyzed to assess the strength of the association between the group and type of spontaneous navigation strategy chosen χ^2 (1) = 4.81, p = .028, φ = -.44, producing a large effect size. The results indicated that a greater proportion of SCZ participants selected a spatial strategy, compared with HC participants (whereas the majority of the HC participants selected the response landmark strategy) (see Figure 1.).

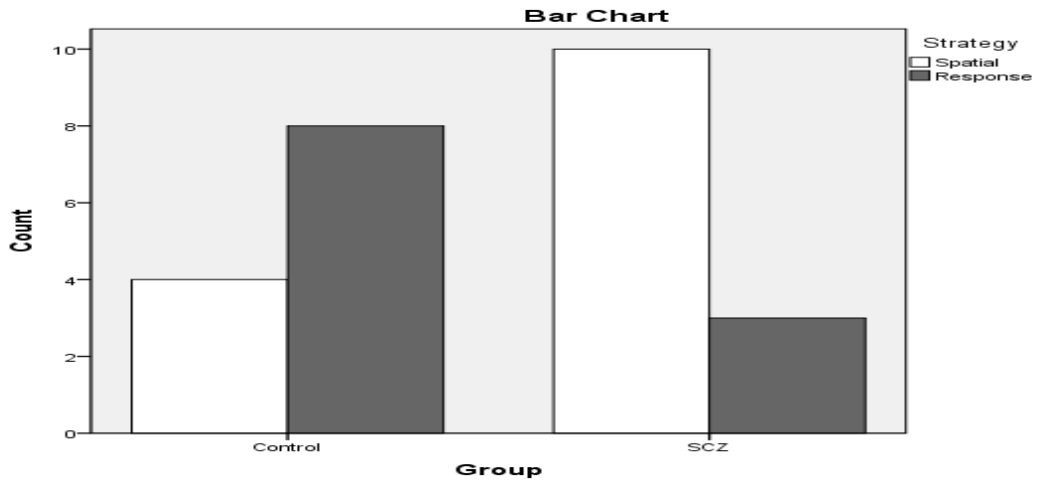


Figure 1. Strategy Assessment -The frequency of strategy chosen by Healthy Controls (HC) and Schizophrenia (SCZ) participants.

Overall Latency

Overall total latencies (length of time it took participants to locate the correct objects across the testing phase trials in minutes) are displayed in Figure 2. There was a significant main effect of Group, $F(1, 21) = 6.51$, p=.019, non-significant effect of Strategy, $F(1,21)= 2.80$, p=.110, and a non-significant interaction of Group x Strategy, $F(1,21) = 1.31$, p=.266. Although

there was a non-significant interaction, the effect size of the interaction was of a medium magnitude, r = .24. The direct comparison indicated that the SCZ spatial group had longer latencies as compared to the HC spatial group, $t(12)$ =-2.52, p=.014, r = .54, but this did not hold for the SCZ vs. HC response landmark contrast, $t(2.07)$=-.67, p=.284, r =.42.

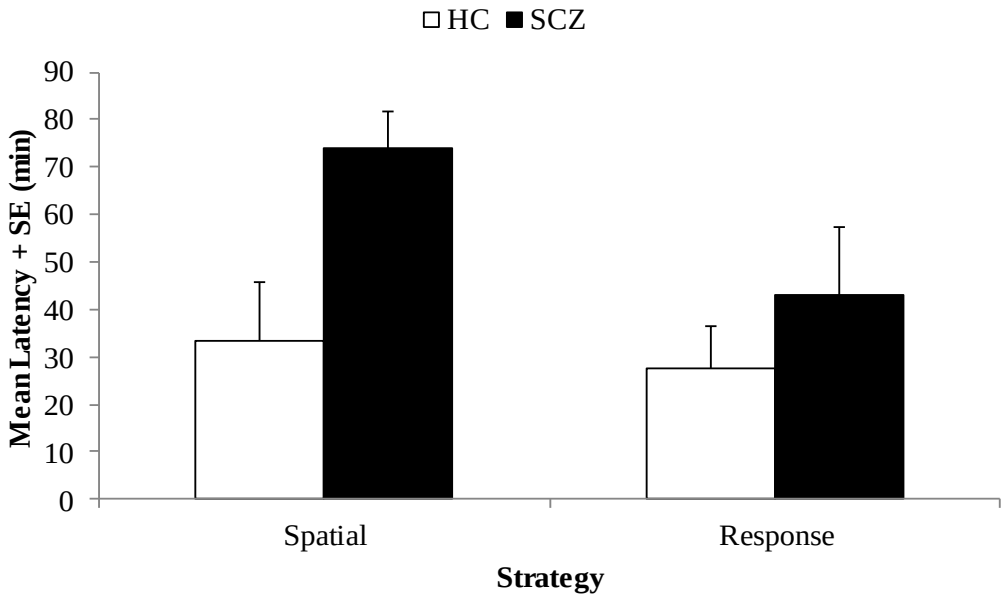


Figure 2. The mean total latency across all study and test phase trials (minutes). Error bars reflect the standard error.

Overall Test Phase Errors

Overall test phase errors (number of errors participants made across the testing phase trials) are displayed in Figure 3. There was a significant main effect of Group, $F(1,21)$ = 6.50, p=.019, non-significant effect of Strategy, $F(1,21)$= 2.85, p=.106, and a non-significant interaction of Group x Strategy, $F(1,21)$ = 1.26, p=.274. Although there was a non-significant

interaction, the effect size of the interaction was of a medium magnitude, r = .24. The direct comparison indicated that the SCZ spatial group made more errors than the HC spatial group, $t(12)$ =-2.19, p=.024, r = .54, but this did not hold for the SCZ vs. HC response landmark contrast, $t(2.12)$= -1.37, p=.149, r =.69.

