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Cortical hyperactivation at low working memory load: A primary processing abnormality in people with schizophrenia?

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ABSTRACT

A frequent finding when studying substrates of working memory (WM) deficits in people with schizophrenia (PSZ) is task-induced hyperactivation relative to healthy control subjects (HCS) when WM load is low. Hyperactivation accompanying similar performance is commonly attributed to cognitive deficits rendering relatively easy operations more resource-consuming. To test if hyperactivation at low load really is secondary to cognitive impairment in PSZ, we reanalyzed functional MRI data showing left posterior parietal cortex (PPC) hyperactivation in PSZ when holding a single color-item in WM. In subgroups matched for the number of items successfully stored in WM (K) by excluding the highest-performing HCS and lowest-performing PSZ, performance was almost identical across all set sizes (1–7). While BOLD activation at the larger set sizes did not differ between groups, PSZ still robustly hyperactivated left PPC when a single item had to be maintained. The same pattern was observed in subgroups matched for model-based estimates of WM capacity or attentional lapse rate. Given that in the K-matched subsamples PSZ performed as well as HCS even in the most challenging load conditions and that no BOLD signal difference was seen at high loads, it is implausible that PSZ over-recruited WM-related neural structures because they were more challenged by maintaining a single item in WM. Instead, the findings are consistent with a primary schizophrenia-related processing abnormality as proposed by the hyperfocusing hypothesis, which suggests that an abnormally narrow but intense focusing of processing resources is central to many aspects of impaired cognition in PSZ.

1. Introduction

Working memory (WM) deficits are considered central to cognitive impairment associated with schizophrenia (Johnson et al., 2013; Lee and Park, 2005), and to psychotic disorders more generally (Gold et al., 2019b). Functional magnetic resonance imaging (fMRI) studies investigating the neural underpinnings of these deficits have found several abnormalities in cortical and subcortical task-related activity. However, the most influential findings have been in dorsolateral prefrontal cortex (DLPFC), where lower activation at high WM load and greater activation at low load were observed in people with schizophrenia (PSZ) as compared with healthy control subjects (HCS) (Glahn et al., 2005; Kraguljac et al., 2013; Manoach, 2003).

Prefrontal *hypo*activation at high WM load is reportedly associated with WM performance deficits (Manoach et al., 2000; Perlstein et al., 2001; Van Snellenberg et al., 2006), although this does not imply that it is a cause of these deficits. Hypoactivation may instead be a consequence of performance deficits. Prefrontal activation generally increases with WM load but decreases when load exceeds an individual's capacity (Callicott et al., 1999; Goldberg et al., 1998). Thus, hypoactivation at high WM load may reflect task demands exceeding capacity more often in PSZ than in HCS. Indeed, several WM studies in which analysis was limited to epochs of correct performance found equal DLPFC recruitment between PSZ and HCS (Eryilmaz et al., 2016; Johnson et al., 2006; Walter et al., 2007).

Prefrontal *hyper*activation at low WM load, too, may be secondary to WM deficits, possibly reflecting task demands at low load being manageable but more effortful and resource-consuming for PSZ (Manoach, 2003). While hyperactivation in PSZ has at times been associated with poorer performance (Callicott et al., 2000), a large multisite study found that DLPFC hyperactivation, although not clearly load-related, persisted in performance-matched subgroups and was

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unrelated to IQ (Potkin et al., 2009). Given that hyperactivation generally tends to be observed only in the lowest WM load conditions, its occurrence against a backdrop of unimpaired performance in more challenging conditions of intermediate difficulty would contradict the interpretation that greater resource expenditure was secondary to WM deficits. The possibility that hyperactivation may indeed reflect a primary schizophrenia-related processing abnormality, and not a phenomenon secondary to other deficits, is intriguing but has received little attention. Greater activation to achieve equal or lower performance has been coined "inefficient" brain function (Callicott et al., 2003). This inefficiency concept is descriptive, however, and does not address the nature or causes underlying hyperactivation.

