Psychiatry Research 278 (2019) 125–128

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Short communication

Spontaneous spatial navigation circuitry in schizophrenia spectrum disorders

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ARTICLE INFO

Keywords:
Spatial memory
Magnetic resonance imaging
Functional neural networks

ABSTRACT

Spatial memory is core to wayfinding and everyday memory. Interestingly, individuals with schizophrenia using spatial navigation strategies (cognitive mapping) are impaired, whereas those using response-based (e.g., single-landmark) strategies show relatively intact memory performance. We observed abnormal brain communication in schizophrenia participants who used a spatial strategy during a virtual-reality navigation task, particularly between temporal and frontal brain regions. In contrast, schizophrenia participants using a response strategy recruited similar brain systems to healthy participants, but to a greater extent to support memory performance. These findings highlight that strategy use is an important consideration for understanding memory systems and navigation in schizophrenia.

1. Introduction

Spatial memory is core to wayfinding in everyday life and to supporting episodic memory, which is a key predictor of functional outcome among persons with Schizophrenia Spectrum Disorders (SSD; Ranganath et al., 2008). SSD is associated with robust spatial-memory deficits. Importantly, however, impairment is particularly observed on tasks involving memory for allocentric spatial relations among environmental cues ("cognitive mapping") with relatively spared performance on tasks involving response-based approaches that rely on body-centered or single landmark-based representations (e.g., Girard et al., 2010; Hanlon et al., 2006). Outside of task constraints, as in the real world, one may flexibly apply these navigation-memory systems. Likewise, the 4-on-8 virtual-maze (4/8VM) task, a human analog of the rodent radial-arm maze, allows for the assessment of individual differences in spontaneous use of these 'spatial' and 'response' strategies, as either is sufficient for remembering target locations to perform this task. As in healthy participants (Bohbot et al., 2004, 2007; Iaria et al., 2003), we found that approximately half of SSD participants also spontaneously adopt each of these strategies on the 4/8VM (Wilkins et al., 2013). However, those who use a spatial-mapping strategy are impaired compared to healthy participants, whereas SSD participants who use a response-based strategy demonstrate relatively intact performance (Wilkins et al., 2013). Thus, strategy used is an important moderator of memory performance in SSD participants.

Interestingly, individual differences in spatial and response strategy use in healthy samples relate to differences in functional and anatomical integrity of the hippocampus and caudate nucleus, respectively (Bohbot et al., 2004, 2007; Iaria et al., 2003), as well as differential relations to ventral and dorsal prefrontal regions (Dahmani and Bohbot, 2015). Extending this work, we recently observed that use of a spatial strategy among SSD participants relates to deficient recruitment of the right hippocampus and lower activation of other temporal, sensorimotor, and cerebellar regions, but greater activation of the left caudate nucleus and inferior frontal cortex (Wilkins et al., 2017). Our prior results (Wilkins et al., 2017) support frontal-temporal disconnection in SSD and again highlight modulation by strategy use. It will be important to understand these strategy-related differences in SSD towards informing cognitive remediation approaches. Given that the above results are based on voxel-wise contrast analyses and on the involvement of multiple brain regions, it is necessary to more directly explore the extent of functional (dis)connectivity in SSD spatial learners

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https://doi.org/10.1016/j.psychres.2019.05.032
Received 15 March 2019; Received in revised form 17 May 2019; Accepted 19 May 2019
Available online 21 May 2019

at a whole-brain level and whether there are also differences in connectivity supporting SSD response learners' intact performance.

Thus, in the current study, we apply whole-brain multivariate spatial-temporal analysis (partial-least squares, PLS) to the data from Wilkins et al. (2017) to directly address the functional connectivity (correlated BOLD activity) among brain regions during initial and later trials of the 4/8VM task, in relation to strategy use and behavioural performance. In previous 4/8VM studies, healthy groups using spatial strategies were distinguished by greater hippocampal activation during early learning (on Trial 1), whereas those using response strategies showed later activation of the caudate-nucleus, by Trial 4 until the learning criterion was reached (Bohbot et al., 2004, 2007; Iaria et al., 2003). Thus, we focus the PLS analyses on the initial (Trial 1) and last (Trial 4) test trials for optimal comparison of group and strategy relations to extended functional brain connectivity. In particular, the current study aimed to identify brain systems associated with the differential use of spontaneous navigation strategies and memory in SSD.

