ABSTRACT: Spatial memory is impaired among persons with schizophrenia (SCZ). However, different strategies may be used to solve most spatial memory and navigation tasks. This study investigated the hypothesis that participants with schizophrenia-spectrum disorders (SSD) would demonstrate differential impairment during acquisition and retrieval of target locations when using a hippocampal-dependent spatial strategy, but not a response strategy, which is more associated with caudate function. Healthy control (CON) and SSD participants were tested using the 4-on-8 virtual maze (4/8VM), a virtual navigation task designed to differentiate between participants’ use of spatial and response strategies. Consistent with our predictions, SSD participants demonstrated a differential deficit such that those who navigated using a spatial strategy made more errors and took longer to locate targets. In contrast, SSD participants who spontaneously used a response strategy performed as well as CON participants. The differential pattern of spatial-memory impairment in SSD provides only indirect support for underlying hippocampal dysfunction. These findings emphasize the importance of considering individual strategies when investigating SSD-related memory and navigation performance. Future cognitive intervention protocols may harness SSD participants’ intact ability to navigate using a response strategy and/or train the deficient ability to navigate using a spatial strategy to improve navigation and memory abilities in participants with SSD. © 2013 Wiley Periodicals, Inc.

KEY WORDS: hippocampus; caudate nucleus; navigational strategies; virtual reality; response learning

INTRODUCTION

Hippocampi and surrounding medial-temporal structures are central to pathophysiological theories of Schizophrenia (SCZ; Christensen and Bilder, 2000; Grace, 2000; Tseng et al., 2009). Moreover, reduced hippocampal volume (Nelson et al., 1998; McCarley et al., 1999; Heckers, 2001) and impaired hippocampal activation during episodic memory tasks have been reliably demonstrated (Heckers et al., 1998). However, characterizing the specificity of hippocampal-dependent memory deficits is important for advancing understanding of the brain-behavior relations affected in SCZ and for developing cognitive remediation strategies.

In this regard, recent studies from our laboratory (Girard et al., 2010; Wilkins et al., 2013) and others (Hanlon et al., 2006; Weniger and Irle, 2008; Folley et al., 2010; Speker et al., 2012) demonstrate robust deficits on tasks associated with hippocampal-dependent learning of allocentric spatial relations among environmental cues in participants with schizophrenia-spectrum disorders (SSDs). These findings are in contrast to relatively spared performance on tasks involving learning to navigate using a body-centered egocentric approach, which involves learning a series of left and right turns or using a stimulus-response approach, which involves identification of a single stimulus (i.e., identification of a landmark), connected with a learned chain of responses, such as left and right body turns. For instance, researchers reported that their SCZ sample performed normally on a virtual water maze under a visible-platform condition, but was impaired at learning to locate a hidden platform relying on knowledge of its allocentric relation to environmental landmarks (i.e., on walls surrounding the maze) (Hanlon et al., 2006). Deficient allocentric learning in the virtual water maze was further correlated with hippocampal grey matter abnormalities in persons with SCZ (Folley et al., 2010). Others had also reported greater deficits among persons with SCZ when learning to navigate a virtual park that demanded formation of an allocentric cognitive map, whereas patients’ performance was intact on a virtual maze that relied on egocentric response-based learning (Weniger and Irle, 2008). Of note, these studies used different tasks to assess spatial and response learning. Thus, we recently extended these findings to demonstrate a within-task differential deficit in allocentric, viewpoint-independent versus viewpoint-dependent memory in an SSD sample.
using both a neuropsychological task (Girard et al., 2010) and an analogous virtual-reality task (Wilkins et al., 2013). Both tasks tested memory for object locations in a three-dimensional spatial array. Taken together, these findings support a differential deficit in hippocampal-dependent spatial memory in SSDs.

However, both spatial and response-based systems can support successful navigation of various environments, albeit using different strategies (Iaria et al., 2003; Bohbot et al., 2004, 2007; Etchamendy and Bohbot, 2007). The spatial memory system involves constructing allocentric relations between landmarks to form a cognitive map. In contrast, the response memory system supports navigation through learning stimulus-response relations such as a series of left and right body turns from a specific starting point.