Task-induced hyperactivation in PSZ has also been observed outside DLPFC. The focus of the above studies on DLPFC may reflect the use of WM paradigms involving manipulation or active rehearsal of the stored material, thus engaging not just storage but also executive control aspects of WM (Barch et al., 2012). For storage-related functions, basic cognitive neuroscience suggests a more central role of the posterior parietal cortex (PPC) (Edin et al., 2009; McNab and Klingberg, 2008; Postle, 2006; Robitaille et al., 2009). Employing visual change detection tasks, which emphasize encoding and maintenance but not manipulation or rehearsal strategies (Luck and Vogel, 1997; Vogel et al., 2001), fMRI studies found that intraparietal and intraoccipital sulcus activation was related to the number of items maintained in WM as inferred from performance (Todd and Marois, 2004).

Employing this same approach to compare WM storage-related processes between PSZ and HCS, Hahn et al. (2018) found that left PPC activity increased linearly with the number of items stored in HCS, but not in PSZ. This lack of activity modulation with WM content was largely due to PCC hyperactivation in PSZ when only 1 or 2 items had to be remembered. The group difference was largest at set size 1, at which PSZ activated and HCS deactivated the left PPC region. There were also trends suggesting PPC hypoactivation in PSZ at larger set sizes. Overall, this pattern mirrored ERP results with this paradigm (Leonard et al., 2013), and was reminiscent of the pattern seen in DLPFC in the fMRI studies described above. Note that, because the task in this study was designed to emphasize WM encoding and maintenance, not manipulation or active rehearsal, no significant DLPFC activation was found.

Until recently, the only conceptualization of hyperactivation during low-load conditions has been in terms of greater effort or resource engagement necessitated by cognitive deficits. However, there is an alternative interpretation. Hyperactivation when only one or two items are maintained in WM would be consistent with the hyperfocusing hypothesis of cognitive dysfunction in schizophrenia (Luck et al., 2019). Based on evidence from various behavioral and electrophysiological paradigms, the hyperfocusing hypothesis suggests that an abnormally narrow but intense focusing of processing resources is at the center of many (although clearly not all) aspects of impaired cognition in PSZ. This includes difficulty distributing attention broadly and maintaining multiple representations in WM. Crucially, the hyperfocusing hypothesis suggests that greater resource expenditure on a narrow band of input represents a primary processing abnormality and is not secondary to WM deficits making the task more challenging for PSZ.

If hyperactivation when maintaining a single item in WM was seen against a background of equal working memory capacity, it would be difficult to explain as secondary to WM deficits. More likely, it would reflect a primary schizophrenia-related processing abnormality, consistent with the hyperfocusing hypothesis. The aim of the present study was to test this possibility.

2. Materials and methods

2.1. Participants

The present data are based on the sample of 37 PSZ and 37 HCS

Table 1
Participant demographics of the full samples and subsamples matched on K at set size 4.

	Full sample PSZ (N = 37)	Full sample HCS (N = 37)	Statistic P-value	Subsample PSZ (N = 23)	Subsample HCS (N = 23)	Statistic P-value
Age	36.3 ± 11.2(range 19–55)	37.0 ± 11.7(range 21–55)	t(72) = 0.25P = 0.80	36.1 ± 11.4(range 21–55)	39.2 ± 10.6(range 21–53)	t(44) = 0.97P = 0.34
Male: Female	23: 14	23: 14	χ^2 = 0P = 1	16: 7	15: 8	χ^2 = 1.0P = 0.75
Afr Am: Cauc: Other	12: 21: 4	14: 23: 0	χ^2 = 4.25P = 0.12	6: 16: 1	10: 13: 0	χ^2 = 2.31P = 0.32
Education (years)	12.8 ± 2.1	15.5 ± 1.9	t(72) = 5.71**P < 0.001**	13.0 ± 2.2	15.5 ± 2.1	t(44) = 3.92**P < 0.001**
Parental Education (yrs)[a]	13.5 ± 2.7	14.7 ± 2.6	t(72) = 1.89P = 0.062	13.6 ± 2.5	15.0 ± 2.5	t(44) = 1.98P = 0.054
Estimated IQ[b,f]	99.5 ± 14.8	115.9 ± 8.8	t(68) = 5.54**P < 0.001**	105.9 ± 12.1	113.7 ± 6.6	t(41) = 2.57**P = 0.014**
MCCB[c,f]	37.1 ± 12.9	53.6 ± 7.8	t(68) = 6.39**P < 0.001**	42.4 ± 10.4	51.1 ± 8.0	t(41) = 3.02**P = 0.004**
WRAT 4[d,f]	98.6 ± 17.0	115.1 ± 13.0	t(68) = 4.53**P < 0.001**	103.8 ± 15.4	113.5 ± 11.4	t(41) = 2.30**P = 0.027**
WTAR[e,f]	100.2 ± 18.2	115.8 ± 7.1	t(68) = 4.61**P < 0.001**	106.0 ± 15.4	115.3 ± 7.1	t(41) = 2.47**P = 0.018**

