FMRI INVESTIGATION OF SPATIAL MEMORY ABILITIES IN INDIVIDUALS LIVING WITH SCHIZOPHRENIA SPECTRUM DISORDERS

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fMRI Investigation of Spatial Memory Abilities in Individuals Living with Schizophrenia Spectrum Disorders

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Abstract

Different strategies dependent on different brain regions may be spontaneously adopted to solve most spatial memory and navigation tasks. For this dissertation, I used brain-imaging and cognitive tasks to test the hypothesis that individuals living with schizophrenia spectrum disorders (SSD) have selective hippocampal-dependent spatial memory impairment. A hippocampal-dependent spatial strategy (locale/allocentric/cognitive map/viewpoint-independent) involves relying on learning the relations between landmarks in the environment, whereas a response strategy (taxon/egocentric/viewpoint-dependent) is more associated with caudate function and involves learning a sequence from a single starting position. In Experiment 1, I examined performance and brain activation with fMRI during the 4-on-8 virtual maze (4/8VM) to test the hypothesis of intact response versus impaired spatial memory in SSD. The SSD participants who adopted a spatial strategy performed more poorly and had less hippocampal activation than other groups. In Experiment 2, I further examined these data using multivariate PLS (partial least squares) analyses to identify whole-brain patterns of activation associated with group and strategy differences on the 4/8VM. Results revealed clusters of correlated activation within the temporal lobe unique to the SSD-Spatial group. The SSD-Response group activated the same regions as the Healthy groups, but to a greater extent

suggesting over-activation. In contrast to the between-subjects nature of strategy differences on the 4/8VM, for Experiment 3 I used the Courtyard Task to seek converging evidence of a selective hippocampal-dependent impairment in spatial memory using a within-subjects design. The Courtyard Task has previously demonstrated impaired performance among individuals with hippocampal lesions under shifted-view (allocentric) but not same-view (egocentric) conditions. Consistent with a profile of hippocampal dysfunction, the SSD group demonstrated a particular deficit under the shifted-view condition. The results support the development of protocols to train impaired hippocampal-dependent abilities and harness non-hippocampal dependent intact abilities. Overall, this dissertation provides valuable information characterizing spatial memory and highlights the importance of strategy use in SSD.

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Chapter 1: General Introduction

The main objective of this body of work is to examine the underlying neural regions associated with spontaneous navigation strategies and spatial memory abilities in individuals living with Schizophrenia Spectrum Disorders (SSD). In Experiment 1 (Chapter 3), I provide fMRI (functional magnetic resonance imaging) evidence of less hippocampal activation and worse navigational memory performance in those SSD participants who spontaneously adopted a spatial strategy compared to a healthy comparison group and patients who used a response strategy. The spatial approach involves learning the relations between landmarks in the environment, whereas the response strategy involves learning a sequence from a single starting position. Applying multivariate analyses in Experiment 2 (Chapter 4), I identify decreased patterns of activation associated with a navigation network in the SSD-Spatial compared to the Healthy and SSD-Response groups. In Experiment 3 (Chapter 5), I provide converging behavioural evidence that SSD participants who have impaired hippocampal-dependent spatial memory can rely on their non-hippocampal dependent response abilities.

SSD refer to a dimensional approach to defining psychosis. Recent changes in DSM-5 (American Psychiatric Association, 2013) led to the removal of subtypes of Schizophrenia (Paranoid, Disorganized, Catatonic, Undifferentiated and Residual) along with some modifications to diagnostic criteria aimed at enhancing reliability. In addition, the broad category for psychosis now incorporates the term 'spectrum' and takes a more dimensional approach. Schizophrenia and Other Psychotic Disorders include Schizoid and Schizotypal Personality, Delusional Disorder, Schizoaffective and Schizophreniform Disorder. Schizophrenia (SCZ) is a devastating and chronic psychiatric disorder that affects approximately one percent of the general population; SSD are more widespread. SSD are typically characterized by positive symptoms of hallucinations and delusions. Despite a focus on research and treatment of psychotic symptoms, the level of functional

disability remains high. Although distortions of reality (e.g., delusions) are the most known symptoms of SSD, this illness is also characterized by cognitive impairment. Cognitive deficits are an important part of SSD, 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 (Bowie & Harvey, 2006; Gold, 2004; Heinrichs, 2005; Ranganath, Minzinberg & Ragland, 2008).

SCZ is associated with widespread cognitive deficit and memory is a seemingly preferential domain of cognitive deficit (Saykin et al., 1991). Declarative memory measures produce large effect sizes approximately ranging from 2-3 standard deviations (*SD*s) below healthy samples (Aleman, Hijman, de Haan & Kahn, 1999; Saykin et al., 1991). These effect sizes reflect the greatest differences in behavioural performance between SSD and healthy participants when we compare their declarative memory performance with other domains of cognition (Gold & Harvey, 1993; Saykin et al., 1991). Declarative memory is also found to be a primary predictor of social and vocational functioning, even more than clinical symptoms or a host of other cognitive and demographic variables (Ranganath et al., 2008). Declarative memory is generally defined as the ability to consciously recall information, such as personal memories for events. Declarative memory impairment in SSD appears to be relatively stable and remains robust even after accounting for moderating variables such as age, medication, duration of illness or severity of psychopathology (Aleman et al., 1999). One type of declarative memory is episodic memory, deficits in which can compromise daily living skills and only show modest improvement with current available therapies in SSD (Ranganath et al, 2008). Episodic memory is generally defined

as the recollection of personally experienced events located within a particular space and time (Tulving, 1972). This type of memory provides the foundation for knowledge about the self and is required to perform daily operations such as recalling when and where you have met someone before, or remembering where your new doctor's office is located.

O'Keefe and Nadel (1978) highlight the importance of investigating spatial memory as a core component of episodic memory. Spatial memory provides information about the relations among spatial locations of objects and their positions with respect to oneself within a specific context (Burgess 2002; Tulving, 1972). Within the SSD literature, episodic memory research has typically involved traditional neuropsychological list-learning paradigms of memory for words (e.g., Christensen, Patrick, Stuss, Gillingham, & Zipursky, 2013; Holthausen et al., 2003). In contrast, the number of studies that focus on spatial components of episodic memory in SSD remains limited.

My dissertation is unique in examining spontaneous adoption of navigational memory strategies by individuals with SSD in relation to brain activation measured with fMRI (Chapters 3 and 4). In addition, I provide converging behavioural evidence of hippocampal-dependent spatial memory impairment relative to intact non-hippocampal dependent memory performance using both between-subjects comparisons of individual differences (Chapters 3 and 4) and within-subjects contrasts across task conditions (Chapter 5). Of note regarding terminology, I use plural terms when speaking generally about brain structures. For example, I use the term hippocampi when discussing these bilateral structures in a general sense. When referring to a specific location in the brain, I indicate whether it is on the left, right, or bilateral.

Before outlining the three empirical chapters, Chapter 2 provides a review of the background for my dissertation. More specifically, I provide an overview of cognition and memory in SSD, a leading animal model of SSD, a multiple-memory framework, spontaneous navigational strategies, and paradigm consideration.

Chapter 2: Literature Review

Hippocampi, Memory and SSD

Characterizing the specific nature of brain-behaviour relations is important for understanding SSD. The hippocampi are central to several pathophysiological theories of SSD (Christensen & Bilder, 2000; Gold & Harvey, 1993; Grace, 2000; Tseng, Chambers & Lipsak 2009). Evidence of reduced hippocampal volume and synaptic disorganization are considered reliable brain abnormalities in SCZ (Conrad, Abebe, Austin, Forsythe & Scheibel, 1991; Nelson, Saykin, Flashman & Riordan, 1998). Consistent with hippocampal dysfunction, episodic forms of memory are particularly affected in SSD (Bowie & Harvey, 2006; Heinrichs, 2005). The pattern of intact non-declarative (e.g., procedural) memory and impaired episodic memory performance in SCZ is similar to individuals with medial-temporal lobe (MTL) lesions and prefrontal cortex (PFC) lesions (Bartholomeusz et al., 2011; Christensen & Bilder, 2000; Christensen et al., 2013; Ornstein, Sahakian & McKenna, 2008). Deficits in contextual binding and episodic memory in SCZ provide further support for the role of hippocampal dysfunction in SSD (Bartholomeusz et al., 2011; Bohbot, Iaria & Petrides, 2004; Boyer, Phillips, Rousseau, & Ilivitsky, 2007; Ledoux, Phillips, Labelle, Smith, Bohbot & Boyer, 2013; Wilkins et al., 2013). There are many converging lines of evidence of episodic memory dysfunction and hippocampal abnormalities in SSD. However, there is limited knowledge regarding the specific relations between hippocampal function and spatial memory abilities in SSD.

SSD has been associated with deficits on hippocampal-dependent spatial memory tasks (Girard, Christensen & Rizvi, 2010; Hanlon et al., 2006; Ledoux et al., 2013; Wilkins et al., 2013). However, more direct brain-based evidence of the relation between memory performance and

hippocampal dysfunction in SSD is required beyond indirect support such as that from comparison of participants' behavioural profiles with those of patients with MTL lesions. Additionally, it is important to attend to the fact that different navigation strategies that are dependent on different brain regions can be used to solve most spatial memory and navigation tasks. This is relevant in the context of investigating relations between spatial memory impairments and brain function in SSD. Moreover, probing the specificity of these relations is important in the context of generalized neurocognitive impairment in SSD. Therefore, in this dissertation, I investigate subtypes of spatial memory dependent on different brain regions. Support for relatively selective hippocampal-dependent spatial memory impairment would inform the development of cognitive interventions that either harness intact abilities or train impaired abilities.

Generalized Cognitive Impairment in SSD

As noted, a major reason why it is important in SSD to compare performance across specific domains of memory as opposed to studying them in isolation, is because there is a backdrop of generalized cognitive deficit in SSD (Dickinson, Iannone, Wilk, & Gold, 2004; Nuechterlein et al., 2004). That is, the neuropsychological profile of individuals living with SSD indicates that across many different cognitive domains such as language, memory, attention, executive functioning, motor and visuospatial performance, the mean difference in behavioural performance of patients relative to healthy participants is approximately 1-1.5 *SDs* (Bilder et al., 2000; Harvey & O'Keefe, 1997; Heinrichs & Zakzanis, 1998; Saykin et al., 1991); impairment on any one task may be a reflection of more widespread cognitive impairment. There is consistent concern within the SSD literature as to whether evidence of cognitive impairment in any one domain reflects a relatively

selective deficit or rather more general neurocognitive dysfunction. Dickinson et al. (2004) administered eighteen cognitive measures to both SCZ and Healthy participants. These researchers found two-thirds of the variance relating a diagnosis of SCZ with cognitive performance was accounted for by a single factor rather than by specific independent effects. These findings were interpreted to suggest that cognitive performance reflects a generalized deficit in SCZ. Chapman (1978) discussed the importance of accounting for these generalized deficits in SCZ, especially when researchers are interpreting differential deficit based on comparison of performance on different tasks. Specific deficits are the potential by-product of two potential confounds associated with comparisons of performance across tasks, rather than true differences in cognitive ability. One potential confound is task difficulty. If task A is more difficult than task B and these tasks are being used as a comparison for intact and impaired domains of ability, this could lead to a false conclusion of a differential deficit. A second potential confound is the discriminating power of the tasks. Tasks with higher true-score variance are better at discriminating between individual levels of ability. Thus, although greater impairment on a task with greater discriminating power compared to a less discriminating task might support a differential deficit, it may only reflect a psychometric confound. As in our previous work (Wilkins et al., 2013), I used the four-on-eight virtual maze (4/8VM) to investigate differential deficit in SSD by comparing performance between groups on the same task, which minimizes concerns about task-related confounds such as difficulty and discriminating power.

Consistent with generalized cognitive deficit, there is also evidence of widespread brain dysfunction in SSD. A meta-analysis reported 2% volume loss of total cortical grey matter in first-episode SCZ relative to healthy groups resulting in a moderate effect size, g = -0.5 (Vita, De Peri,

Deste & Sacchetti, 2012). However, meta-analyses indicate an even more robust 4% hippocampal volume loss in SCZ (Nelson, Syakin, Flashman & Riordan, 1998; Vita et al., 2006). Functional connectivity studies provide evidence of disruption in connection between the PFC and thalamus (Woodward, Karbas, Foroushan & Heckers, 2012), PFC and parietal (Zhou et al., 2007), PFC and temporal regions (Friston & Frith, 1995), and overall reduced connectivity across the brain in SSD (Brennan, Harris & Williams, 2013; Pettersson-Teo, Allen, Benetti, McGuire & Michelli, 2011). These theories and findings will be discussed further below (Chapter 6, General Discussion).

In sum, it is important to recognize that a spatial memory deficit may reflect a generalized deficit. The presence of both an impaired and relatively intact ability provides better evidence for a relatively specific deficit, but potential task-related psychometric confounds need to be considered. There is evidence to suggest a greater magnitude of impairment in declarative memory (2-3 *SD*) in SCZ (Aleman, Hijman, de Haan & Kahn, 1999; Saykin et al., 1991), compared to a generalized cognitive deficit (1-1.5 *SD*) (Bilder et al., 2000; Harvey & O'Keefe, 1997; Heinrichs & Zakzanis, 1998; Saykin et al., 1991). In order to directly address the specificity of hippocampal-dependent spatial memory impairment in SSD, here I assess performance within the same tasks across different strategies (Experiment 1, Chapter 3) and conditions equated on difficulty (Experiment 3, Chapter 5).

Neonatal Ventral-Hippocampal Lesion Model

Consistent with the hippocampal abnormalities noted above, a leading pathophysiological and neurodevelopmental model of SSD is based on neonatal ventral hippocampal lesions in rats (Lipska, Jaskiw & Weinberger, 1993). In this model, seven-day old rat pups receive lesions to their ventral hippocampi during a critical phase of hippocampal development. The lesion triggers a

cascade of deficits in the brain leading to observable behavioural and cognitive features deemed similar to those in persons living with SSD. Importantly, these animals do not exhibit deficits until at least puberty, which is viewed as akin to the delayed onset of psychosis in humans. For instance, lesions of the neonatal ventral hippocampi impact the development of multiple surrounding brain regions similar to SSD (Tseng, Chambers & Lipska, 2009). Over the course of development, this lesion produces downstream disruption in the connective paths between the hippocampi and PFC and nucleus accumbens, as these are primary targets of the hippocampi (Brady, Saul & Wiest, 2010; Tseng et al., 2009). The neonatal ventral hippocampal lesion model is also considered a strong candidate as a model for cognitive impairments in SSD, as these lesions trigger behavioural (hypersensitivity to psychostimulants, impaired grooming and social isolation) and cognitive features (prepulse inhibition, sensory gating, spatial working memory, set-shifting and memory for space) similar to those in persons living with SSD (Al-Amin, Weickert, Weinberger & Lipska, 2001; Chambers, Moore, McEvoy & Levin, 1996; Flores, Silva-Gomez, Iranez, Quirian & Srivastava, 2005; Hanlon & Sutherland, 2000; Lipska, 2012; LePen et al., 2000; Tseng et al., 2009).

Of particular relevance to my dissertation, spatial memory performance is poor in adult rodents that had lesions applied to their ventral hippocampi during the neonatal stage of development. Specifically, they 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). Similarly, hippocampal volume reduction is a consistent structural abnormality found in SSD (Grace, Moore, & O'Donnell, 2010; Heckers, 2001) and SSD individuals are also significantly impaired on virtual-reality analogs of both the Morris water maze (Hanlon et al., 2006) and spatial radial arm maze (i.e., the 4/8VM; Wilkins et al., 2013). It is notable that the neonatal lesion model also highlights the

connectivity between multiple brain regions involved in spatial memory (Brady et al., 2010). Therefore, in addition to targeted analyses of hippocampal and striatal activation, I also investigate patterns of activation across the brain during spatial memory performance in SSD (Chapters 3 and 4).

Multiple Spatial Memory Framework

The hippocampi have long been recognized as integral to spatial memory performance (O'Keefe & Nadel, 1978). However, there are also forms of spatial memory that are more reliant on other brain regions, as elaborated on below. This section reviews the historical development of the multiple spatial memory framework. Spatial memory is traditionally defined as the ability to remember the spatial contexts of an event by forming an allocentric "cognitive map" of the world (O'Keefe & Nadel, 1978; Tolman, 1948). An allocentric map is a representation held in memory that is composed of the elements that make up the spatial array of an environment. The right hippocampus plays a key role in supporting the formation, recognition, and flexible use of this allocentric cognitive map (O'Keefe & Nadel, 1978). One initial line of evidence for this theory is that neurons called place cells in the hippocampi of freely moving rats fire most when the rats visit particular locations. That is, these neurons appear to code spatial locations (O'Keefe & Dostrovsky, 1971).

O'Keefe and Nadel (1978) further identified the composition of spatial memory as consisting of both locale and taxon forms of learning. Locale learning is another term for allocentric spatial mapping that is dependent on the hippocampi and refers to learning the relations among environmental cues to navigate to a target end goal. In contrast, taxon learning is not dependent on

hippocampal function and refers to a response approach that involves the use of a single cue to direct oneself to a target goal. Evidence of these two distinct spatial memory approaches stems from research with rodents tested on the Morris water maze (Morris, Garrud, Rawlins & O'Keefe, 1982). The Morris water maze consists of a pool filled with water. Rodents are placed in different starting positions across trials in the pool and are required to locate a platform in order to escape the maze. The platform is submerged beneath opaque water and the rodents are required to locate the platform by utilizing the distal cues available in the environment. Rats with lesions to the hippocampi typically fail to locate the submerged platform (Morris et al., 1982), supporting the claim that learning the relations among cues in the environment to aid navigation is dependent on intact hippocampal function. On the other hand, in the presence of a single distal cue rodents will utilize a taxon approach. The taxon approach requires learning the location of the submerged platform relative to a single permanent distal cue such as a triangle on the extra-maze wall or a single permanent proximal cue such as a beacon within the maze, near or attached to the visible platform. The taxon approach is unaffected by hippocampal lesions.

More direct evidence for a double dissociation between the brain regions involved in utilizing a locale or taxon approach to navigate in rats was observed by Packard & McGaugh (1992) following lesions to the caudate nucleus or the fimbria-fornix. The fimbria-fornix is a major subcortical output/input pathway to each hippocampus; therefore, a lesion of this nature is considered a functional lesion to the hippocampi. The caudate nucleus is located within the basal ganglia, and is a key part of the nigro-striatal dopamine pathway that plays a role in voluntary motor control and habit learning. In each of two versions of the water-maze task used by Packard & McGaugh (1992), there were different starting positions across trials requiring rats to use visual

cues (vs. egocentric/kinaesthetic motor paths) to locate the platform. There was a correct cue for the escape platform and an incorrect cue for a platform the rodents were unable to mount; the cues were balls located above the platforms. In the allocentric task, the correct cue/platform was always located in the same position in the maze, but the visual pattern of the cue varied across trials (vertical versus horizontal stripes). Thus, rats were required to identify the correct cue by its location relative to distal cues in the extra-maze environment and not the visual identity of the ball. In the response/taxon version of the task, the spatial location of the correct cue varied, but the visual pattern remained consistent demanding the rodents identify the platform based on the cue's visual pattern rather than its spatial location. Rats with lesions to the fimbria fornix (tail hippocampi) performed well in the response version, but poorly in the allocentric/spatial version. Rats with lesions to the caudate nucleus showed the reverse pattern of performance (Packard & McGaugh, 1992), thus providing evidence of dissociable brain regions supporting allocentric/spatial and response-based memory.

Some researchers suggest a role for the PFC in connection with the above types of spatial memory as an executive system controlling the spatially guided behaviour of the rats (Kolb, Sutherland & Whishaw, 1983). For example, deBruin, Sanchez-Santed, Heinsbroek, Donker, & Postmas (1994) placed rats with lesions to the medial PFC (MPFC) in the Morris water maze. After learning the location of the escape platform, the rats were given reversal training and expected to learn to locate a submerged platform in the opposite quadrant (the visible platform was removed). Rodents with MPFC lesions compared to the sham-operated rats were less able to learn the reversal training (deBruin et al., 1994). Evidence of poor reversal learning indicated that these rodents were unable to adapt to changes in the environment, suggesting that there is a potential executive

functioning role of MPFC during spatial navigation. Executive function deficit has also been found in SCZ on the Wisconsin Card Sorting Task, but patients improved their performance when aided with verbalizing their sorting strategy (Perry et al., 2001). Additionally, damage to ventromedial PFC (VMPFC) led to a dissociable impact on spatial learning and memory in rats (Kolb, Buhrmann, McDonald & Sutherland, 1994; Kolb, Pittman, Sutherland & Whishaw, 1982). That is, Delatour and Gisquet-Verrier (2000) tested rodents with lesions to their VMPFC on a spatial version of the Morris water maze and found impaired performance, but intact performance on the response version of the Morris water maze. In contrast, rodents with lesions to their dorsomedial PFC (DMPFC) performed poorly when response learning was required, but showed intact performance when spatial learning was required (deBruin, Swinkerls & de Brabander, 1997). These rodent lesion studies provide evidence of dissociable memory systems and dissociable PFC region involvement dependent on the spatial navigation approach (spatial versus response). Therefore, the involvement of these regions in the impaired spatial ability in SSD requires empirical attention. I address this objective with brain imaging technology in Chapters 3 and 4.

Importantly, there are also human neuroimaging studies that have identified several brain regions involved in spatial navigation. Spreng, Mar and Kim (2008) reported a meta-analysis of fMRI studies of healthy individuals who completed spatial navigation tasks. Based on conjunction analyses they found overlapping brain regions that included significant peak clusters in the hippocampus, parahippocampus, retrosplenial cortex, posterior cingulate cortex, precuneus, temporoparietal junction, ventrolateral PFC (VLPFC), superior frontal sulcus, thalamus, inferior temporal lobe, superior parietal and posterior MPFC. In this vein, there is human work investigating how multiple brain regions support adoption of spontaneous navigation strategies in humans

(Bohbot, Lerch, Thorndycraft, Iaria & Zijanbos, 2007; Iaria, Petrides, Dagher, Pike & Bohbot, 2003).

Spontaneous Strategy Use: The 4/8VM

Healthy human studies further support the role of the hippocampi in flexibly forming and using an allocentric cognitive map of space (Bohbot, Iaria, & Petrides, 2004; Hartley, Maguire, Spiers, & Burgess, 2003). For example, individual differences in spatial navigation abilities on the 4/8VM task correlate with measures of hippocampal integrity, such that better ability to form a cognitive map is correlated with higher fractional anisotropy in the right hippocampus (Iaria, Lanyon, Fox, Giasschi, & Barton, 2008). Researchers also found evidence that whether humans utilized either a spatial or response approach could depend on the task or the nature of the environmental context. Under normal circumstances, in order to successfully navigate one's environment one can use different strategies and approaches to learn to reach a target goal location. For example, some individuals might spontaneously adopt a spatial approach (allocentric) dependent on learning the relation between landmarks, a stimulus-response approach dependent on identifying a single landmark in conjunction with a sequence of body turns, or an egocentric response approach dependent on learning a series of body turns independent of landmarks in the environment. As reviewed below, human brain-imaging studies have found that healthy individuals who performed the 4/8VM reported spontaneously adopting multiple different strategies to learn to navigate their environment.

The 4/8VM task consists of a virtual environment with a central starting position surrounded by extra-maze landmarks (e.g. tree, rock, mountain, and valley). To obtain hidden target objects, participants walk down a staircase to a small pit at the end of the arm. Testing involves a series of

two-part trials. In the first part, participants visit four open pathways to retrieve target objects. In the second part of each trial, participants are able to visit all eight open pathways and are asked to avoid the previously visited pathways to find the target objects down the previously closed pathways. Importantly, individuals can utilize either a spatial or response approach to solve the navigation task. The spatial approach involves learning the location of the rewarded arms based on their relation with multiple landmarks in the environment, such as the tree and the rock. An example response approach involves using a specific landmark (i.e. tree) and learning the sequence of open and closed arms (e.g., open-closed-open-closed). Participants are then administered a probe trial that differs at test in that the walls around the maze are raised to conceal the landscape, so the extra-maze landmarks are no longer visible. On this probe trial, a higher error rate is expected among those spontaneously adopting a spatial strategy given the removal of allocentric landmarks compared to the response strategy group. Bohbot et al. (2007) found that 50% of healthy participants spontaneously adopted the spatial approach and 50% spontaneously adopted the response approach.

Those individuals who reported spontaneously adopting an allocentric/spatial strategy reported learning the relations between landmarks in the environment (i.e., tree and rock). These individuals had more grey matter and greater task-related blood oxygenation level-dependent (BOLD) signal in the right hippocampus in comparison to the response group as measured by voxel-based morphometry and fMRI, respectively (Bohbot et al., 2007; Iaria et al., 2003). Others reported spontaneously adopting a response approach. There were two different response subtypes described by these individuals (Bohbot et al., 2007; Iaria et al., 2003). The first was a response-landmark approach that involved identifying and using a single landmark (i.e., tree) to start their

sequence of responses (open-closed-open-closed pathways). The second response strategy was an egocentric approach; independent of any landmarks in the environment (no cues) these individuals reported learning to navigate using a sequence (i.e., left and right or open-closed-open-closed pathways) from a constant start orientation. For both these response approaches, the caudate and posterior parietal cortex appeared preferentially active relative to a baseline control condition (Bohbot et al., 2007; Iaria et al., 2003). Across the majority of studies both the response landmark and egocentric approach were grouped together as the response strategy group (Bohbot et al., 2004, 2007, 2011; Iaria et al., 2003). Individuals in these latter studies who spontaneously adopted a response approach appeared to have more grey matter and fMRI BOLD responses in the caudate nucleus relative to the spatial group (Bohbot et al., 2007; Etchamendy & Bohbot, 2007; Iaria et al., 2003). Interestingly, both the spatial and response groups were found to have shared activation in the parietal cortex and PFC (Iaria et al., 2003), consistent with involvement of a large-scale navigation network.