The 4-on-8 virtual maze (4/8VM) task is a human analog of a rodent eight-arm radial maze designed for ascertaining individual differences associated with spontaneous navigational strategies (Iaria et al., 2003; Bohbot et al., 2007; Etchamendy and Bohbot, 2007). Briefly, task trials begin with participants navigating to target objects located at the end of four open pathways (the other four closed). Subsequently, participants are returned to the maze centre with all eight pathways open and required to remember previously visited pathways to avoid them and retrieve targets hidden down the previously closed pathways. The maze is surrounded by extra-maze landmarks (e.g., tree, rock, mountain, valley) allowing participants to use a spatial strategy by forming an allocentric representation of the configuration of target pathways relative to the distal landmarks. However, participants may also apply a response-based strategy such as remembering the within-maze sequence of target pathways relative to their starting position or a single landmark. In previous studies, approximately half of young adults spontaneously adopted a spatial strategy and half a response strategy on this task (Iaria et al., 2003). Those who spontaneously used a spatial strategy had higher hippocampal gray matter and fMRI activity while navigating a virtual environment; whereas, spontaneous use of a response strategy was associated with higher gray matter and sustained fMRI activity of the caudate nucleus (Iaria et al., 2003; Bohbot et al., 2004, 2007). Patients with medial temporal lobe lesions who also used a spatial strategy performed the 4/8VM with longer latencies and more errors relative to healthy participants, whereas those who used a response strategy performed similarly to controls (Bohbot et al., 2004). In summary, spontaneous adoption of a given strategy has been associated with different brain systems and can be an important determinant of successful navigation and spatial memory performance in clinical populations. Thus, this study employed the 4/8VM to assess the contribution of spontaneous strategy on spatial-memory performance in persons with SSDs.

Since individuals with SSDs are known to have structural and functional abnormalities in the hippocampi, we predicted that individuals with SSDs who spontaneously use a hippocampal-dependent spatial strategy to solve the 4/8VM would be impaired relative to those who spontaneously use a caudate nucleus-dependent response strategy. Given the integral role of locating oneself in space to episodic memory, navigation and efficient day-to-day functioning, understanding the role of spontaneous strategies used by SSD individuals is important for advancing the development of effective neurocognitive interventions.

MATERIALS AND METHODS

Participants

SSD participants (n = 21) were recruited through a research database 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 control (CON) participants (n = 24) were recruited from the Hamilton (Ontario) community via newspaper, Craigslist, and poster advertisements. Participants were excluded 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. SSD participants met criteria for a DSM-IV psychotic disorder (SCZ, Schizoaffective Disorder, Schizophreniform Disorder, Delusional Disorder), as ascertained using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Diagnostic interviews were conducted by trained research assistants or trained senior graduate students. Additionally, all SSD participants were clinically and pharmaco logically 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 lifetime or current nonpsychotic Axis I psychiatric disorder (including alcohol or substance dependence or abuse). CON participants with a first-degree relative with a psychotic disorder were also excluded. Four SSD participants were excluded from analyses due to a failure to meet experimental criterion on acquisition of the 4/8VM (detailed below). Although they failed to meet criterion, we assessed their spontaneous strategy selection. Of those excluded, two SSD participants self-reported using a spatial strategy and two using a response strategy. To equate sample sizes and better match samples on demographic and cognitive measures seven CON were also omitted from the analyses. Data from the remaining SSD (n = 17; 13 male) and CON (n = 17; 8 male) participants are reported below.

Participant characteristics are summarized in Tables (1–3). To assess group and strategy differences across demographic, cognitive, and clinical measures, we ran independent sample t tests and Chi-square tests for continuous and categorical variables, respectively. Overall, the SSD group reported fewer years of education (M = 13.3) and had fewer participants with experience playing three-dimensional games (n = 6) than the CON group (M = 15.2; n = 13), but there were no other demographic differences between groups (CON, SSD) or strategy types (spatial, response), ps > 0.05 (see Table 1). Also, the groups did not differ significantly across global measures of cognition (FSIQe, estimated Full Scale Intelligence Quotient based on Information and Matrix Reasoning subtests from the

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Wechsler Adult Intelligence Scale, Third Edition, Sattler and Ryan, 1998; WRAT-reading, Reading subtest from the Wide Range Achievement Test, Fourth Edition, (Robertson, 2006)) visual-spatial skills (3D mental rotation, Vandenberg, 1978; RBANS-visual spatial index, The Repeatable Battery for Assessment of Neuropsychological Status, (Randolph et al., 1998)), or global functioning (WHODAS, The World Health Organization Disability Assessment Schedule, (Janca et al., 1996)), but persons with SSDs demonstrated poorer episodic memory, attention, and language ability on the RBANS (see Table 2 for descriptive statistics and definitions of abbreviations). Importantly, however, these cognitive differences between groups (CON, SSD) did not interact with navigational strategies (Group ×; Strategy, n.s.) (see Table 2).

