Short communication

Dorso- and ventro-lateral prefrontal volume and spatial working memory in schizotypal personality disorder

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ABSTRACT

Schizotypal personality disorder (SPD) individuals and borderline personality disorder (BPD) individuals have been reported to show neuropsychological impairments and abnormalities in brain structure. However, relationships between neuropsychological function and brain structure in these groups are not well understood. This study compared visual–spatial working memory (SWM) and its associations with dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) gray matter volume in 18 unmedicated SPD patients with no BPD traits, 18 unmedicated BPD patients with no SPD traits, and 16 healthy controls (HC). Results showed impaired SWM in SPD but not BPD, compared with HC. Moreover, among the HC group, but not SPD patients, better SWM performance was associated with larger VLPFC (BA44/45) gray matter volume (Fisher's Z p-values <0.05). Findings suggest spatial working memory impairments may be a core neuropsychological deficit specific to SPD patients and highlight the role of VLPFC subcomponents in normal and dysfunctional memory performance.

Published by Elsevier B.V.

Schizotypal personality disorder (SPD) is characterized by asocial tendencies, difficulties with language, paranoia, odd behavior, and magical thinking. Borderline personality disorder (BPD), on the other hand, is characterized by affective instability and impulsive behavior and was first included in DSM-III [1,2]. Many of the earlier SPD studies included symptoms related to conceptions of BPD, but diagnostic overlap was somewhat modified when the criterion of paranoid ideation under stress in BPD was introduced in DSM-III-R [3,4]. Nonetheless, co-morbidity of SPD and BPD is not uncommon [5], which may be due to overlapping areas of impairment [6] or to similar diagnostic nomenclature. Given the potentially overlapping and diverging neurobiological and phenotypic aspects of SPD and BPD, as well as the inherent complexity of both, this study worked to clarify commonalities and distinctions among SPD, BPD and HC individuals on one specific type of neuropsychological functioning, visual–spatial working memory, and the dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) morphometric correlates.

Previous studies reviewing neuropsychological impairments in individuals with SPD consistently document disruptions in working memory [7–12]. Neuropsychological investigations of individuals with BPD also reveal deficits in non-verbal domains of functioning [13–17], including visual–spatial working memory [18]. Nonetheless, although a meta-analysis of neuropsychological findings in BPD by Ruocco [16] revealed that BPD deficits seem to be primarily lateralized to the right hemisphere [19], it also included studies that failed to detect any neuropsychological difficulties in BPD. Ruocco [16] concluded that further examination of brain–behavior relationships is required to better characterize and elucidate neurocognitive functioning in BPD and personality disorders in general. In the current study, our aim was to investigate one aspect of this brain–behavior relationship, namely volume of DLPFC and VLPFC regions subserving visual–spatial working memory function in SPD and BPD—two personality disorder groups shown to exhibit cognitive deficits and frontal lobe dysfunction [20,21]—as compared

Table 1
Clinical interview and self-report ratings in healthy control, borderline personality disorder, schizotypal personality disorder groups.

	Healthy controls			Borderline PD patients			Schizotypal PD patients		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Symptom severity[a]	16	–	–	18	7.53	0.98	18	7.14	1.22
State-Trait Anxiety Inventory for Adults-Trait (STAI-T)	13	30.46$_a$	7.47	18	51.22$_a$	11.75	17	41.53$_a$	11.69

	Healthy controls		Borderline PD patients		Schizotypal PD patients	
	n	%	n	%	n	%
Past MDD[b]	–	–	10$_b$	56%	4$_b$	22%

Means in same row that share subscripts differ at $p < 0.05$. Given these group differences, we correlated STAI-Trait [65] as well as Past MDD with SWM performance, and they were not significant. Thus, STAI-T and Past MDD were not used as covariates.

[a] Symptom severity = total of individual symptom ratings for each DSM-IV diagnostic criterion.