Dahmani and Bohbot (2015) extended their investigation to further understand relevant spatial navigation and memory-related networks of brain regions. Their inquiry was centered on regions active in conjunction with critical regions-of-interest (ROI) that may have selectively contributed to these multiple memory-related regions during spatial navigation. Most importantly, they explored whether there was a dissociable contribution of the PFC dependent on spontaneous selection of a spatial navigation strategy. For this purpose, they used the Concurrent Spatial Discrimination Learning Task (CSDLT), which is a virtual-reality paradigm like the 4/8VM, but involves a 12 arm-radial maze that is surrounded by landscape and landmarks (mountains, trees and rocks). The researchers analyzed behavioural performance along with fMRI and voxel-based

morphometry. Individuals who adopted a spatial approach had increased activation in the hippocampus and increased grey matter density in the VMPFC. In contrast, those individuals who adopted a response approach showed increased activation in the caudate and increased grey matter density in the DMPFC. The pattern of results replicates the dissociation between hippocampal and caudate-based involvement on strategy, but also highlights a strategy-based dissociation in the PFC.

Dissociation between use of spatial and response strategies also comes from lesion studies. For example, participants with MTL lesions (critically including the hippocampus) who spontaneously adopted the spatial strategy made more errors and had longer latencies compared to MTL patients using a response strategy (Bohbot et al., 2004). Contrary to expectations that patients might spontaneously harness intact brain regions, a majority (60%) of the MTL patients (unsuccessfully) adopted the more hippocampal-dependent spatial strategy.

Selective Spatial memory Deficits in SSD

As mentioned previously, there is consistent evidence of hippocampal abnormalities in SSD (Heckers, 2001; McCarley et al., 1999). Therefore, one expects and does find robust spatial memory impairments in this population (Ledoux et al., 2013; Rizzo, Danion, van der Linden, & Grange, 1996; Waters, Maybery, Badcock, & Michie, 2004). However, only a few studies have assessed whether this is a selective or general behavioural impairment across multiple types of spatial memory in SSD. Studies from our lab and others have found evidence in favour of a selective deficit in SSD on tasks that required allocentric spatial relations within an environment (Folley, Astur, Jagannathan, Calhoun, & Pearlson, 2010; Girard et al., 2010; Hanlon et al., 2006; Weniger & Irle, 2008).

For example, Weniger and Irle (2008) tested 25 participants with recent-onset SCZ on the Virtual Park and Virtual Maze tasks. The Virtual Park required participants to locate a pot of money in the presence of landmarks in the environment and was associated with hippocampal-dependent cognitive mapping. In comparison, the Virtual Maze required participants to locate a pot of money in the absence of landmarks and was linked to dorsal-striatal and parietal cortex-dependent response learning. In support of deficient hippocampal-dependent memory and preserved response learning, individuals living with SCZ were found to be impaired on the Virtual Park, but relatively intact on the Virtual Maze compared to healthy participants. Harnessing the intact egocentric system in the presence of a hippocampal-dependent spatial memory deficit could be an important rehabilitative approach to circumvent spatial memory deficits in SCZ. Of note, their Virtual Maze task, on which the SCZ group was not impaired, was the more difficult task (based on healthy performance), indicating that the differential impairment in allocentric spatial memory was not due to a difficulty confound. However, this between-task comparison presents a confound that challenges clear interpretation. Thus, in the current dissertation, I form comparisons between strategies applied to the same task (Experiment 1 and 2) or between conditions within the same task (Experiment 3).

Prior work from our lab (Girard et al., 2010) also indicates that persons with SSD demonstrated similar selective impairments on tests demanding viewer-independent (allocentric) learning, but intact performance on viewer-dependent (egocentric) forms of learning within the same experimental paradigm, the Bin Task. In this paradigm participants were seated at one of four identical chairs surrounding a table in the centre of a room filled with environmental features such as artwork, computers, desks and shelves. On the table were nine visually identical bins arranged in a circle on top of the table in front of the participant. At study the participant watched an

experimenter randomly place four everyday objects into four of the nine bins. The goal of the task was for the participant to remember the location in which the experimenter placed each individual object following a distractor-filled delay during which the participant either remained in the same location as study (viewer-dependent position) or the participant was moved to another seat around the table (allocentric viewer-independent position). Having the participant moved to another location to recall the location of the objects targeted the ability to form an allocentric representation. That is, to successfully perform this condition the participant had to learn the location of the objects and bins in relation to the landmarks available in the environment, independent of their viewing position in the room. Individuals living with SSD performed well on the egocentric viewer-dependent version of the task (i.e., study and test location the same), but were impaired on the allocentric viewer-independent version of the task (i.e., test location different from study). Moreover, these conditions did not differ in discriminating power, indicating that the differential deficit was not a psychometric artifact (Girard et al., 2010).

The above experiments are among the first to provide direct support for a differential deficit across multiple memory systems in SSD. Importantly, the Bin task used by Girard et al. (2010) presents these memory conditions within the same paradigm (i.e., without a task confound) and the conditions do not differ with respect to discriminating power (i.e., without a psychometric confound). However, clear interpretation of these findings is limited by the possibility that participants could have continually updated their relevant locations in relation to their body-centered axis as they physically moved around the array of bins, as opposed to using a truly viewpoint-independent perspective (Burgess, 2006; Wang & Simmons, 1999). Although SSD and healthy participants reported equal use of environmental and body-centered cues, data regarding

reported strategies were collapsed across view conditions (Girard et al., 2010). Thus, it is unclear to what extent the observed SSD-related deficit reflects impaired viewpoint-independent memory, difficulty updating a viewpoint-dependent representation, or differential strategy use across conditions between SSD and healthy participants. Thus, these issues are targeted by my dissertation. As my dissertation further follows my previous work (Wilkins et al., 2013), I will review that study in the next section leading into the rationale for the current dissertation.

Selective Spontaneous Spatial Navigation Strategy Deficit in SSD

In my previous work (Wilkins et al., 2013), I utilized the well-validated 4/8VM task as a human analogue of the radial-arm maze long used to study rodent spatial memory (Bohbot et al., 2004, 2007). For example, the rodent version was used in studies demonstrating spatial-memory deficits in the neonatal ventral-hippocampal lesion model of SCZ (Brady et al., 2010; Chambers et al., 1996). This human analogue is a useful tool to investigate the role of hippocampi in selective spatial cognitive deficits. This makes this paradigm an ideal tool for the goals of the current dissertation to investigate selective spatial deficits in SSD.

As reviewed above, under normal circumstances individuals can navigate their environment using different types of strategies and individual differences in hippocampal and caudate integrity relate to spontaneous use of spatial and response strategies, respectively (Bohbot et al., 2007; Etchamendy & Bohbot, 2007; Iaria et al., 2003). However, this relation is less clear among clinical populations. For example, over half of patients with MTL lesions tended to preferentially adopt a less efficient hippocampal-dependent spatial strategy approach. They reported using the relation between multiple landmarks to help find a target location (Bohbot et al., 2007). In adopting this approach, these individuals committed more errors and had longer latencies when solving the task

compared to the healthy group and MTL-response group. Given robust evidence of abnormal hippocampal function in SSD, we predicted that SSD participants adopting the spatial approach would also make more errors and have longer latencies on the 4/8VM task compared to the Healthy-Spatial group and SSD-Response group. Consistent with this hypothesis the SSD-Spatial group took significantly longer to locate all targets, made more pathway-entry errors during the learning phase, and required more trials to learn the task than the Healthy-Spatial group. In contrast, SSD-Response learners were not impaired relative to Healthy groups (Figure 1; Wilkins et al., 2013). Overall, we provided behavioural evidence to support the hypotheses of a selective allocentric memory dysfunction in SSD, relative to an intact functioning response-based system (Wilkins et al., 2013). The behavioural findings suggest that the caudate system is intact, however, the relations between 4/8VM performance in SSD and brain function were not assessed.

The major limitation with my previous work is that we did not measure brain activation while participants performed the 4/8VM. Based on previous fMRI and behavioural findings on the 4/8VM, this is a useful approach to probe hippocampal and caudate function in SSD more directly. Understanding these relations may provide insight regarding underlying neural bases for individual differences in both navigational strategy use and spatial memory performance in SSD.

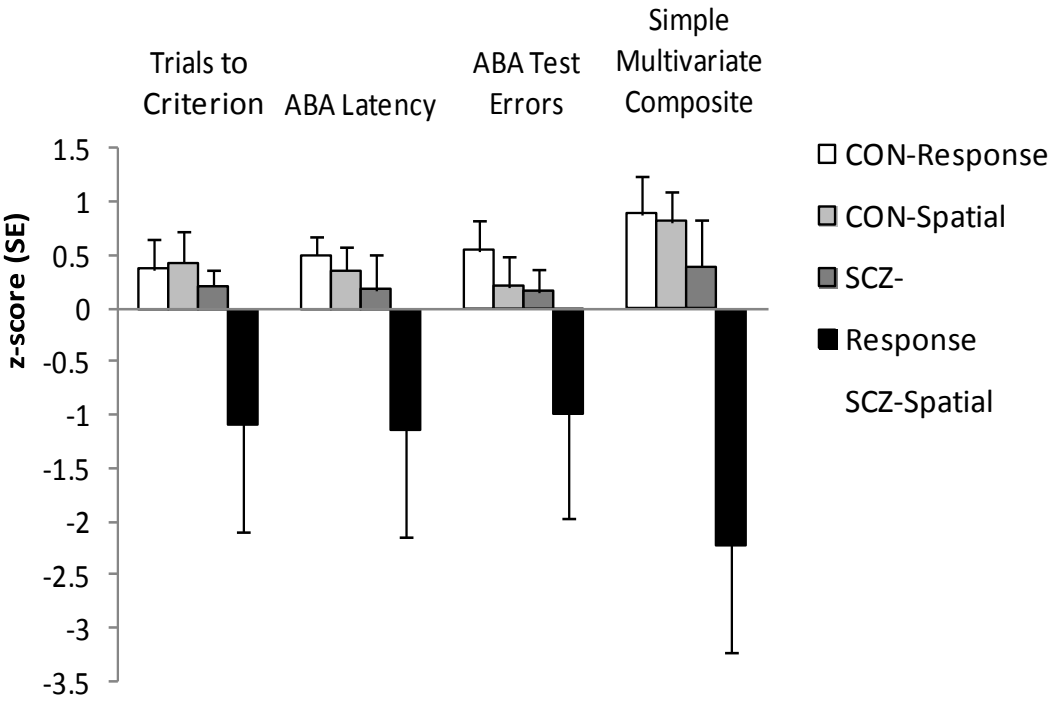

Figure 1. Differential deficit among SSD participants reporting spontaneous use of a Spatial versus Response strategy during acquisition of the 4/8VM task. Data represent standardized means (and standard errors) by Group and Strategy on the measures of Trials to criterion, latency to find targets and test errors on the initial three ABA trials. The z-scores are signed such that negative scores reflect poorer performance (below the overall mean for each measure). The simple multivariate composite reflects a linear combination of the Trials to criterion and ABA Latency measures. This figure was reproduced with permission (Wilkins et al., 2013). SCZ = SSD; CON = Healthy.

In Experiment 1, I compare performance and brain activation (using fMRI) between participants on the 4/8VM to assess hippocampal and caudate activation and their relation to navigational strategy use and spatial memory performance in SSD. Whereas rat lesion work highlights dissociations between these regions, fMRI research in healthy human participants provides a more complex picture, with dissociable neural regions that extend beyond the hippocampi and caudate. In Experiment 2, I assess multivariate patterns of brain activation among

SSD participants using a spatial strategy. This study suggests disconnectivity among the hippocampi and navigation-related brain areas in SSD.

Within Group Comparison: The Courtyard Task

A limitation of the 4/8VM paradigm was that between-group comparisons were based on individual differences in spontaneous strategy use, rather than comparing performance within-subjects on the same paradigm. Thus, it is unclear whether differential performance reflects individual differences or brain system differences. For example, between-group comparisons on the 4/8VM failed to inform whether those SSD individuals who spontaneously adopted a spatial strategy had an intact or impaired caudate-dependent response system. This possibility is important to note because the spatial strategy impairment may reflect a general impairment of regions associated with both spatial and response learning specific to this group, whereas those in the response group may have intact regions associated with the spatial approach. Addressing this limitation will be informative about the extent to which these brain regions are coordinated when one system is intact and the other is impaired. Spatial memory paradigms that are able to provide convergence of evidence on within-subject performance differences are thus important to strengthen our understanding of multiple spatial memory abilities in SSD.

Some experiments on SSD have provided within-subjects comparisons across spatial memory conditions. For example, Weniger and Irle (2008) demonstrated SSD-related impairment on the Virtual Park task requiring allocentric learning, but not the Virtual Maze that relies on egocentric processing (as reviewed above). Conversely, these researchers have reported that individuals with lesions to the parietal cortex are impaired at learning to locate the pot of money in the Virtual Maze, but are intact in the Virtual Park (cognitive mapping). Likewise, on these same

tasks smaller precuneus (parietal) volumes and striatal lesions were related to impaired performance on this condition alone (Wengier, Ruhleder, Lange, Wolf, & Irle, 2011). These findings support the utility of within-subject comparisons for identifying differential abilities across patient groups. However, as noted, one limitation is that these findings are confounded by the use of different experimental tasks.

Therefore, in Experiment 3, I assess SSD performance on a within-subject comparison of allocentric/viewer-independent and response/viewer-dependent memory abilities using a single task, the Courtyard task developed by King and colleagues (King, Burgess, Hartley & Vargha-Khadem, 2002; King, Trinkler, Hartley & Vargha-Khadem, 2004). Viewer-dependent memory is an aspect of the response system. Viewer-dependent forms of memory involve relying on learning the egocentric locations of objects in space relative to one's own body-centered axes or fixed sensory-perceptual representations of landmark objects within a scene (King et al., 2002, 2004). Under viewer-dependent task conditions, participants often either start or view object-location pairings from a consistent starting location across study and test (Burgess, 2006). In contrast, tasks that tap into viewer-independent memory measure the ability of the individual to learn the spatial relations among elements in the environment independent of one's location in space. Viewer-independent memory is an aspect of the allocentric system and thus, is designed to recruit the hippocampi. In this approach, one can flexibly recall or recognize object-location associations regardless of viewpoint. This type of spatial memory is essential for navigating detours from familiar navigation routes and orienting environments that are different between study and test phase. Although this type of memory involves a network of brain regions, the hippocampi are core to this type of flexible navigation. CA1 subregions in the hippocampi have also been particularly associated with viewer-

independent allocentric spatial learning (Suthana, Ekstrom, Moshivaziri, Knowlton, & Bookheimer, 2009).

The virtual reality Courtyard Task is one task able to measure both viewer-dependent and viewer-independent memory. The Courtyard Task is valuable as it permits a within-subject comparison of hippocampal-dependent and non-hippocampal dependent spatial memory performance, reducing task-related confounds. In this task, the participants are allowed to move along a rooftop of a building that provides a clear view of the placeholders in the centre of the environment. Objects are presented randomly above the place holders at study and test. Participants are asked to remember the location of the objects presented above one of the 21 static red place holders located in the courtyard environment at study. However, at test the participant either view the object-placeholder pairing from the same-viewpoint seen at study or are teleported across the courtyard to a different view that places demands on allocentric processing. Both conditions are equated for difficulty. King and colleagues tested a bilateral hippocampal lesion participant on this paradigm (King et al., 2002, 2004). The lesion was a result of perinatal anoxia. The hippocampal lesion participant was able to identify the correct location of the objects in the viewer-dependent condition of this Courtyard Task, but was unable to identify the location of the objects in the viewer-independent condition when he was teleported into a different viewing location (King et al., 2002, 2004).

In sum, lesion of the MTL in humans impairs performance on a task that is requiring allocentric learning abilities and lesions of the striatum and parietal cortex impair performance on a task requiring response learning abilities, but not vice-versa. However, these studies only provide indirect evidence of a double dissociation because the results stem from testing different

lesion groups on different tasks. These confounds highlight the importance of testing the same clinical population across conditions within a single task. Convergence of evidence across rodents, healthy human and lesion studies support engagement of multiple forms of memory to support navigation that appear coordinated. That is, when one ability is impaired, the other may support learning within a spatial context. Given the potential for such regulation, it remains imperative to study spatial navigation at the whole brain level. Although brain function of individuals living with SSD is quite complicated, there is substantial variation across brain regions with differential effects on neurocognitive functioning. Thus, by using tasks that are able to clearly dissociate spatial and response approaches, my dissertation advances understanding of SSD with stronger conclusions about preferential dysfunction within a multiple memory framework.

Summary

In sum, my dissertation will provide insight into the role of underlying neural regions involved in spontaneous adoption of a navigation strategy. In Experiment 1, I provide fMRI evidence of reduced hippocampal activation in those SSD participants who spontaneously adopt the spatial strategy and equivalent caudate activation in SSD-response learners compared to Healthy groups. In Experiment 2, I apply multivariate analyses to characterize patterns of brain activation within the context of spatial memory and spatial navigation in SSD. In Experiment 3, I provide converging behavioural evidence that SSD participants who have impaired viewer-independent memory can rely on their viewer-dependent response abilities. Together these studies provide supporting evidence of relatively intact response learning and impaired spatial memory in SSD.

Chapter 3: An fMRI Investigation of Spontaneous Navigation Strategy Use in Schizophrenia Spectrum Disorders

Taken together, research supports a selective hippocampal-dependent spatial memory deficit in SSD. These findings are in line with the idea of the existence of multiple types of spatial memory. The use of a cognitive map strategy requires intact recruitment of the hippocampi (O'Keefe & Nadel, 1978), whereas response strategies are associated with the caudate nuclei in humans (Bohbot et al., 2004, 2007; Hartley et al., 2003; Iaria et al., 2003). For example, in the study by Wilkins et al. (2013), I observed impaired performance among SSD participants using a spatial, but not response strategy. However, we did not include a brain measure to verify hippocampal and caudate function while participants performed the 4/8VM. Understanding these brain-behaviour relations may provide insight regarding underlying neural bases for individual differences in both navigational strategy use and spatial memory performance in SSD. Therefore, the purpose of Experiment 1 is to assess brain activation using fMRI during performance on the 4/8VM. As in Wilkins et al. (2013), I expected that SSD participants who spontaneously adopt a spatial strategy would make more errors and have longer latencies on the 4/8VM compared to SSD-Response and Healthy participants. Supporting this behavioural profile, I further predicted that the SSD participants who spontaneously adopt the spatial strategy would have less hippocampal activation compared to the Healthy-Spatial group, whereas SSD participants who spontaneously adopt the response strategy would have intact recruitment of the caudate similar to the Healthy-Response group. These hypotheses are based on an indirect connection between abnormal hippocampal function and spatial memory impairments through assessing behavioural impairment on the virtual Morris water maze (Hanlon et al., 2006) and fMRI to assess way-finding performance in SSD (Folley et al., 2010; Ledoux et al., 2013). However, previous studies have not investigated associations between hippocampal dysfunction and spontaneous strategy use in SSD.

Methods

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 SCZ. Healthy participants (n =16) were recruited from the community via newspaper, Craigslist, and poster advertisements. Participants were included if 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. SSD participants met criteria for a DSM-IV psychotic disorder, as ascertained using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Diagnostic interviews were conducted by trained senior graduate students. All SSD participants were clinically and pharmacologically stable (i.e., no recent change in medication or patient status in the past 6 weeks). Exclusion criteria consisted of a 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. Participants were also screened for MRI scanning requirements (e.g., no metal implants, not pregnant; please see fMRI screening form Appendix A).

All participants completed two days of testing. On Day 1 of testing, participants gave informed consent and were administered a battery of tests to determine clinical, cognitive and demographic information. Clinical information was gathered using the MINI to confirm diagnoses and the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opfer, 1987) was used to

assess current symptomatology. The neuropsychological/cognitive measures assessed general cognition, memory abilities and visual-spatial processing. Participant characteristics are summarized in Tables 1-3. Overall, the SSD group had fewer years of education (*M*=13.6) than the Healthy group (*M*=17.0). Also, the SSD-Spatial group was older (M = 44.4) than the SSD-Response group (M = 34.6), on average. But, there were no other demographic differences between groups (Healthy, SSD) or strategy types (Spatial, Response), *p*s > 0.05 (see Table 1).

The groups did not differ in terms of estimated intelligence or 3D mental rotation abilities (See Table 2). The SSD group scored lower (M= 95.2), however, than the Healthy group (M=109) on the reading subtest (See Table 2). Importantly, cognitive differences between groups did not interact with strategy.

The SSD group included participants with SCZ (*n* = 10) and Schizoaffective Disorder (*n* = 6). There were no differences between these subgroups on the experimental, cognitive, or demographic variables (*ps* >.05; data not shown). There were also no significant differences between the SSD-Spatial and SSD-Response group on symptom measures (see Table 3). The SSD-Spatial group took higher dosages of antipsychotics based on CPZe (chlorpromazine equivalent) conversions (SSD-Spatial = 239.1; SSD-Response = 104.0) (Virani et al., 2011), but not with respect to types of medications used (see Table 3). As detailed in the Results, accounting for the variables showing group differences, including education and WRAT-Reading, in the analyses did not affect the pattern of findings.

Table 1.

Demographic Characteristics of Healthy and SSD Groups by Strategy (Spatial, Response)

	Healthy		SSD			
Characteristics[a]	Spatial	Response	Spatial	Response	*Effect(s)*[b]	η^2
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)	17.6 (.9)	16.5 (4.1)	13.4 (1.7)	13.7 (2.0)	G	.34
SES[c]	42.2 (11.9)	47.1 (11.4)	44.3 (9.3)	39.6 (8.6)		
Video Game Experience[d]						
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*)	4	8	3	5		

Note. [a]Continuous data are presented as means (standard deviation), *M* (*SD*). Sex and experience with first-person immersive three-dimensional video-game experience (3D) are reported as frequency data (*n*). I evaluated Group x Strategy effects using ANOVAs for continuous variables and the Cochran-Mantel-Haenszel test for categorical variables. [b]G represents a significant ($p < .05$) main effect of Group for education. There were no other main effects or interactions. [c]Socioeconomic status (SES) calculations were based on parental occupations (appropriate data were unavailable for one healthy participant). 3D Gamer frequency was determined based on the Video Game Questionnaire (Bohbot et al., 2004; Appendix B). The SSD-Response group consisted of one participant who used a sequence without awareness of a central starting location.

Table 2.

Cognitive Characteristics of Healthy and SSD Groups by Strategy (Spatial, Response)

	CON		SSD			
Characteristics	Spatial	Response	Spatial	Response	*Effect(s)*[a]	η^2
FSIQe[b]	114.0 (18.2)	115.1 (19.6)	104.4 (15.1)	105.3 (17.7)		
WRAT-Reading[b]	107.3 (9.2)	110.3 (13.8)	93.0 (10.7)	98.4 (12.5)	G	.26
MRT	9.4 (6.9)	9.5 (3.4)	7.8 (6.7)	8.0 (5.3)		

Note. Data are presented as *M* (*SD*). [a] G represents a significant ($p < .05$) main effect of Group on the WRAT-Reading subtest. There were no other main effects or Group x Strategy interactions. [b] Data were missing for two Healthy (Spatial) on WRAT-Reading and FSIQe. Abbreviations: FSIQe = Estimated Full-Scale Intelligence Quotient derived from the Matrix Reasoning and Information subtests of the Wechsler Adult Intelligence Scale – Third Edition (Wechsler, 1997) as per Sattler and Ryan (1998); MRT = Mental Rotation Test (Peters et al., 1995); WRAT-Reading = Reading subtest from the Wide Range Achievement Test- Fourth Edition (Wilkinson & Robertson, 2006).

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Table 3.

Clinical Characteristics of the SCZ Sample by Strategy (Spatial, Response)

Measure [a]	Spatial	Response
Diagnoses (Schizophrenia, Schizoaffective disorder)	5, 4	5, 2
Medication		
CPZe*	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)

[a]Continuous data are presented 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) *$p < .05$.

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

Materials and Procedure

The 4/8VM task. On Day 1 participants completed an assessment of cognitive, clinical and demographic variables (See Tables 1-3). Participants returned on Day 2 to complete the 4/8VM paradigm (Bohbot et al., 2004, 2007; Etchamendy & Bohbot, 2007; Iaria et al., 2003; Wilkins et al., 2013). The 4/8VM was a computerized virtual environment (created using Unreal Tournament, Epic Games Inc., Raleigh, N.C.) comprising an eight-arm radial maze with a central starting position, surrounded by extra-maze landmarks (e.g., tree, rock, mountain, and valley; see Figure 1). Participants navigated with forward, left turn, and right turn buttons on a keypad.