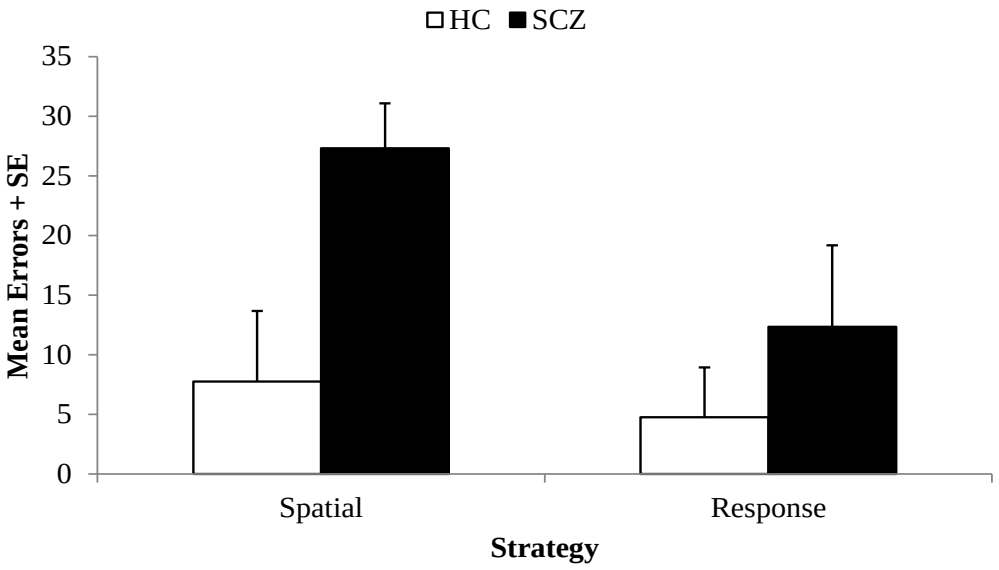


Figure 3. The mean total errors committed across all test phase trials. Error bars reflect the standard error.

ABA Latency

ABA test and study phase latencies (length of time it took participants to locate the correct objects across the ABA trials, in seconds) are displayed in Figure 4. There was a non-significant main effect of Group, $F(1,21)$ = 4.23, p=.053, non-significant effect of Strategy, $F(1,21)$= 1.39, p=.251, and a non-significant interaction of Group x Strategy, $F(1,21)$ = 1.72,

p=.204. Although there was a non-significant interaction, the effect size of the interaction was of a medium magnitude, *r* = .28. The direct comparison indicated that the SCZ spatial group had longer ABA latencies than the HC spatial group, *t*(12) =-2.20, *p*=.024, *r* = .54, but this did not hold for the SCZ vs. HC response landmark contrast, t(9)=-.67, *p*=.259, *r* = .21.

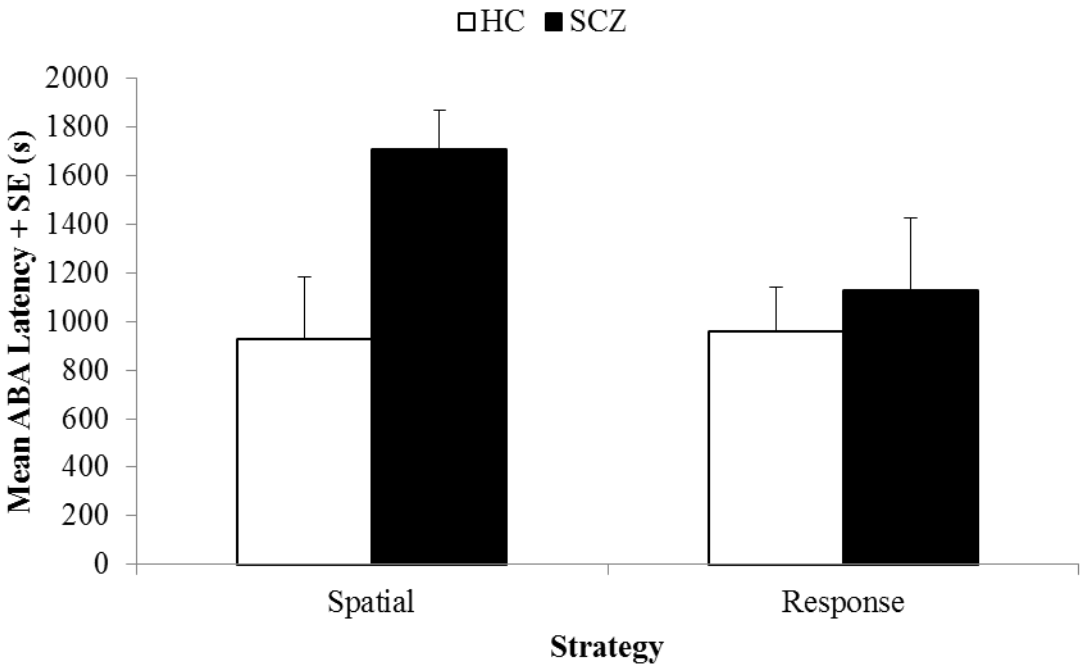


Figure 4. The mean ABA Latency (seconds) for study and test phases. Error bars reflect the standard error.