The SSD group comprised mainly participants with SCZ or Schizoaffective Disorder, along with one diagnosed with

### TABLE 1.

<table>
<thead>
<tr>
<th>Characteristicsa</th>
<th>CON</th>
<th>SSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (n males/females)</td>
<td>6/2</td>
<td>3/6</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>36.0 (11.5)</td>
<td>36.4 (15.0)</td>
</tr>
<tr>
<td>Education</td>
<td>15.9 (2.0)</td>
<td>14.6 (2.2)</td>
</tr>
<tr>
<td>SESd</td>
<td>44.8 (10.7)</td>
<td>39.9 (13.3)</td>
</tr>
<tr>
<td>Video game experienced</td>
<td>11.3 (10.4)</td>
<td>13.7 (9.1)</td>
</tr>
<tr>
<td>Hours played/week</td>
<td>1.3 (1.4)</td>
<td>14.4 (25.3)</td>
</tr>
<tr>
<td>3D (n)</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

aContinuous data are presented as means (standard deviation), M (SD), and evaluated using independent-samples t tests. Sex and experience with first-person immersive three-dimensional video-game experience (3D) are reported as frequency data (n) and evaluated with $\chi^2$ tests. We evaluated Group × Strategy ANOVAs for continuous variables. We evaluated Group × Strategy for categorical variables with the Cochran–Mantel–Haenszel test.

bG represents significant ($P < 0.05$) main effects of Group; there were no main effects of Strategy or Group × Strategy interactions.

cSocioeconomic status (SES) calculations were based on parental occupations (Blishen et al., 1987).

dAppropriate data were unavailable for three SCZ participants on SES (1 spatial, 2 response) and one CON (spatial) on video game experience.

### TABLE 2.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CON</th>
<th>SSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Characteristics of CON and SSD Groups by Strategy (Spatial, Response)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQe</td>
<td>113.1 (11.2)</td>
<td>110.6 (18.7)</td>
</tr>
<tr>
<td>WRAT-reading</td>
<td>106.8 (10.6)</td>
<td>101.6 (13.0)</td>
</tr>
<tr>
<td>3D Rotationb</td>
<td>14.3 (9.8)</td>
<td>9.9 (6.4)</td>
</tr>
<tr>
<td>WHODAS</td>
<td>13.6 (19.4)</td>
<td>13.6 (14.2)</td>
</tr>
<tr>
<td>RBANS indices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate memory</td>
<td>108.0 (15.4)</td>
<td>93.4 (23.7)</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>98.9 (24.9)</td>
<td>94.0 (20.2)</td>
</tr>
<tr>
<td>Language</td>
<td>108.6 (8.5)</td>
<td>98.7 (10.7)</td>
</tr>
<tr>
<td>Attention</td>
<td>102.4 (11.9)</td>
<td>96.6 (17.2)</td>
</tr>
<tr>
<td>Delayed memory</td>
<td>106.1 (13.4)</td>
<td>97.0 (14.7)</td>
</tr>
</tbody>
</table>

Data are presented as M (SD). We evaluated Group × Strategy interactions for continuous variables using ANOVA and for categorical variables with the Cochran–Mantel–Haenszel test.

bG represents significant ($P < 0.05$) main effects of Group; there were no main effects of Strategy or Group × Strategy interactions.

data were missing for one SCZ participant (response) and one CON (spatial) on 3D rotation.

Abbreviations: FSIQe = Prorated estimate of Full-Scale Intelligence Quotient derived from the Matrix Reasoning and Information subtests of the Wechsler Adult Intelligence Scale—Third Edition, Sattler and Ryan, 1998; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, Randolph et al., 1998); 3D rotation = Mental rotation of three-dimensional geometric shapes, Vandenberg et al., 1978; WRAT-Reading = Reading subtest from the Wide Range Achievement Test–Fourth Edition, Robertson and Wilkinson, 2006; World Health Organization Short Disability Assessment Schedule, Janca et al., 1996.

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Delusional Disorder (see Table 3). There were no differences between these subgroups listed above on the experimental, cognitive, or demographic variables ($p > 0.05$). Interestingly, all of the SSD participants who used a spatial strategy were on a combination of both atypical and typical antipsychotics, whereas those using a response strategy were more likely to be on one type of medication (atypical or typical; see Table 3). The participant with delusional disorder was on an antidepressant, but not antipsychotic medication. On average, participants using a spatial strategy were on higher dosages of antipsychotics and were more symptomatic as measured by the Positive and Negative Symptom Scale (PANSS; Kay et al., 1987), than the SSD group reporting a response strategy (see Table 3). However, as detailed in the Results, accounting for dose and symptomology in the analyses did not affect the pattern of findings. Moreover, the SSD groups were symptomatically stable, scoring below average relative to patient norms on the PANSS (Kay et al., 1987).