[a] Average over maternal and paternal education.
[b] Based on the Wechsler Abbreviated Scale of Intelligence – II (Wechsler, 2011).
[c] Composite score on the MATRICS Consensus Cognitive Battery (Nuechterlein and Green, 2006).
[d] Wide Range Achievement Test (Wilkinson and Robertson, 2006).
[e] Wechsler Test of Adult Reading (Wechsler, 2001).
[f] Data missing for 4 HCS of the full sample and 3 HCS of the subsample.

described in Hahn et al. (2018). Briefly, PSZ were outpatients meeting Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)[41] criteria for schizophrenia (n = 30) or schizoaffective disorder (N = 7). PSZ were stably medicated (no change in the preceding four weeks); 28 received second-generation antipsychotics, 4 first-generation antipsychotics, and 5 both. Sixteen PSZ additionally received antidepressant medication, 5 mood stabilizers, 13 anxiolytic and 7 antiparkinsonian medication. HCS had no Axis 1 or 2 diagnoses and no self-reported family history of psychosis, and were not taking psychotropic medication. Drug or alcohol abuse within the last six months was exclusionary, as was color blindness. Participants provided informed consent for a protocol approved by the Institutional Review Board of the University of Maryland Baltimore. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Table 1 summarizes demographic characteristics. In both the full samples and in the performance-matched subsamples, groups were matched on age, sex, and ethnicity, but PSZ had fewer years of education and scored lower on neuropsychological tests of cognitive functioning. There was also a trend toward lower parental education in PSZ relative to HCS.

2.2. Procedure

Prior to the scan, participants received task instructions and performed a short practice version of the change detection task on a desktop computer. Eight blocks of the change detection task were then performed in the MRI scanner. An anatomical scan was obtained after the first four blocks. The entire scan took approximately one hour. Neuropsychological testing and psychiatric ratings were completed on a separate day; ratings and neuropsychological test scores were described previously (Hahn et al., 2018).

2.3. Task paradigm

An encoding array of 1, 2, 4, 6, or 7 squares (~1 × 1° of visual angle) was presented against a black background for 200 ms (Fig. 1). Each square was painted in a different color, chosen randomly from a pool of red, magenta, purple, blue, teal, cyan, green, olive, yellow, and white. After a blank-screen delay of variable duration (1100, 1650, 2200, 2750, 3300, 3850, or 4400 ms), one of the squares reappeared for 2000 ms at its original location. Participants were instructed to make an index finger response if the color of this item had changed relative to the original presentation, and a middle finger response if the color stayed the same (50% probability). The intertrial interval was variable (2000, 2500, 3000, 3500, 4000, 4500, or 5000 ms). A white fixation cross (~0.66 × 0.66° of visual angle) remained at the center of the display throughout the task to serve as a spatial reference point. The task was presented in eight runs of 35 trials each. Seven trials of each set size were presented per run, in random order. Each run was 4:56-minutes long, separated by short breaks. Total task length was ~45 min.

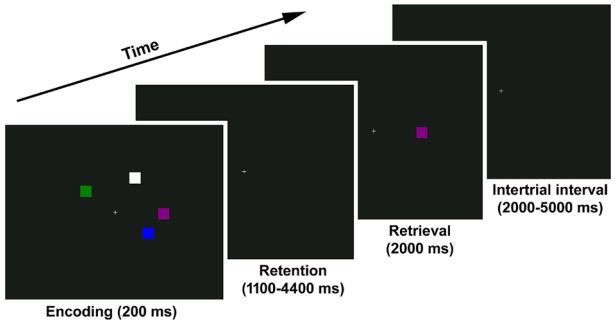

Fig. 1. A single trial of the change detection task. Each encoding array contained 1, 2, 4, 6, or 7 items. The task was to report whether the test item was of the same color as the corresponding item from the encoding array or had changed to a new color. Shown here is a no-change trial at set size 4. The size of the squares is not to scale, for better discernibility in the figure.