ABA Errors

ABA errors (number of errors participants made across the first three trials ABA) are displayed in Figure 5. There was a non-significant main effect of Group, *F*(1, 21) = 2.79, *p*=.110, non-significant effect of Strategy, *F*(1,21)= 2.88, *p*=.104, and a non-significant interaction of Group x Strategy, *F*(1,21) = .96, *p*=.335. In addition to the non-significant interaction the effect

size of the interaction was of a medium magnitude, r = .21. The direct comparison between the SCZ vs. HC spatial group was nearing significance. This indicated that the SCZ spatial group was trending towards making more errors on ABA trials, $t(12)$ =-1.57, p=.071, r = .41, but this did not hold for the response landmark contrast, $t(9)$ =-1.24, p=.121, r = .38.

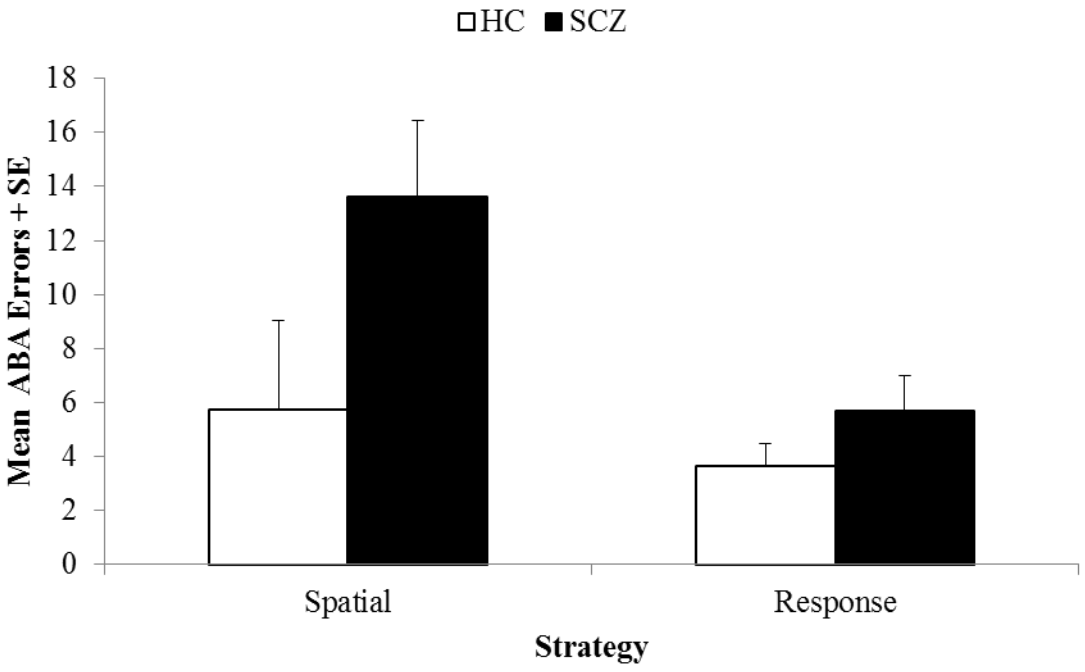


Figure 5. The mean number of ABA Errors for study and test phases. Error bars reflect the standard error.

Extra Trials to Criterion

Extra trials necessary to meet criterion (two perfect A trials) are displayed in Figure 6. There was a significant main effect of Group, $F(1, 21) = 4.57$, p=.044, and non-significant effect of Strategy, $F(1,21)= 2.50$, p=.129, and a non-significant interaction of Group x Strategy, $F(1,21) = .75$, p=.396. In addition to the non-significant interaction, the effect size of the

interaction was of a small magnitude, r = .18. However, there was a visible trend (see Figure 6.) consistent with the pattern of preferential impairment of the SCZ spatial group, which is statistically supported by the significance of the direct contrast, $t(12)$=-1.93, p=.039, r = .49, but not for the SCZ response landmark group, $t(2.04)$=-.715, p=.123, r = .69.

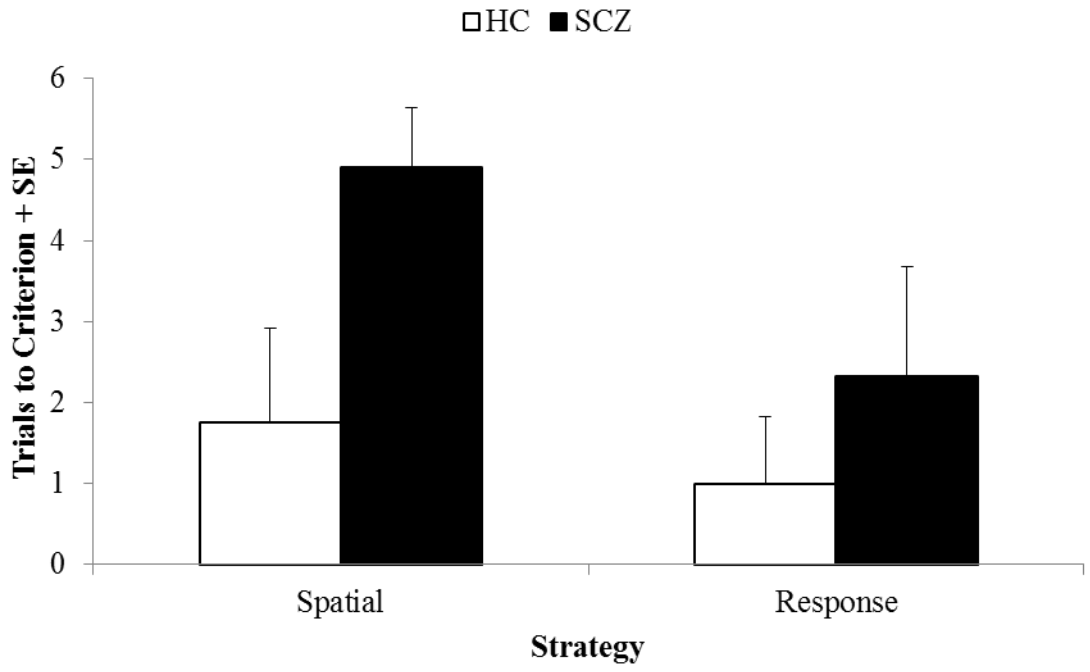


Figure 6. The mean number of extra trials needed to meet Criterion. Errors bars reflect standard error.