As noted above, four SSD participants failed to reach this criterion within the first three trials, testing continued using the A configuration until participants met this criterion. As noted above, four SSD participants failed to reach this criterion within 3 h and were excluded from analyses.

The probe test was administered to further confirm navigational strategies. This trial differed at test in that walls around the radial maze were raised to conceal the landscape and the other landmarks were removed. Testing was discontinued after participants entered four different pathways. The probe test dissociates between spatial and response strategies because a higher error rate is expected among participants using a spatial strategy given the removal of allocentric landmarks.

At the end of the experiment, participants were interviewed to identify their spontaneous navigational strategy. Interviews were audio taped and two independent raters confirmed agreement on the coding of participant strategies. Spatial strategies were operationalized by indication of remembering the positions of target pathways relative to two or more landmarks and the absence of any reference to using a sequence of open and closed pathways from a single position. For example, a participant would be assigned to the spatial strategy group if they mentioned remembering the target pathways in relation to the tree, rock or mountain. In contrast, response strategies were defined as remembering the within-maze sequence of target pathways relative to their starting position or to a single landmark. For example, a participant using a response strategy may report locating the tree as a starting position for their memorized clockwise sequence of open and closed pathways.

The 4/8VM Task

The 4/8VM paradigm has been thoroughly described previously (Iaria et al., 2003; Bobbot et al., 2004, 2007; Etchemendy and Bobbot, 2007). Briefly, the 4/8VM is a computerized virtual environment (created using Unreal Tournament, Epic Games Inc., Raleigh, N.C.) comprised of a virtual eight-arm radial maze with a central starting position, surrounded by extra-maze landmarks (e.g., tree, rock, mountain, and valley). Participants use a keypad with forward, left turn, and right turn buttons to move within the environment. To obtain hidden target objects, participants are required to navigate to the end of the maze arms and down a staircase to a small pit. Prior to testing, participants practiced navigating with the keyboard by exploring a similar environment to the 4/8 task, but without landmarks.

Testing involved a series of two-part trials from a constant start position. In the first part, participants visited four open pathways to retrieve target objects (the other four were blocked). In the second part of each trial, participants were presented with all eight pathways opened and had to avoid the previously visited pathways to find the target objects down the previously closed pathways. All participants completed an initial sequence of three trials across which the configuration of pathways containing target objects changed between the first (configuration A) and second trial (configuration B), with the third trial having the same configuration as the first (configuration A). Thus, we refer to this initial key sequence of trials as the ABA trials. Participants were required to perform two type-A trials without error before proceeding with a probe test. If participants did not meet this criterion within the first three trials, testing continued using the A configuration until participants met this criterion. As noted above, four SSD participants failed to reach this criterion within 3 h and were excluded from analyses.

TABLE 3. Clinical Characteristics of the SCZ-Spectrum Sample by Strategy (Spatial, Response)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Spatial</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnoses (SCZ, schizoaffective, delusional disorder)</td>
<td>3, 5, 0</td>
<td>4, 4, 1</td>
</tr>
<tr>
<td>Medication*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPZ* chlorpromazine equivalents</td>
<td>300.8 (209.7)</td>
<td>102.6 (115.1)</td>
</tr>
<tr>
<td>Atypical, typical, neither, or both antipsychotic types*</td>
<td>0, 0, 0, 8</td>
<td>4, 2, 1, 2</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>PANSS T-scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General*</td>
<td>38.8 (4.3)</td>
<td>33.9 (2.0)</td>
</tr>
<tr>
<td>Negative</td>
<td>39.5 (8.5)</td>
<td>34.7 (5.3)</td>
</tr>
<tr>
<td>Positive</td>
<td>40.0 (13.2)</td>
<td>35.9 (4.7)</td>
</tr>
</tbody>
</table>

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

Appropriate medication data were unavailable for two SSD participants.

Abbreviations: CPZ = chlorpromazine equivalents (Virani et al., 2011; Woods, 2003), PANSS = Positive and Negative Symptom Scale (Kay et al., 1987).

*p < 0.05.