2.4. Magnetic resonance imaging

Whole-brain EPI images for measuring T2*-weighted BOLD effects [37 4-mm oblique (13.5°) axial slices, 128 × 128 matrix, FOV = 22 × 22 cm, TR = 2 s, TE = 27 ms, FA = 90°] were acquired on a 3-Tesla Siemens Tim Trio scanner (Erlangen, Germany). GeneRalized Autocalibrating Partial Parallel Acquisition (GRAPPA) with an acceleration factor of four was used to reduce the number of phase encoding lines and keep the TR at 2 s.

Anatomical reference was obtained from an axial T1-weighted image (MPRAGE; 0.8-mm^3 voxels, TR = 2.2 s, TE = 2.83 ms, FA = 13°). Data were processed using AFNI (Cox, 1996). Each volume was registered to a base volume. Several control analyses based on the six motion correction parameters were described by Hahn et al. (2018), verifying that head motion did not differ between HCS and PSZ.

The time series was analyzed as an event-related design by voxel-wise multiple regression. Regressors were expressed as a delta function, time-locked to the onset of each encoding array, convolved with a model hemodynamic response function and its temporal derivative. Regressors corresponded to the five set sizes. Additionally, regressors of no interest corresponded to the onset of the retrieval array, to the onset of the encoding and retrieval array on trials in which the participant did not respond or responded prematurely, and to the six motion parameter curves. For each subject, the voxel-wise average amplitude of signal change produced by each of the five set sizes was determined. These maps were re-sampled to a 1-μL resolution, converted to a standard coordinate system (Talairach and Tournoux, 1988), and spatially blurred using a Gaussian 5-mm root mean square (RMS) isotropic kernel.

Second-level analyses: Whole-brain voxel-wise multiple linear regression was performed on these maps, designed to identify regions in which set size-related activity differed between PSZ and HCS. Accordingly, the group × set size interaction was the regressor of interest, with group, set size and subject also included in the statistical model as regressors. Voxel-wise $P < 0.001$ combined with a 687-μL cluster size threshold yielded overall $P < 0.05$ based on Monte Carlo simulations. Within the resulting cluster, BOLD activity was averaged across voxels for each subject at each set size.

2.5. Statistical analysis

The number of items stored in working memory (K) at each set size was derived from the following formula (Cowan, 2001): K = set size * (hit rate − false alarm rate).

According to this formula, complete guessing would result in a K estimate of 0. At the smaller set sizes (1 and 2), the K values are limited primarily by the number of items presented because K cannot exceed the number of items in the array. As set size increases, K typically increases and plateaus close to the individual's WM capacity. Often, after reaching plateau, K declines with even larger set sizes as a sub-portion of the array must be selected for encoding.

Performance matching was first performed on the basis of K at set size 4, which is least limited by the number of items presented or reduced by an individual's difficulty selecting a subset of items for storage. Performance matching was achieved by sequentially excluding the best-performing HCS, followed by the worst-performing PSZ, followed by the next-best performing HCS, etc. until the average K value at set size 4 for the remaining subjects differed the least between groups, i.e., until excluding another subject would begin to increase the absolute group difference again. Excluding the 14 HCS with the highest and the 14 PSZ with the lowest K at set size 4 led to almost identical K