Probe C

Probe C errors are displayed in Figure 7. There was a non-significant main effect of Group, $F(1,18)$ = .08, p=.777, non-significant effect of Strategy, $F(1,18)$= .08, p=.777, but a significant interaction of Group x Strategy, $F(1,18)$ = 4.52, p=.048. The effect size of the interaction was of a medium-large magnitude, r = .28. The direct comparison indicated that the

HC response landmark group made fewer errors on Probe C compared to the SCZ response landmark group, t (7)= -2.50, p=.021, *r* = .49, and there was a trend indicating that the SCZ spatial group were making fewer errors than the HC spatial on Probe C, *t*(8) =1.60, *p*=.074, *r* = .45.

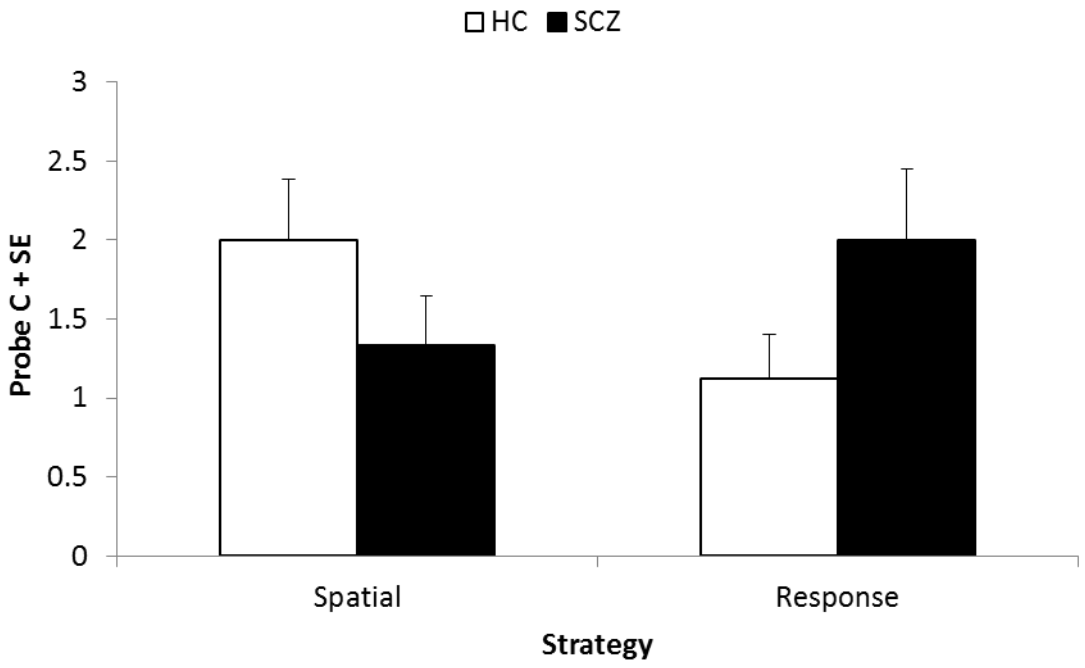


Figure 7. The mean number of errors committed on Probe C (test phase). Error bars reflect the standard error.

Discussion

The first objective of the current thesis was to identify the types of spontaneous navigation strategies individuals living with schizophrenia used to solve the 4 on 8 task. Previous literature with the 4 on 8 task found that HC participants self-report having spontaneously used the response landmark strategy as often as the spatial strategy during the initial ABA trials.

However, with practice almost 50% of the HC spatial strategy group shifted to using a response landmark approach to solve the task, whereas no response landmark participants shifted to the spatial strategy approach with practice (Bohbot et al., 2004; Iaria et al., 2003). Previous studies reported that MTL patients reported preferring to use the spatial strategy to solve the task (60%), while 45% of these same individuals shifted to the response strategy with practice on extra trials. In the current study three-quarters of the SCZ group chose to solve the task using a spatial strategy, while only one-third of the HC group chose the spatial strategy during the ABA trials. These findings are in line with predictions that SCZ participants spontaneously choose the spatial strategy more often, as found with the MTL lesion patients, indicating a natural bias in SCZ towards using a spatial strategy to navigate within a virtual environment.