[b] MDD = past major depressive disorder (MDD) was defined as prior episode occurring >2 months from time of fMRI scan.

with HC. Thus, our goal was to investigate the association between spatial working memory functioning and volume of frontal brain regions thought to subserve working memory function.

Given this aim to explore the potential association between non-verbal deficits and prefrontal cortex morphometric correlates, it is important to note previous studies implicating the DLPFC Brodmann areas (BA9/10/46) and VLPFC Brodmann areas (BA44/45) in working memory processes [22–26]. In addition to this work, functional neuroimaging studies examining SPD and BPD patients provide additional support for the idea that abnormalities in DLPFC and VLPFC may underlie neuropsychological impairments [27–31]. Evidence also exists for DLPFC and VLPFC volumetric abnormalities in BPD and SPD [32–35]. Further, research supports the notion that smaller prefrontal regions in SPD are associated with executive function deficits in a healthy control group with schizotypal personality features [36] and reduced volume of BA10 is related to increased impulsiveness in BPD [32].

To date, there is little work comparing neurocognitive function across different personality disorder groups and its relationship with prefrontal cortex volume. The current study sought to determine whether performance on measures of visual–spatial working memory differs for both patient groups, as compared with HC, and/or if deficits are specific to one personality disorder, and characterize the relationship between visual–spatial working memory and DLPFC/VLPFC volume. As such, this study works to advance our limited understanding of the phenotypic and endophenotypic aspects among and within SPD and BPD patients, respectively. We hypothesized that both groups would evidence visual–spatial working memory deficits but, given more consistent reporting of poor performance in SPD [10,31] patients, we predicted more impairment in this group. The second goal of this study was to explore the volumetric correlates of visual–spatial working memory function in these groups. Because both DLPFC and VLPFC have been shown to play a role in working memory in HC, and both regions have been shown to be dysfunctional in SPD and BPD patients, we hypothesized that, among HC, larger prefrontal cortex volume would be associated with better performance on measures of visual–spatial working memory, but these relationships would not be evidenced in SPD nor BPD patients.

All diagnoses were made through interviews by a psychologist using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [37] and the Structured Interview for DSM-IV Personality Disorders (SIDP) [38] followed by a consensus meeting. Diagnostic methods have been reported previously [39]. Patients with a history of schizophrenia, a psychotic disorder, bipolar (type I) affective disorder, substance abuse within 6 months of study entry or current (in the last 6 months) major depressive disorder (MDD) were excluded. All patients were unmedicated at the time of the study (>2 weeks prior to testing sessions). Healthy volunteers diagnosed with an Axis I or II psychiatric illness or an Axis I diagnosis in a first-

degree relative were excluded from this study. Exclusion criteria for all participants included: severe medical illness, neurological illness, head injury, past substance dependence, as well as substance abuse in the past 6 months, positive urine toxicology test on scan day, and females with a positive pregnancy test on scan day. Written informed consent approved by the Mount Sinai Institutional Review Board was provided by all participants.

A total of 52 adults participated in the study. We excluded one HC who was >2 SD from the healthy control mean on SWM performance. There were two additional HC participants who approached 2 SD on SWM so we conducted all analyses with and without these participants, and the results were essentially the same and significant either way. Therefore, we present analyses with these two HC subjects included in order to be more conservative. We studied 18 SPD patients with no BPD traits (11 M/7 F; mean age = 35.33 ± 11.0); 18 BPD patients with no SPD traits (7 M/11 F; mean age = 33.50 ± 9.52); and 16 HC (9 M/7 F; mean age = 30.63 ± 8.11). Participants in the three groups did not differ on age, sex, years of education (SPD mean = 14.94 ± 3.32; BPD mean = 14.0 ± 2.50; HC mean = 15.63 ± 3.28), or Wechsler Abbreviated Scale of Intelligence Full Scale (WASI FSIQ) [40] (SPD mean = 104.76 ± 9.91; BPD mean = 107.07 ± 17.62; HC mean = 108.19 ± 18.13), all p's > 0.11.