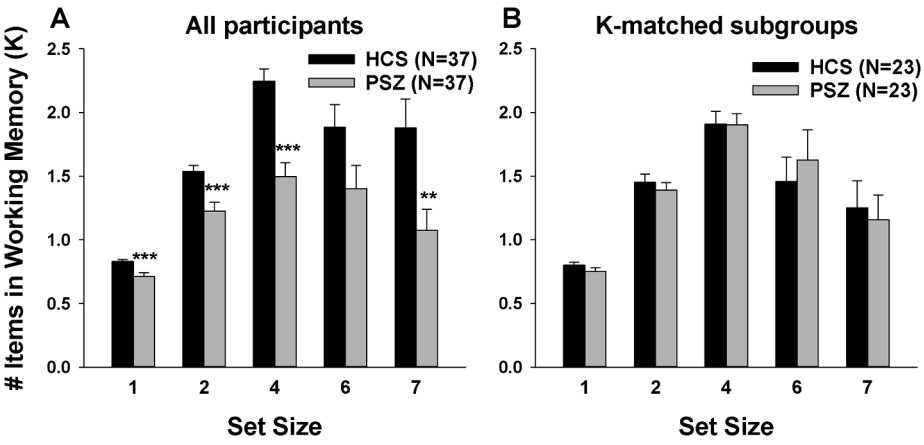

Fig. 2. Average (± SEM) number of items stored in working memory (*K*) in people with schizophrenia (PSZ) and healthy control subjects (HCS) at each of five set sizes. Subpanel A shows K values in the full samples (N = 37 per group), subpanel B in K-matched subsamples (N = 23 per group). **P < 0.01 and ***P < 0.001 in independent-samples t-tests comparing HCS and PSZ.

values across set sizes in the remaining participants (Fig. 2B).

Performance as reflected by K is dependent on both WM capacity and attentional engagement. Thus, in addition to matching performance based on K at set size 4, we also derived estimates of WM capacity using a model which assumes that errors in a working memory task are driven both by the true working memory capacity limit and by lapses of attention (Rouder et al., 2008). We fit the model individually to obtain a maximum likelihood estimates of working memory capacity and attentional lapse rate for each participant from the data across all set sizes. The attentional lapse rate parameter reflects the proportion of trials in which responses were incorrect because of an attentional lapse. Values ranged from 0 to 1 with larger values reflecting worse attention. Deficits in either WM capacity or attentional lapse rate would make performance more challenging and could explain hyperactivation in PSZ. Thus, after excluding one outlier in each group (each with a WM capacity estimate of 7, over four standard deviations above each group mean), each parameter estimate was used separately to match performance between the two groups. Matching was performed by sequential exclusion as described above.

K values and the BOLD signal were analyzed by 2-factor ANOVA for repeated measures, with diagnostic group as between-subject factor and set size as within-subject factor. Reaction times were not recorded.

3. Results

3.1. Full samples

Fig. 2A displays published data (Hahn et al., 2018), showing the inverted U-shaped dose-response relationship of the number of items stored in WM (*K*) with set size in HCS and PSZ [main effect of set size: F(4,288) = 27.9, P < 0.001]. *K* was lower in PSZ than HCS throughout [main effect of group: F(1,72) = 535.5; P < 0.001], but especially at the larger set sizes [group × set size interaction: F(4,288) = 3.47, P = 0.009].

Voxel-wise whole-brain ANOVA identified a single cluster (4833 μl), located in left PPC and including superior parietal lobule, inferior parietal lobule, intraparietal sulcus, and precuneus (center of mass: LR 23.3 mm, PA 59.0 mm, IS 44.4 mm), as showing a group × set size interaction (Fig. 3). This cluster largely overlapped with the region previously identified as displaying an interaction of group with *K*, i.e. with the number of items actually stored independent of set size (Hahn et al., 2018). Fig. 3A shows the basis for the group × set size interaction. In these full-group analyses, PSZ significantly hyperactivated the left PPC relative to HCS at set sizes 1 and 2. The largest group difference was seen at set size 1, at which HCS displayed significant deactivation and PSZ significant activation relative to baseline. At the larger set sizes (4, 6, and 7), there were numeric trends toward less activation in PSZ than in HCS.

3.2. Performance-matched subsamples

To test whether hyperactivation in PSZ at low WM load may have been secondary to performance deficits (leading to greater cognitive effort), we performance-matched the groups by excluding the 14 HCS with the largest and the 14 PSZ with the smallest K values at set size 4, as detailed above. Fig. 2B illustrates K across set sizes in the remaining participants (N = 23 per group). Performance was closely matched between groups at each set size. A 2-factor ANOVA on the *K* values confirmed a significant main effect of set size across groups [F(4,176) = 22.4, P = 0.001], but there was no main effect of group [F(1,44) < 0.01, P = 0.95] and no group × set size interaction [F(4,176) = 0.35, P = 0.85].