Previous studies reported that with practice on the extra A trials, HC participant's natural habit based learning systems overrode the spontaneous choice of the spatial strategy and participants reported switching to using a response landmark approach. This switch in strategies is in line with findings of a change in brain activation from the hippocampus to the caudate nucleus (Iaria et al., 2003). In addition, this flexible approach confers an advantage as the response strategy was found to be more efficient than the spatial memory strategy in solving the task (Iaria et al., 2003). However, in the current study the SCZ spatial group on average performed five extra A trials in order to meet criteria, and despite the extra practice on these trials, none of the SCZ spatial participant reported switching to a response landmark strategy. These findings indicated that their navigation strategy was less flexible and that the SCZ spatial participants were not able to learn to use the more efficient strategy to solve the task. In addition, two SCZ participants in the shifter group initially started using a response landmark strategy, but shifted to the spatial strategy with practice on the extra A trials. This observation is in contrast to

HC literature that found that no participants shifted from the response approach to using a spatial strategy approach (Bohbot et al., 2004). These findings support the hypothesis that SCZ participants predominantly use the spatial strategy as seen with MTL lesion patients, supporting the link between SCZ and hippocampal neuropathology. However, replication and further studies would be necessary to fully explore the findings of a strategy bias in SCZ. This issue of a strategy bias in SCZ deserves further attention. There are three possible reasons an individual might choose a particular strategy: 1) random, 2) genetic predisposition, 3) experience based learning bias, and 4) differential effects of medication. Any of the above might bias strategy choice and provide some potential avenues for further explanation within this population (Bohbot et al., 2004).

Lastly, two SCZ participants reported using a counting strategy independent of landmarks within their environment. However, these individuals also reported that they did not believe they were starting in the same position within the arena or facing the same direction. There are no reports published indicating participants having tried to use a response starting position strategy without the knowledge of the starting position being static. Anecdotally, when asking the participants if there was something available in their environment that might suggest whether or not the starting position was the same or different these participants indicated that there was nothing available. We further probed these individuals by asking them to take their time and look at their surroundings to see if there was some marker available to suggest a static starting position. Despite the fact that there was a large cherry tree in front of the participants in the environment, these two individuals reported a failure to notice this object directly in front of them. These individuals did notice the pillars and barriers along the pathways, but failed to

attend holistically to their virtual environment. These two individuals performed poorly, making on average a total of 31 errors and took 89 minutes to solve the task across all of the trials.

The second objective of the current thesis was to investigate whether these different types of strategies corresponded to differences in the number of errors and latency for the SCZ participants across the trials. Previous research found that the MTL lesion patients that used the spatial strategy made predominantly more errors and had longer latencies compared to those MTL lesion patients who used the response learning strategy (Bohbot et al., 2004). Based on these findings we predicted that the SCZ participants who spontaneously chose the spatial strategy to solve the task would have the longest latencies and would commit the most errors as compared to those that spontaneously chose the response landmark strategy. Four out of five of the dependent variables assessed relating to the main task produced a medium magnitude effect size (Probe C trial discussed in the following section). Although the fifth was of small magnitude the pattern of findings was the same. These measures indicated that there was a differential deficit between the SCZ spatial strategy participants and the HC spatial strategy participants that was not found with the SCZ vs. HC response landmark participants. These findings are in direct support of the hypothesis of a preferential hippocampal-dependent spatial memory deficit in SCZ.

Analysis of Probe C, the trial where the landmarks are removed from the environment, produced a medium-large magnitude effect size. The purpose of including the probe in the experiment was to provide an objective measure of the types of strategies participants used to solve the task to supplement the subjective reported strategies. In previous literature with HC participants, those individuals that spontaneously chose the spatial strategy reported learning to

solve the task by learning the relationship between the landmarks in the environment. When the landmarks were removed in Probe C, the HC spatial participants reported being unable to solve the task and were found to make the largest number of errors (Bohbot et al., 2007; Iaria et al., 2003). However, those individuals who reported using a response strategy were less dependent on the landmarks available in the environment and made the fewest errors on the probe trial. In the current thesis I found the same trend with the HC participants (see Figure 7.). However, in the current thesis the SCZ participants who reported using the spatial strategy made the least number of Probe C errors and the SCZ participants that reported using the response landmark strategy made the highest number of Probe C errors. There were only two SCZ participants that were not able to meet criteria of two perfect A trials and were not given Probe C. These two SCZ participants that were unable to meet criteria reported having used a spatial strategy to solve the task.

Overall, the findings with the SCZ participants who were able to make it to the probe trial indicate an opposite trend to the HC participants. Because the SCZ spatial participants made the most errors while solving the task, they were also required to complete the most extra trials to meet criteria. Given the extra practice trials, it is possible that although these participants continued to report using an explicit spatial strategy, but their implicit habit learning system actually did learn the task more gradually, as indicated by the minimal number of Probe C errors committed (Bohot et al., 2004; Iaria et al., 2003). These findings are potentially indirectly in line with the current hypothesis that although SCZ participants should primarily have a cognitive mapping deficit due to hippocampal impairment, the striatum and stimulus response implicit habit learning system remain intact in SCZ. These findings tentatively provide support for a differential deficit in SCZ explicit spatial strategy system vs. their implicit habit learning

response system (Keri et al., 2005). However, one way to support the interpretation of the current findings would be to provide all groups with equal training opportunities (extra A trials) prior to administering Probe C trial.

Limitations

The effect sizes across five of the dependent measures indicated that there was greater impairment in the SCZ spatial group, than for the SCZ response landmark participants. The findings also provided support for the hypothesis that SCZ participants more often choose to spontaneously navigate using a spatial learning strategy. However, these are tentative findings given the relatively small sample size for SCZ response landmark group. The fact that the current paradigm was based on spontaneous strategies presented a challenge as one cannot recruit for one group or the other. A larger sample remains necessary to confirm the findings and would provide further opportunities to explore and interrogate data and the role of potential covariates (age, sex, SES and 3D video game experience) and their relations with other clinical and cognitive variables (i.e., medications and smoking).