SWM performance errors were significantly correlated with WASI FSIQ ($r = -0.51$, $p < 0.05$), years of education ($r = -0.29$, $p < 0.05$), and age ($r = 0.46$, $p < 0.05$) across all participants regardless of group. Therefore, we used two covariates: age and years of education, instead of WASI FSIQ, because we had data for all participants on this variable, whereas five of the 52 participants were missing WASI data. See Table 1 for clinical symptom severity ratings and self-report ratings. To calculate the level of clinical symptom severity, we added up the individual symptom ratings for each DSM-IV diagnostic criterion. Ratings were on a 4-point scale (0 = absent, 0.5 = somewhat present, 1.0 = definitely present/prototypic, 2.0 = severe, pervasive).

Gray matter volume [39] in the Brodmann areas and diffusion tensor imaging (DTI) [41] has been reported previously for this sample. Neuropsychological measures were not a component of the study initially and thus were administered only to a subset of the original sample published previously [39].

All participants completed the Spatial Working Memory (SWM) subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB) [42], a standardized computer battery, as part of the full CANTAB battery. Findings from the remaining tests of the battery are reported elsewhere [43,44]. The CANTAB has demonstrated adequate reliability [45,46].

Spatial Working Memory (SWM). See Fig. 1A for details on the test. There are two outcome measures: a 'Between Search Error' involving the number of errors made (i.e. touching boxes that are empty or revisiting boxes that have already been checked) and
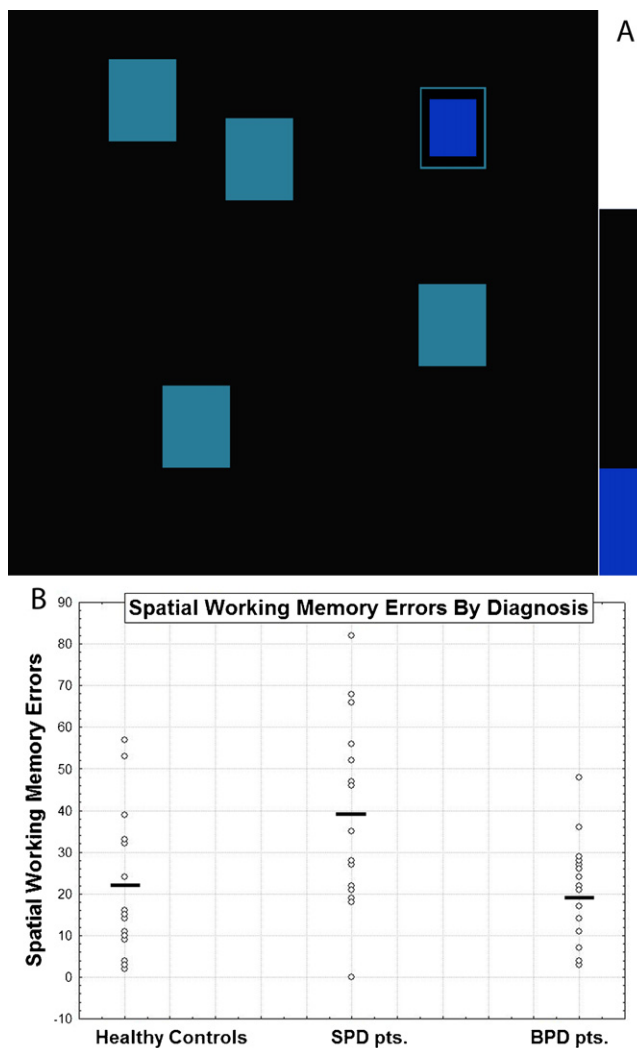
Fig. 1. Spatial working memory task and performance in healthy controls, schizotypal personality disorder patients and borderline personality disorder patients. (A) An example of the visual–spatial working memory task is shown. In the task, blue tokens are "hidden" behind colored squares on the screen and the participant is asked to locate the tokens using the process of elimination until they have found enough tokens to fill up an empty column on the side of the screen. Only one token is hidden on each trial and a token is never hidden more than once in the same location. (B) Scatterplot for performance scores on the spatial working memory task is shown for healthy control, SPD, and BPD participants. The horizontal bar represents the unadjusted means for each group that are as follows: SPD: 38.67 ± 25.14; BPD: 19.33 ± 12.04 and HC: 22.13 ± 17.24. Note that two participants had a score of 32 in the HC group; two participants had a score of 0, two had a score of 27, two had a score of 82 in the SPD group; and two participants had a score of 17, three had a score of 7 in the BPD group. Adjusted means (adjusted for age and years of education) are as follows: SPD: 37.16 ± 16.32; BPD: 17.47 ± 16.37 and HC: 25.93 ± 16.52. There was a significant group $\times$ error score interaction, $F(2,47) = 6.54$, $p = 0.003$ and SPD participants performed significantly worse than the BPD participants ($p = 0.0008$, Fisher's LSD test) and healthy controls ($p = 0.005$, Fisher's LSD test).