Fig. 3B shows that BOLD activity in the performance-matched subgroups was now almost identical between groups at set sizes 4, 6, and 7. However, BOLD activity at set size 1 was still higher in PSZ than in HCS. A 2-factor ANOVA indicated that the group × set size interaction remained significant in these matched subgroups [F(4,176) = 3.21, P = 0.014]. Moreover, a post-hoc *t*-test indicated that BOLD activity was significantly greater in PSZ than in HCS at set size 1 [t(44) = 3.11, P = 0.003], and this effect remained significant after Bonferroni correction for comparison at five set sizes (P = 0.015). It is important to note that the greater BOLD activity for PSZ at set size 1 occurred even though in these subsamples PSZ performed as well as HCS even in the most challenging WM load conditions, and no BOLD signal difference was seen between groups at any of the larger set sizes [t(44) = 1.48, P = 0.145 at set size 2; P > 0.69 at all larger set sizes]. This pattern of results provides evidence against the interpretation that PSZ over-recruited WM storage systems at set size 1 because they were more challenged by maintaining a single item in WM. If hyperactivation represented extra effort to achieve the same performance, the same pattern of increased response in PSZ would be found across all set sizes in the performance-matched subgroups.

Because K at set size 4 is not a pure reflection of WM capacity but is also influenced by attentional lapses, as a next step we matched the two groups based on a purer index of WM capacity derived from a model that makes use of the data from all set sizes (Rouder et al., 2008). Table 2 summarizes each group's average WM capacity and attentional lapse rate after matching for either WM capacity or for attentional lapse rate. In each pair of subsamples, we found higher BOLD activity in PSZ than in HCS at set size 1 (Fig. 4), as seen above for the K-matched subsamples. BOLD activity did not differ significantly between PSZ and HCS at set sizes 4, 6, and 7, although numerical trends were seen whose direction depended on the type of matching. In two-factor ANOVA, the group × set size interaction was significant both in WM capacity-matched [F(4,208) = 5.17, P < 0.001] and attention-matched subsamples [F(4,216) = 7.38, P < 0.001]. In each case, the group difference at set size 1 remained significant after Bonferroni correction for comparison at five set sizes.