A second potential limitation may be related to standard definitions created for the 4 on 8 task. The protocol allows people to mention both the tree and the rock as landmarks used to aid navigation, which makes it difficult to differentiate between spatial and response landmark strategies. The primary way to differentiate between the two types of strategies was the sequence of open and closed barriers used by the participant. If an individual learned one single sequence of open and closed arms surrounding the maze this ensured being classified in the response landmark group. If an individual learned two different sequences in relation to both the tree and the rock (i.e., two open pathways by the tree and two closed pathways by the rock), this ensured

being classified in the spatial group. However, it is entirely possible that some individuals learned two different sequences in relation to the tree and the rock, but never learned the relationship between the tree and the rock. These individuals would have been classified in the spatial strategy group, when it might be more appropriate to have reclassified these individuals as having used a response landmark strategy. This possibility raised the potential importance of probing more deeply into potential sub-strategies used by participants. However, as this was the first study with SCZ participants aimed at investigating spontaneous navigation strategies, it was essential to stick with these standard definitions to attain consistency across studies.

A third potential limitation with the current 4 on 8 task protocol was how the shifters were categorized. In previous studies (Bohbot et al., 2004; Iaria et al., 2003), if an individual reported that they had changed strategies during any stage of navigation they were removed from data analysis. In the current study there were two individuals in the SCZ group that initially used a response landmark strategy. However, these two individuals also completed multiple extra trials to meet criteria. Initially it seemed to make sense not to eliminate the "shift group" and create a new set of rules. If a participant used a strategy at least 60% of the time they would be classified within this group. Data were analyzed with this new classification system and the old classification system and there were no meaningful differences in the results.

A few individuals in the SCZ group reported across the few initial trials having used a guessing strategy. The SCZ participants seemed to take more time to settle into either a spatial or response landmark strategy compared to controls. Given the variability in strategies, memory deficits, and typically poorer insight in SCZ, it perhaps would have been advantageous to assess

spontaneous strategies throughout testing, rather than at the end of the task, to more accurately assess these fluctuations.

Future Directions

The current thesis was a behavioural investigation of the spontaneous navigation strategies that SCZ participants use to solve the 4 on 8 task. The predictions of the current thesis were grounded in the neurodevelopmental hippocampal pathophysiological model of schizophrenia (Lipska, 2004). Although the current thesis found behavioural evidence that those SCZ participants who chose a spatial navigation strategy made the largest number of errors and took the longest time to solve (as found with MTL lesion patients), there was no direct evidence that deficient recruitment of the hippocampus in SCZ accounted for these behavioural differences. A future study that includes functional magnetic resonance (fMRI) and voxel-based morphometry (VBM) imaging analysis would be required to provide direct support for the hypothesis that these differences in behavioural performance are associated with to either deficient recruitment of the hippocampus or intact recruitment of the striatum in SCZ.

In addition, based on the findings that SCZ participant chose to spontaneously navigate using a spatial strategy, one would assume that these individuals also choose this strategy to navigate in a real-world setting. If a SCZ participant had difficulties navigating in the real world, one might assume that this impairment was due to over reliance on a deficient spatial strategy. However, the overlap between the spontaneous navigation strategies individuals use to solve the 4 on 8 task and the types of spontaneous navigation strategies relied on during real-world navigation has not been investigated. In order to provide stronger connections between the

behavioural performance on this task and functional outcome there would have to be stronger evidence of the ecological validity of this and other relevant virtual navigation tasks.

In the future it would be beneficial to include an additional questionnaire that assessed how individuals navigate in the real-world and the types of strategies used to solve real-world navigation problems. During the course of testing I anecdotally discovered that there was quite a bit of variability in the mode of transportation used in the SCZ group. One SCZ participant had a license and drove a car, a few took the bus and others required being transported by Wheel-Trans or by cab. The current thesis did not measure or account for differences in real-world navigation experiences across the participants. This variable would be vital to include in the future as a potential covariate in statistical analysis.

Additional covariates might include antipsychotic medications, given there has been mixed evidence as to whether illness or medications might affect intact recruitment of the striatum (Konradi & Heckers, 2001; Ebdrup et al., 2011). Despite evidence of a selective deficit for MTL dependent learning (Keri et al., 2005), there has been mixed evidence of potential striatal dysfunction in SCZ, which may be due to either illness or medications. Given the current findings, this task appears useful for future work to better investigate the relative role of hippocampal and striatal (habit learning) dependent learning systems in this population.

Lastly, it is important to investigate differential performance on tasks that measure specific subdivisions of spatial navigation such as spatial and response learning. Identifying specific memory deficits associated with SCZ will inform the development of more specific cognitive rehabilitation programs. Based on the findings of the current thesis, spatial memory performance in SCZ appears to be impaired, whereas response landmark performance appears to

be intact. In the future cognitive rehabilitation specialists might specifically develop a training protocol that harnesses the intact ability (navigating using a response landmark strategy) and/or trains the deficient ability (navigating using a spatial strategy) in order to improve navigation abilities.

Appendix A

Behavioural Instructions for the 4 on 8 Radial Arm Maze

Habituation:

Place subject in the trial environment to habituate them to the keyboard touches. "*You will be in a virtual environment in which you will have to navigate. Please familiarize yourself with the keys that will allow you to move around. You may use the forward, left and right keys.* ***Do not use the backwards key****. Please stay on the carpet and practice following the pathways and turning around. There are different pathways, and when you start going down a pathway, you have to go all the way to the pit at the end. When you get to the end of a pathway, you can turn around using the arrows keys and go back up the stairs. You can now practice moving around the platform."* When you are satisfied that the subject knows how to navigate with the keys ask if they are ready to start the test. If the subject is unsure, ask them to repeat what they are supposed to do back to you.