Data Analyses

To test the hypothesized Group × Strategy interaction of differential 4/8VM task impairment in the SDD-Spatial group
RESULTS

Univariate Analyses

Results revealed that SSD participants who reported spontaneous use of a spatial strategy produced longer latencies and more errors on the initial ABA trials, and required more additional trials to meet the acquisition criterion of two correct A

on each performance measure, we conducted univariate analyses on four key dependent variables ( DVs): (1) Trials to Criterion: The number of additional trials required to perform two error-free A trials following the initial ABA sequence. (2) ABA Latency: The summed duration (in minutes) of the initial ABA sequence of trials. (3) ABA Errors: Errors of commission at test across the ABA trials comprised entries into a pathway without a target (incorrect) and repeat pathway entries within a trial. (4) Errors on the probe test: The total number of incorrect pathways visited during the probe test (out of a maximum of four).

We evaluated the first three DVs using a 2 (Group: SSD and CON) × 2 (Strategy: Spatial and Response) factorial analysis of variance (ANOVAs). However, given the discrete and limited scale for probe-test errors, we analyzed these errors using nonparametric statistics. Because of small cell counts across error rates other than perfect performance, we further dichotomized this variable prior to the analysis (error free versus at least one error). We assessed whether Group error differences were contingent on Strategy using the Cochran–Mantel–Haenszel test; homogeneity of the odds ratios across Strategy were confirmed with the Breslow–Day statistic. Of note, we corroborated the probe test results using a 2 × 2 ANOVA on the original full-scale data, but only report the more appropriate nonparametric results below. All results were evaluated at an alpha level of 0.05.

Given overlapping variance among the three 4/8VM acquisition variables, we also applied the multivariate analysis of variance (MANOVA) approach (Grice and Iwasaki, 2007) to assess the extent to which a more comprehensive linear combination of the acquisition parameters account for the Group × Strategy interaction. Moreover, this linear composite was used to minimize redundancy in assessing correlations between task performance and demographic, cognitive, and clinical attributes, along with follow-up covariate analyses. That is, the two-factor between-subjects MANOVA provides a single multivariate composite that maximally accounts for the Group × Strategy interaction across measures, allowing for unified correlational analyses, rather than performing multiple redundant analyses for each of the variables within each subsample. Given the different measurement scales, the dependent measures were standardized prior to analysis. Our data met the required assumptions of independence, univariate and multivariate normality, and homogeneity of variance-covariance matrices (Grice and Iwasaki, 2007).

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. Please see text for further description of these measures.
$\eta^2 = 0.18$. However, the Group × Strategy interaction failed to reach significance, $F(1,30) = 1.83, P = 0.19, \eta^2 = 0.06$. Nonetheless, follow-up analyses revealed that the SSD-Spatial group was impaired relative to the CON-Spatial group, $t(14) = -2.18, P = 0.047, d = -1.17$. The Response SSD and CON groups did not differ significantly, $t(16) = -1.45, P = 0.166, d = -0.73$.

Finally, the probe test did not reveal differential patterns of errors in the Group by Strategy analysis, $\chi^2_{CHI}(1) = 0.625, P = 0.429$. There was no overall Group difference on this measure, $\chi^2(1) = 1.36, P = 0.244, \phi = 0.20$. Across groups, there was a moderate, but nonsignificant, tendency in the expected direction for more participants in the Response groups to perform error-free on the probe test, $\chi^2(1) = 3.03, P = 0.081, \phi = 0.30$.

### Multivariate Analyses

Supporting the composite univariate analyses, the MANOVA revealed a statistically significant Group × Strategy interaction, Wilks’ $\lambda = 0.73, F(3, 28) = 3.41, P = 0.031$. The multivariate composite of the dependent measures (Trials to criterion, ABA latency, ABA errors) accounted for 27% of the variance pertaining to the Group × Strategy interaction, according to Roy’s greatest characteristic root, g.c.r. ($s = 1, m = 1/2, n = 13) = 0.27, P < 0.05$. As such, the MANOVA approach yielded a multivariate gain of 11% in accounting for the Group × Strategy interaction beyond that detected by the univariate analyses above (Grice and Iwasaki, 2007). Consistent with the univariate results, the standardized discriminant function coefficients identified Trials to criterion (ws = −0.86) and ABA latency (ws = −0.74) as main contributors to the interaction effect, with ABA errors adding substantially less to the overall function (ws = 0.24). Following the approach outlined by Grice and Iwasaki (2007), we created a simplified multivariate composite = (−1) (Trials to Criterion) + (−1) (ABA Latency) + (0) (ABA errors). Conceptually, this simplified composite reflects an equally weighted combination of the criterion and latency measures as an index of overall performance on the 4/8VM. Further analyses of the full and simplified models revealed near-identical results, with the latter only resulting in a loss of 1% explanatory power. Given the greater stability and general applicability to future studies, we present results from the simplified composite here.