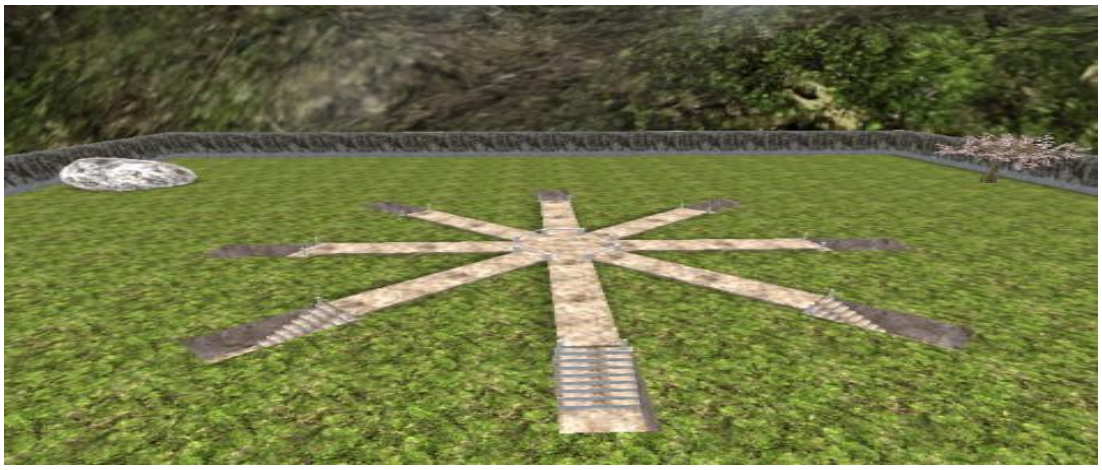

Figure 1. Image of 4/8VM virtual environment. The environment contains the tree, mountain and rock as landmarks surrounding the eight open pathways.

Participants were required to navigate towards the end of the maze arms and down a staircase to a small pit to locate hidden target objects. Prior to testing, participants practiced navigating with the keyboard in an environment similar to the 4/8VM. The practice maze consisted of eight open pathways without target objects at the end of each arm. The environment included a grey background wall without landmarks.

Testing consisted of two-part trials from a constant starting position. In the Study Phase, participants visited four open pathways to retrieve target objects hidden at their ends (the other four pathways were blocked). In the Test Phase, all eight pathways were open and the participants avoided the paths previously visited and found the hidden objects down the pathways previously closed. Following practice and any clarification of the task, participants completed an initial sequence of four trials during the fMRI scan. The configuration of pathways that contained the target objects changed across these four trials. The first (trial A1) and second configuration (trial B1) differ, whereas the third and fourth trial (trial A2, trial A3) had the same configuration as the first (trial A1) (See Figure 2).

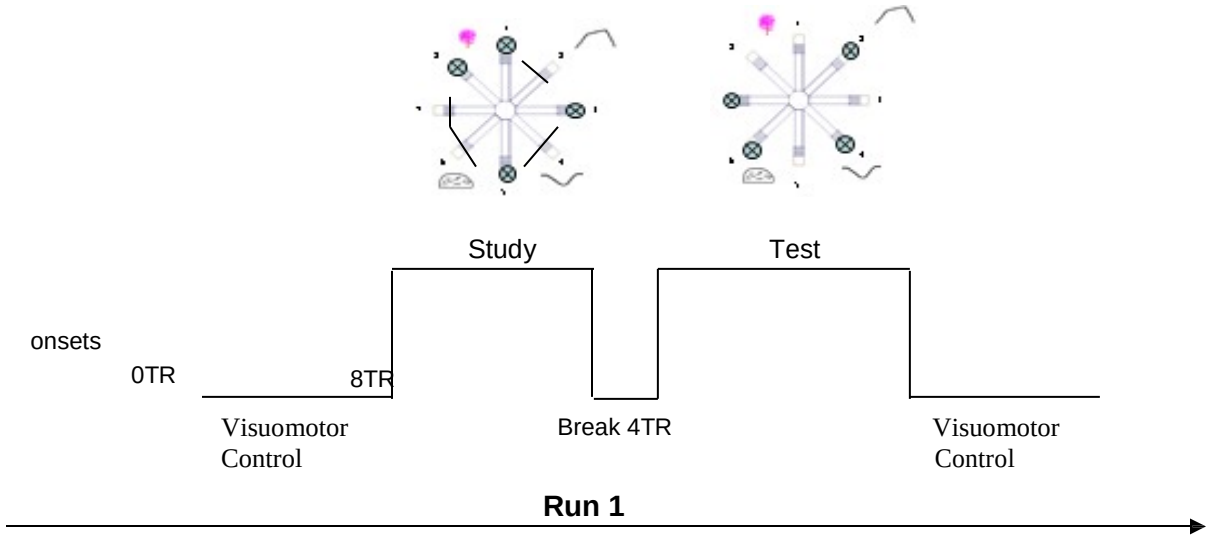

Figure 2. 4/8VM fMRI block design for trial A1 in the scanner. Study Phase block is the configuration of pathways closed by barriers with a dark line through the arm. The circles at the end of the pathway reflect target arms. The Test Phase is the configuration of eight open pathways and the circles at the end reflect the target arms that were previously blocked by barriers in the Study Phase. The landmarks (mountains, tree and rock) are depicted in the image.

The purpose of the change in configuration across the first two trials was to further promote the spatial strategy use amongst the spatial learners. The change in configuration promotes activation of the hippocampus because encoding of novel relations between target objects and environmental landmarks is required. After these initial two trials, the configuration repeated until participants reached criterion. I refer to the sequence participants performed in the scanner as the ABAA trials. Prior to the beginning and end of each run there was a Visuo-Motor Control condition. Participants were instructed to count backwards by threes starting at 1000 and were informed that there was nothing to learn during this Control task; they were presented with eight open arms, but just needed to visit any four arms to obtain the objects at the end of the pathway. All additional trials were completed outside of the scanner. Participants who met a criterion of two A-type trials without error proceeded to the probe test. If criterion was not met within the first four trials, testing continued outside of the scanner until the participant met this criterion.

The probe test was designed to assess participants' reliance on the extramaze cues. This trial (type C) differed from other trials at test in that the walls around the radial maze were unexpectedly raised and the landscape and landmarks were no longer available to aid navigation. Testing was discontinued after participants entered four different pathways. A higher error rate was expected among participants relying on a spatial strategy given the occlusion of allocentric landmarks (Bohbot et al., 2004, 2007; Iaria et al., 2003).

At the end of the experiment, spontaneous navigation strategies were assessed with an interview. Interviews were audio-taped and two independent raters confirmed agreement on the coding of participant strategies. Spatial strategies were defined as remembering the position of target pathways relative to two or more landmarks and the absence of reference to using a sequence

of open and closed pathways from a single position. For example, a spatial strategy was remembering the target pathways by their spatial relations to the tree, rock and mountain. In contrast, a response strategy was defined as remembering the within-maze sequence of target pathways relative to the participant's starting orientation or a single landmark such as the tree in combination with a series of clockwise sequences of open and closed pathways. For example, remembering the target pathways based on a memorized sequence of open and closed barriers that started at the pink tree would be coded as a response strategy. No participants switched strategies while in the scanner and all participants reported use of a strategy.

Scanning session. Participants lay in the scanner with padding to minimize movement. The virtual environment was back-projected onto a screen and a mirror allowed participants to see the 4/8VM. Participants responded with one of three keys on an MR-compatible five-button response box. Four 15-minute runs were administered in total (one for each of the ABAA trials). Total time in the scanner was approximately 1.5 hours, which also includes anatomical and B0 scans.

fMRI Acquisition Parameters. Images were acquired with a 3T Signa MRI scanner (GE Medical Systems, Milwaukee, WI). T1-weighted anatomical images were acquired with a multiplanar rapidly acquired gradient echo (MP-RAGE) sequence with a spatial resolution of 1x1x1 mm^3. Functional data were obtained using T2*-weighted high-resolution echo planar imaging (EPI) scans on an oblique angle perpendicular to the long axis of the hippocampi with 34 contiguous 3-mm thick slices covering the whole brain (TR = 4000 ms, TE = 30 ms, FA = 90°, 128 x 128 matrix, FOV = 25.6). The first four functional scans were collected as dummy scans prior to administration of the task. The dummy scans were required for scanner and tissue equilibrium and were not included in data processing. The 4/8 VM task components were presented in four 15-minute fMRI

sessions separated by short breaks. The order of the scanning trials were A, B, A, and A, corresponding to the trials described above. B0 field maps were obtained to correct for inhomogeneity-induced image displacement in the functional scans (<5 mins). This entire scanning protocol was completed in 1.5h. The protocol was developed and was consistent with previous protocols (Bohbot et al., 2004) for various clinical populations, including medial temporal lobe lesions and individuals living with SCZ.

Behavioural data analysis. Given the current focus on imaging data, I applied the MANOVA approach by Grice and Iwasaki (2007) used in our prior behavioural study (Wilkins et al., 2013) to succinctly summarize the current 4/8VM performance data. I used a MANOVA to assess Group (SSD, Healthy) × Strategy (Spatial, Response) effects using three key dependent variables (1) ABAA Latency = The summed duration (in minutes) of the initial ABAA sequence of test trials, and (2) ABAA errors = Errors of commission at test across the ABAA trials, including entries into a pathway without a target and repeat entries into a pathway within a trial, (3) Trials to Criterion = Number of trials after ABAA required to perform two error-free A trials (Wilkins et al., 2013). The linear composite of these variables contributing to the Group × Strategy interaction also provided a single index of performance for subsequent univariate and correlation analyses, thereby minimizing redundancy. The standardized discriminate function coefficients were Trials to Criterion, *ws* = -1.22479, ABAA latency, *ws* = -0.35467, and ABAA errors, *ws* = 0.7804 (see MANOVA SPSS Script in Appendix C). In my previous study (Wilkins et al., 2013), errors did not contribute substantial unique variance to the equation, but in the current analyses all three measures contributed to the multivariate composite. Given the different measurement scales, the dependent

measures were standardized prior to this analysis. My data met the required assumptions of independence, multivariate normality, and homogeneity of variance-covariance matrices (Grice & Iwasaki, 2007). I separately assessed the total number of incorrect pathways entered in the probe test (maximum four pathways entered) using a 2 Group (Healthy, SSD) x 2 Strategy (Spatial, Response) ANOVA.

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

Anatomically based ROI masks of the hippocampi and caudate nuclei were created using MARINA (Tzourio-Mazoyer et al., 2002). Hippocampal and caudate ROIs were interrogated separately for locations of peak activation of significant clusters within each region. Within these ROIs, I applied a voxel-wise threshold of $p < .05$ (uncorrected) and extent threshold of 5 voxels to assess the Group x Strategy interaction of a priori interest. More exploratory whole-brain data were employed at a statistical threshold of $p < .005$, uncorrected with a cluster extent threshold of 15 voxels.

Trials were self-paced and many SSD participants did not complete the final Visuo-Motor Control phase that followed the Test phase. Due to variability in the Visuo-Motor Control duration across participants, I included only the first 30 s of the initial (pre-Study) Visuo-Motor Control phase in our analyses. For the purpose of the current dissertation I focused analyses on the Test Phase data for Trials 1 and 4 (i.e., A1 and A3). These were the trials in previous studies where groups were distinguished by maximal hippocampal activation in A1 for the Healthy-Spatial group and caudate activation in A3 for the Healthy- Response group (Bohbot et al., 2004, 2007; Iaria et al., 2003). The data were analyzed as a block design.

Univariate analysis. SPM analysis is based on a general linear model (GLM) to analyze fMRI data. Second-level fMRI analyses targeted the differential profile of the SSD-Spatial group. That is, the current results (see below) and previous studies (Ledoux et al., 2013; Wilkins et al., 2013) indicate a selective impairment in the SSD-Spatial group. First-level (individual) analysis consisted of t-test contrasts entered for each trial: Test Phase > Visuo-Motor Control (A1) and Test Phase > Visuo-Motor Control (A3). A primary goal of the current study is to assess the extent to which this selective deficit relates to hippocampal under or over activation. As such, this question was best addressed with specific hypothesis-driven a priori contrasts comparing the SSD-Spatial group to the other three groups, as opposed to exploratory omnibus approaches (Rosnow & Rosenthal, 1989; Rosnow, Rosenthal & Rubin, 2000). More specifically, I weighted the data for the Healthy-Spatial, Healthy-Response, SSD-Spatial, and SSD-Response groups with the SSD-Spatial "hypoactivation" contrast 1, 1, -3, 1 and SSD-Spatial "hyperactivation" contrast,-1, -1, 3, -1. Given the differential weighting of the SSD-Spatial group (-3/+3) and lack of direct comparison between

Response groups in these full-sample analyses, follow-up pairwise contrasts using equal weights directly addressed differences between the Healthy and SSD Spatial groups, and between the Healthy and SSD Response groups.

Data were visualized and localized using SPM8, xjview (Ciu, X., http://www.alivelearn.net, Stanford, United States of America), and the WFU_ PickAtlas (Department of Radiological Sciences, Wake Forest University, Winston-Salem, USA) toolboxes via Matlab (version 2013A, The Mathworks Inc).

Results

Behavioural Results

Group × Strategy ANOVA. A Group (Healthy, SSD) × Strategy (Spatial, Response) between-subject univariate ANOVA of the multivariate composite based on Trials to Criterion, ABAA latency and ABAA errors confirmed a Group x Strategy interaction, $F(1,28) = 8.80$, $p = .006$, $\eta^2 = .24$, and main effect of Group, $F(1,28) = 9.21$, $p = .005$, $\eta^2 = .25$. As shown in Figure 3, the interaction indicated the SSD-Spatial group was impaired relative to the other three groups. Most importantly, the SSD-Spatial group was impaired relative to the Healthy-Spatial, $t(14) = -3.24$, $p = .006$, $d = -1.73$, and SSD-Response groups, $t(14) = -2.58$, $p = .022$, $d = -1.34$, whereas the SSD-Response group performed near-equivalently to the Healthy-Response group, $t(14) = -0.45$, $p = .965$. $d = -0.24$ (See Figure 3).

Probe Test. Analysis of the probe errors failed to yield a significant Group × Strategy interaction, $F(1,28) = .669$, $p = .420$, $\eta^2 = .02$, or main effects of Group, $F(1,28) = 2.065$, $p = .162$, $\eta^2 = .07$, or Strategy, $F(1,28) = 1.080$, $p = .308$, $\eta^2 = .04$.

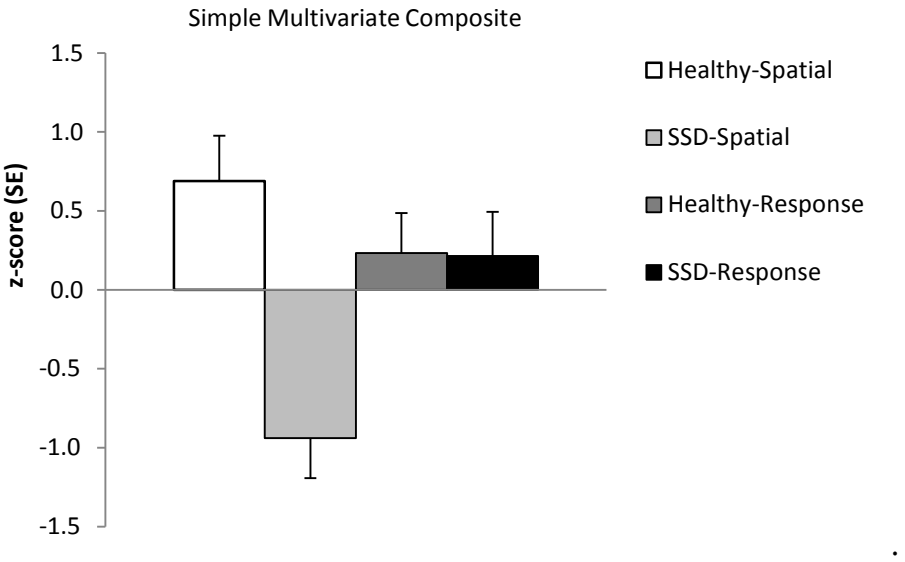

Figure 3. Differential deficit among SSD participants reporting spontaneous use of a Spatial strategy. The composite score reflects a multivariate composite of Trials to Criterion, ABAA Latency and ABAA Errors for the Group × Strategy interaction. Data represent standardized means and standard errors. Scores with a negative value indicate poor performance (below overall mean for each measure).

Correlational Analyses. Relationships between demographic, cognitive and clinical variables with the multivariate composite of 4/8VM performance were explored via bivariate correlations within groups. In the Healthy group, participants with higher scores on the WRAT-Reading subtest performed better on the 4/8VM, $r = .72$, $p = .009$. Within the SSD group, higher scores on both WRAT-Reading and FSIQe were associated with better performance on the 4/8VM,

r = .53, p = .036, and r = .55, p = .026, respectively, whereas higher doses of CPZe related to worse performance on the 4/8VM, r = -.59, p = .017.

In light of these correlations and group differences in WRAT-Reading and FSIQe (Healthy > SSD), we explored the impact of these variables on the Group × Strategy interaction reported above using a covariate analysis. Accounting for the variance associated with these covariates enhanced the relative variance accounted for by the Group × Strategy interaction by 15%, $F(1,22)$ = 14.01, p <.001, η^2 =.39 (compare to η^2 = .24 from ANOVA).

Following up on the CPZe correlation, the SSD-Spatial group had higher CPZe values compared to the SSD-Response group, $t(13)$=2.95, p =.011, d = 1.58 (see Table 3). The difference in 4/8VM performance between the SSD-Spatial and SSD-Response groups remained a large effect, but did not reach statistical significance, when covarying for CPZe, $F(1,13)$ = 2.22, p =.160, d = 0.84. This result suggests that correlation with CPZe at least partially reflects the differences between the SSD-Spatial and Response groups. However, inspection of the data also supported a continuous linear relation between antipsychotic dose and performance (i.e., not a basic heterogenous subsampling issue). Moreover, the large negative correlation observed within the SSD-Spatial group alone, r = -.59, suggests increased dosage relates to worse performance on the 4/8VM.

Additional follow-up assessment regarding use of other medications (coding use of antidepressant, anxiolytic, neither or both) and type of antipsychotic (atypical, typical, both, none) did not reveal differential performance. For an Other Medication × Strategy ANOVA there remained a main effect of Strategy, $F(1,9)$=7.91, p = .02, η^2 = .47, but there was neither an effect of

Drugs, $F(3,9) = 1.44$, $p = .295$, $\eta^2 = .32$, nor Drug × Strategy interaction, $F(2,9) = .34$, $p = .723$, $\eta^2 = .07$.

fMRI Results

Hippocampal ROI. At Trials A1 and A3 we found significant clusters of activation bilaterally in the hippocampi during the test phase for the SSD-Spatial hypoactivation contrast, particularly in the right anterior hippocampus at Trial A3 (Table 4). The SSD-Spatial group had less activation in the right anterior hippocampus compared to all other groups (see Figure 4).

Table 4.

Clusters of lower hippocampal activation in the SSD-Spatial group

		MNI Coordinates				
Trial	Left/Right	x	Y	z	*t*	k
A1	R	34	-14	-26	2.61*	85
	R	32	-40	-2	2.43*	11
	L	-22	-16	-22	1.82	7
A3	R	32	-14	-16	3.69**	344
	L	-24	-14	-20	1.83	15
	L	-24	-38	8	1.77	18

$p<.05$, uncorrected. $p<.01$, ** $p<.001$.* k = number of 2-mm^3 voxels in the respective cluster.

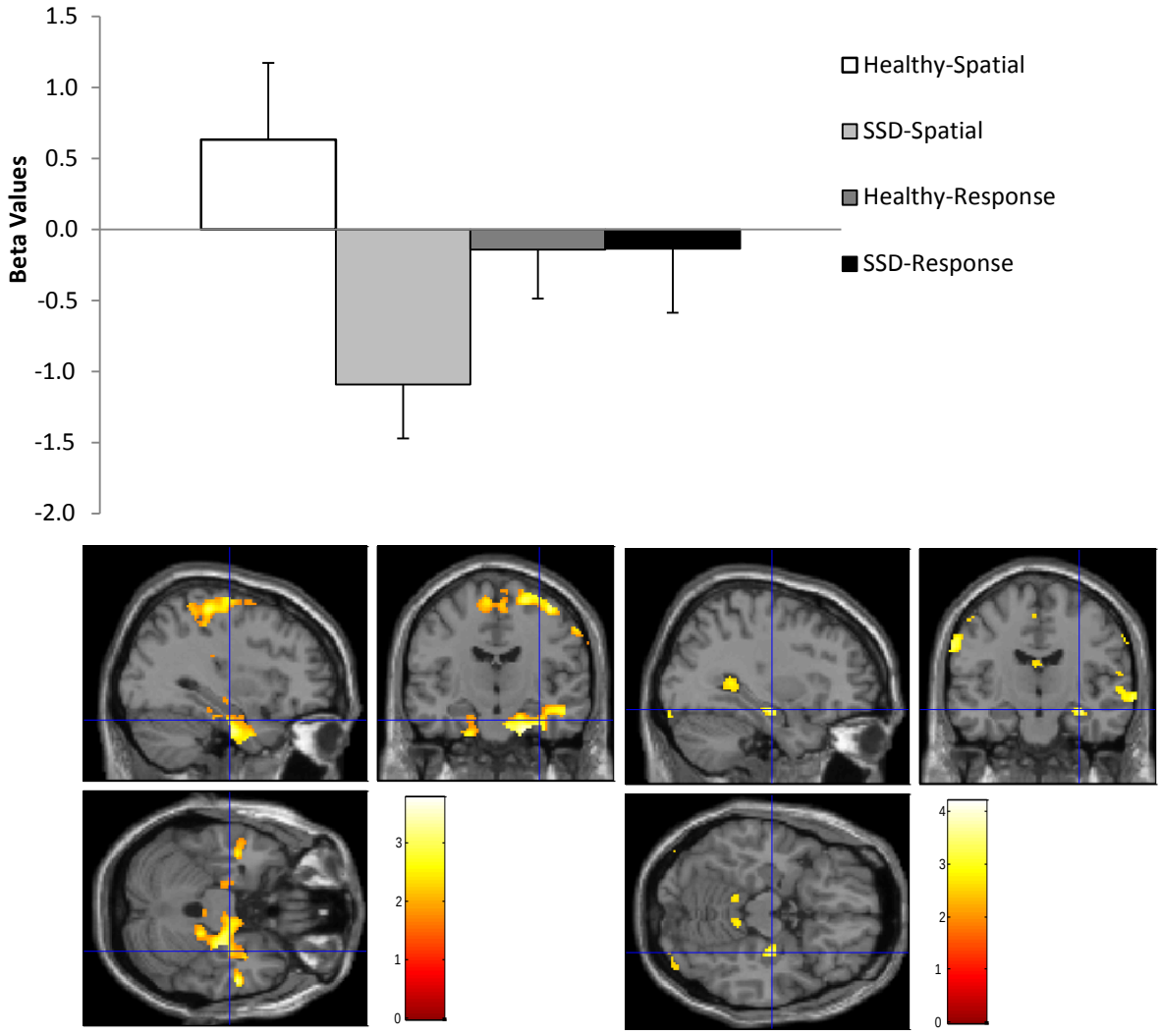

Figure 4. Clusters with lower hippocampal activation in the SSD-Spatial group (hypoactivation contrast). Bar plot at top based on mean beta values extracted from Trial A1 peak hippocampal cluster; error bars reflect 90% confidence intervals. Images below: Left, Trial A1 peak hippocampal activation, t = 2.61, *xyz*: 34, -14, -26, p<.001 uncorrected; right, A3 peak hippocampal activation, t = 3.69, *xyz*: 32, -14, -16, p<.001, uncorrected. The scale bar represents colour-coded t values. The brain images are thresholded at p < .05 (left) and p < .01 (right). As displayed, subsequent whole-brain analyses revealed that the cluster yielding the peak right-hippocampal activation at Trial A1 had its maxima in the neighboring parahippocampal gyrus; the peak hippocampal cluster at Trial A3, however, was well centered in the right hippocampus (see also Tables 7 and 8).

At Trials A1and A3 for the SSD-Spatial hyperactivation contrast we also found bilateral hippocampal clusters, but particularly on the left at Trial A3 (Table 5). The SSD-Spatial group had greater activation in these clusters, whereas the SSD-Response group showed hypoactivation and the two healthy groups were near baseline (see Figure 5).

Table 5.