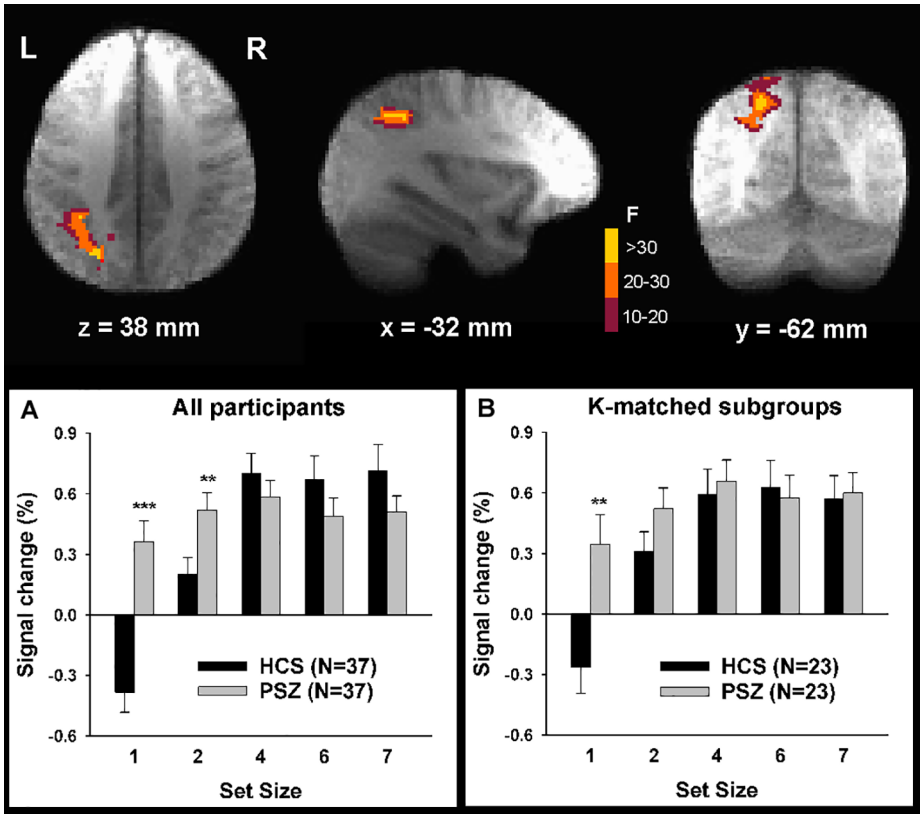

Fig. 3. Left posterior parietal cortex (PPC) region identified as displaying a group × set size interaction in a whole-brain voxel-wise regression analysis conducted in the full samples of healthy controls subjects (HCS) and people with schizophrenia (PSZ). Group activation maps are overlaid onto anatomical scans in Talairach space averaged over all 74 participants. Subpanel A shows the average (± SEM) BOLD activity at each set size in this region for the full samples. Subpanel B shows the averages (± SEM) for the K-matched subsamples. **P < 0.01 and ***P < 0.001 in independent-samples t-tests comparing HCS and PSZ.

3.3. Correlations

To test whether hyperactivity of the left PPC region at set size 1 was related to WM capacity, we correlated the BOLD signal at set size 1 with the algorithmically derived WM capacity estimate in the full samples. There were no significant correlations in either HCS (R = −0.30, P = 0.072) or PSZ (R = 0.03, P = 0.86). Chlorpromazine-equivalents (Andreasen et al., 2010) were not significantly correlated with BOLD activity at set size 1 or with the WM capacity estimate (both Ps > 0.2), suggesting that antipsychotic medication is unlikely to account for the observed hyperactivation, or for WM deficits.

4. Discussion

The present findings suggest an alternative explanation to the common view that hyperactivation of PSZ at low WM load is a secondary consequence of cognitive deficits, which make task performance more effortful and resource consuming in PSZ than in HCS. Specifically, in the posterior parietal region that has been linked with WM encoding and maintenance, we found that hyperactivation in PSZ relative to HCS when holding a single item in WM remained robust in subgroups matched for performance based on the number of items held in WM (K), and in subgroups matched more specifically for WM capacity or attentional lapse rate. Thus, even when PSZ and HCS were equally able to remember the colors and locations of 4, 6, or even 7 items, PSZ displayed significantly more activation when a single item had to be remembered. Hyperactivation was sometimes observed also at set size 2, but, importantly, not at larger set sizes at which it would be most expected if it reflected greater effort and resource engagement to perform equally well. The finding that hyperactivation at set size 1 remained robust also in subgroups matched for WM capacity and attentional lapse rate suggests that it cannot be explained by WM deficits or by greater effort to sustain attention to the task. Thus, hyperactivation at low WM load in PPC appears to reflect a primary schizophrenia-related processing abnormality, as opposed to being secondary to WM or sustained attention deficits necessitating additional cognitive effort.

We suggest that this kind of hyperactivation reflects a hyperfocusing abnormality that may underlie many aspects of impaired cognition in PSZ. The hyperfocusing hypothesis is based on many sources of evidence for an excessively narrow and exclusive attentional window in PSZ with regards to both attended and internally represented stimuli (Hahn et al., 2012a,b; Kreither et al., 2017). Importantly, it appears that the narrow set of information that *is* selected by PSZ is represented with greater intensity. This is supported by findings that features of single stimuli that are attended or stored in WM have a greater measurable influence on other cognitive processes in PSZ (Gold et al., 2019a; Luck

Table 2
WM capacity and attentional lapse rate as derived algorithmically (Rouder et al., 2008) in the full samples or in subsamples matched on either WM capacity or attentional lapse rate.

		HCS (mean ± stdev)	PSZ (mean ± stdev)	Statistic
Full samples (36 HCS, 36 PSZ)	WM capacity	2.50 ± 0.80	1.96 ± 0.72	t(70) = 3.05, P = 0.003
	Attentional lapse rate	0.18 ± 0.12	0.29 ± 0.17	t(70) = 3.15, P = 0.002
Matched on WM capacity (27 HCS, 27 PSZ)	WM capacity	2.16 ± 0.56	2.18 ± 0.68	t(52) = 0.12, P = 0.902
	Attentional lapse rate	17.1% ± 11.3	27.1% ± 17.2	t(52) = 2.52, P = 0.015
Matched on attentional lapse rate (28 HCS, 28 PSZ)	WM capacity	2.67 ± 1.16	1.90 ± 0.57	t(54) = 3.17, P = 0.003
	Attentional lapse rate	21.3% ± 11.3	21.5% ± 11.7	t(54) = 0.07, P = 0.944