2. Method

2.1. Participants

Detailed sample characteristics are described in Wilkins et al. (2017). In brief, 16 SSD participants (10 Schizophrenia, 6 Schizoaffective; 6 female) were recruited from St. Joseph's Healthcare Hamilton and the Hamilton Program for Schizophrenia, and 16 healthy participants (10 female) were recruited via community advertisement. On average, the SSD group was older (Mean ± SD = 40 ± 6), less educated (13.5 ± 2 years), and had lower premorbid intelligence (95 ± 11.5) than the healthy sample (31 ± 14; 17 ± 3; 109 ± 12), ps < 0.05, but the means reflect a high functioning SSD sample. Patients were on an average dose of 180 ± 91 mg (chlorpromazine equivalents); 12 were on atypical antipsychotics, 2 on typical, 1 on both, and 1 on neither. All participants provided informed consent and the study was approved by the Research Ethics Boards at Ryerson University and St. Joseph's Healthcare Hamilton.

2.2. The 4/8VM task

The 4/8VM is a computerized virtual environment analogue of the rodent eight-arm radial maze with a central starting position, surrounded by extra-maze landmarks (e.g., tree, mountain). Participants completed four study-test trial pairs in the scanner, each starting with a Visuo-Motor Control (see Wilkins et al., 2017 for further details).

2.3. fMRI acquisition and preprocessing

fMRI data were obtained using T2*-weighted EPI acquisition at 3T on an oblique angle perpendicular to the long axis of the hippocampi (34 contiguous 3-mm slices; TR = 4000 ms, TE = 30 ms, FA = 90°, 128 × 128 matrix, FOV = 25.6). Standard preprocessing of functional images was completed using SPM8. Functional scans were co-registered to T1 anatomical MRIs (1-mm^3), resampled to 2-mm^3 and B0 field maps were applied to correct for inhomogeneity. Images were normalized based on grey-matter segmentation parameters and smoothed with an 8-mm Gaussian filter.

2.4. PLS analyses

PLS is a multivariate technique adapted for brain-imaging analyses introduced by McIntosh et al. (1996) to identify patterns of activity that covary across space (brain voxels) and time. We used mean-centered PLS, which is an exploratory (non-seed based) analysis, to extract patterns (latent variables, LVs) of correlated brain activity in relation to Group, Strategy use, and Condition (Memory Test Phase, Visuo-Motor Control). We also used behaviour PLS to assess brain-behaviour correlations across voxels associated with 4/8VM performance scores. As in previous studies (Wilkins et al., 2013, 2017), performance was indexed by a multivariate composite of Latency and Errors of commission on the Test Trials 1 and 4.

For both analyses, 500 permutations (DeBrigard et al., 2013) and 300 bootstrap resampling estimations (Addis et al., 2009) were used to derive 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). MNI coordinates for these clusters were imported to SPM8 and anatomical labels were determined via the WFU_ PickAtlas (Wake Forest University).

3. Results

3.1. PLS results

3.1.1. fMRI mean-centered PLS at trial 1

The mean-centered PLS identified one significant pattern (LV) of correlated brain activity at Trial 1 that accounts for 63.38% of the covariance between brain activity and the Group × Strategy × Condition design, $p < .005$, SV = 194.50. The brain regions involved in this functional network comprised primarily temporal-lobe regions (including the hippocampus), an occipital cluster, small cerebellar clusters, and very little prefrontal involvement (See Fig. 1 and Supplementary Table 1). As shown by the pattern of brain scores in Fig. 1, this functional network was primarily driven by the SSD-Spatial group, such that these regions were significantly more active than the same contrast in the other groups, i.e., during retrieval on the Test Phase vs. Visuo-Motor Control condition. Interestingly, the interaction effect is such that the SSD-Response participants showed the reverse pattern for this correlated network (Test < Visuo-Motor). This pattern of mainly temporal-lobe connectivity across task Conditions and Strategy also held for the respective Healthy groups, but was much less prominent.

3.1.2. fMRI mean-centered PLS at trial 4

The mean-centered PLS also identified only one significant pattern of functional connectivity at Trial 4, accounting for 61.34% of the variance, $p < .001$, SV = 195.40. This LV reflects predominantly frontal-parietal regions (see Supplementary Figure S1 and Table S2) that were more active during the Test Phase than Visuo-Motor Control for the SSD-Response group. The brain scores for both Healthy groups and the SSD-Spatial group were not significant.