Clusters of greater hippocampal activation in the SSD-Spatial group

		MNI Coordinates				
Trial	Left/Right	x	y	z	*t*	k
A1	L	-28	-36	-6	1.91	9
A3	L	-34	-18	-12	2.65*	29
	R	36	-12	-26	2.05	21

*p<.05, uncorrected. * p<.01.*

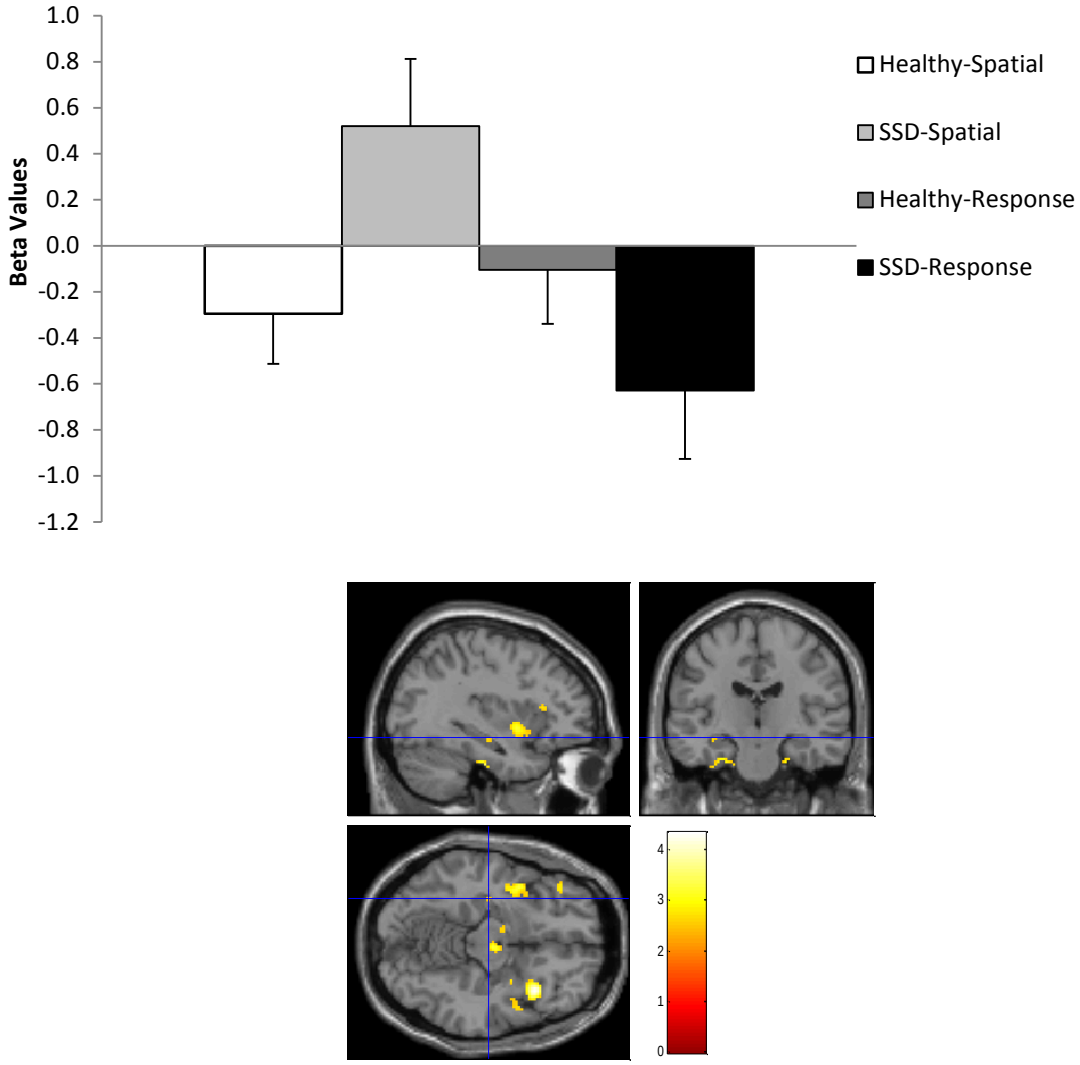

Figure 5. Clusters with greater hippocampal activation in the SSD-Spatial group (hyperactivation contrast). Bar plot at top based on mean beta values extracted from Trial A3 peak hippocampal cluster; error bars reflect 90% confidence intervals. Images at bottom display the Trial A3 peak left-hippocampal activation, t = 2.65, *xyz*: 34, -18, -12, p<.01, uncorrected. The scale bar represents colour-coded t values.

When comparing Healthy-Spatial and SSD-Spatial groups using a hippocampal ROI, we found a significant right anterior hippocampal cluster for the contrast identifying greater activation in the Healthy-Spatial group compared to the SSD-Spatial group at Trials A1 and A3, but not with the reverse (hyperactivation) contrast (See Figure 6).

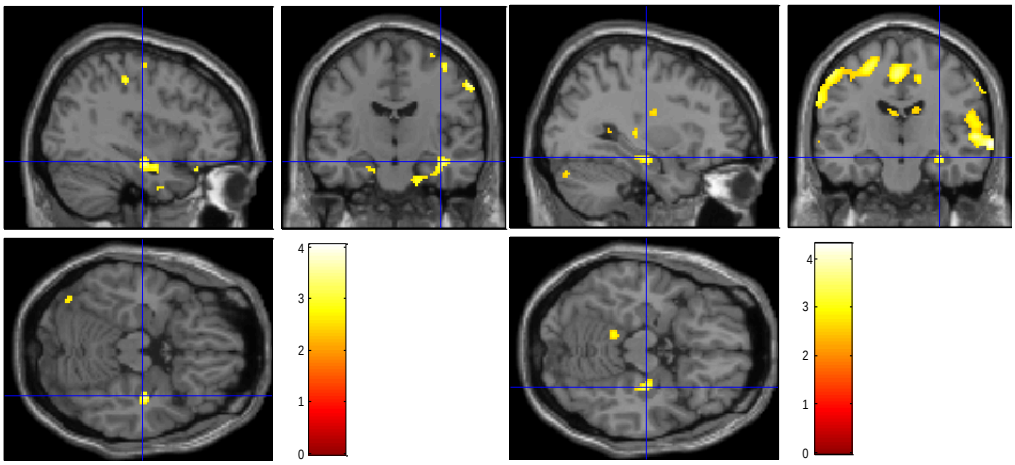

Figure 6. Clusters with greater hippocampal activation in the Healthy-Spatial than SSD-Spatial group. The scale bar represents colour-coded *t* values. Left: Trial A1, xyz: 38, -14, -18, *t* =3.43, *p* <.001, k = 61. Right: Trial A3, xyz: 32, -16, -16, *t* = 3.60, *p* <.001, k = 61.

Caudate ROI. At Trials A1 and A3 for the SSD-Spatial hypoactivation contrast we found right clusters in the caudate, as well as a small left cluster at Trial A3 (see Table 6). For the SSD-Spatial hyperactivation contrast, there was a robust left caudate cluster and small right cluster at Trial A3. Follow-up direct comparisons of the Healthy-Response and SSD-Response groups revealed different clusters of greater activation for each group at Trials A1 and A3, but such that the overall activation in the caudate was similar for both groups (data not shown).

Table 6.

Caudate activation at Trials A1 and A3

		MNI Coordinates				
Contrast / Trial	Left/Right	x	y	z	*t*	k
Hypoactivation						
A1	R	8	22	2	2.08	31
A3	R	16	-14	22	2.36	54
	L	-18	-22	20	1.76	5
Hyperactivation						
A3	L	-16	26	-2	2.97*	235
	R	22	20	8	1.74	6

*p<.05, uncorrected. * p<.01.*

Whole Brain Data. At Trial A1 for the SSD-Spatial hypoactivation contrast there was less whole brain activation relative to the healthy groups and SSD-Response group in the temporal lobe including clusters in the parahippocampus, inferior and middle temporal gyri. Additional clusters were in precentral, paracentral and cerebellar regions. In contrast, at Trial A1 for the SSD-Spatial hyperactivation contrast there was more activation in the frontal inferior orbital regions only (see Table 7).

Table 7.

Whole brain results at Trial A1 for the SSD-Spatial group hypoactivation and hyperactivation contrasts

		MNI Coordinates				
Analyses	Label	x	y	z	*t*	k
Hypoactivation						
Frontal	Precentral	-28	-36	-6	3.76	374
	Precentral	42	-12	62	3.32	50
Parietal	Paracentral	-20	-26	68	3.75	89
Temporal	Parahippocampal*	22	-16	-32	3.68	179
	Middle Temporal Gyrus	56	-8	-24	3.43	28
	Inferior Temporal Gyrus	38	2	-38	3.07	25
Cerebellum	Cerebellum	26	-36	-34	3.48	17
Hyperactivation						
Frontal	Inferior Orbital	-52	32	-10	4.79	406

$p < .005$, k > 15. * Parahippocampal cluster extended into right hippocampus.

At Trial A3, the SSD-Spatial hypoactivation contrast showed reduced activation in temporal regions including the hippocampus, as well as parietal and frontal regions, whereas for the SSD-Spatial hyperactivation contrast there was increased activation in the insula, cingulate, pallidum, temporal lobe and inferior frontal regions (see Table 8).

Table 8. *Whole brain results at Trial A3 for the SSD-Spatial hypoactivation and hyperactivation contrasts*

		MNI Coordinates				
Analyses	Label	X	y	z	*t*	k
Hypoactivation						
Frontal	Precentral	-58	12	38	4.2	104
	Precentral	62	8	34	3.73	85
	Paracentral	-62	-10	38	3.73	130
Parietal	Inferior Parietal	-60	-28	50	3.49	111
Occipital	Inferior Occipital	54	-78	-6	3.46	54
Temporal	Hippocampus	32	-14	-16	3.69	27
	Hippocampus	26	-42	0	2.94	39
	Superior Temporal Gyrus	74	-18	-4	3.56	122
	Superior Temporal Gyrus	48	-34	14	2.99	25
Hyperactivation						
Frontal	Inferior Opercularis	52	18	2	3.37	61
	Inferior Orbitalis	-42	38	-6	3.31	37
	Cingulate	-14	38	-4	3.73	161
	Cingulate	14	46	4	3.27	50
Insula	Insula	38	16	-14	4.43	132
	Insula	-14	8	-8	3.68	190
	Insula	-26	22	-4	3.3	82
Temporal	Fusiform	-26	-12	-32	3.9	81
	Middle Temporal Gyrus	54	-4	-24	3.9	108
	Inferior Temporal Gyrus	-56	-38	-16	3.6	35
Subcortical	Pallidum	-12	-6	-8	3.1	31

$p < .005$, $k > 15$

Discussion

The goal of Experiment 1 was to provide insight into the role of underlying neural regions involved in spontaneous navigation strategies. Our behavioural results replicate our findings from Wilkins et al. (2013), revealing a differential deficit among SSD participants who spontaneously adopted the spatial strategy (SSD-Spatial) compared to all other groups. The SSD-Spatial group performed significantly worse relative to all other groups on the 4/8VM. In contrast, the SSD-Response group was not impaired relative to all other groups. Regardless, the overall performance measures provided further behavioural support for hippocampal-dependent spatial memory dysfunction in SSD. The findings from the current study further corroborate hippocampal dysfunction among those in the SSD-Spatial group with fMRI evidence. The brain-imaging results revealed lower right anterior hippocampal activation in the SSD-Spatial group during test trials compared to the other groups that may account for the selective behavioural impairment found in this group. Most importantly, the SSD-Response and Healthy-Response groups yielded relatively equivalent patterns of activation in both the hippocampi and caudate and performed similarly on the 4/8VM task. These data support the hypothesis that caudate-based functioning in the SSD-Response group is relatively intact.

Whole-brain analyses further confirmed the ROI results that the SSD-Spatial group had less hippocampal activation compared to the Healthy-Spatial group. The SSD-Spatial group had greater activation of the inferior orbital-frontal region during Trial A1 compared to the Healthy and SSD-Response groups, whereas the Healthy and SSD-Response groups activated temporal lobe regions more so than the SSD-Spatial group. These differential patterns of PFC and temporal activation

associated with navigation in the SSD-Spatial group may point to disconnection between PFC and medial-temporal regions (Ledoux et al., 2013, 2014).

During Trial A3, the SSD-Spatial group activated some regions associated with the Default Mode Network (DMN) including the insula and inferior frontal region, more so than the Healthy and SSD-Response groups. These regions are typically more active during passive states (e.g., 'rest' conditions) or conditions involving internal mental processes such as mind wandering and self-projection; these regions are typically deactivated during attention-demanding task performance (Andrews-Hanna, Reidler, Sepulcre, Pulin & Buckner, 2010; Menon, 2011). In contrast, the SSD-Spatial group showed lower activation than the Healthy and SSD-Response groups in locations associated with an MTL subsystem of the DMN. The MTL subsystem that included the hippocampi has been found to be activated when participants were engaged in constructing mental scenes based on memory and during spatial navigation (Andrews-Hanna et al., 2010; Menon, 2011; Spreng et. al, 2008). Based on these findings, there appears to be hyperactivation in frontal regions and hypoactivation in temporal lobe regions, suggesting frontal-temporal disconnectivity.

Functional integrity of the parahippocampus, anterior hippocampus, and precuneus are associated with spatial navigation ability (Ohnishi et al., 2006). In most spatial navigation tasks, frontal, parietal and temporal regions are activated (Hartley, Maguire, Spiers and Burgess, 2003; Spreng et al., 2008; Viard, Doeller, Hartley, Bird & Burgess, 2011). Lower activation in the hippocampus and parahippocampus in the SSD-Spatial group is consistent with the behavioural impairment in using a cognitive map on the 4/8VM. Moreover, it is possible that any spatial

representation is not being adequately transferred to PFC regions to support appropriate adoption and continued use of a successful spatial strategy.

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

In the current study, the lower hippocampal activation in the SSD-Spatial group was particularly robust in the right anterior hippocampus. Previous literature has associated the right and the left hippocampi with different functions during spatial navigation. For instance, the right hippocampus was deemed central for spatial navigation as Spiers, Burgess, Hartley, Vargha-Khadem and O'Keefe (2001) showed that individuals with right temporal lobectomies were impaired on spatial navigation tasks and those with left temporal lobectomies were impaired on episodic memory tasks that were more verbal in nature. The right hippocampus has been more centrally involved in spatial navigation (Bohbot et al., 1998) and decline in function of the right has been associated with poorer navigation abilities (Nedelska et al., 2012). Igloi, Zaoui, Berthoz and Rondi-Reig (2010) showed that the right hippocampus was involved during tasks requiring allocentric spatial representations, whereas the left hippocampus is involved in conditions requiring

sequential egocentric representations such as learning a sequence of turns to find a target location. Therefore, it makes sense that poor navigation performance in the SSD-Spatial compared to the Healthy-Spatial group would be associated with deficient recruitment of the right hippocampus.

In contrast to the lower right-hippocampal activation, it is interesting that the SSD-Spatial group activated a cluster in the left hippocampus more than the SSD-Response group. Atypical lateralization of the hippocampi in SSD has been noted in the literature (Petty, 1999). For example, Hanlon et al. (2011) reported that SSD participants activated the left hippocampus and PFC during a relational mnemonic transverse patterning task, whereas the healthy group activated these structures in the right hemisphere. They interpreted these results as indicating either that the left activation was compensating for deficient right activation or the left was overactive in SSD. In this context, compensation refers to additional recruitment of unique areas activated in the impaired SSD group not found in the Healthy group. In contrast, overactivation reflects that the same region is activated in both groups, but significantly more active in SSD group compared to the Healthy group. Both over recruitment or under recruitment (i.e., a deviation from the Healthy group) could reflect neural inefficiency. Similarly, our data showed lower right hippocampal activation and greater left orbital PFC activation in the SSD-Spatial compared to the Healthy and SSD-Response groups. These results suggest potential compensation in the left orbital PFC in the face of dysfunctional hippocampal involvement in the SSD-Spatial group.

The lower hippocampal activation in the SSD-Spatial group may also reflect delayed formulation of a strategy while solving the 4/8VM. During post-test session interview, reports from four of the nine SSD-Spatial participants support a delay in formulating a strategy (See Appendix D). A late onset in the formulation of a spatial strategy in the SSD-Spatial group is consistent with

literature suggesting that individuals living with SSD struggle with selection, generation and use of strategies necessary to solve cognitive tasks (Iddon, McKenna, Sahakian & Robbins, 1998). For example, Bonner-Jackson, Yodkovik, Csernansky & Barch (2008) found that SSD participants had better episodic memory performance in an incidental compared to intentional encoding condition and concluded that the general episodic memory impairment in SSD is primarily due to a failure to select an optimal processing strategy (deep versus shallow levels of processing). Poor strategy selection was also identified by Iddon et al. (1998) where it was hypothesized that if SCZ participants were left to self-generate a strategy they would not have generated an effective strategy. Iddon et al. (1998) concluded that their pattern of memory performance in SCZ was similar to that seen in frontal lobe excision patients and Parkinson's Disease. Many researchers propose that PFC dysfunction contributes to impaired performance on episodic memory tasks (Ragland et al., 2009), and improvement in PFC function should lead to improvements in episodic memory. It is clear from the literature that there is indeed a PFC-related deficit in SSD that stems from impaired generation of an appropriate strategy (Iddon et al., 1998; Ragland et al., 2009). In the current study there is only anecdotal evidence of a problem with delayed development and generation of the spatial strategy. Therefore, we are left with the prospect that the impairment in the SSD-Spatial group is primarily associated with under-recruitment of the hippocampi and potentially also the PFC. Regardless of its potentially delayed onset, this group does not appear to select the optimal strategy, which goes against our expectations that individuals harness their optimal system. Those reporting the Response approach were not initially impaired in their selection and use of a strategy. The differential performance and imaging findings from Trial A1 are meaningful as the deficit in the

SSD-Spatial group seems to be more immediately related to decreased recruitment of brain regions involved in navigation and memory.

During Trial A3, the Healthy and SSD-Response groups activated the right hippocampus, DLPFC, motor, temporal and parietal cortices more than the SSD-Spatial group. The difference in DLPFC activation is notable in that it has been associated with the formation of a response landmark approach that is acquired over time (Dahmani & Bohbot, 2015). My similar findings provide cross-task convergence. Previously researchers found decreased DLPFC activation associated with poor executive function in SSD (Kim et al. 2010). In this thesis, the DLPFC activation suggests intact formulation and application of a response strategy in the SSD-Response group.

Limitations/Future Directions

In Experiment 1 there are multiple potential limitations. First, strategies were assessed via interview outside of the scanner after participants met the criterion of two perfect A trials without error and the probe trial. The strategy assessment required participants to remember if there were any changes in their adopted strategy across the trials, and if so, what the changes were and when they occurred. This was a very straightforward assessment with the healthy participants because they required very few trials to meet criterion. However, the SSD participants appeared to have more difficulty explaining the strategy they adopted and recalling when and what changes occurred across the trials. Therefore, I cannot be certain as to trial-by-trial changes that may have taken place in this group. In the future when working with individuals living with SSD, it might be advantageous to develop a modification of the current paradigm to concurrently assess strategy after every trial. However, one would also have to be cautious because questioning during the course of

the task could influence a change in strategy that is not natural or spontaneous. Currently I only have anecdotal evidence that the SSD-Spatial group took longer to formulate a spatial strategy. Having a report of strategy across trials would allow better quantification of these observations. This is critical to provide evidence that deficits in self-generation and cognitive control of strategy may also play a role in the selective SSD-Spatial navigation impairment.

Another limitation relates to the Probe Test, which has previously distinguished between Healthy Spatial and Response groups and been used to validate subjective measures of strategy (Bohbot et al., 2004). However, as in my previous work (Wilkins et al., 2013), the current experiment yielded null results when comparing group differences in error rates during the Probe Test. This may have been due to the fact participants did not complete the Probe until they met criterion on two successive trials. Therefore, participants completed different numbers of trials prior to the Probe. Those with more trials prior to the Probe may have switched to the response based habit system. Therefore, with this protocol, the probe may not be an effective measure to distinguish strategy. Regardless, if it is the case that individuals living with SSD are not able to choose the optimal approach to navigate, this would be a means for intervention. Cognitive rehabilitation practitioners could focus on training the hippocampal-dependent function or harness the intact response function. A third approach would be to train participants to select different strategies and learn to be aware that the spatial approach of relying on landmarks is more deficient and learn to self-monitor and switch to a body-based response landmark approach.

Information about deficits associated with strategy warrant more direct exploration of the role of both the PFC and the hippocampi in SSD-Spatial memory impairments on the 4/8VM. The disconnection between these regions could be tested functionally and anatomically. One way to

explore the role of anatomical disconnection or disruption between brain regions would be to follow the procedure by Hanlon et al. (2012). In their investigation they used fractional anisotropy (FA) to measure the uncinate fasciculus to assess whether relational-working memory impairment in SSD was related to disconnection between the PFC and the hippocampi.

I have also reported results of the whole-brain analysis. The whole brain contrasts assess voxel-wise activation averaged across the Test Phase. This analysis allows us to look at group and condition differences in magnitude of voxel activation across the entire brain. The SSD-Spatial impairment may not simply be due to deficient recruitment and formation of a spatial map, but rather due to improper generation and control of a mnemonic navigation strategy. As in Chapter 4 (below), studies should utilize techniques such as the spatiotemporal PLS multivariate technique (McIntosh, Bookstein, Haxby & Grady, 1996) to investigate activation among brain regions during navigational memory in SSD. This would promote understanding of the patterns of association between hippocampi and caudate nuclei with each other and with brain regions such as the PFC. Complementing the current GLM approach, PLS analysis would allow insight, for example, regarding whether the SSD-Spatial group has a pattern of activation similar to the Healthy-Spatial group. This would inform about neural correlates associated with each strategy approach that may be targeted for the development of remediation/intervention. Therefore, in Experiment 2 I investigate patterns of activation across the whole brain.

The current and previous studies have not directly assessed temporal dynamics across brain regions involved in spatial navigation. Very little is known about the temporal sequence of activation among these regions on the 4/8VM. Literature has yet to identify whether the PFC precedes hippocampal activation to initiate a strategy, or whether the hippocampus incidentally

encodes spatial relations prior to activation of PFC regions. Additionally, researchers have suggested that the PFC suppresses striatal activation during early stages of navigation-based learning, while PFC activation decreases and striatal activation increases as habitual (response-based) learning increases (Alobouy, King, Maquet & Doyon, 2013). There also might be times when both the caudate and hippocampi work together in a complementary fashion to aid navigation (Brown, Ross, Tobyne & Stern, 2012; Brown & Stern, 2014).

The groups were matched relatively well on demographic, cognitive and clinical variables. Nevertheless, I included WRAT and FSIQe as covariates in analysis of behavioural data and the Group × Strategy interaction remained robust. There was a difference in dosage of antipsychotic drugs (CPZe) with SSD-Spatial participants taking significantly higher dosages of medication compared to the SSD-Response group. Including CPZe as a covariate substantially decreased the effective difference in performance between the SSD-Spatial and SSD-Response groups. Therefore, spatial strategy use in SSD and medication dose are confounded. One possibility is that those who take higher doses of antipsychotics might preferentially select the deficient hippocampal-dependent strategy and those who take lower doses of antipsychotics select the intact caudate-dependent strategy. Although it is unclear why such a relation might exist, there is evidence that second generation atypical antipsychotics including ziprasidone, risperidone and olanazapine, and the first generation typical antipsychotic haloperidol, impair spatial navigation on the Morris water maze in rodents with degree of impairment associated with dose (Skarsfeldt, 1995). Nonetheless, it is unclear whether higher dosages of antipsychotics are the reason for poorer performance. SSD participants have similar stable levels of symptoms as measured by the PANSS. However, higher CPZe values may potentially be a proxy for greater illness severity. A future study with a larger

sample of participants taking a wide range of typical and atypical antipsychotics alongside a drug-naïve control group would be needed to parse apart these relations.

Conclusion

In Experiment 1, I provide direct behavioural and fMRI evidence of hippocampal under-activation in those SSD participants who spontaneously adopt the spatial strategy. I replicated our previous findings of a selective hippocampal-dependent spatial navigation deficit in SSD on the 4/8VM (Wilkins et al., 2013). The SSD-Spatial group that reported relying on the allocentric relations among landmarks in the environment to solve the 4/8VM performed worse relative to all other groups. Moreover, fMRI data revealed deficient recruitment of the right anterior hippocampus in the SSD-Spatial group relative to all other groups during both the early and later trials. In contrast, the SSD-Response group performed in an equivalent fashion to its healthy counterpart and they did not differ in terms of hippocampal or overall caudate activation. These findings provide direct evidence of a hippocampal-dependent dissociation in the SSD group. Additionally, at the whole brain level the SSD-Spatial group recruited more PFC regions and fewer temporal lobe regions than the other groups while navigating the 4/8VM. Further investigation of the relations among these regions and the hippocampi (e.g., Chapter 4) are important for understanding the strategy-related deficits observed in the SSD group. It is imperative to answer these questions as they will inform the development of cognitive rehabilitation paradigms.

Chapter 4: Spontaneous Spatial Navigation Circuitry in Schizophrenia Spectrum Disorders

Abnormal hippocampal structure and function are reliable findings among individuals living with SSD (Weiss, DeWitt, Ditman & Heckers, 2005) and that are associated with severe episodic memory impairments in this population (Achim & Lepage, 2005; Bonner-Jackson et al., 2008). However, evidence of generalized cognitive and neural impairments in this population means that characterizing specificity of memory deficits is essential for advancing our understanding of the neuropsychology of SSD. For instance, SSD are associated with deficiencies in large-scale brain networks (Menon, 2011). Therefore, it is essential to identify not only selective hippocampal-dependent memory deficits in this population, but to explore more extended neural regions that may play a role in these episodic memory deficits.

Consistent with evidence that individuals with SSD have both structural and functional abnormalities in the hippocampi, the SSD-Spatial group performed poorly relative to all other groups in Experiment 1 (Chapter 3). Additionally, in Experiment 1, I observed deficient recruitment of the right hippocampus in the SSD-Spatial group during navigation at test compared to the Healthy-Spatial group. Interestingly, the SSD-Spatial group recruited the left hippocampus more while performing the 4/8VM. In previous studies, the left hippocampus has been associated with sequence learning, whereas the right was associated with the formation of a cognitive map (Igoli et al., 2009). These findings are consistent with evidence of altered lateralization of hippocampal function in SSD (Hanlon et al., 2011). On the other hand, both the Healthy-Response and SSD-Response groups performed equivalently on the 4/8VM and had comparable levels of hippocampal and overall caudate activation. These findings provide evidence of a selective hippocampal-dependent deficit in SSD. Better understanding of the mechanisms underlying these individual differences associated with spontaneous strategy use will set the stage for developing interventions

that target strengthening the hippocampal system to directly improve real-world navigation and spatial memory abilities.