4 ON 8

Note: Never mention the number of remaining objects to find. If people think they are finished before collecting all objects, just tell them that "there are objects that remain to be picked up."

Start the first exercise 1a. : Note to participants that they will be asked questions regarding their understanding of the task after this paragraph, so they should pay close attention.

> "*You are at the center of a platform from which branch out several pathways. At the end of these pathways are stairs that lead to a small pit. You will notice that there are 4 paths closed by barriers, as you can see, and 4 paths that are accessible. You must visit the 4 accessible pathways and pick up the objects located at the end of the stairs. Look carefully because you have to remember in which pathways the objects are located. You must* ***remember which pathways you have taken****, because in the next step, all 8 pathways will be accessible, there will not be any barriers to block your way and you will have to avoid the paths that you had initially gone into to find objects. You have to go in the pathways and try to make as few errors as possible. If you enter the same pathway twice, this will be counted as an error; if you go into a pathway that does not contain an object, it also counts as an error. This task is not a race, it is important that you understand that the goal is to find the objects in the right*

pathways during stage one when the 4 arms are open and avoid those pathways during stage two when all 8 arms are open.

Remember, go into all the accessible paths to get the objects located at the end, take all the time you need, this isn't about speed. Once you have visited all available paths, let me know when you are ready to go on to the next trial."

These instructions were amended from the original instructions by Dr. Veronique Bohbot. After piloting a few participants living with SCZ it became clear that the key to administering the task was to ensure participants understood what was being required. Participants were asked the following questions. If the participant was not able to answer all the questions below without being prompted, then the instructions were repeated.

Question: Do you understand what I have just explained to you?

Question: Can you tell me in your own words your understanding of the task?

Question: Can you tell me in your own words what an error is?

Question: What are we asking you to do during the "first" stage of the task?

Question: What are we asking you to do during the "second" stage of the task?

Question: What is the main goal of the task? Is speed important?

Start the timer when the subject starts the exercise, take down the order of visits and/or revisits, stop the exercise when the subject has finished, and note the total time taken.

"Now that you have picked up all the objects, you can go back to the centre, look around you to learn where all the objects are located." Please take your time to look around to try to remember the paths you had taken.

Start the next level and remind the directions:

"***All 8 paths are now available, you have to remember where you have been and avoid these pathways in order to retrieve the objects***. *If you go down a pathway and there is no object located at the end, this indicates that you have taken an incorrect pathway that you had previously visited in the last stage.*

Start the timer when the subject begins, take down the order of visits and/or revisits, and stop the trial when the subject has acquired all 4 objects (maximum 10 visits).

- For part one of the second trial (when 4 arms are blocked again) say:

> *"Now we are going to start over. You must visit all the accessible pathways and pick up the objects located at the end of the stairs. You must* ***remember which pathways you have taken."***

- Start the next level and remind the directions:

> "***All the paths are now available, you have to remember where you have been and avoid these pathways in order to retrieve the objects****."*

Repeat bulleted instructions for every trial if necessary (e.g. elderly participants).

Continue the following trials, by briefly restating the objectives each time. Upon reaching the 8th exercise (**probe**), the subject may wonder what is happening, due to the lack of landmark and the appearance of surrounding walls. Simply tell him:

> "*The goal is still the same. You must* ***avoid the paths that you had previously visited to collect the objects****."*

If participants make a remark to the effect that they do not believe this is doable, then say *"Just do the best you can".*

Continue with the last two trials (5a and 5b) and note order of visits and revisits.

Appendix B

Experience with Video and Computer Games Questionnaire

1. Have you ever played video games? Yes No

2. What type of games have you played? 2D 3D

3. How many hours per week do you spend on the video game system? ___hours

4. How long have you been playing on the video game system? ___months/years

5. Have you ever played computer games? Yes No

6. What type of games have you played? 2D 3D

7. How many hours per week do you spend playing video games on the computer? ___hours

8. How long have you been playing video games on the computer? ___months/years

9. What type of games do you play on the computer/video game system (please check, multiple answers possible)?

Role-playing games (e.g. World of Warcraft, Final Fantasy)

2-D action game (e.g. Super Mario Bros)

First-person 3-D games (e.g. Wolfenstein 3D, Halo3)

Life simulation (e.g. SimLife)

Strategy (e.g. Civilization)

Management simulation (e.g. Simcity)

Vehicle simulation (e.g. Flight simulator)

Adventure (e.g. Myst)

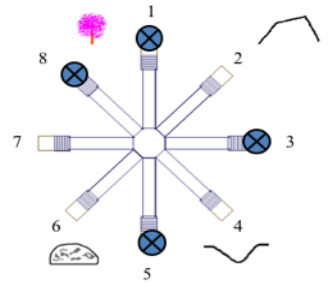
Examples of previous games played:

10. What games are you playing right now?

Appendix C

4 on 8 Radial Arm Maze Scoring Sheet

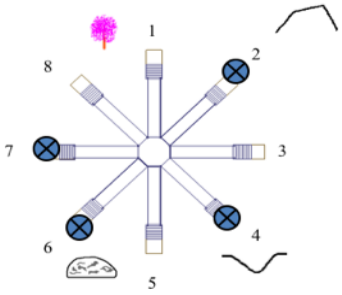
1a



T:
WMc:

Visits:

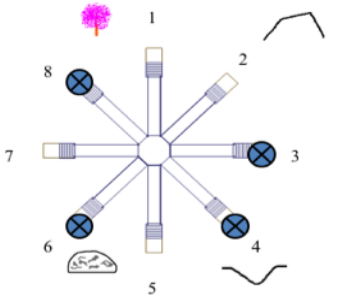
1b



T:
RM:
WMc:
WMi:
Total:

Visits:

2a



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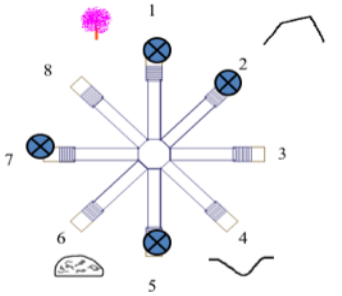
WMc:

Visits:

2b



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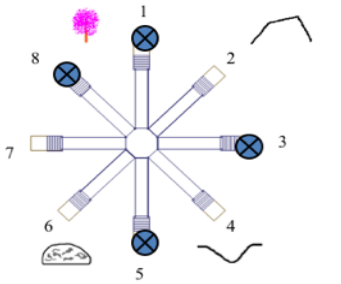
WMi:
Total:

Visits:

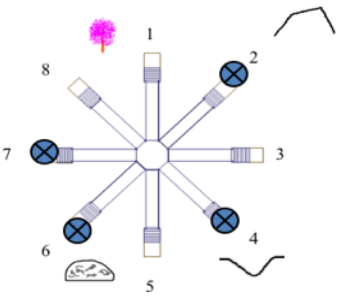
3a



T:
WMc:

Visits:

3b



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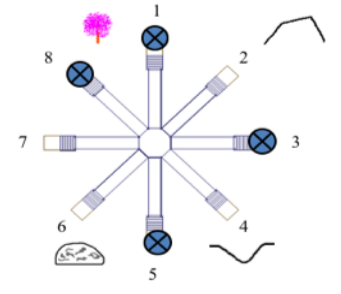
Total:

Visits:

Ex1a



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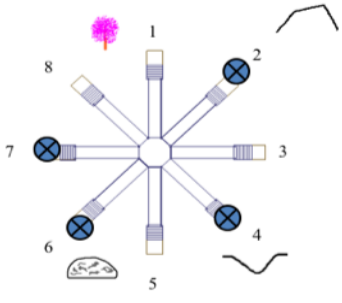
Visits:

Ex1b



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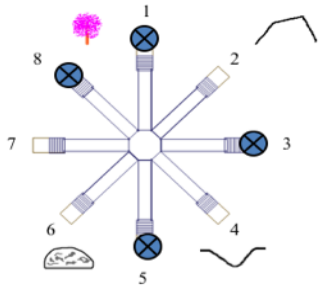
Visits:

Ex2a



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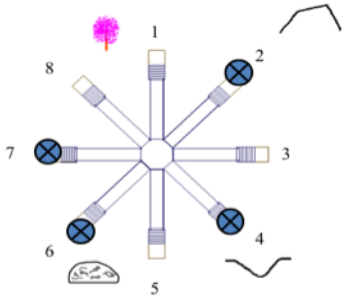
WMc:

Visits:

Ex2b



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RM:

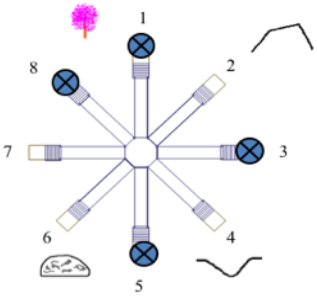
WMc:

WMi:

Total:

Visits:

5a

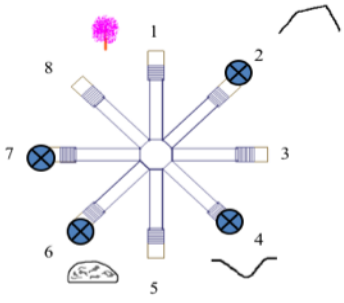


T:

WMc:

Visits:

5b



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RM:

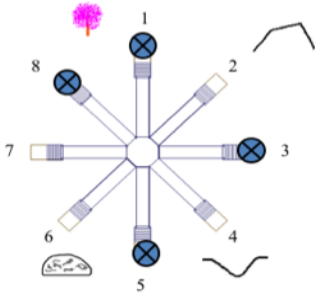
WMc:

WMi:

Total:

Visits:

4a

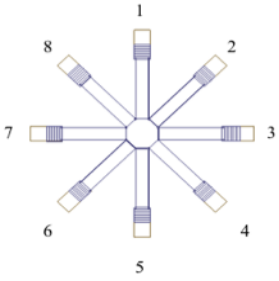


T:

WMc:

Visits:

4b



T:

Abs. Errors:

Rot. Errors:

Visits:

Appendix D

Verbal Strategy Questionnaire

This step is VERY important, you must write down **WORD FOR WORD** what the subject says, and not interpret what he says and write this down. Your own interpretation can be included AFTERWARDS, and someone else may do it also, for inter-rater reliability. In addition, you should record the verbal report using a laptop/mp3 player/digital recorder, so that inter-raters have access to the original discussion in case of disagreement.

1- **What did you do to learn which paths to take and which ones to avoid?**

Let the subject answer until he has finished. If the subject mentions one or more landmarks, push further: **Which ones?**

If only one landmark is mentioned: **Is that the only one you used?**

If no landmark is mentioned: **Can you be more specific about how you counted the arms? Where did your sequence start?**

2- **Did you do this throughout all trials, from beginning to end?**

If the subject says he changed his method: **How did you change? When did you change?**

3- **Was the starting position always the same, or did it change?**

Representation: Ask the participant to draw a bird's eye view of the platform, the pathways and all the landmarks that he remembers, taking care to place them in their correct relative position.

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