a 'Strategy Score' which consists of how often a predetermined search sequence was employed by beginning with the same box during each trial (a low score indicates a more effective use of this strategy).

As described in Goldstein et al. [39], imaging in this sample was conducted on a head-dedicated Siemens Allegra 3-T scanner. T1-weighted MP-RAGE (Magnetization Prepared Rapid Gradient Echo) scans were acquired with the following parameters: 208 slices with slice thickness = 0.82 mm, matrix size = $256 \times 256 \times 208$, FOV = 21 cm, TR = 2500 ms, TE = 4.38 ms, T1 = 1100 ms, and an 8° flip angle FLASH acquisition.

Volumes for the correlational analyses were obtained for gray matter within each individual BA in the DLPFC and VLPFC using a semi-automated parcellation technique described in detail elsewhere [28,47,48] and based upon a digital version of a histologically based atlas [49].

FSL-FAST was used to segment the images into matter type (gray, white, CSF). Validation of the segmentation method is reported elsewhere [48,50]. Volume measures were expressed in mm^3 and obtained by computing relative size as the ratio of (area of ROI)/(volume of brain) $\times$ 1000. The intraclass correlation coefficients for gray and white matter components for two tracers were 0.98 and 0.99. To address the current study's primary hypotheses, we examined gray matter volume in BAs within the DLPFC (BA9/10/46) and VLPFC (BA44/45) which were developed on a theoretical and anatomical basis.

Neurocognitive data were analyzed using one-way analysis of covariance (ANCOVA). Follow-up Fisher's Least Significant Difference (LSD) tests were conducted to determine the nature of significant main effects and interactions with group. Pearson r product–moment correlations were used to examine the association between specific BA gray matter volumes and performance on the neurocognitive measures. To minimize the number of tests, we ran correlations in diagnostic groups where we found significant between-group differences from HC on the SWM task. A Bonferroni correction was applied for multiple comparisons (alpha level of $p = 0.0025$ to account for the number of comparisons conducted), and a Fisher's Z test was used to assess between-group differences in correlation coefficients. All significance tests were two-tailed. Correlation coefficients that did not survive Bonferroni correction but were significantly different between groups are mentioned.

1. Neurocognitive measures

A one-way ANCOVA was performed on the Spatial Working Memory (SWM) test and, controlling for age and years of education, results revealed a significant main effect of group, $F(2,47) = 6.54$, $p = 0.003$. As hypothesized, SPD patients showed more impaired performance (more SWM errors) than BPD patients ($p < 0.01$) and HC ($p < 0.01$) (see Fig. 1B). BPD patients and HC did not differ, $p = 0.62$. Results from analyses without age and education covariates also revealed a significant main effect of group ($F(2,49) = 5.38$, $p < 0.01$). SPD patients had significantly more SWM errors than HC ($p < 0.05$) and BPD patients ($p < 0.01$). The three groups did not differ in strategy use whether controlling for age and education or not, Fs < 1. The 'Strategy Use' Score is based on how frequently a searching sequence was initiated from the same box during a trial. Thus, a low strategy score is indicative of searching systematically and using a more extensive strategy whereas a high score represents poor use of this strategy.