ANOVA on the simplified composite yielded a Group × Strategy interaction, $F(1,30) = 10.48, P = 0.003, \eta^2 = 0.26$, as well as main effects of Group, $F(1,30) = 20.19, P < 0.001, \eta^2 = 0.40$, and Strategy, $F(1,30) = 11.81, P = 0.002, \eta^2 = 0.28$. As shown in Figure 1, the interaction reflected that the SSD-Spatial group was impaired relative to the other three groups, $t(30) = 6.13, P < 0.001, d = 2.31$, which did not differ from one another, $F(2,23) = 0.52, P = 0.603, \eta^2 = 0.04$.

### Correlation and Covariate Analyses

The relationships between demographic, cognitive, and clinical variables (as listed in Tables 1–3, respectively) with the simplified composite measure of 4/8VM performance were explored via bivariate correlations within the SSD and CON groups. Better performance among CON participants was significantly associated with sex (male > female), $r_{pb} = 0.53, P = 0.041$, 3D videogame experience, $r_{pb} = 0.52, P = 0.033$, and higher visual-spatial abilities (3D mental rotation, $r = 0.65, P = 0.007$; RBANS visuospatial index, $r = 0.55, P = 0.022$). Among the SSD sample, better performance was significantly related to younger age, $r = -0.50, P = 0.041$, WRAT-Reading scores, $r = 0.54, P = 0.026$, and 3D Mental Rotation abilities, $r = 0.52, P = 0.041$. Consistent with the higher symptom ratings and antipsychotic dosage among SSD participants who used a spatial strategy compared to those using a response strategy (see Table 3), General PANSS scores, $r = -0.53, P = 0.044$, and CPZe, $r = -0.54, P = 0.024$, were related to worse 4/8VM performance.

In light of these correlations and group differences, the impact of these variables (i.e., sex, 3D gaming experience, 3D mental rotation scores, RBANS visuospatial index scores, age, and WRAT-Reading scores) on the main Group × Strategy interaction was explored using covariate analysis. Importantly, the Group × Strategy interaction remained significant, $F(1, 21) = 15.46, P < 0.001, \eta^2 = 0.42$, as did the main effects of Group, $F(1, 21) = 7.16, P = 0.014, \eta^2 = 0.25$, and Strategy, $F(1, 21) = 14.80, P < 0.001, \eta^2 = 0.41$. In addition, we ran two-way ANOVAs on matched subsamples regarding sex and 3D gaming experience: The Group × Strategy interaction remained robust among females, $F(1, 9) = 10.67, P < 0.010, \eta^2 = 0.54$, males, $F(1, 17) = 6.34, P = 0.022, \eta^2 = 0.27$, and among those with, $F(1, 15) = 8.96, P = 0.009, \eta^2 = 0.37$, and without 3D-gaming experience, $F(1, 11) = 8.76, P = 0.013, \eta^2 = 0.44$ (see Fig. 2).

Within the SSD sample, the mean deficit among SSD-Spatial versus SSD-Response participants remained significant when covarying the variance shared with antipsychotic dosage (CPZe), $F(1, 14) = 9.52, P = 0.008, \eta^2 = 0.41$, and differences in symptomatology (PANSS-General), $F(1, 12) = 6.98, P = 0.022, \eta^2 = 0.37$. Moreover, inspection of the data indicated that among SSD participants matched on symptomatology or CPZe, as well as types of medication, those in the SSD-spatial subgroup consistently performed worse than their response subgroup counterparts. These results suggest that the Group × Strategy interaction cannot be fully explained by the SSD spatial group having a higher General PANSS and CPZe. Figure 3 illustrates the relation between dosage (CPZe) and 4/8VM task performance.

Likewise, follow-up assessment regarding anti-depressant and anxiolytic use (coding subgroups as using an antidepressant, anxiolytic, neither, or both) failed to reveal any differential effects on performance. Within the SSD group, a Drugs × Strategy ANOVA maintained a robust main effect of Strategy (Response > Spatial), $F(1, 11) = 8.10, P = 0.016, \eta^2 = 0.42$, but neither an effect of Drugs, $F(3, 11) = 0.17, P = 0.916, \eta^2 = 0.04$, nor Drugs × Strategy interaction, $F(1, 11) = 0.33, P = 0.580, \eta^2 = 0.03$. 