3.1.3. fMRI behaviour PLS

At Trial 1 only, behaviour PLS analysis yielded a significant LV ($p < .002$; SV = 241.81) that accounted for 50.38% of the covariance between brain activity and memory performance during the Test Phase. The LV 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 Healthy-Spatial ($r = .87$), Healthy-Response ($r = .76$) and SSD-Response ($r = .72$). Better performance was related to higher brain scores in the distributed pattern of activity across the neocortex, left hippocampus, right dorsal striatum, thalamus, and cerebellum (see Supplementary Figure S2 and Table S3) in these groups.

4. Discussion

Mean-centered analysis revealed a pattern of hyperactive connectivity during the first Test Phase in the SSD-Spatial group, focusing largely on temporal lobe activation with little frontal involvement, suggesting inefficient use of medial-temporal regions and frontal-

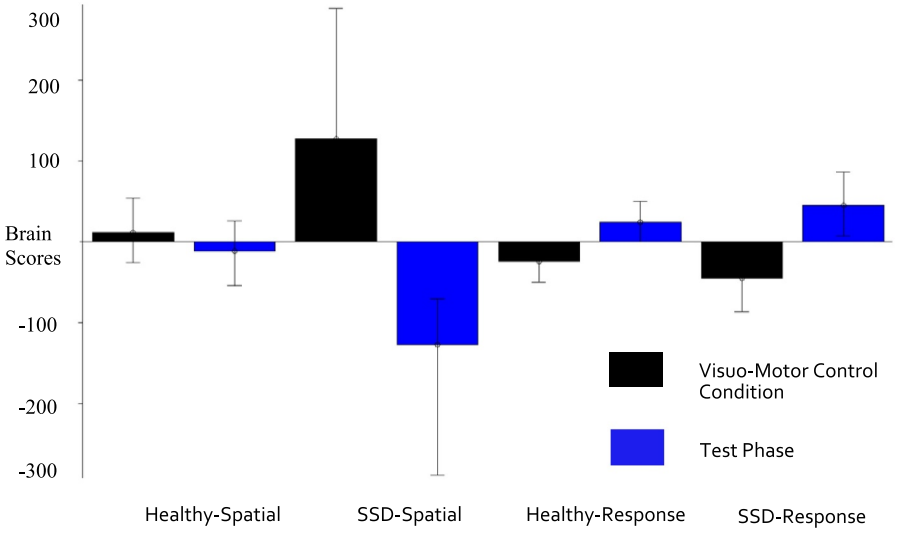
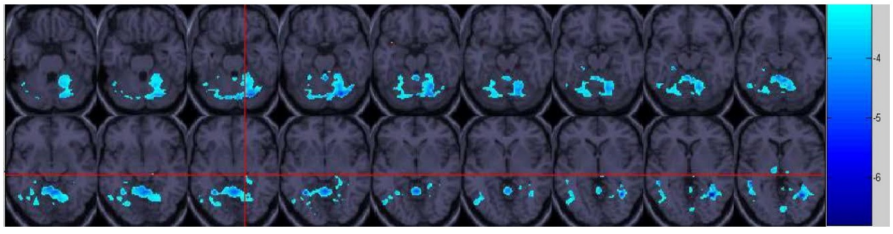


Fig. 1. Functional connectivity during the initial (Trial 1). The graph at top highlights that this network predominantly reflects brain regions in the SSD (schizophrenia spectrum disorders) participants who used a Spatial Strategy that were more involved during the Test Phase than Visuo-Motor Control condition. This network comprised largely temporal brain regions, as well as cerebellar and occipital regions, but little frontal involvement (shown in cool colours at bottom; see Table S1). To orient the viewer, the crosshairs are located in the right-hippocampal cluster, which arose from the PLS analysis. The colour-coded scale reflects BSR (bootstrap ratio) values thresholded at $p < .001$.



temporal disconnection. The SSD-Spatial group also stood out in the behaviour PLS, whereas the two Healthy and SSD-Response groups displayed a similar relation between performance and a network of activity spanning both hippocampal and dorsal-striatal clusters, as well as frontal, temporal, insular, parietal, and occipital, and cerebellar clusters. Interestingly, whereas prior behavioural and contrast analyses (Wilkins et al., 2013, 2017) did not differentiate the SSD-Response group from healthy participants, functional connectivity at Trial 4 distinguished the SSD-Response group, including a large, robust frontal-parietal network, which may indicate more neural effort directed toward adoption of a habit-based navigation strategy following practice across trials. These results may also indicate overcompensation involved in selecting the appropriate strategy due to neural inefficiencies in the SSD-Response group.