2. Neurocognitive correlates

Given our finding of normal-SPD differences in SWM, Pearson's correlations were calculated for these groups to examine the association between DLPFC/VLPFC volume and task performance. All of the following correlational analyses controlled for age and education. Among the healthy control participants but not the SPD patients, fewer errors on the SWM test was associated with larger gray matter volume: right BA44 (HC: $r = -0.89$, $p < 0.005$, Fig. 2A; SPD: $r = 0.04$, $p = $ ns; HC vs SPD, Fisher's Z test = -3.86, $p < 0.01$) and right BA45 (HC: $r = -0.68$, $p < 0.01$; SPD: $r = -0.02$, $p = $ ns; HC vs SPD, Fisher's Z test = -2.14 $p < 0.05$). The association between right BA44 and SWM in HC survived the Bonferroni correction of 0.0025, but the relation between BA45 and SWM in HC did not.

In order to see if there was utility in PFC volumes predicting SWM performance, we also calculated the correlation coefficient
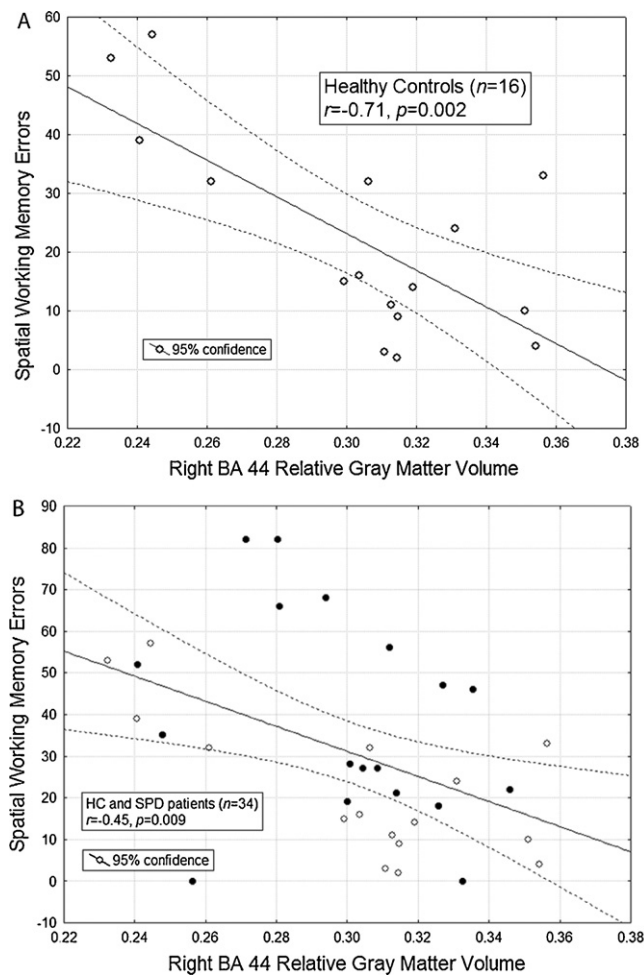
Fig. 2. Individual differences in right BA 44 volume and spatial working memory errors. (A) The scatterplot for the correlation between relative right BA 44 gray matter volume and spatial working memory errors in healthy controls is shown ($r(16) = -0.71$, $p = 0.002$). Solid black circles represent schizotypal personality disorder (SPD) participants and white circles represent healthy controls (HC). When controlling for age and education, the correlation between relative right BA 44 gray matter volume and spatial working memory errors is $r(12) = -0.89$, $p = 0.0001$. The r for healthy controls ($n = 16$) was significantly different from the $r = 0.04$ for SPD patients ($n = 18$), $p < 0.01$. (B) The scatterplot for the correlation between relative right BA 44 gray matter volume and spatial working memory errors in the entire sample of HC and SPD participants is shown ($r(34) = -0.45$, $p = 0.007$). When controlling for age and education, the correlation remains significant ($r(30) = -0.45$, $p = 0.009$).