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We also addressed potential differences across diagnostic subtypes. Because there was only a single patient with the diagnosis of Delusional Disorder and this patient was not taking antipsychotics, we repeated our analyses without this participant. All results and conclusions were replicated. For example, the ANOVA on the simplified composite measure of 4/8VM performance yielded identical \( P \)-values and effect sizes to the analysis with this participant included (reported above), e.g., Group \( \times \) Strategy interaction omitting this patient, \( F(1,29) = 10.17, P = 0.003, \eta^2 = 0.26 \). This participant scored in the middle of the overall distribution on the simplified composite (score = 0.08), falling close to her SCZ (\( M = 0.04 \)) Response group counterparts and slightly below those with Schizoaffective disorder (\( M = 0.80 \)). Although patients diagnosed with Schizoaffective disorder performed better than those with SCZ, this difference was not significant, \( F(1, 12) = 1.32, P = 0.413 \), and of small magnitude, \( \eta^2 = 0.06 \). Moreover, this relation was consistent across Strategies, Group \( \times \) Strategy, \( F(1, 12) = 0.12, P = 0.801, \eta^2 < 0.01 \): The SSD-Spatial group performed significantly and substantially worse than their SSD-Response counterparts across diagnoses, \( F(1, 12) = 28.17, P = 0.002, \eta^2 = 0.56 \).

**FIGURE 2.** The greater impairment among SSD participants reporting spontaneous use of a Spatial versus Response strategy remained robust across subsamples matched by (A) sex and (B) those with (yes) and without (no) 3D videogame experience.

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**FIGURE 3.** Scatter plot of the correlations between medication dosage (CPZe) and 4/8VM performance. Overall, greater dosage was significantly correlated with poorer performance in the SSD group (\( r = -0.54 \)). However, this relation failed to account for the behavioral difference between SSD subgroups. Regression lines for the SSD response and spatial subgroups are similar and less robust: SSD-Spatial, \( r = -0.30 \); SSD-Response, \( r = -0.22 \). Comparison between SSD-spatial and SSD-response individuals with comparable CPZe levels indicates that those with a spatial strategy consistently perform worse (with one exception).
Hanlon et al., 2006; Weniger and Irl, 2008; Girard et al., 2010; Wilkins et al., 2013). This conclusion is in line with evidence that use of a spatial strategy depends on the integrity and recruitment of the hippocampal system (O’Keefe, 1978; Smith and Milner, 1989), whereas response strategies are associated with the caudate nucleus in humans (Hartley et al., 2003; Iaria et al., 2003; Bohbot et al., 2004, 2007) and striatum (Packard et al., 1989; McDonald and White, 1994). These data further support that the hippocampus and caudate nucleus memory systems can function independently of each other (McDonald and White, 1994; Bohbot et al., 2004).

Beyond corroborating previous studies reporting deficient allocentric spatial memory in SCZ, these results are consistent with evidence of selective behavioral deficits in hippocampal-dependent spatial and episodic memory and contextual processing (Boyer et al., 2007). Indeed, hippocampal abnormalities and deficient episodic memory are reliably reported in the SCZ literature (Heckers, 2001; Heinrichs, 2005; Bowie and Harvey, 2006). For example, reduced hippocampal volume is a reliable finding (Nelson et al., 1998; McCarley et al., 1999) and individuals living with SCZ show impaired recruitment of this brain region during performance on episodic memory tasks (Heckers, 2001). The overall pattern of memory impairment in some SCZ samples appears comparable to that of individuals with medial-temporal lobe (MTL) lesions (Ornstein et al., 2008; Bartholomew et al., 2011). This study builds upon this literature and our findings of episodic and allocentric spatial memory deficits in SCZ (Girard et al., 2010; Wilkins et al., 2013) by demonstrating the importance of strategy use.

The observation that participants with SSD demonstrated normal performance when utilizing a strategy dependent on the caudate nucleus memory system has important clinical implications. Keri et al. (2005) also found evidence of spared stimulus-response learning in SCZ. In their study, stimulus-response learning was assessed using the Rutgers acquired equivalence task, which requires participants learn associations between faces and different colored fish. Using the same task, stimulus generalization required participants to learn to equate the value of two stimuli when they had been associated with the same response. SSD participants performed better on stimulus-response learning compared to more hippocampal-dependent stimulus-generalization learning. These findings are consistent with our data, which suggest that variability in memory performance in SCZ may be related in part, to the variability in learning strategies available to solve a given task. In other words, the current data may help explain individual differences in participants with SSD, in terms of autonomy to navigate to places without getting lost.