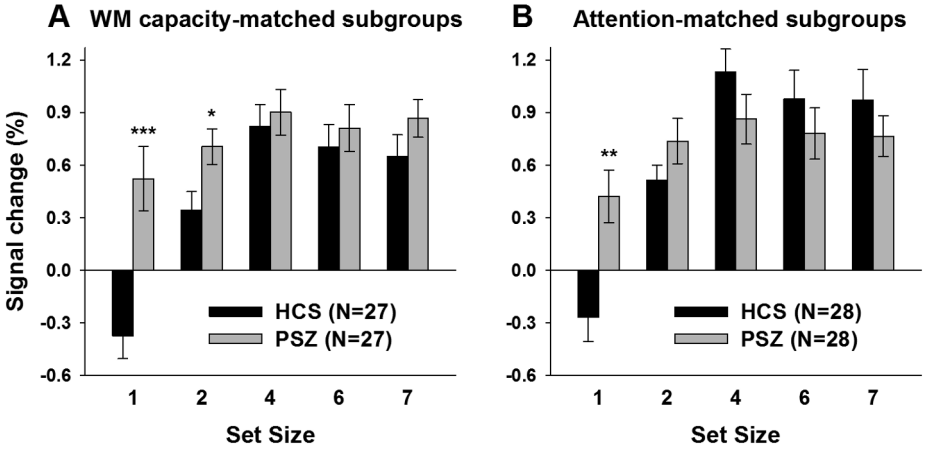

Fig. 4. Mean (± SEM) BOLD activity at each set size in the left posterior parietal cortex region for subsamples matched on WM capacity (A) and subsamples matched on the attentional lapse rate (B). *P < 0.05, **P < 0.01, and ***P < 0.001 in independent-samples t-tests comparing HCS and PSZ.

et al., 2014; Sawaki et al., 2017). This more intense, resource-consuming focus on a narrow selection would be reflected in increased neuronal activity when processing a small number of stimuli, consistent with the hyperactivation at low WM load described here.

The propensity to over-recruit processing resources for one item (or a narrow selection) would be expected to be detrimental to performance under conditions requiring resources to be spread over several items, such as when trying to maintain multiple items in WM. Thus, we predicted that hyperactivation at set size 1 would be associated with lower WM capacity. However, the correlation between BOLD activity at set size 1 and WM capacity was only a negative trend in HCS, and almost zero in PSZ. While this finding suggests that other sources of cognitive dysfunction, such as primary storage deficits, may play a larger role in explaining WM deficits, it also reinforces the conclusion that greater neuronal activity when processing a small number of stimuli is not secondary to WM deficits in PSZ.

Hyperactivation of PSZ at low WM load, especially in the DLPFC, has been described repeatedly for over two decades and has been framed as “inefficiency”, i.e., the need for more neuronal activation to achieve equal or lower performance, or “less bang for the buck” (e.g., Callicott et al., 2003; Karch et al., 2009; Manoach, 2003). The inefficiency interpretation does not imply any specific mental operation that is disproportionately engaged as the basis for the higher neuronal discharge reflected by the greater BOLD signal. Findings in support of the hyperfocusing hypothesis provide such an account of hyperactivations, suggesting a maladaptive processing strategy of focusing high resources on a narrow input selection. However, the present paradigm was not designed to activate the DLPFC, and our conclusions may or may not generalize to DLPFC.

The present finding that hyperactivation at low WM load in PSZ was not a secondary phenomenon to WM deficits, combined with the growing evidence for a core cognitive processing abnormality that would directly predict such hyperactivation, may guide investigation on the pathology underlying this phenomenon. Although the present findings require replication in larger samples and a broader population of PSZ, including first-episode and unmedicated patients, they suggest that there is more to hyperactivations in PSZ than previously met the eye.

CRediT authorship contribution statement

Britta Hahn: Conceptualization, Methodology, Formal analysis, Data curation, Visualization, Writing. **Gi-Yeul Bae:** Formal analysis. **Benjamin M. Robinson:** Software, Investigation, Data curation. **Carly J. Leonard:** Conceptualization, Methodology, Writing - review & editing. **Steven J. Luck:** Conceptualization, Methodology, Writing - review & editing, Supervision, Funding acquisition. **James M. Gold:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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