for the entire sample of HC and SPD participants, given that they showed significant differences in SWM performance. The correlation coefficient was significant conventionally (but did not survive Bonferroni correction of 0.0025) and, as expected, greater right BA44 volume was associated with better SWM performance (see Fig. 2B; $r = -0.45$, $p = 0.009$).

Correlations between SWM performance, DLPFC/VLPFC gray matter volume and clinical symptomatology (as assessed by interview and self report) for SPD patients did not reach significance.

The first novel finding of this study is that patients with SPD demonstrate visual–spatial working memory impairment relative to BPD patients and HC. These results add to previous work by suggesting that SWM abilities may help differentiate SPD patients from BPD. SWM may thus represent a core neuropsychological deficit in SPD [8] and potentially serve as an important biomarker for differentiating between personality disorders. The second major finding is that, consistent with our hypothesis, larger volume of right BA44 was associated with better task performance (fewer errors)

in HC but not in the SPD group alone, the diagnostic group that showed significantly impaired performance. However, the association between larger right BA 44 volume and better SWM was observed across the HC–SPD spectrum.

Our finding of visual–spatial working memory impairment in SPD patients is consistent with prior work [7,8,11] as well as studies involving schizophrenia patients [51,52] thought to evidence similar genetic, neurobiological and neuropsychological abnormalities as those with SPD [53]. Although some previous studies report intact visual–spatial working memory in individuals with BPD [16,54–56], a few studies have reported BPD deficits in this domain [18]. However, much of this work included BPD patients who met criteria for other Axis II disorders, including SPD, thus rendering it difficult to establish a clear neurocognitive profile for BPD. The present study addressed these comorbidity issues by including BPD patients without SPD traits (i.e. no more than three SPD diagnostic criteria with two items rated as 1.0 (definitely present) and one item rated as 0.5 (somewhat present)) and SPD patients without BPD traits. Taken together, our findings indicate SPD but not BPD patients exhibit SWM deficits and underscore the diagnostic specificity of this deficit.

SPD patients demonstrated a specific type of spatial working memory deficit in this study, involving a high number of erroneous returns to previously searched locations. On the 'Strategy Use' score, however, SPD patients performed within normal limits. These findings suggest that SPD patients can adopt a spatial-search strategy, but it does not aid in the accuracy of their performance. Thus, while caution is necessary in drawing conclusions from these results, it is possible to argue that SPD erroneous re-visits to boxes where they previously had found tokens may be better attributed to difficulties in executive functioning, such as perseverative behavior and/or temporary storage and/or manipulation of spatial and/or visual information deficits [57], rather than impairments in strategy use. Consistent with this idea, Raine et al. [36] reported that individuals with high scores on schizotypal personality measures demonstrated more perseverative errors on an executive functioning task. Further research is needed to understand executive functioning difficulties in SPD patients and potential ways in which cognitive interventions, e.g., cognitive remediation and/or training in strategy-use abilities might improve function.