A limitation is that our samples were not demographically matched. Although prior studies found that these variables did not account for the key strategy-related differences on the 4/8VM (Wilkins et al., 2013, 2017), it will be informative to assess the generalizability of these findings across a range of samples in future.

These differential patterns of functional connectivity highlight the importance of strategy use as a moderator of extended neural networks involved in spatial memory in SSD. It will be important to understand these strategy-related differences in SSD towards informing cognitive remediation approaches.

Further research will investigate whether specific subtypes of SSD guide intervention avenues while considering clinical factors (disease onset, progression, symptoms, medications), and whether they extend to other SSDs, subclinical, and unaffected relatives. Future work may also explore relations to functional outcome and amenability to cognitive training.

Acknowledgements

This research was supported, in part, by grants from NARSAD (The Brain and Behaviour Research Foundation, Grant #16343) and the Faculty of Arts at Ryerson University to TAG.

Conflict of interest

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

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.05.032.

References

Addis, D.R., Pan, L., Vu, M.A., Laiser, N., Schacter, D.L., 2009. Constructive episodic simulation of the future and the past: distinct subsystems of a core brain network mediate imagining and remembering. Neuropsychologia 47, 2222–2238. https://doi:10.1016/j.neuropsychologia.2008.10.026.

Bohbot, V.D., Iaria, G., Petrides, M., 2004. Hippocampal function and spatial memory: evidence from functional neuroimaging in healthy participants and performance of patients with medial temporal lobe resection. Neuropsychology 18https://doi.org/10.1037/0894-4105.18.3.418. 428-425.

Bohbot, V.D., Lerch, J., Thorndycraft, B., Iaria, G., Zijdenbos, A., 2007. Gray matter differences correlate with spontaneous strategies in a human virtual navigation task. J. Neurosci. 27, 10078–10083. https://doi.org/10.1523/jneurosci.1763-07.2007.

Dahmani, L., Bohbot, V., 2015. Dissociable contributions of the prefrontal cortex to hippocampus and caudate nucleus-dependent virtual navigation strategies. Neurobiol. Learn. Mem. 117, 42–50. http://dx.doi.org/10.1016/j.nlm.2014.07.002.

DeBrigard, F., Addis, D.R., Ford, J.H., Schacter, D.L., Giovanello, K.S., 2013. Remembering what could have happened: neural correlates of episodic counterfactual thinking. Neuropsychologia 51, 2401–2414. https://doi:10.1016/j.neuropsychologia.2013.01.015.

Girard, T.A., Christensen, B.K., Rizvi, S., 2010. Visual–spatial episodic memory in

schizophrenia: a multiple systems framework. Neuropsychology 24, 368–378. https://doi.org/10.1037/a0018313.

Hanlon, F.M., Weisend, M.P., Hamilton, D.A., Jones, A.P., Thoma, R.J., Huang, M., Martin, K., Yeo, R.A., Miller, G.A., Canive, J.M., 2006. Impairment on the hippocampal-dependent virtual morris water task in schizophrenia. Schizophr. Res. 87, 67–80. https://doi.org/10.1016/j.schres.2006.05.021.

Iaria, G., Petrides, M., Dagher, A., Pike, B., Bohbot, V.D., 2003. Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. J. Neurosci. 23, 5945–5952. https://doi.org/10.1523/jneurosci.23-13-05945.2003.

McIntosh, A.R., Bookstein, F.L., Haxby, J.V., Grady, C.L., 1996. Spatial pattern analysis of functional brain images using partial least squares. Neuroimage 3, 43–157. https://doi:10.1006/nimg.1996.0016.

Ranganath, C., Minzinberg, M., Ragland, J.D., 2008. The cognitive neuroscience of memory function and dysfunction in schizophrenia. Biol. Psychiatry 64, 18–25. https://doi.org/10.1016/j.biopsych.2008.04.011.

Wilkins, L.K., Girard, T.A., Herdman, K.A., Christensen, B.K., King, J., Kiang, M., Bohbot, V.D., 2017. Hippocampal activation and memory performance in schizophrenia depend on strategy use in a virtual maze. Psychiatry Res. Neuroimag. 268, 1–8. http://dx.doi.org/10.1016/j.pscychresns.2017.07.007.

Wilkins, L.K., Girard, T.A., Konishi, K., King, M., Herdman, K.A., King, J., Christensen, B.K., Bohbot, V.D., 2013. Selective deficit in spatial memory strategies contrast to intact response strategies in patients with schizophrenia spectrum disorders tested in a virtual navigation task. Hippocampus 23, 1015–1024. https://doi.org/10.1002/hipo.22189.