Beyond the hippocampi and caudate nuclei, however, there are other regions involved in spatial navigation (Bohbot et al., 2007; Spreng et al., 2008). Both the PFC and parietal cortex were activated in both spatial and response learners on the 4/8VM (Bohbot et al., 2004), indicating these regions are core to what might be considered a spatial navigation neural network. Both the hippocampi and caudate have connections to each other via the PFC (Burianova, McIntosh & Grady, 2009; Cavada, Company, Tejedor, Cruz-Rissolo & Reinoso-Suarez, 2000; Haber, Kim, Mally & Calzavra, 2006) and all three of these brain regions are activated when having to disambiguate between highly similar environments to reach a target (Brown & Stern, 2012). In this regard, evidence points to functional cooperation between medial-temporal and caudate regions on tasks thought to tap into either of these regions (Moses, Brown, & Ryan, 2010; Voermans et al., 2004). Allocentric and egocentric memory can combine to support navigation abilities and may be coordinated via mediation by the PFC (Brown & Stern, 2012; Burgess, 2006). A meta-analysis of fMRI studies that tested healthy participants on spatial navigation tasks identified a more extensive pattern of regions in the brain activated during tasks that required the formation of a cognitive map (Spreng et al., 2008). Spatial navigation consistently activated regions that include the MPFC, precuneus, cingulate, retrosplenial cortex, temporoparietal junction, VLPFC, hippocampi and parahippocampi (Spreng et al., 2008). However, these studies did not investigate spontaneous navigation strategies on a task that allowed adoption of either a spatial or response approach, or assess functional differentiation between the regions supporting these strategies.

Dahmani and Bohbot (2015) were the first to report on a pattern of correlated brain regions associated with spontaneous navigation strategies based on regression analyses with grey matter and probe-trial scores. These researchers investigated BOLD signal and grey-matter density in ROIs that consisted of the hippocampi, caudate, VMPFC and DMPFC, ventral and dorsal anterior cingulate. As in prior work, healthy individuals who spontaneously adopted the spatial approach had greater BOLD activation in the VMPFC, orbitofrontal cortex and right hippocampus during initial trials, whereas their Response group revealed greater activation in the caudate and DMPFC after the first three trials. Moreover, grey matter in the former regions correlated with worse performance on a probe test (reflecting reliance on allocentric cues), whereas grey matter in the latter regions correlated with better probe-test performance (consistent with a response strategy). These findings suggest distinct brain regions associated with the spatial and response approach. Given involvement of other regions in successful spatial navigation, it is essential to explore the extent to which SSD-Spatial deficits reflect impairment beyond the hippocampi that may involve disconnections or dysfunction across larger neural networks.

There is evidence of disconnections in SSD between the PFC and the temporal lobe and between the PFC and the parietal lobes (Fletcher, McKenna, Friston, & Frith, 1999; Friston & Frith, 1995; Magnotta et al., 2008; Menon, 2011). Therefore, the purpose of the current analyses is to explore relations between the SSD-Spatial group performance deficit found in previous work (Wilkins et al., 2013a) and this dissertation (Chapter 3) and regions activated during spatial navigation. Beyond the voxel-wise comparisons presented in Chapter 3, here I use PLS analyses (McIntosh et al., 1996) to explore the relations between 4/8VM strategy use, performance and brain activation at a multivariate level. I focus on the initial (A1) and last (A3) scan trials because these

were the trials in previous studies for which groups were distinguished by maximal hippocampal activation in Trial 1 (A1) for the Healthy-Spatial group and caudate activation in Trial 4 (A3) for the Healthy- Response group (Bohbot et al., 2004, 2007; Iaria et al., 2003).

PLS Analyses

The current study involves further analysis of data from Experiment 1 using PLS (Please see Chapter 3 for other methodological details). PLS is a multivariate analytic technique that involves identifying maximal covariances and minimization of residuals between sets of dependent measures (McIntosh & Lobaugh, 2004). This multivariate technique was adapted for brain-imaging analyses by McIntosh and colleagues (McIntosh et al., 1996) to identify patterns of activation that differ across space (brain voxels) and time. In the current study I employed both a mean-centered and behavioural PLS analysis. The mean-centered PLS analysis provides information about how brain activity and conditions (Test Phase, Visuomotor Control) covary within the 4/8VM task. In these analyses, a cross-covariance matrix is computed based on the design and data matrix. The data matrix consists of a single row for each participant that consists of voxel activation information nested within each condition block. There is a signal extracted for each voxel at each time point for the selected conditions, which is used to create column averages. The mean-centered PLS identifies patterns of correlations among voxels across the brain and task conditions (brain and task condition correlation). This pattern provides information about patterns of activation that are differentially correlated with the Visuo-Motor Control and Test Phase conditions across groups. In addition, behaviour PLS was used to assess correlations across voxels associated with 4/8VM performance (brain and behaviour correlation). For this behaviour PLS analysis I examined the relations among

fMRI data from the Test Phase with composite performance scores from Trial 1 and 4 as described below.

Mean-centered PLS. Singular value decomposition (SVD) provides a matrix produced from the cross-covariance computation. The mean-centered PLS solution yields three latent variable (LV) components: design LV (how well the task relates to each LV), singular LV (how SV corresponds to each LV) and brain LV (how well each voxel relates to the LV). The SVD extracts rank LVs from the covariance matrix based on brain activity and conditions. The LV provides information about the optimal relation between design and brain activity (McIntosh et al., 2004). For each LV, a brain image is produced showing how voxels in the brain covary uniquely with each task condition (Test Phase, Visuo-Motor Control). These unique patterns of correlations across task conditions are ranked for significance. The SV indicates the amount of covariance accounted for by each LV. The brain score is based on the product of the raw images and singular images on a specific LV for each participant. This cross-product via matrix multiplication indicates the degree to which each participant has a similar pattern for each LV (McIntosh, 1999; McIntosh et al., 1996, 2004).

The significance of the SV for each LV is tested with permutation sampling comparing each SV to a noise distribution (McIntosh & Lobaugh, 2004). New LVs are generated by random re-ordering of information in the data matrix. The participants are randomly reassigned to the imaging dataset and the LV is recalculated. The purpose of the comparison is to calculate a probability value based on the number of times the experimental LV is greater than the statistic from the permutation

(McIntosh & Lobaugh, 2004; McIntosh et al., 1996). For the mean centered analyses 500 permutations were calculated (DeBrigard, Addis, Ford, Schacter & Giovanello, 2013).

Bootstrapping is also applied to resample the data set with replacements to derive an estimated standard error of the LV saliences for each voxel. The purpose of this bootstrapping method is to identify areas that reliably relate to the LV correlation pattern. The bootstrapping method also reduces the influence of outliers on the data (McIntosh et al., 2004). For the mean centered analyses, bootstrap estimations were conducted 300 times (Addis et al., 2009).Using the ratio of each voxel's salience to its standard error yields a critical ratio termed the bootstrap ratio (BSR). We applied a common threshold of BSR = ±3.3 (corresponding to $p < .001$) to extract clusters of significantly correlated activation (Addis et al., 2009; DeBrigard et al., 2013).

Behaviour PLS. I also conducted a behaviour PLS analysis to provide complementary examination of brain-behaviour relations by correlating patterns of brain activation with 4/8VM task performance. More specifically, I analyzed the pattern of correlated brain activation during the Test phase with the corresponding composite performance measure for Trials 1 and 4. As in Experiment 1, a multivariate composite measure of performance was derived using the MANOVA approach outlined by Grice and Iwasaki (2007). To assess the brain-behaviour relations during initial and later trials, I created separate composites for the Group × Strategy interaction term at Trials 1 and 4 based on a combination of Latency (minutes) and Errors of commission during the Test Phase for the respective trial. In this case the LV represents brain activity that covaries with task performance across Group and Strategy. For the behaviour PLS I also used 500 permutations and used 300 bootstrapping estimates.

The MNI coordinates for maximum clusters were imported to SPM8 and anatomical labels were determined via the WFU_ PickAtlas (Department of Radiological Sciences, Wake Forest University, Winston-Salem, USA) databases and corroborated by visual inspection.

Behavioural Results

Consistent with overall performance measure in Experiment 1, the results of the multivariate composite measures of performance based on Trial 1 and Trial 4 test latency and errors yielded significant Group x Strategy interactions, $F_{Trial1}(1,28) = 5.96$, $p = .021$, $\eta^2 = .18$, and $F_{Trial4}(1,28) = 7.79$, $p = .009$, $\eta^2 = .22$, with a main effect of Group for Trial 4, $F(1,28) = 17.13$, $p < .001$, $\eta^2 = .38$. As shown in Figure 1, the interaction indicates that the SSD-Spatial group is impaired relative to the other three groups.

PLS Results

fMRI Mean-Centered PLS at Trial 1. The mean-centered analysis at Trial 1 yielded one significant LV that accounted for 63.38% of the covariance between brain activation and the Group × Strategy × Condition design, $p < .005$, SV = 194.50. As shown in Figure 2, the pattern of brain scores defined by this LV distinguished between the Spatial and Response strategies in terms of the relative activation during the Test Phase versus Visuo-Motor Control condition, particularly within the SSD group. That is, brain regions (see Figure 2 and Table 1) that were more active during the Test Phase than Visuo-Motor Control for SSD-Spatial subgroup were less active during the Test Phase among the SSD-Response participants (although to a lesser extent). The general pattern was

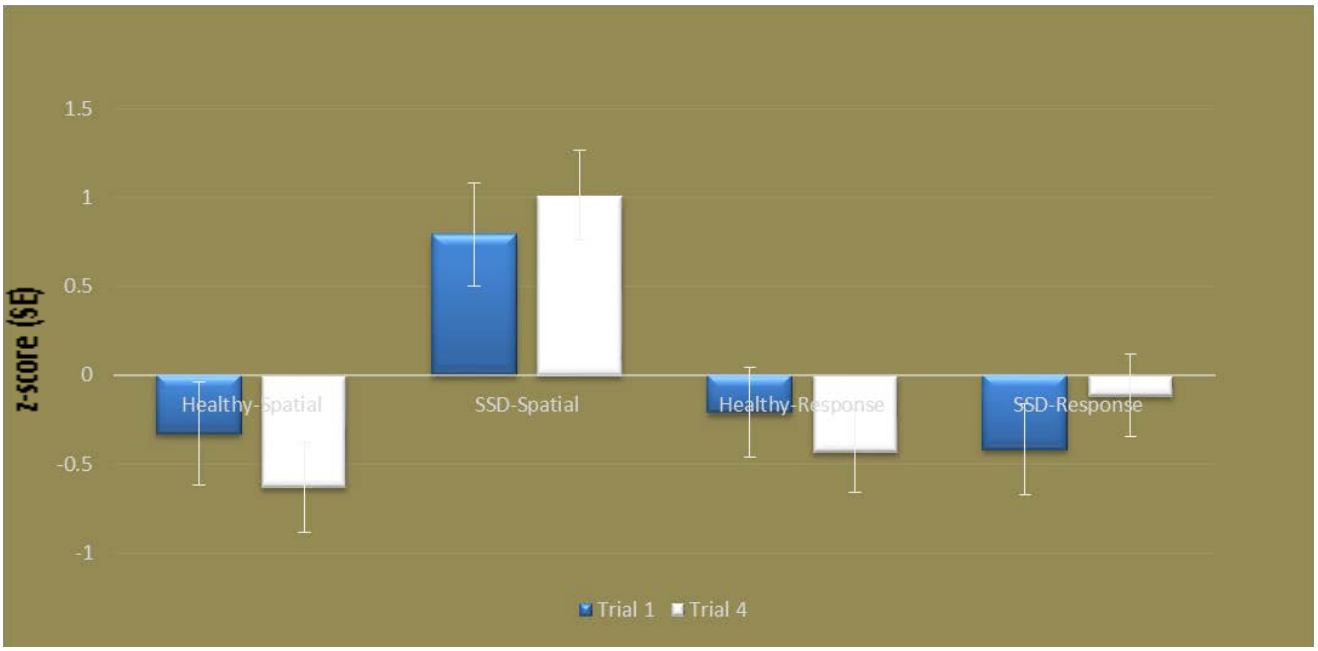

Figure 1. Differential deficit among SSD participants reporting spontaneous use of a Spatial strategy for Trial 1 and Trial 4, respectively. The multivariate composite of 4/8VM performance is based on a linear combination of Test Latency and Errors for each of Trial 1 and Trial 4 as they maximally relate to a Group x Strategy interaction. Data represent standardized means and standard errors. The z-scores with a positive value indicate poor performance.

for the respective Healthy groups, but much less prominent; for example, the deflections for the Healthy-Spatial group were not significant (95% CI overlapping zero; see Brain Score Plot, Figure 2). The CIs also indicated that there was no significant difference between the Healthy-Response and SDD-Response groups; whereas there was a more robust difference in magnitude of brain scores for this LV between the SSD-Spatial and Healthy-Spatial groups. The regions shown in cool (blue) colours in Figure 2 and listed with negative BSR values in Table 1 reflect the pattern of correlated activation corresponding to greater involvement during the Test Phase in the SSD-Spatial group. This pattern was largely characterized by medial-temporal, thalamic, and cerebellar clusters.

fMRI Mean-Centered PLS at Trial 4. The mean-centered analysis at Trial 4 yielded one significant LV that accounted for 61.34% of the variance. The LV ($p < .001$; SV = 195.40) reflects brain regions (see Figure 3 and Table 2) that were more active during the Test Phase than Visuo-

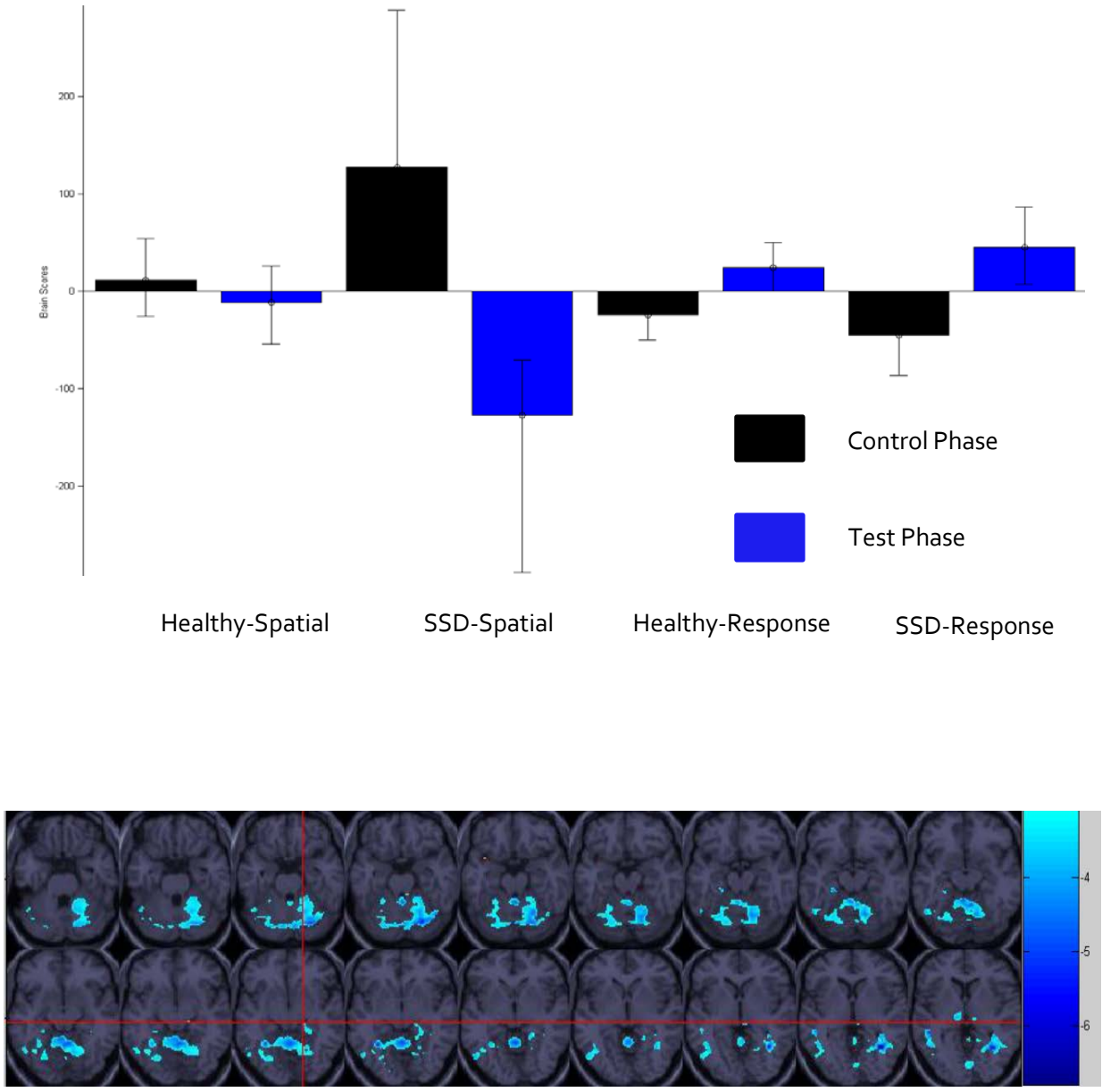

Figure 2. Pattern of activation corresponding to greater involvement during the Test Phase than Visuo-Motor Control condition in the SSD-Spatial group at Trial 1. The graph at top highlights the specificity of the LV from the mean-centered PLS distinguishing the SSD-Spatial from Response groups. Brain regions where activation was positively associated with Test Phase in SSD-Spatial are shown in cool colours ($p < .001$; at bottom). The colour-coded scale reflects BSR values for the LV.

Table 1.

Mean-centered PLS results differentiated regions showing greater activation during the Trial 1 Test Phase particularly in the SSD-Spatial group

		MNI Coordinates				
	Brain Region	x(mm)	y(mm)	z(mm)	BSR	k
Frontal						
	Rolandic Operculus	-50	-8	8	-4.22	29
Temporal						
	Fusiform Gyrus	-32	-52	-10	-5.54	3679
	Middle Temporal Gyrus	-50	-36	2	-4.99	363
	Parahippocampus	-26	-32	-18	-4.64	29
	Hippocampus	20	-24	-10	-4.08	76
	Middle Temporal Gyrus	-54	-48	20	-3.53	32
Occipital	Calcarine	8	-82	6	-4.26	293
Cerebellum						
	Cerebellum_8	-10	-62	-50	-3.96	31
	Cerebellum_Crus1	-48	-56	-30	-3.96	25
	Cerebellum_Crus2	46	-68	-40	-3.51	17

Note. Only clusters with a BSR greater than -3.3, ($p < .001$) and cluster size of at least 15 voxels are reported. All peak coordinates were significant at $p < .0001$. MNI =Montreal Neurological Institute.

Motor Control for the SSD-Response group. The brain scores for both Healthy groups and the SSD-Spatial group were not significant (95% CI overlapping zero; see Brain Score Plot Figure 3). The regions shown in hot (yellow) colours in Figure 3 and listed with positive BSR values in Table 2

reflect the pattern of activation corresponding to greater involvement during the Test Phase in the SSD-Response group. The regions positively correlated with the greater activation in the Test Phase in the SSD-Response group consisted of regions distributed primarily across the left side of the brain. The regions included the motor (A2), cingulate (medial frontal), precuneus, insula, frontal, and temporal regions; of note this pattern of activation also included the right hippocampus.

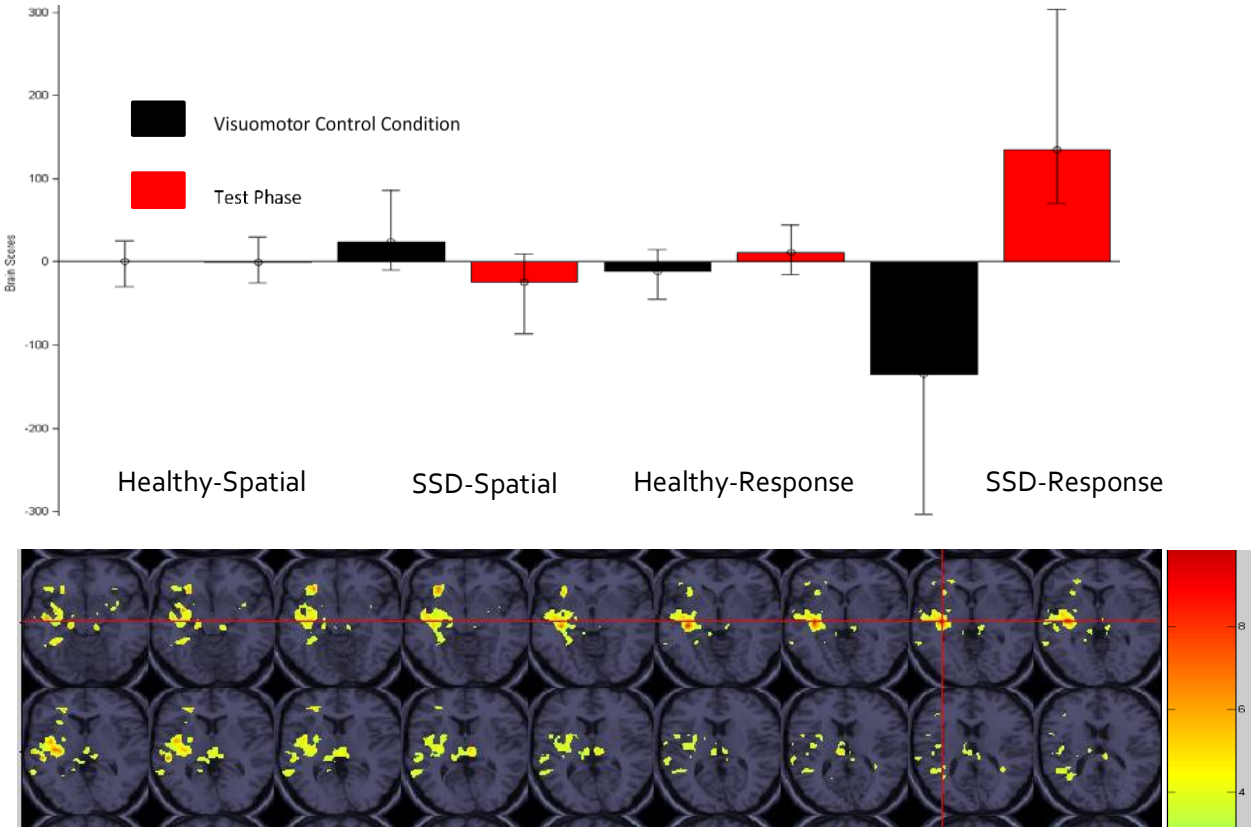

Figure 3. Pattern of activation corresponding to greater involvement during the Test Phase in the SSD-Response group at Trial 4. The graph at top highlights the specificity of the LV from the mean-centered PLS distinguishing the SSD-Response group. Brain regions where activation was positively associated with Test Phase in SSD-Response group are shown in hot colours ($p < .001$; at bottom). The colour-coded scale reflects BSR values for the LV.

Table 2. *Mean-centered PLS results differentiated regions showing greater activation during the Trial 4 Test Phase in the SSD-Response group*

		MNI Coordinates				
	Brain Region	x(mm)	y(mm)	z(mm)	BSR	k
Insula	Insula	-36	-16	0	9.88	4335
Frontal						
	Inferior	-30	32	-10	6.68	391
	Inferior	28	10	-16	6.32	152
	Middle	-24	22	44	5.55	35
	Inferior Triangularis	-46	40	-2	4.59	17
	Middle	-44	20	38	4.01	27
	Cingulate	0	6	32	3.95	69
	Middle	-40	38	20	3.61	13
	Inferior Orbitalis	38	32	-16	3.53	18
Temporal						
	Superior Temporal Gyrus	-62	0	0	3.65	15
	Superior Temporal Gyrus	-14	-44	4	3.63	21
	Hippocampus	16	-4	-14	3.55	15
Parietal						
	BA 2	-24	-52	58	7.35	2526
	Supramarginal	-66	-26	34	5.93	479
	Precuneus	18	-58	32	4.72	57
	Inferior Parietal	42	-50	48	3.53	45

Note. Only clusters with a BSR of greater than +3.3 ($p < .001$) and cluster size of at least 15 voxels reported. BSR = boostrap ratio; MNI =Montreal Neurological Institute. BA = Brodmann's Area.

fMRI Behaviour PLS. The behaviour PLS analysis yielded one significant LV that accounted for 50.38% of the cross-block covariance between brain activation during the Test Phase and 4/8VM performance. The LV ($p < .002$; SV = 241.81) distinguished between the SSD-Spatial and all other groups such that only the former failed to yield a significant brain-behaviour correlation, although it was of medium effect size, $r = .45$, $p > .05$. There were significant brain-behaviour correlations within each of the other three groups, but no significant difference among them (see Figure 4): Healthy-Spatial ($r = .87$), Healthy-Response ($r = .76$) and SSD-Response ($r = .72$). For these groups, better performance (lower composite scores) on the 4/8VM composite was related to higher brain scores in the distributed pattern of activation across the neocortex, left hippocampus, right dorsal striatum, thalamus, and cerebellum. There were no significant LVs at Trial 4.