The present study's visual–spatial working memory task and its measures of errors and strategy use have been shown to be primarily sensitive to frontal-lobe functioning [58]. Additionally, Petrides and colleagues [59,60] have proposed that working memory processes can be mapped onto two distinct cytoarchitectonic regions—VLPFC, where information is maintained in working memory, and DLPFC, where information is monitored and manipulated in working memory [61]. Consistent with the above-mentioned research, as well as animal and human work demonstrating dorsolateral and ventral prefrontal cortex involvement in spatial working memory [23,62], this study showed that larger right BA44 volume was associated with better spatial working memory performance in HC. This same relationship was not observed in the SPD group alone. Given these findings, it is important to note our most recent paper reporting brain volume in this same sample [39] did not detect SPD–HC group differences in VLPFC (i.e. BA44) volume. Although some prior work suggests VLPFC volumetric abnormalities in SPD individuals [35], our failure to find group differences in this region is not entirely surprising given our previous work [34] and other research reporting no SPD–HC prefrontal volume differences, suggesting these regions may be relatively preserved in SPD individuals [53]. However, in the absence of group differences in prefrontal volume, the current study's correlational results across the HC–SPD spectrum suggest there is an association between volume and neurocognitive performance. Our data provide support for the new NIMH Research Domain Criteria (RDoC)

strategic plan which calls for studies to classify psychopathology based on dimensions of "observable behavior and neurobiological measures."

Although this study did not include fMRI to determine whether SPD patients demonstrate dysfunctional prefrontal cortex activation during spatial working memory processing, our previous imaging work implicates disrupted right BA44 and BA45 function in SPD patients during visual–spatial working memory tasks [31]. Koenigsberg et al. [31] demonstrated that HC showed increased activation in right BA44/45/47, bilateral premotor areas (BA6), as well as additional parietal regions during a visual–spatial working memory task. SPD patients, on the other hand, showed reduced activation during the maintenance period of a visual–spatial working memory task in left BA44/45/47/10, left intraparietal cortex, and left posterior inferior gyrus. Importantly, our prior finding of an SPD-related deficit in right BA44/45 activation [31] is consistent with our current finding of a lack of association between volume of BA44 and SWM performance in SPD. One potential explanation for our results may be differential recruitment of the neuronal network subserving this function in SPD patients. For example, research in HC provides evidence of VLPFC (i.e. BA44/45) connections with posterior sensory association areas [59,60] and reports VLPFC's role in the process of maintaining visual information in working memory [63]. It is also significant that our results were localized to the right hemisphere, consistent with research linking hemispheric lateralization with type of task (i.e. spatial with right, verbal with left) [59,60].

Our study has several limitations. First, given the constraints of the task, we were not able to offer greater specificity regarding the exact component of spatial working memory that is impaired in SPD patients. For example, our prior study [31] reported that during the encoding and maintenance period of a SWM task, HC showed increased activation in right BA44/45/47, among other prefrontal and parietal regions. In contrast, SPD patients showed decreased activation in left BA44/45/47 and other regions during this same period of maintaining the spatial locations in memory. Taken together with these findings and evidence of BA44/45 involvement in maintenance functions in HC [63], we can only speculate that SPD patients experience difficulty during the maintenance period in particular but cannot offer evidence to support this idea. Future research needs to investigate potential SWM deficits in greater detail and ideally include a spectrum sample examining HC, SPD, and schizophrenia patients. Despite the present study's significant results, the findings need to be replicated in a larger sample, and it would be beneficial to include a group of schizophrenia patients to examine the full schizophrenia spectrum. Lastly, research suggests that stress, which is thought to play an important role in the etiology and course of personality disorders, may impair prefrontal cortex working memory performance in humans and animals [64]. Thus, further research examining the effect of stress on prefrontal cortex functioning in BPD and SPD patient groups would help better characterize SWM abnormalities in these disorders.

The present study's findings highlight visual–spatial working memory deficits in SPD patients and, given the complexity of personality disorder groups and their many overlapping and diverging aspects, suggest that SWM may be a potential biomarker for differentiating among/between them. Also, given our finding of a relation between prefrontal cortex volume and SWM performance, these results suggest the need to further investigate functional prefrontal correlates of different working memory tests and how they may or may not contribute to cognitive, behavioral and emotional disturbances that may underpin SPD and BPD traits, respectively. Use of the SWM test in personality disorder studies examining change with treatment may help, and baseline predictors of treatment response may be fruitful.

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