Interestingly, our data suggest the caudate nucleus in participants with SSD is less affected by the disease when compared to hippocampal systems. However, the extant literature shows inconsistent findings with respect to caudate nucleus abnormalities in SSD (Beninger et al., 2003; Purdon et al., 2003). Evidence suggests volumes of the caudate nucleus among individuals experiencing first episode psychosis do not differ from CON volumes, but that delay in treatment of antipsychotics and positive symptomology relate to reduced volume in the caudate nucleus (Crespo-Facorro et al., 2007). Additionally, an antipsychotic-naive SCZ sample had reduced caudate nucleus volumes relative to a CON group (Banner et al., 2011), indicating that duration of untreated illness might adversely affect the caudate nucleus. Conversely, treatment with atypical antipsychotics was associated with increased caudate nucleus volume (Okugawa et al., 2007). Given the particular relation of response-based strategies to the caudate nucleus, the 4/8VM offers a valuable tool for future investigation regarding the functional relevance of the above volumetric findings and their associations with the course of illness and medications in SSD and SCZ.

**LIMITATIONS AND FUTURE DIRECTIONS**

In this study, we sampled across the SCZ spectrum and found a consistent pattern of differential performance within a small heterogeneous sample of SSD participants. In the future, a larger study with a greater representation of diagnostic subgroups will be valuable to assess whether the differential pattern remains consistent across subgroups. However, it remains interesting that half of our SSD sample used a spatial strategy, despite their robust impairment in doing so; whereas, the other half of our SSD sample used a response strategy and performed as well as the CON group. It is of potential interest that the SSD-Spatial group was slightly more symptomatic and substantially more medicated (in terms of dosage, and taking a combination of typical and atypical antipsychotics) than the SSD-Response group. Follow-up analyses indicate that these variables failed to fully account for the difference in behavioral impairment within the SSD-Spatial group. Nonetheless, it is an intriguing possibility that more severe disease and/or higher medication dosage might influence spontaneous navigation strategy. For example, higher blockage of dopamine receptors in the striatum due to antipsychotic medication, may lead to a shift in spontaneous adoption from a successful response approach to a deficient hippocampal-dependent spatial approach. In addition, we did not have the statistical power to assess the influence of combined usage of antipsychotics and antidepressants/anxiolytics on behavioral performance on the 4/8VM. It remains plausible, that use of antidepressants in combination with antipsychotics could ameliorate the SSD-spatial deficit or prevent an antipsychotic induced shift from a response to a spatial strategy. Understanding the mechanisms underlying idiosyncratic spontaneous strategies in CON and SSD populations, and their relations to symptoms and medication, may shed light on important individual difference factors that might inform early detection, monitoring disease progression, or treatment strategies for cognitive impairment in SSD.

Based on the current findings, along with its previously demonstrated sensitivity to both hippocampal and striatal system functioning and their inter-relations, the 4/8VM promises a valuable tool for such further investigation.

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The role of prefrontal regions in regulating and coordinating hippocampal and caudate nucleus memory systems’ involvement in navigation and memory also deserves further attention (Brown et al., 2012; Dahmani and Bohbot, 2012). In this regard, participants may flexibly shift their strategies on the 4/8VM and in real life. However, individuals with SSD who adopt a deficient spatial strategy may perseverate in doing so rather than shift to a response strategy without external cuing or instruction. This hypothesis is in line with models supporting SSD as a prefrontal-medial temporal lobe disconnection syndrome (Spieker et al., 2012). Future studies will be necessary to further explore the role of shifting strategies and navigation in SSD. Cognitive and brain imaging studies will also help to uncover the extent to which differences in behavioral performance in the SSD-Spatial and -Response groups reflect hippocampal, caudate nucleus, and prefrontal networks.

**CONCLUSION**

In summary, our results reveal a selective deficit among SSD participants using a Spatial strategy, compared to those using a Response strategy, despite the fact that all SSD participants were tested on the same dual-solution task with the same instructions. These findings corroborate previous reports of impaired episodic memory and spatial navigation abilities in SCZ. Moreover, the results highlight the importance of assessing strategies among individuals with SSD as important determinants of navigational and memorial performance and possibly the related functional integrity of underlying neural mechanisms such as the caudate-nucleus and hippocampi. Given the integral roles of spatial memory and navigation, use of response-based versus spatial strategies may afford more functional ability in everyday life among those with SSD. Thus, these findings set the stage for developing interventions that target strengthening the hippocampal system and spatial-strategies or explore methods that might train SSD participants to adopt the intact response system during real-world navigation. An important next step, however, will be to better understand the mechanisms underlying individual differences in spontaneous strategies and their relations to progression of psychosis and antipsychotic medication related factors. Emerging findings indicate that it will also be important to take into consideration genetic (Banner et al., 2011), hormonal (Bohbott et al., 2011), and lifespan development factors (Bohbott et al., 2012; Schwabe et al., 2012).

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