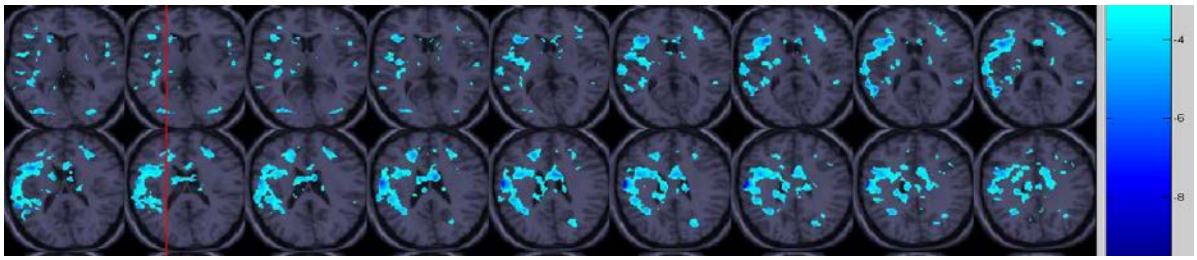

Figure 4. Pattern of activation identified from the behaviour PLS analysis reflects greater involvement during the Trial 1 Test Phase in the Healthy and SSD-Response groups. Brain regions where activation was positively associated with performance are shown in cool colours ($p < .001$). The colour-coded scale reflects BSR values for the LV.

Table 3.

Behaviour PLS identified negative relations between regional brain activation and performance on the Trial 1 Test Phase in the Healthy and SSD-Response groups

		MNI Coordinates				
	Brain Region	x(mm)	y(mm)	z(mm)	BSR	k
Frontal						
	Middle	-24	16	60	-9.52	12761
	Inferior Orbital	-32	34	-8	-5.58	303
	Middle	36	44	16	-4.77	325
	Superior Medial	8	40	52	-4.23	71
	Middle	-34	46	4	-3.79	21
	Inferior Triangularis	58	20	4	-3.63	27
Temporal						
	Superior Temporal Gyrus	-56	-4	-12	-6.94	107
	Superior Pole	-30	4	-22	-6.59	84
	Superior Temporal Gyrus	-52	-24	2	-5.85	258
	Middle Temporal Gyrus	-52	-62	0	-4.66	91
	Superior Temporal Gyrus	64	-12	10	-4.51	32
	Superior Temporal Gyrus	62	-38	18	-4.04	44
	Hippocampus	-32	-34	-10	-4.00	23
Insula						
	Insula	50	10	-8	-4.39	243
Subcortical						
	Caudate	20	-14	24	-3.79	74

	Putamen	32	-6	0	-3.75	39
	Thalamus	-18	-24	8	-3.66	15
Parietal						
	Postcentral	56	-22	44	-4.77	53
	Superior	38	-44	56	-4.09	79
	Angular	42	-56	36	-3.62	32
Occipital						
	Middle	32	-70	34	-4.31	92
	Middle	36	-86	8	-4.20	139
Cerebellum						
	Cerebellum_Crus2	-38	-76	-36	-6.51	1437
	Cerebellum_Crus1	38	-78	-20	-5.81	70

Note. Only clusters with a BSR of greater than -3.3, ($p < .001$) and cluster size of at least 15 voxels reported. BSR = boostrap ratio; MNI =Montreal Neurological Institute.

Discussion

The goal of the current study was to explore whether the SSD-Spatial group performance deficit found in previous studies (Wilkins et al., 2013) and this dissertation (Chapter 3) reflected atypical recruitment of a hippocampal-dependent spatial navigation network compared to the Healthy-Spatial group. Beyond the voxel-wise comparisons presented in Chapter 3, here I used multivariate analyses (PLS; McIntosh et al., 1996) to explore the relations between 4/8VM strategy use, performance and brain activation. I observed that the SSD-Spatial group consistently performed significantly worse on both Trial 1 and Trial 4 relative to all other groups on the 4/8VM. The PLS results for the mean-centered analyses of Trial 1 and Trial 4 provide evidence of a

distinction between the SSD-Spatial and SSD-Response groups. During Trial 1, the correlated pattern of brain activation revealed a pattern of regions that were more active in the Test Phase than the Visuo-Motor Control condition in the SSD-Spatial group. The pattern of greater recruitment during the Test Phase included the MTL (hippocampus and parahippocampus). PFC regions were associated with spatial navigation in healthy individuals (Bohbot et al., 2004; Dahmani & Bohbot 2015), but were notably absent from the neural pattern associated with the Test Phase in the SSD-Spatial group. Findings of greater involvement in MTL regions and lesser activation in PFC across these distributed regions suggests inefficient use of MTL regions and potential disconnection between MTL and PFC regions.

The behaviour PLS, as predicted, also distinguished the SSD-Spatial from the Healthy and SSD-Response groups at Trial 1. Only the former yielded a non-significant brain-behaviour correlation. The Healthy and SSD-Response groups displayed a similar relation to a similar group of brain regions. The SSD-Spatial group performance was less tied to the pattern of activation. The brain regions activated in the Healthy and SSD-Response groups reflected that higher overall levels of activation were associated with better 4/8VM performance (lower latency and fewer errors of commission on Test Phase). This neural pattern consisted of both hippocampal and dorsal striatal clusters (caudate and putamen), along with frontal, temporal, insula, parietal, and occipital cortices, and cerebellar clusters. This suggests that successful performance on the 4/8VM involves coordinated activation of hippocampal, caudate and PFC regions, among others.

Healthy adults typically activate a temporal-parietal-frontal network of brain regions during spatial navigation (Hassabis & Maguire, 2007). This network reliably activates MPFC, DLPFC, VLPFC, parahippocampal, hippocampal, insula, cingulate, retrosplenial, precuneus, and other parietal regions (Burgess, Maguire & O'Keefe, 2002; Hassabis & Maguire, 2007; Spreng et al., 2008). The pattern of activation in the SSD-Spatial group did not extend to key regions beyond the temporal lobe and cerebellum. This limited pattern of activation in the SSD-Spatial group compared to the Healthy and SSD-Response group suggests potential disconnection between regions involved in spatial navigation. This interpretation is consistent with proposals of a disconnection in SSD between PFC and temporal regions, which may stem from dysfunction in the hippocampi or PFC (Friston, 1998; Pettersson-Yeo et al., 2011; Zhou et al., 2007). Other researchers have found abnormalities with functional integration that may explain the manifestation of cognitive symptoms in SCZ (Dolan, 1999).

The result from the behaviour PLS also provides evidence of a potential disconnection between critical regions involved in spatial navigation. This analysis identified correlated regions across the whole brain that showed higher activation with enhanced behavioural performance on the 4/8VM. This pattern thus provides a marker related to successful navigation and memory on the 4/8VM. Interestingly, this pattern yielded a significant correlation for the Healthy and SSD-Response groups only. The regions involved were generally consistent with those associated with spatial navigation in healthy individuals in the literature (Spreng et al., 2008). Based on the Trial 1 mean-centered analysis and behaviour PLS, the SSD-Spatial group activated only a portion of a navigation network with a brain-behaviour covariance that deviated from all other groups.

In Experiment 1 and previous studies (e.g., Wilkins et al., 2013), the SSD-Response group performed similarly and activated similar brain regions to the Healthy groups. Interestingly, however, in the current analyses the SSD-Response group stands out on Trial 4 relative to the Healthy and SSD-Spatial groups. This is a novel finding and contrary to what I predicted based on behavioural findings. The Trial 4 LV revealed a group of brain regions reflecting greater activation in the Test Phase than the Visuo-Motor Control in the SSD-Response group. Regions activated were the motor (A2), cingulate (medial frontal), precuneus, insula, frontal and temporal regions. The SSD-Response group activated brain regions that included robust clusters in a frontal-temporal-parietal network that is generally consistent with regions associated with navigation in healthy individuals (Burgess, Maguire & O'Keefe, 2002; Hassabis & Maguire, 2007; Spreng et al., 2008). However, inconsistent with their intact behavioural performance at Trial 4 relative to the Healthy groups, the PLS analysis revealed a pattern of brain activation that distinguished the SSD-Response group from all other groups. This deviation in brain activation was masked in our previous behavioural and contrast analyses in Experiment 1. More specifically, the SSD- Response group appears to be over-recruiting these regions to attain similar levels of performance to the Healthy groups. Thus, this pattern of results may also indicate neural inefficiencies in the SSD-Response group.

On the other hand, the SSD-Spatial group appears to preferentially activate the MTL system hypothesized to be impaired (Achim & LePage, 2005; Bonner-Jackson et al., 2008; Hanlon et al., 2011). Isolated activation of temporal lobe regions with minimal or absent correlations with prefrontal and parietal networks suggest potential disconnection with regions beyond the hippocampi that are involved and may be necessary for successful spatial navigation. These patterns

of impairments that include, but also extend beyond the hippocampi may contribute to the selective SSD-Spatial deficit.

Future Directions. There are several aspects of the current study that warrant future study. First, this study highlights need for further exploration of the role of both the PFC and the hippocampi, along with their connectivity, in SSD-Spatial memory impairment. One way to explore the role of anatomical disconnection or disruption between brain regions would be utilize diffusion tensor imaging (DTI). DTI provides valuable information about abnormal white matter connectivity across brain regions and could provide insight regarding the integrity of anatomical connections associated with spontaneous navigation strategies and spatial memory impairment in SSD. Additionally, effective connectivity techniques such as structural equation modeling (SEM) can assess directional relations between regions to provide insight into the potential origins and relations among brain regions underlying spatial navigation and memory abilities in SSD. These approaches will further inform us about normal and abnormal neural correlates associated with each strategy approach that may be targeted for the development of remediation/intervention. Additionally, the SSD-Response group deserves more attention. The differences between the SSD-Response and Healthy and SSD-Spatial groups is potentially quite interesting and warrants further understanding of potential neural compensatory mechanisms that may account for intact behavioural performance in this group.

Conclusion

In Experiment 2, I applied multivariate brain-imaging analyses to characterize whole-brain patterns of activation within the context of spatial memory and navigation strategy in SSD. Results provided further evidence of a distinction between the SSD-Spatial and SSD-Response groups. The

SSD-Spatial group performed worse behaviourally relative to the Healthy and SSD-Response groups. They also preferentially activated temporal lobe regions, with minimal activation in other regions associated with successful spatial navigation. The SSD-Response group performed equivalent to the Healthy groups behaviourally, but appeared to be over-activating brain regions that included frontal-temporal and parietal regions to achieve the same level of performance, suggesting neural inefficiency. Together these studies provide supporting evidence of how large-scale neural networks are associated with intact/and or impaired spatial memory performance and strategy use in SSD. Accurately characterizing intact and impaired abilities that are either due to specific circuits or general neural deficit in SSD is vital. Future studies require more direct examination of effective and anatomical connectivity across navigation and memory networks in both the SSD-Spatial and SSD-Response groups.

Chapter 5: Spatial-Memory Deficit in Schizophrenia Spectrum Disorders Under Viewpoint-Independent Demands in the Virtual Courtyard Task

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Note. Chapter presents minor inconsistencies from the other chapters (e.g., use of "we" versus "I") and includes some redundant definitions, but this chapter was left in the form it was published.

On a backdrop of a generalized cognitive impairment, deficits in declarative memory appear particularly severe among persons with chronic and first-episode schizophrenia spectrum disorders (SSD; Aleman, Hijman, de Haan & Kahn, 1999; Heinrichs & Zakzanis, 1998; Karnik-Henry et al., 2012; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Weiss & Heckers, 2001). Moreover, memory performance is one of the strongest predictors of functional outcome, as compared to a host of other cognitive measures, clinical symptoms, and demographic variables (Ranganath, Minzinberg, & Ragland, 2008). Memory impairments compromise daily living skills and show only modest improvement with current therapies in Schizophrenia (Ranganath et al., 2008). Importantly, however, there are different forms and processes of memory that relate with varying degrees to different underlying brain systems. Therefore, identification of the specific profile of relatively deficient and intact memory abilities is important for developing more tailored interventions.

Consistent with their core roles in declarative memory deficits, the medial temporal lobes, and particularly the hippocampi, are brain structures central to pathophysiological theories of Schizophrenia (Boyer, Phillips, Rousseau, & Ilivitsky, 2007; Christensen & Bilder, 2000; Grace, 2000; Tseng, Chambers & Lipska, 2009). Moreover, reduced hippocampal volume and functional recruitment are robust findings in the Schizophrenia literature (Heckers, 2001; McCarley et al., 1999; Nelson, Saykin, Flashman, & Riordan, 1998; Vita, De Peri, Silenzi & Dieci, &2006). Similarly, the medial temporal lobes have been identified as an important vulnerability indicator in Schizophrenia (Seidman et al., 2003).

Supporting the specificity of hippocampal-dependent memory deficits, persons with SSD demonstrate robust impairment on tests demanding viewer-independent or allocentric spatial memory, whereas viewer-dependent cue-based or egocentric forms of learning are relatively intact (Folley, Astur, Jagannathan, Calhoun & Pearlson, 2010; Hanlon et al., 2006; Landgraf et al.,2010; Weniger & Irle, 2008). Viewpoint-independent memory requires learning the spatial relations among elements in the environment, such that one can flexibly recall or recognize object-location associations regardless of viewpoint (i.e., participants' viewing location and/or orientation in the environment differs between study and test phases). Although this type of memory involves a network of brain regions, the hippocampi are core to flexible navigation and allocentric spatial memory. Patients with hippocampal lesions are particularly impaired on allocentric versus egocentric spatial memory tasks (della Rocchetta et al., 2004; Holdstock et al., 2000; King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002; King, Trinkler, Hartley, Vargha-Khadem, & Burgess, 2004). Additionally, hippocampal place cells in rodents fire preferentially when in particular locations within an environment (O'Keefe & Dostrovsky, 1971) and human hippocampal activation in the CA1 region has been observed more so during allocentric than egocentric learning (Suthana, Ekstrom, Saba, Knowlton, & Bookheimer, 2009). Moreover, morphological indices of hippocampal integrity relate to individual differences in the acquisition and use of view-independent spatial memory (Bohbot et al., 2007; Woollett & Maguire, 2011; Zuzana et al., 2012). In contrast, viewpoint-dependent forms of spatial memory rely on learning the egocentric locations of objects in space relative to one's own body-centered axes and/or fixed sensory-perceptual representations of landmark objects within a scene (King et al., 2002, 2004), as maximized when participants' viewing or starting location remains consistent across study and test phases (Burgess,

2006). Parietal and dorsal-striatal functioning are particularly associated with egocentric and landmark-based response learning, as compared to forming allocentric spatial representations (Burgess, 2006; Doeller, King, & Burgess, 2008; McDonald & White, 1994; Packard & McGaugh, 1992). For example, individuals using a response-based navigational memory strategy showed greater grey matter and activation in the caudate compared to those using a more allocentric spatial strategy (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003). Weniger and colleagues (Weniger, Ruhleder, Wolf, Lange, & Irle, 2009) observed that patients with parietal cortex lesions were impaired on a virtual maze task requiring viewpoint-dependent memory, but not on a virtual task of viewpoint-independent spatial memory. Likewise, they found that smaller precuneus (parietal) volumes and presence of striatal lesions related to impaired performance on the same viewpoint-dependent, but not viewpoint-independent, task (Weniger, Ruhleder, Lange, Wolf, & Irle, E., 2011). Although these systems operate in parallel and interact under normal circumstances in healthy brains (Burgess, 2006; McDonald & White, 1994), experimental manipulation of viewpoint permits comparison of hippocampal viewpoint-independent versus parietal and striatal viewpoint-dependent spatial learning and memory systems.

Applying this approach, we previously assessed viewpoint-independent and -dependent memory in SSD using the Bin Task, a human analog of rodent maze tasks (Girard, Christensen, & Rizvi, 2010). Importantly, this task allowed us to directly compare these memory conditions within the same paradigm (i.e., without a task confound) and the conditions did not differ with respect to discriminating power (i.e., without a psychometric confound). Supporting a differential deficit in viewpoint-dependent memory, we observed a robust deficit in SSD when participants were required

to move to a new viewpoint before recalling the locations and identities of objects hidden among an array of nine identical bins, but intact performance when viewpoint remained stationary. However, clear interpretation of these findings is limited by the possibility that participants could have continually updated their relevant locations in relation to their body-centered axis as they physically moved around the array, as opposed to using a truly viewpoint-independent perspective (Burgess, 2006; Wang & Simmons, 1999). Although SSD and healthy participants reported equal use of environmental and body-centered cues in our previous study, these data were collapsed across view conditions (Girard et al., 2010). Thus, it is unclear to what extent the observed SSD-related deficit reflects impaired viewpoint-independent memory, difficulty updating a viewpoint-dependent representation, and/or differential strategy use across conditions between SSD and healthy participants.

The goal of the current study was to extend our previous findings by assessing viewpoint-independent and -dependent spatial memory in SSD, while addressing the above methodological issues associated with physical movement in the viewpoint-independent condition of the Bin Task. More specifically, in the current study we harness virtual-reality to "teleport" participants to a new vantage point between encoding and retrieval. For this purpose, we use the Courtyard Task developed by King et al. (2002) to assess viewpoint-independent and -dependent spatial episodic memory within a computerized three-dimensional virtual environment. During each trial, objects are presented sequentially in different locations within an enclosed virtual town square (see Figure 1). Participants are required to recognize the objects' locations when viewed either from the same viewpoint or a shifted viewpoint. The Same-view condition can be solved using viewpoint-

dependent memory, the latter Shifted-view condition demands viewpoint-independent spatial memory. We previously observed a specific deficit in viewpoint-independent versus -dependent spatial memory on this task in a patient with developmental amnesia associated with bilateral hippocampal damage (King et al., 2002). Additional clinical studies have further confirmed the task as a reliable indicator of hippocampal dysfunction (Bisby, King, Brewin, Burgess, & Curran, 2010; King et al., 2004). In sum, this study examines viewpoint-independent and -dependent memory in SSD using the well-established virtual Courtyard Task, thereby addressing some of the interpretive confounds from previous studies.

Methods

Participants. Twenty individuals living with Schizophrenia or Schizoaffective Disorder (SSD group) were recruited through a research registry at St. Joseph's Healthcare, Hamilton (SJHH) and by direct referrals from outpatient clinics at SJHH and the Hamilton Program for Schizophrenia. Twenty healthy comparison participants were recruited from the Hamilton, Ontario community via newspaper, Craigslist and poster advertisements. Participants 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. Exclusion criteria consisted of a self-reported lifetime history of a neurological condition or current nonpsychotic Axis I psychiatric disorder (including alcohol or substance dependence or abuse) as ascertained by graduate students trained to administer the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). In addition, healthy comparison participants were excluded if they reported having a first-degree relative with a psychotic disorder. Only SSD participants with no recent changes in medication or clinical symptomology were recruited. Overall, the SSD group included more males,

was older, and had fewer years of education compared to the healthy comparison group (see Table 1 for demographics).

The SSD group was mildly symptomatic with respect to patient symptom norms from the Positive and Negative Symptom Scale (PANSS; Kay, Fiszbein, & Opfer, 1987), reflected minimal functional disability (personal, occupational, social) on the WHO DAS-S (World Health Organization Short Disability Assessment Schedule; Janca et al., 1996), and all were on stable medication (see Table 2). The SSD group comprised a mix of individuals with Schizophrenia and Schizoaffective Disorder; there were no differences between these subgroups on any of the demographic, cognitive or clinical measures (*ps* > .05). All participants were compensated with a cash honorarium of $10 dollars per hour. This study was approved by Ryerson University's Research Ethics Board and the SJHH Research Ethics Board. All participants gave voluntary, written consent to participate.

Table 1. *Demographic and Cognitive Characteristics of the Healthy Comparison and Schizophrenia Spectrum Disorder (SSD) Groups*

Characteristics	Healthy	SSD	*D*
Demographics			
Sex (*n* males/ females)	7/13	16/4	1.02*
Age (Years)	32.25± 12.59	42± 8.52	0.99*
Education	15.35± 2.23	13.05± 1.72	1.18**
SES	42.78± 12.22	40.68± 7.40	0.09
Cognition			
FSIQe	111.36± 9.56	98.9± 16.95	0.95*
WRAT-4 Reading	103.21± 9.72	94.5± 12.01	0.81*
3D Rotation	13.1 ± 7.23	6.4± 5.1	1.15**
RBANS			
Immediate Memory	101.32± 15.94	79.1± 16.15	1.42**
Visuospatial	103.37± 12.95	92.4± 20.74	0.56
Language	101.58± 9.16	85.75± 10.29	1.60**
Attention	99.32± 16.14	79.85± 18.96	1.13**
Delayed Memory	102± 10.4	89.95± 19.89	1.22**

* $p < .05$, ** $p < .0045$ (corrected). *Note*. With the exception of Sex, data are presented as means ± standard deviation (*M* ± *SD*) and tested using independent t tests; Sex was evaluated with a χ^2 test; *d*, effect size of group difference. Socioeconomic status (SES) calculations were based on parental occupations and calculated according to the method of Blishen, Carroll, and Moore (1987). Prorated estimates of full-scale intelligence quotients (FSIQe) were derived from the Matrix Reasoning and Information subtests of the WAIS-III (Sattler & Ryan, 1998; Wechsler, 1997). Additional abbreviations: WRAT-4 Reading = Reading subtest from the Wide Range Achievement Test-Fourth Edition (Wilkinson & Robertson, 2006; 3D Rotation = Mental rotation of three dimensional geometric shapes (Vandenberg & Kuse, 1978); RBANS = Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, 1998).

Table 2

Clinical Characteristics of the Schizophrenia Spectrum Group

Characteristics	
Diagnoses (*n*)	11 schizophrenia, 9 schizoaffective
Antipsychotic medication	
CPZe	236 ± 191
Atypicals (*n*)	16
Typicals (*n*)	5
Antidepressants (*n*)	10
Anxiolytics (*n*)	13
PANSS	
General	26.63 ± 4.63
Negative	12.74 ± 4.45
Positive	14.05 ± 5.22
WHO DAS-S	12.05 ± 7.72

Note.; CPZe (Chlorpromazine equivalents; Virani, Bezchlibnyk-Butler, Jeffries, & Procyshyn, 2011), PANSS (Positive and Negative Symptom Scale; Kay et al., 1987), and WHO DAS-S (World Health Organization Short Disability Assessment Schedule; Janca et al., 1996) measures are reported as means ± standard deviation (*M* ± *SD*).

Table 3

Correlations (r) of Demographic and Cognitive Variables with Courtyard Task Performance

Characteristics	Same View		Shifted View		Same-Shifted	
	Healthy	SSD	Healthy	SSD	Healthy	SSD
Demographics						
Age (Years)	.18	-.33	-.05	-.53*	.28	.43
Education	.30	.26	.47*	.33	-.35	-.22
SES	.06	-.02	.39	-.06	-.50*	.06
Cognition						
FSIQe	-.12	**.64****	.28	**.64****	-.55*	-.35
WRAT-4 Reading	.20	.48*	.37	.49*	-.32	-.27
3D Rotation	-.23	.47*	.03	**.63****	-.30	-.46*
RBANS						
Immediate Memory	**.73****	**.61****	.57*	.35	-.01	-.01
Visuospatial	.20	.45*	.42	.30	-.39	-.06
Language	.32	.61*	.11	.41	.21	-.09
Attention	**.69****	.57*	.59*	.43	.-.08	-.13
Delayed Memory	**.64****	.52*	.59*	.19	-.13	.13

* $p < .05$, ** $p < .0045$ (corrected for multiple analyses)

Note. Data represent Pearson's correlation coefficients, *r*, between demographic and cognitive variables with the proportion of correct responses on the Courtyard task performance under Same-view and Shifted-view conditions, as well as with the difference scores between these View conditions. Variables and abbreviations are as detailed in Table 1.

Neuropsychological Testing. Following the collection of consent and demographic information, the above clinical (MINI, PANSS) measures were administered along with a neuropsychological battery to characterize participants' general cognitive abilities (with test order randomized across participants). Measures of general intellectual function included the WRAT-4 (Wide Range Achievement Test 4; Wilkinson & Robertson, 2006) and estimated Full-Scale IQ (FSIQe) based on the Information and Matrix Reasoning subtests (Sattler & Ryan, 1998) of the WAIS-III (Wechsler Adult Intelligence Scale – 3rd Edition; Wechsler, 1997). The RBANS (Repeatable Battery for the Assessment of Neuropsychological Status; Randolph, Tierney, Mohr, & Chase, 1998) provided more comprehensive assessment across five cognitive 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); RBANS data were incomplete for one SSD and one healthy comparison participant. Given the visual-spatial nature of this study, we also included the Mental Rotation Test (MRT-A; Peters, Laeng, Latham, Jackson, Zaiyouna, & Richardson , 1978), a paper and pencil task requiring participants to match target objects by mentally constructing and rotating three-dimensional representations of drawn cuboid shapes from among foil stimuli.

Virtual Courtyard Task. We tested participants on the virtual courtyard task on a separate day from the neuropsychological battery. The virtual environment for the Courtyard Task is a modified version of the computer game Quake2 (© Id Software; King et al., 2002) presented in a first-person perspective using a Dell Latitude E6510 15.6 computer on a standard 17-inch monitor

at a resolution of 800 x 600 pixels. The environment consists of a courtyard surrounded on all sides by visually distinct buildings. Inside the courtyard are 21 randomly distributed placeholders, upon which the test stimuli appear (see Figure 1).

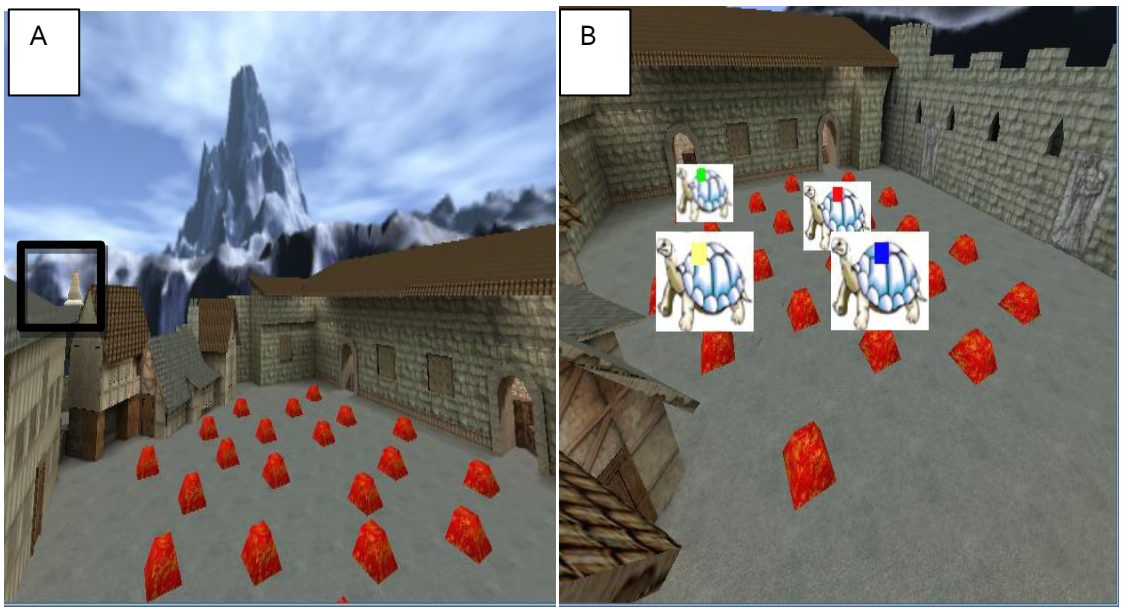

Figure 1. Image of virtual Courtyard Task study and test phase. A) Image of the virtual courtyard environment with 21 placeholders positioned in the centre and the orange cone (in back left corner at rooftop level) to mark the central starting location across trials. B) Sample image of test stimuli positioned above the placeholders in the centre of the courtyard.

Participants first familiarized themselves with the virtual environment through five minutes of exploration. Participants were able to navigate along two of the perimeter walls at the rooftop level. In the centre of the courtyard, 21 red placeholders were randomly distributed. Test stimuli were presented above the red place holders (see Figure 1). There were two different starting locations, each counterbalanced across trials. The starting locations occurred at opposite corners of

the courtyard and were identified by markers (orange cones; see Figure 1). Participants were instructed to walk to the marker and, on contact with the marker, their viewpoint was adjusted to a standard view with all the placeholders visible. Also prior to testing, participants were trained on both Same-view and Shifted-view trials with a memory load of only one object-location pairing to ensure understanding of the task demands. Everyday objects were presented in turn for 3000 ms, each with an inter-stimulus interval of 1000 ms. Each object appeared over a randomly chosen placeholder. Participants were instructed to remember the original locations of each object. After the presentation phase, recognition memory was immediately probed from the same viewpoint or from a viewpoint shifted by 140° by presenting each target along with three duplicates at foil locations. During test trials, task difficulty was varied across three memory span lengths (n = 3, 6, or 9 items presented at study). In addition, the Same- and Shifted-view conditions were previously matched for task difficulty by varying the spacing of target and foils (King et al, 2004). Within each trial, a given location was used only once. Participants received four trials at each span twice (once per each view condition) for a total of 24 trials, with span length counterbalanced across trials. Participants recalled object-location mappings orally. Following testing, we asked participants about their awareness of viewpoint shifts and the strategies that they employed during both conditions of the task (see Appendix E). As we predicted that SSD participants would be particularly impaired in viewpoint-independent processing, we coded these data according to whether participants reported any use of a viewpoint-independent strategy during testing.

Data Analyses. In order to analyze data across span lengths on a common scale, the proportion of correct responses were obtained by dividing the mean number of correct responses for

each span per viewpoint condition by the respective span length. Given sex differences in object-location memory in the general population (Voyer, Postman, Brake, & Imperato-McGinley, 2007) and in spatial working-memory strategy use among persons with Schizophrenia (Lecardeur, Mendrek, & Stip, 2010), we included sex as a factor in the analyses. More specifically, we conducted a four-way analysis of variance (ANOVA) on between-subjects factors of Group (healthy comparison group, SSD) and Sex, and within-subject factors of Span (3, 6 or 9) and View (Same, Shifted). Due to deviations from normality and sphericity on some measures, we corroborated the pattern of results reported below using Greenhouse-Geisser corrections for ANOVA results and nonparametric Mann-Whitney analyses of Group contrasts within each condition (data not shown). Results were evaluated at an alpha level of .05; however, Bonferroni corrections were also applied for multiple comparisons between groups and exploratory correlations with sample characteristic variables.

Results

SSD Group Demonstrated a Differential Deficit in Viewpoint-Independent Spatial Memory.

The omnibus ANOVA on the proportions of correct responses revealed main effects of Group, $F(1, 36) = 18.67$, $p < .001$, η^2_p (partial η^2) = .34, View, $F(1, 36) = 40.00$, $p < .001$, $\eta^2 = .53$, and Span, $F(2, 72) = 16.13$, $p < .001$, $\eta^2 = .31$. More importantly, there was a significant interaction of View x Group, $F(1, 36) = 8.97$, $p = .005$, $\eta^2 = .20$, supporting a disproportionately greater spatial memory deficit in the Shifted- than Same-view condition in SSD (see Figure 2). Of note, this Group x View interaction was not influenced by difficulty level, Group x View x Span, $F(2, 76) = 0.07$, $p = .93$, $\eta^2 < .01$. Follow-up t-tests indicated that the group difference was significant and of large

effect size in both the Same-, $t(38) = 3.72$, $p = .001$, $d = 1.21$, and Shifted-view conditions, $t(38) = 4.85$, $p < .001$, $d = 1.57$, but such that the mean difference between groups was twice as large in the Shifted- ($M = .30$) than Same-view condition ($M = .14$). Moreover, although the difference between conditions was significant for both the healthy comparison group, $t(19) = 4.48$, $p < .001$, $d = 0.79$, and SSD group $t(19) = 6.15$, $p <. 001$, $d = 1.39$, the effect size for the SSD group was almost twice that for the healthy comparison group (see Figure 2). Indeed, consistent with the Group x View interaction, the magnitude of the mean difference score between Same versus Shifted-view conditions was significantly greater in the SSD than healthy comparison group, $t(38) = -3.28$, $p = .002$, $d = -1.06$. Further assessment of the pattern of Shifted versus Same-view performance on an individual level revealed that all SSD participants had higher Same versus Shifted-view scores (100%), whereas this pattern was less consistent among healthy comparison participants such that only three-quarters (75%) demonstrated higher Same versus Shifted-view scores, $\chi^2 = -3.69$, $p = .023$.

The omnibus ANOVA also revealed a significant interaction of View x Span, $F(2, 72) = 4.94$, $p = .010$, $\eta^2 = .12$, which further interacted with Sex, $F(2, 72) = 6.28$, $p = .003$, $\eta^2 = .15$. These interactions reflected that performance was particularly high in the Same-view condition with a span of three items and worst in the Shifted-view condition with a span of nine items, and that this pattern was slightly more pronounced among males. Notably, Sex failed to interact with any effects or interactions involving Group, e.g., Sex x Group, $F(1, 36) = 1.53$, $p = .224$, $\eta^2 = .04$.

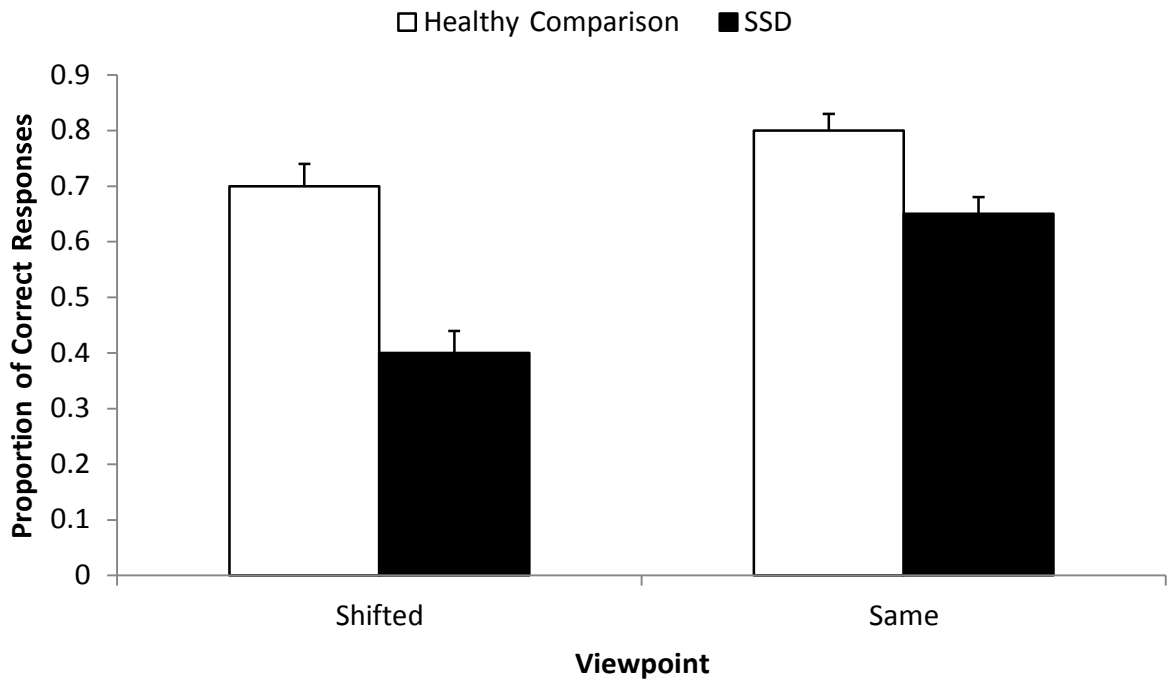

Figure 2. The proportion of correct responses for SSD and healthy comparison groups by Viewpoint condition. Note that the SSD group was disproportionately impaired under Shifted-view task demands, Group x View, $p = .005$, $\eta^2 = .20$. Error bars reflect standard errors.

Demographic and Neuropsychological Measures Failed to Account for the Differential Deficit in Viewpoint-Independent Spatial Memory. Although our recruitment procedures typically yield demographically matched samples, this was not the case in the present study. Thus, due to potential concerns regarding demographic differences (see Table 1) and the limitations of covariate analysis in this regard (Miller & Chapman, 2001), we replicated our analyses using a subsample of demographically matched participants. For this purpose, we reviewed our data to find a healthy comparison match for as many SSD participants as possible under the constraints of matching them on sex, age (within 5 years), and education (within 2 years). This yielded 9 pairs of

matched participants, who were perfectly matched by sex and did not differ significantly by sex or education. Matched-samples ANOVA yielded the View x Group interaction, $F(1,8) = 11.34$, $p = .010$, $\eta^2 = .59$, such that the SSD sample was significantly impaired under the Shifted-view condition, $t(8) = 2.98$, $p = .018$, with a large effect size, $d = 0.99$, whereas the Group difference under the Same-view condition failed to reach significance, $t(8) = 1.64$, $p = .140$, and was of approximately half the effect size, $d = 0.55$.

To further explore the potential impact of demographic and cognitive variables on task performance, we ran within-group bivariate correlations between these variables and the proportion of correct responses in the Same-view and Shifted-view conditions, as well as with the key condition comparison of interest based on Same-Shifted view difference scores. As reported in Table 3, performance on the Same-view condition was highly and significantly correlated with the RBANS indices of attention, immediate and delayed memory within the healthy comparison group. Within the SSD sample, all cognitive measures correlated positively with Same-view performance, with the correlations with FSIQe and immediate memory surviving Bonferroni correction. For the Shifted-view condition, the same three RBANS measures of attention, immediate and delayed memory demonstrated significant positive correlations with performance among the healthy comparison group, along with education; none of these survived correction for the multiple analyses. Within the SSD group, Shifted-view performance correlated highly with FSIQe and mental rotation scores, and to a lesser degree with WRAT-4 reading and age, but in contrast to the Same-view condition all RBANS measures failed to correlate significantly. Lastly, analyses with the Same-Shifted difference scores revealed negative correlations with socioeconomic status and

FSIQe for the healthy group and only with mental rotation scores for the SSD group. That is, lower scores on these measures related to relatively poorer Shifted-view than Same-view performance (although none of these relations survived statistical correction).

Given the above correlations (Table 3) and group differences (Table 1), we derived partial correlations to examine the extent to which sample characteristics accounted for the observed group differences on the proportion of correct responses on the Courtyard task. To minimize redundancy, we selected the five most robust and consistent correlates with performance as control variables: FSIQe, mental rotation, attention, immediate and delayed memory (bolded in Table 3). These variables demonstrated significant correlations across at least three columns in Table 3, with at least one of these surviving Bonferroni correction. After partialing out variance shared with these five measures, there was no longer a Group difference on the Same-view condition, r_{pb} = -.08, p = .654. In contrast, the SSD group remained significantly impaired compared to the healthy group on Shifted-view trials, r_{pb} = -.35, p = .046. Moreover, the greater impairment in Shifted < Same-view difference scores among the SSD group compared to the healthy sample also remained significant, r_{pb} = -.372, p = .030. These results support the Group x View interaction and further indicate that although more global cognitive deficits associated with SSD contribute to impaired performance on the Courtyard task, the degree to which they account for group differences depends on View condition. Whereas SSD deficits in the Same-view condition are largely accounted for by more global cognitive deficits, the deficits observed in the Shifted-view condition remained robust after partialing out variance accounted for by five key covariates.

Courtyard Task Performance Related to Symptoms and Functioning among Patients. With respect to the clinical measures summarized in Table 2, symptoms and functional disability

related to task performance within the SSD group. More specifically, although the SSD group was characterized by mild symptomology overall, worse performance in both the Shifted-view (r = -.50, p = .036) and Same-view condition (r = -.51, p = .030) correlated with greater negative symptoms of psychosis (PANSS). However, inspection of the data revealed that the large magnitude of these correlations was driven by two participants with more extreme symptoms (albeit at the patient normative mean with PANSS T-scores of 54 and 50). Without these participants, the correlation with Same-view performance was negligible (r = -.01), but that with Shifted-view performance remained moderate (r = -.40). In addition, Shifted-view performance correlated negatively with PANSS-General scores (r = -.55, p = .018); neither condition related significantly with positive symptoms. Overall WHO DAS-S scores revealed that greater disability correlated similarly with worse Shifted- and Same-view performance (rs = -.46, -.45; ps = .004). Interestingly, inspection of individual indices revealed that Shifted-view performance was most strongly related to Mobility scores (r = -.53, p = .001) and Same-view performance to Life Activities (r = -.47, p = .003). Chlorpromazine equivalent dosages (Virani et al., 2011) did not correlate significantly with either Shifted- or Same-view conditions. Additionally, there were no significant differences between those SSD subjects taking atypical or typical antipsychotics, or between specific diagnostic subtypes, on either condition.

Incongruent Strategy Use Contributed to Impaired Same-View Performance in SSD. Reports from one healthy comparison and five SSD participants were insufficient to properly code strategy types. Of the remaining 34 participants, there were no group differences in the spontaneous use of a viewpoint-independent strategy, χ^2 (1) = 0.19, p = .667. Just under half of the participants reported clear use of a viewpoint-independent strategy (40% SSD, 47% healthy comparison).

Further analysis of the impact of strategy on the performance of SSD participants revealed that their performance was related to their strategy selection. That is, SSD participants reporting use of a viewpoint-independent strategy in the Same-view condition performed significantly worse than their healthy comparison counterparts, $t(13) = -4.36$, $p = .001$, with a very large effect size, $d = -2.42$. Although the effect size of SSD-related impairment was also large among those who employed a viewpoint-dependent strategy in the congruent Same-view condition, the magnitude of the effect was smaller by over three times, $d = -0.78$, and was not significant, $t(17) = -1.60$, $p = .128$. The SSD group performed equally poorly in the Shifted-view condition regardless of strategy.

Discussion

The current results demonstrate greater impairment in viewpoint-independent versus -dependent spatial memory in SSD. Importantly, this finding was independent of difficulty level across the three memory spans. Group differences on the Same-view trials were accounted for by global cognitive deficits, but SSD-related deficits on the Shifted-view trials remained robust. Correlation analyses also revealed that viewpoint-independent deficits in SSD related to psychotic symptomology and both task conditions predicted functional disability.

These results extend upon previous studies that have involved movement or navigation within a virtual environment or a real-world setting (Folley et al., 2010; Girard et al., 2010; Hanlon, 2006; Weniger & Irle, 2008), but here with the movement component removed. The ability to virtually "teleport" participants in the Courtyard Task eliminates the potential strategy available in navigation paradigms of continuously updating a body-centered, viewpoint-dependent representation of target locations (Burgess, 2006; Wang & Simmons, 1999) in support of the interpretation of particular viewpoint-independent memory deficits in SSD. In this regard, it is

notable that the role of strategy has received little attention in studies comparing viewpoint-independent and -dependent memory. Although we have previously probed overall strategy use (Girard et al., 2010), it was unclear to what extent the observed SSD-related deficit reflected differential strategy use across conditions. Thus, in the current study we more specifically probed and coded the application of a viewpoint-independent strategy within conditions. That is, while the teleportation feature of the Courtyard is intended to minimize use of viewpoint-dependent strategy on Shifted-view trials, nothing precludes the use of a viewpoint-independent strategy on Same-view trials despite not being necessary for the task at hand. Interestingly, SSD participants reporting a viewpoint-dependent strategy in the congruent Same-view condition performed at a more comparable level to the healthy comparison group, but those patients who reported applying a (less-efficient) viewpoint-independent strategy were significantly impaired. These findings further underscore the need to consider strategy selection and implementation in SSD (Bryan & Christensen, 2003; Christensen et al., 2006; Wilkins et al., in press).

The virtual environment used for the Courtyard paradigm affords future extensions using functional neuroimaging to further clarify the contribution of hippocampal and other brain systems to viewpoint-independent and viewpoint-dependent spatial memory in SSD. Nonetheless, previous investigations using the Courtyard Task with other populations support that performance under the Shifted-view condition is preferentially sensitive to disruption of the hippocampal system (Bisby et al., 2010; King et al., 2002, 2004). For instance, King et al. (2002) reported on a patient with focal bilateral hippocampal pathology who was particularly impaired in the Shifted-view condition. Although this task has not been directly used to assess the involvement of other regions, paradigms with similar objectives indicate that viewpoint-dependent memory is reliant on the integrity of

parietal and dorsal-striatal regions (e.g., Weniger et al., 2009, 2011). Interestingly, Siemerkus, Irle, Schmidt-Samoa, Dechent, and Weniger (2012) recently observed correlations between precuneus (parietal) activation during their egocentric maze task with worse performance and greater positive symptoms among participants with Schizophrenia. While a SSD-related egocentric deficit in this latter study appeared to contradict their earlier findings of intact performance on the same task (Weniger et al., 2008), the authors suggest that the difference may relate to sample differences (Siemerkus et al., 2012). The specificity of their observed egocentric deficit is unclear as they did not assess allocentric processing, which has also been linked to precuneus function (Frings et al., 2006). Nonetheless, these findings suggest that it will be important to further investigate the relations between both viewpoint-independent and viewpoint-dependent spatial memory in SSD and their relations to regional brain function. The ability of the virtual Courtyard task to assess these memory conditions within the same paradigm and unconfounded by movement (supporting egocentric updating) is an attractive feature. However, the role of active navigation in spatial memory abilities in SSD also deserves further attention.

Another advantage of virtual-reality is the ability to investigate neuropsychological functions, including spatial navigation and memory, in a more ecologically valid manner (Zakzanis, Mraz, Campbell, & Graham, 2004). That is, standardized neuropsychological measures of spatial memory tasks often provide limited evidence of the ecological validity or how deficits identified in these paradigms might relate to poorer navigation and spatial memory abilities in the real-world. Use of virtual environments is a strong first step to understanding cognition in SSD in a real-world, albeit controlled virtual setting. Nonetheless, real-world contexts present more complexity than modeled by virtual environments. Thus, future studies will also more directly explore the link

between behavioural performance in virtual environments and the approaches individuals with SSD use to navigate in day-to-day life.

A limitation of the current study is that our SSD sample differed from the healthy comparison sample across demographic and cognitive measures, presenting potential confounds to the observed deficits on the Courtyard task. Addressing this concern, we confirmed the pattern of more robust impairment in SSD under the Shifted-view condition than Same-view condition among a subsample of demographically matched participants. In addition, the differential impairment under Shifted-view versus Same-view trials remained after statistically controlling for measures of general intelligence, attention, memory, and mental-rotation ability. Furthermore, the current findings converge with our previous findings of preferential impairment in viewpoint-independent memory in SSD on the Bin Task, where SSD and healthy groups were matched on sex, age, education, general intelligence, among other factors (Girard et al., 2010). While matched samples minimize sources of confound, they also limit generalizability in that, on the whole, SSD populations are cognitively impaired relative to normative groups. On the other hand, statistically controlling for factors such as generalized cognitive deficits results in over-correction as it partials out true-score variance inherent to the disorder (Miller & Chapman, 2001). Thus, despite these lines of support for the interpretation of a differential deficit in viewpoint-independent memory, it will be important to more directly assess the potential contributions of demographic and cognitive factors on task performance in future studies. That is, the group differences observed across demographic and cognitive measures were in the same direction as overall deficits on the Courtyard task, and we observed some specific relations among these measures with task performance (see Tables 1 and 3). Although sex failed to interact significantly with group, it did interact with the task factors of

viewpoint and span length, and sex differences in spatial memory abilities have been observed with other paradigms (Lecardeur et al., 2010; Voyer et al., 2007). Larger samples will be beneficial towards supporting the reliability and enhancing the generalizability of the findings, as well as for more in-depth investigations regarding relations among neurocognitive mechanisms of spatial memory with individual difference factors and functional outcome measures among patients. Such research would benefit from experimental manipulation of amenable factors (e.g., via cognitive training) and longitudinal examination.

In sum, current results corroborate prior findings of preferential deficits in viewpoint-independent memory in SSD. It should be clarified at this point that the presence of a differential deficit in viewpoint-independent memory does not mean that viewpoint-dependent memory is necessarily intact among patients with SSD. Although demographic and cognitive confounds appear to account for substantial variance in viewpoint-dependent performance, such factors are also inherently associated with the illness (e.g., lower average education and intelligence). Nonetheless, the differential pattern of performance observed suggests that cognitive rehabilitation specialists might develop a training protocol that harnesses the less impaired viewpoint-dependent spatial memory and/or trains the more deficient ability to employ a viewpoint-independent cognitive map in order to improve visual-spatial memory and navigation abilities in real-world daily functioning.

Chapter 6: General Discussion

A main purpose of my dissertation was to use fMRI to investigate a selective hippocampal-dependent spatial navigation deficit in SSD. This fMRI investigation was a follow-up from previous studies from our lab supporting the hypothesis of selective allocentric memory dysfunction in SSD, relative to an intact response-based system (Girard et al., 2010; Wilkins et al., 2013). Consistent with hippocampal abnormalities associated with SSD, I observed that the SSD-Response group performed in an equivalent manner to the Healthy-Response group, whereas the SSD-Spatial group performed more poorly relative to the Healthy-Spatial group on the 4/8VM. These findings provide behavioural support for selective-hippocampal dependent memory dysfunction in SSD relative to intact response learning. These findings further support the SSD literature indicating selective behavioural deficits in spatial and contextual processing (Boyer et al., 2007).

The major limitation with my previous work (Wilkins et al., 2013) is that I did not include a direct measure of hippocampal and caudate function while participants performed the 4/8VM. My dissertation thus provides important data regarding these brain-behaviour relations to enhance insight regarding underlying neural bases for individual differences in both navigational strategy use and spatial memory performance in SSD. This is the first imaging-based study of SSD participants who spontaneously adopt a spatial approach to navigate.

In Experiment 1, I replicated our previous findings of a selective hippocampal-dependent spatial navigation deficit in SSD on the 4/8VM (Wilkins et al., 2013). The SSD-Spatial group who reported relying on the allocentric relations among landmarks in the environment to solve the 4/8VM performed worse relative to the Healthy and SSD-Response groups. Moreover, fMRI data revealed deficient recruitment of the right anterior hippocampus in the SSD-Spatial group relative

to all other groups during both the early and later trials. In contrast, the SSD-Response group performed as well as its healthy counterpart and they did not differ in terms of hippocampal or caudate activation. Additionally, at the whole-brain level the SSD-Spatial group failed to recruit both the prefrontal and temporal lobe regions to the same extent as the Healthy and SSD-Response groups. I interpret the whole-brain findings as supporting the hypothesis of deficient hippocampal activation in the SSD-Spatial group. They had lower activation of both anterior hippocampi, as well as deficient recruitment of additional brain regions normally involved in navigation. These results may reflect functional disconnection between the frontal and temporal lobe regions (Friston, 1998; Pettersson-Yeo et al., 2010; Zhou et al., 2007). These interpretations are based on analysis using a general linear model to investigate fMRI data and are unable to provide answers about connectivity across regions. Therefore, a follow-up study was necessary to investigate patterns of activation associated with the selective SSD-Spatial deficit.

The purpose of Experiment 2 was to explore how the pattern of brain activation in the SSD-Spatial group differs from the other groups using multivariate PLS analyses (McIntosh et al., 1996). The results provide evidence of a distinction between the SSD-Spatial and SSD-Response groups. The SSD-Spatial group was associated with a pattern of temporal-lobe activation, but minimal integration of extra-temporal lobe regions typically associated with successful spatial navigation. The SSD-Response group performed similar to the Healthy groups behaviourally, but appeared to be over-recruiting a pattern of brain regions that included frontal-temporal and parietal regions to achieve the same level of performance as the Healthy groups. In the SSD-Spatial group, both Experiment 1 and 2 provided evidence of isolated activation of temporal-lobe regions with minimal functional activation across prefrontal and parietal regions, which further suggests potential

disconnection among regions involved in successful spatial navigation. These profiles of activation that include, but also extend beyond the hippocampi, appear to contribute to the selective SSD-Spatial deficit. There appears to be a breakdown in activation across the spatial navigation network. These individuals are not just activating the hippocampi less and performing worse, rather there is a loss in the relation between performance on the 4/8VM and use of this extended network. Thus, although the hypothesis of hippocampal dysfunction is supported, together these studies further indicate that extended neural patterns of over-recruitment and under- recruitment are associated with intact and impaired spatial memory and spatial navigation performance in SSD. Although the SSD-Response group revealed a pattern of activation similar to the Healthy groups, it must not be ignored that they activated these regions to a greater extent. These findings warrant future investigation to understand their potential mechanisms.

In Experiments 1 and 2, performance between groups defined by individual differences in strategy use was used to assess relative functioning of multiple memory types rather than comparing performance within-subjects on the same paradigm. That is, it is unclear the extent to which differential performance between the Spatial and Response SSD groups reflects individual differences and/or brain system differences. With respect to between-group comparisons on the 4/8VM, deficient hippocampal recruitment among SSD individuals who spontaneously adopted a spatial strategy is supported. However, there is no direct evidence to speak to whether they have an intact or impaired caudate-dependent response system. Likewise, the ability of spontaneous Response learners to adequately use an allocentric spatial strategies is not addressed in these studies. These limitations are important because, for example, the impairment observed in the

Spatial-SSD group may reflect a general impairment of both spatial and response learning specific to this subgroup of patients, whereas, it is possible that those in the Response group may have intact spatial learning. Alternatively, the SSD group may be more homogenous in terms of deficient spatial and relatively intact response learning, and such that the differences observed merely reflect individual differences in strategy use. Addressing this limitation is informative about the extent to which these types of learning are coordinated when one is intact and the other is impaired. Spatial memory paradigms that are able to provide convergence of evidence on within-subject performance differences are thus important to solidify and strengthen our understanding of multiple spatial memory abilities.

Therefore, in Experiment 3, I assessed SSD performance on a within-subject comparison of allocentric/viewer-independent and response/viewer-dependent memory abilities using the Courtyard task (King et al., 2002, 2004). Results provided convergent evidence for the profile of intact viewer-dependent and impaired viewer-independent spatial memory abilities in SSD. Importantly, this finding was independent of difficulty level across the three memory spans. In sum, Experiment 3 corroborated Experiments 1 and 2 in demonstrating selective deficits in hippocampal-dependent memory in SSD.

Together, this dissertation is valuable in providing the first set of studies aimed at better understanding the mechanisms and neural circuits underlying individual differences in spontaneous strategy use in SSD. Although brain function of individuals living with SSD is quite complicated and functional deficiencies are dispersed across the brain, there is substantial variation across brain regions with differential effects on neurocognitive functioning. Thus, by using tasks that are able to clearly dissociate these brain-behaviour relations, my dissertation has advanced our understanding

of SSD with stronger conclusions about preferential dysfunction within a multiple memory framework.

Spatial Navigation Impairment and SSD Disconnectivity Literature

In my dissertation, evidence was provided of under-recruitment of the right anterior hippocampus in the SSD-Spatial relative to the Healthy-Spatial group, but also a pattern of over-recruitment of additional temporal lobe regions. In contrast to the Healthy-Spatial group, SSD-Spatial failed to activate both PFC and hippocampal regions while performing the 4/8VM. In contrast, they do appear to have preferentially activated the left orbital-frontal cortex. Although previous studies have not investigated spontaneous strategy use systematically, the current findings are consistent with previous SSD spatial navigation literature that also reported selective impairment in hippocampal-dependent memory (Folley et al., 2010; Ledoux et al., 2013, 2014).

Folley et al. (2010) tested SCZ participants using the virtual Morris water maze with fMRI. SCZ participants made more errors and required more time in the maze to solve the task, similar to the findings of the current dissertation. Also, they found a positive correlation between hippocampal activation and efficiency in solving the task in the controls only. There was no relation between the hippocampi and behavioural efficiency in the SCZ group. The SCZ group recruited different brain regions compared to the Healthy group while solving the virtual water maze suggesting the SCZ group was compensating by utilizing a different neural circuit. Their independent component analysis revealed one similar ICA component between groups, but further identified the SCZ group as having a different pattern in four different circuits compared to the Healthy group suggesting the SCZ group activates anomalous neural circuits. The SCZ group failed

to activate hippocampal regions comparable to the Healthy group. These findings are consistent with decreased hippocampal activation found in the SSD-Spatial group compared to all other groups.

In addition, Ledoux et al. (2014) compared performance between Healthy and SCZ participants on the Way-Finding Task. In this experiment they measured grey matter in hippocampal, caudate and PFC regions and regressed these volumes with performance on the Way-Finding Task. Similar to this dissertation, they found that the right hippocampus correlated with performance in the Healthy group, whereas the left hippocampus correlated with performance in the SCZ group. For the regression analysis they found that the hippocampus covaried with the parahippocampus, amygdala, medial and orbital PFC in the Healthy group. In contrast, activation in the cuneus and cingulate covaried with the hippocampi, but with no activation in the orbital PFC in the SCZ group. These findings of reduced hippocampal grey matter in the SSD group were thought to potentially account for the contextual binding deficit associated with poor spatial navigation, while the lack of activation in the orbital PFC was hypothesized to reflect potential disconnection between the PFC and temporal lobe in SSD. Although they did not investigate strategy, their findings are consistent with my SSD-Spatial findings of a difference in activation patterns in the temporal and PFC regions compared to the healthy groups.

In contrast, the SSD-Response group performed at an equivalent level to the Healthy groups. The SSD-Response group also had a similar pattern of brain regions activated during performance on the 4/8VM. However, they activated these regions to a greater extent. Over-recruitment of these brain regions to perform at the same level as the Healthy groups suggested

neural inefficiency. This unique finding warrants future investigation into the mechanisms and reasons for their relatively intact performance and further characterizing their pattern of hyperactivation of neural regions compared to the Healthy and SSD-Spatial group.

Previous meta-analysis of working memory studies in SSD have identified patterns of both hypoactivation and hyperactivation in different regions (Glahn et al., 2005). Hypo- and hyper-activation were considered to mean there was difficulty immobilizing neural resources for best performance and deemed this to reflect neural inefficiency (Kim et al., 2010). Given inconsistent literature with respect to regions that are hypo and hyperactive (Glahn et al. 2005), Kim et al. (2010) investigated how manipulating load in a working memory task would affect activation patterns at a whole-brain level. They found evidence of hypoactivation at low load and hyperactivation at higher loads. In addition, whether they measured the probe or encoding phase also changed the pattern of hypo and hyperactivation relative to healthy participants. Different manipulations of load and condition within a working memory task provided different patterns of activation. This is consistent with my findings of different patterns of recruitment based on the spontaneously adopted strategy. My findings thus bolster support for the need to investigate individual difference based on strategy in SSD at the neural level.

Evidence of hyper and hypoactivation patterns across the whole brain are consistent with findings of structural abnormalities and functional impairments at the whole-brain level in SSD. In terms of structure, meta-analysis revealed a 2% volume loss total of grey matter relative to healthy participants (Vita et al., 2012). There has also been evidence reported of a functional disconnection between the PFC and thalamus (Woodward et al., 2012), PFC and parietal lobe (Zhou et al., 2007)

and PFC and temporal lobe (Friston and Frith, 1995). Connectivity disturbances in frontal, parietal and temporal cortices have been associated with left hemisphere dysfunction (Pettersson-Yeo et al., 2011; Ellison-Wright & Bullmore, 2009). Dynamic causal modeling also provided evidence for an alteration in frontal-temporal coupling in SCZ; however, temporal dysfunction was hypothesized to be a secondary effect of PFC dysfunction (Crossley et al., 2009). Thus, the disconnectivity hypothesis of SCZ is based on findings of alterations in brain connectivity patterns and deficient integration between brain regions not typically found in healthy participants. Failure to activate the hippocampi and PFC in the current dissertation, suggest potential disconnectivity between these regions for the SSD-Spatial group. These interpretations are in line with Friston and Frith's (1995) theory explaining cognitive and clinical symptomology in SSD. However, my results are unable to address whether the hippocampal or PFC dysfunction is primary or secondary to disturbance in the other region.

Diffusion spectrum imaging (DSI) has the capacity to measure effective connectivity and integration between areas in the brain as it measures diffusion of water molecules along white matter tracts. Researchers have started to apply graph theory to analyze data collected with DSI to create a connectome map across the brain (Crossley et al., 2009, 2014; Griffa, Baumann, Ferrari, Kim & Conus, 2015; Whitford, 2011), which may be a valuable tool to assess disconnectivity patterns in SSD. Graph theory can quantify and visually represent integration and segregation among brain regions. In graph theory, regions are placed on both the x and y axis of a graph and lines are drawn showing regions effectively connected. Hubs are depicted in these graphs, which are nodes that appear to be key to communication across the brain. These hubs are tagged based on

their disproportionate connectivity to other brain tracts. Graphs developed for both healthy and SCZ brain show that the SCZ brain has less efficient network organization and limited capacity for functional integration compared to a healthy brain (Fornito et al., 2012). Collins et al. (2014) assessed changes in connectome patterns in relation to PANSS, IQ scores and a measure of real-world function across 3 years in SCZ. SCZ had reduced connectivity in their nodes, suggesting potential disruptions within their hub, and these network alterations were correlated with both an increase in total symptoms as measured by PANSS and decline in IQ. These findings also suggest the level of connectivity in the hubs may predict progressive changes in real-world function. SCZ has distributions concentrated in both frontal and temporal cortical hubs (Crossley et al. 2014). Both the thalamus and hippocampus are the only two hubs consistently implicated in SCZ (Crossley et al., 2014). Graph theory could be used to compare connectivity between SSD-Spatial and SSD-Response participants to identify where there may be differences at hubs or differences in hub connectivity that correlates with performance on the 4/8VM and real-world spatial navigation performance overtime or may predict group membership.

Limitations/Future Directions

As this is the first study to investigate regional brain activation associated with spontaneous navigation strategies in SSD, it holds incredible implications to inform future researchers of the importance of assessing strategy. In the past, the majority of spatial memory and spatial navigation studies have not assessed the role of strategy on performance. It is clear from the dissertation that individual differences play an important role in the spatial navigation impairment found in SSD. However, a key question that was not addressed in the current dissertation remains: What underlies

spontaneous adoption of a particular strategy? Literature based on healthy samples shows greater hippocampal integrity in those who spontaneously adopt a spatial strategy (Bohbot et al., 2007; Iaria, Lanyon, Fox, Giaschi & Barton, 2008) and caudate integrity in those who spontaneously adopt a response approach (Bohbot et al., 2007). The question remains whether spontaneous adoption of a spatial strategy precedes hippocampal integrity or vice-versa.

Nonetheless, the healthy data would predict adoption of a response approach in SSD, given the lack of hippocampal integrity. However, similar to our Experiments 1 and 2, Bohbot et al. (2007) found that 60% of their sample of individuals with MTL resection spontaneously adopted the spatial strategy. This finding is incompatible with understanding of spontaneous adoption of the spatial approach being dependent on intact hippocampal integrity. The SSD and MTL participants had abnormal hippocampal structure and function and therefore, were not expected to adopt the spatial approach under the integrity model outlined above. Rather, the current results highlight a dissociation between spontaneous use of a strategy and its successful application. That is, half of my patient sample spontaneously adopted the spatial approach, but these individuals were impaired on the 4/8VM. The question remains, why do these individuals adopt and continue to use an approach that does not lead to optimal performance? The relation between brain regions and behavioural performance is more complicated and raises the question as to how well the results and interpretation from the healthy samples do extend to clinical populations or conversely, whether the patient data challenge those original interpretations. In the current study, it may be that SSD participants have both deficient hippocampal activation and deficient strategy selection, which may be related to decreased PFC function or hippocampal-PFC connectivity. Healthy participants with intact brain function may inform better strategy selection. In the presence of dysfunction, patients may be

impaired due to communication or coordination breakdowns. The SSD-Spatial impairment in strategy appears to extend to the whole brain. These individuals do not activate key regions involved in successful spatial navigation to the same extent as the Healthy and SSD-Response groups.

Interestingly, I see from Experiment 3 that across the whole SSD sample there is a dissociation more related to impaired view-independent than view-dependent memory. In Experiment 3, the SSD sample performed poorly on the hippocampal-dependent version of the task but were able to perform the non-hippocampal dependent version of the task at a similar level as the Healthy participants. Therefore, it appears that SSD is generally associated with an impaired hippocampal-dependent system and a relatively intact response learning system. Therefore, the critical question remains, why do individuals choose to adopt the non-optimal strategy? Bohbot and colleagues have theorized that strategy selection may be a random process or it may be due to genetic predisposition (BDNF Val gene and spatial strategies; Banner et al., 2011) or experience-dependent learning (drug use, Bohbot et al., 2013; video game playing, Drisdele et al., 2015; spatial training, Lerch et al., 2007; acute and chronic stress, Schwabe & Wolf, 2009). Future studies will be required to assess whether some SSD participants are predisposed to adopt a spatial approach and if so, why they continue to maintain this bias in presence of failure. Moreover, cognitive rehabilitation specialists should investigate whether there is the potential to train or use the more efficient non-hippocampal dependent strategy.

Another limitation with studying spontaneous strategy use is that the SSD participants appeared to have more difficulty explaining the strategy they adopted and recalling when and what changes occurred across the trials. Therefore, I cannot be certain as to trial-by-trial changes that

may have taken place in this group. However, I have some anecdotal evidence that the SSD-Spatial group took longer to formulate a spatial strategy. Having a report of strategy across trials would allow us to quantify these observations. This would be informative towards understanding whether deficits in self-generation and cognitive control of strategy may also play a role in the selective SSD-Spatial navigation impairment. If it is the case that individuals living with SSD are not able to choose the optimal approach to navigate, this could be a promising area to further investigate as a means for rehabilitation.

Another limitation of Experiment 1 is that the probe-trial data from our Healthy groups did not replicate findings from Bohbot et al. (2004, 2007). The probe trial (Trial C) was completed outside of the scanner after participants were able to finish two A trials without the commission of an error on the Test Phase. The Test Phase in the probe trial only differed from the other trials because the landmarks were concealed. In the probe trial the eight arms were surrounded by a grey wall. Occlusion of the landmarks is believed to have impaired performance for those who adopted the spatial approach and relied on the landmarks. The number of errors on the probe has been used by Bohbot and colleagues to distinguish healthy response and spatial groups (Dahmani & Bohbot, 2015; Iaria et. al., 2003). In Experiment 1, I did not find a significant difference in errors on the probe between those individuals who reported the spatial and response strategy. Finding the distinction on the probe trial between the healthy groups would have provided additional convergence of group assignment. This discrepancy might be due to use of a different protocol from Bohbot et al. (2004, 2007). In Dr. Bohbot's previous studies she administered probe trials twice in the scanner. The sequence of trials administered were ABCAAABC. Our probe trial was administered outside of the scanner after participants had

completed at least four trials (ABAA) and until they performed two error-free 'A' trials. The habit-based response learning system may have come online for those individuals who had initially adopted a spatial approach prior to the probe. Both our protocol and that of Bohbot and colleagues are valuable as they provide answers for separate questions. Protocols with early probe tests are able to provide converging evidence for assignment of members to a strategy. Later probe tests can also be used to assess whether patient populations show a persistence in adopting the inefficient strategy, which may indicate a breakdown in cooperation with key brain regions.

Compared to the SSD-Spatial group, the SSD-Response group demonstrated relatively intact performance, supporting relatively intact caudate-dependent system, albeit with indication of potential compensatory activation of the spatial navigation network. However, there is some controversy as to whether the caudate system is intact in SSD. 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). Some report smaller caudate volume in drug-naïve first episode psychosis (Edrupt et al., 2011), reduced volume with atypical antipsychotic use and increased volume with typical antipsychotics (Scheepers,Gispen, Hulshoff & Kahn, 2001). Others have found the opposite, reporting increased striatal enlargement after chronic atypical use (Anderssen et al., 2002). Although the literature is inconsistent, it is clear that symptomology, length of illness and type of medication may affect caudate volume and function. Andersson and colleagues (2002) explain that the inconsistent findings within the atypical and typical antipsychotic drug literatures may be remedied if researchers look at the pharmacological properties (i.e., occupancy of D_2 or 5-HT_{2A} receptors) at different therapeutic doses rather than gross classes of medication and dosage to assess their impact on brain and behaviour. In the current study, most participants took similar types

of atypical antipsychotics. Given the current findings, the 4/8VM task may be useful for future work to better investigate the relative role of type and dosage of medication, length of illness and length of treatment on intact caudate function in SSD.

In a similar vein, the SSD-Spatial group in Experiment 1 was on a higher average dosage of antipsychotic medication compared to the SSD-Response group. Including CPZe as a covariate eliminated the significant difference in performance between the SSD-Spatial and SSD-Response groups. It is unclear whether this finding reflects a meaningful relation between antipsychotic dosage and spontaneous strategy selection or whether dosage is an indirect proxy of illness severity, which in turn may affect strategy use as discussed above. There is evidence that second generation atypical antipsychotics, including ziprasidone, risperidone, and olanzapine impair performance in rats on spatial navigation in a dose-dependent manner (Morris water maze; Skarsfeldt, 1995). Higher doses of antipsychotics in and of themselves may impair spatial navigation performance in rodents. However, other researchers have found a neuroprotective effect of atypical antipsychotics on cognition and memory (He et al., 2009). Similar to the discussion above about the influence antipsychotics on caudate function, there are also inconsistent findings regarding the influence of atypical antipsychotics on hippocampal function (Panenka et al., 2007; Pillai, Terry & Mahadik, 2006; Rizos et. al., 2014). There are only a limited number of studies that investigated not only the type, but also the effect of dosage on cognitive function. Therefore, it unclear how dose and type of medication, and severity of illness relate to hippocampal integrity and spatial abilities. A future study with larger subsamples of participants taking different types of typical and atypical antipsychotics, across a range of CPZe doses, alongside a drug-naïve patient group would be ideal

to parse apart these relations. In Experiment 1, there appeared to be a linear relation between antipsychotic dosage and performance on the 4/8VM. In our previous research (Wilkins et al., 2013), when covarying CPZe, our selective hippocampal-deficit remained significant. Even when I matched SSD subgroups on symptomatology, CPZe and types of medication, the SSD-Spatial remained impaired. In addition, I observed a within-subject difference showing impaired spatial and intact response-based performance in Experiment 3 (Courtyard) as in previous work from our lab (Girard et al., 2010) and others (Hanlon et al., 2006, Ledoux et al., 2014). Therefore, medication as a confound cannot fully explain these selective deficits. However, medication may differentially affect these brain regions influencing these impaired and intact abilities.

In addition, in the future there needs to be more direct exploration of the role of both the PFC and the hippocampi in SSD-Spatial memory impairments. DTI would provide valuable information about abnormal white matter connectivity across brain regions anatomically connected. Additionally, SEM could be utilized to assess directional relations between these regions. This would inform us about normal and abnormal neural correlates associated with each strategy in healthy and clinical populations. It would be beneficial in the future to follow-up using both the 4/8VM and Courtyard Task with fMRI, DTI and SEM to exam effective connectivity to further corroborate the observed pattern of whole brain findings.

Conclusion

My dissertation supports selective hippocampal-dependent spatial navigation impairments relative to other non-hippocampal dependent forms of navigation in SSD. In Experiment 1, fMRI data revealed deficient recruitment of the right anterior hippocampus in the SSD-Spatial group. Additionally, at the whole-brain level the SSD-Spatial group failed to recruit additional prefrontal

and temporal-lobe regions to the same extent as the Healthy and SSD-Response groups. In Experiment 2, multivariate whole-brain analyses revealed a profile of covaried activation unique to the SSD-spatial group suggesting a disconnection between MTL and frontal regions. Interestingly, the SSD-Response group activated the same pattern of activated brain regions as the Healthy groups, but to a greater extent than other groups during the Test Phase, suggesting neural inefficiency in order to support their intact performance. In Study 3, I found converging behavioural evidence that SSD participants who have impaired hippocampal-dependent spatial memory can rely on non-hippocampal dependent forms of spatial memory.

These findings have set the stage for the development of interventions to directly improve real-world navigation and memory abilities. The differential pattern of performance observed suggests that cognitive rehabilitation specialists might develop a training protocol that harnesses the less impaired non-hippocampal dependent spatial memory and/or trains the more deficient ability to employ a hippocampal-dependent cognitive map in order to improve visual-spatial memory and navigation abilities in real-world daily functioning. This dissertation further highlights the importance of strategy use. Thus, a third approach might be to train participants to select different strategies and learn to be aware that the spatial approach of relying on relations among landmarks is more deficient and learn to self-monitor and switch to a body-based response landmark approach. Given evidence of dysfunctional connectivity across the spatial navigation neural circuit, it will also be valuable for researchers to further investigate dissociable brain regions involved in spontaneous strategy use and examine the roles of each contributing brain region in this spatial navigation impairment in SSD. It is important to distinguish the relative roles of individual brain regions as

well as their functioning across the whole brain. For instance, large-scale dysfunction might point more towards neurological rehabilitation and cognitive remediation targeting multiple regions; whereas, intensive training of the hippocampal system more specifically may be apt if core hippocampal dysfunction primarily underlies the larger-scale neural abnormalities and behavioural impairment.

Appendix A: MRI Patient Screening

NAME: _____

FOR PATIENT SAFETY, THESE QUESTIONS MUST BE ANSWERED:

YES NO

1. Have you ever worked with metal;

- Occupational/Hobby?

2. Has metal ever gone into your eyes?

Do you have any of the following?

3. Pacemaker / Defibrillator/ Heart operation
4. Brain Aneurysm clip(s)
5. Cochlear implants/ Hearing aids
6. Neurostimulators (Tens Unit) Spinal implant ?
7. Have you had any surgery

Describe_____

Any within the last six weeks (describe)_____

8. Shrapnel / bullets / body piercing
9. Medication patches?
10. Any implanted devices? Specify _____
11. Do you have any permanent tattoos or eyeliner
12. Are you pregnant?

- The above information is correct to the best of my knowledge. I have read and understand the entire contents of this form and have had the opportunity to ask questions regarding the information on this form:

Signature of Patient: _____ Date:_____

Form reviewed by: _____ Date:_____

- Please remove all metal objects including body piercing, jewelry, hair-pieces/pins. Place all belongings in locker provided. Nothing except the locker key goes into the MRI scan room.
- Please consult the MRI Technologist if you have any concerns or questions BEFORE entering the magnet room

Appendix B: Video Game 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?

11. [POST] Have you been playing games in the past 2 months? Which ones?

12. [6MF-UP] Have you been playing games in the past 6 months? Which ones?

Appendix C: MANOVA SPSS Script

```
Title 'Grice & Iwasaki MANOVA results on Z-scored data'.

Subtitle 'Step 1 Analyses'.

* Both univariate and multivariate results will be printed from the MANOVA

* command below.

MANOVA ZCriterion ZABAA_latency_b ZABAA_errors_b by group(1,2) strategy(1,2)

/print cellinfo(means) homogeneity

/discrim(raw stan) alpha(1.0) /* 'alpha(1.0)' insures all discriminant functions will be printed */

/design.


Subtitle 'Step 2 Analyses for multivariate composite of G x S'.

* Compute the 1st full multivariate composite.

COMPUTE CompositeGXS=(ZCriterion * -1.22479) + (ZABAA_latency_b * -.35467) + (ZABAA_errors_b *
.7804).

MANOVA CompositeGXS BY group(1,2) strategy(1,2)

/design.
```

Appendix D: Strategy Delay Report

Participant 1: “First two trials I was trying to remember what I was supposed to do. It was random. I tried all pathways with no pattern. By third time started using tree and stone.”

Participant 2: “As I was going in the beginning, I guessed and did not use a strategy. I was trying randomly and towards the end I was more aware of the environment.”

Participant 3: “On the second trial, I became more motivated.”

Participant 4: “In the beginning I just tried to memorize barriers and then I used mountains and peaks.”

Appendix E: Courtyard Assessment

Courtyard Spatial Strategies:

- What sorts of thing did you use to try to help you remember where the objects were located?
- Did you use this same strategy from the beginning to the end? If you did change strategies, when did this change occur? How did your strategy/strategies change?
- Did you notice that there were times when your location changed or remained the same?

After recording their answer, clarification and/or elaboration of any aspects could be probed further:

ON THE TRIALS WHERE YOUR LOCATION CHANGED, WHAT SORTS OF THINGS DID YOU USE TO TRY AND HELP YOU REMEMBER WHERE THE OBJECTS WERE LOCATED?

- Did you try to remember how things looked in relation to yourself in the original starting location?
- Did you try and update the location of the objects in relation to yourself in the new starting position?
- Did you try to recall the location of the objects based on the relationship with specific cues on the walls? (Provide Example)

Try to probe whether the individual has either rotated themselves or rotated the environment

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Expected size (number of pages)	180

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28 July 2015

Dear Leanne Wilkins,

Material requested: “Spatial-memory deficit in schizophrenia spectrum disorders under viewpoint-independent demands in the virtual courtyard task”, by Leanne Wilkins, published in Journal of Clinical and Experimental Neuropsychology, Vol35:10, pp1082-1093(2013)

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Sincerely,

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