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Clinical utility of the dual n-back task in schizophrenia: A functional imaging approach

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ABSTRACT

The neural correlate of working memory (WM) impairment in schizophrenia is key to the understanding of the cognitive deficits observed in this disorder. We sought to determine the clinical validity of the dual version n-back paradigm in patients with schizophrenia, and whether schizophrenia patients exhibit altered brain activation patterns compared with healthy controls in this dual version WM measure using functional magnetic resonance imaging. Patients with schizophrenia (n = 20) and healthy controls (n = 24) performed the dual n-back task that consists of both visuospatial and auditory-verbal *n*-back streams, in which participants were required to monitor and update the contents from these two different inputs simultaneously. Significant positive correlations were found between performance in the dual 2-back condition and another measure of WM capacity and IQ estimates. Moreover, hypoactivation was observed at the right middle frontal gyrus and the posterior parietal regions in schizophrenia participants compared with healthy controls. The right hippocampus was less deactivated in schizophrenia patients compared with healthy controls. Our results support the clinical utility of the dual n-back task in schizophrenia and may have implications for the development of specific cognitive training targeting these impaired neural substrates in relation to WM in patients with schizophrenia.

1. Introduction

Working memory (WM) refers to one's capacity in maintaining and manipulating information for a limited period of time which is essential to many human behaviors. WM impairment has been recognized as a core neurocognitive dysfunction in patients with schizophrenia, which impacts considerably on their daily functioning and quality of life (Rajji et al., 2014). Moreover, WM impairment typically precedes the onset of psychotic symptoms in schizophrenia and has been reported in individuals with schizotypy (Schmidt-Hansen and Honey, 2009) and unaffected first-degree relatives of patients with schizophrenia (Callicott, et al., 2003a), suggesting that WM impairment may be a potential endophenotype of schizophrenia (Park and Gooding, 2014), rather than a consequence of symptoms or pharmacological treatment (Green et al., 2004). However, the underlying neurobiological mechanisms of WM impairment remain unclear.

In Baddeley's model of WM (Baddeley, 2007), the central executive is considered responsible for the allocation and coordination of attentional resources, while the temporary maintenance of mental representations is supported by two modality-specific subsystems, i.e. the phonological loop and the visuospatial sketchpad. Previous meta-analytic examination of modality-specific deficits of WM in schizophrenia did not reveal any statistically significant results. However, some evidence suggests that there is more consistent impairment in visuospatial WM tasks than in verbal WM tasks in patients with schizophrenia (Lee and Park, 2005; Piskulic et al., 2007). On the other hand, functional imaging studies have revealed altered activation at the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC) and the

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thalamus in schizophrenia patients, even in the absence of behavioral deficits (Minzenberg et al., 2009). However, it should be noted that some studies have reported hypoactivation at the DLPFC and parietal regions in schizophrenia (Barch et al., 2001), while some have identified hyperactivation in these nodes of the WM network (Manoach et al., 2000). Other researchers have also suggested an inverted U-shaped function between WM performance and prefrontal activation (Callicott et al., 2003b; Deserno et al., 2012; Manoach et al., 2003). Despite the well-replicated impairment in WM and a strong focus on prefrontal-parietal dysfunction in schizophrenia, the contribution of this dysfunction to WM impairment seen in schizophrenia patients remains unclear. One of the main reasons for this discrepancy between the large amount of available data and the relatively little knowledge gained from them might be the heterogeneity of tasks used and discrepancies in task difficulty between WM experiments.

Thus far, WM paradigms have exclusively tapped into either the verbal/auditory (Deserno et al., 2012; Manoach et al., 2000) or visual modality (Quide et al., 2013). In some studies, both modalities have been investigated, but they did so separately (Quee et al., 2011; Zilles et al., 2010). The fact that studies in healthy volunteers have reported a different activation pattern in WM tasks employing verbal and non-verbal materials (Rottschy et al., 2012) suggests that WM may be modality-specific. Moreover, there is ample evidence suggesting that group differences increase as a function of task complexity and the inclusion of different process types. One possibility to increase task complexity and the number of tapped processes is to include concurrent input from two different modalities. An example of such a task, the dual n-back task, with two simultaneous n-back streams: the visuospatial and auditory-verbal n-back tasks, requires participants to monitor and update WM contents from two different input sources. The visuospatial and the auditory-verbal tasks are independent from each other although they are presented simultaneously. Consequently, the dual n-back task combines maintenance and active manipulation because of the necessity to continuously encode, update and discard the information held in WM with the presentation of each new stimuli (Jaeggi et al., 2003). Due to the inclusion of multi-modal components, the task is demanding to the human cognitive system. It has been proposed that dual task performance yields a relative better estimate of inter-individual differences regarding WM function because the dual-task procedure prevents the use of task-related strategies that considerably confound performance in single n-back tasks (Jaeggi et al., 2008b). Several lines of evidence indicate that the measure of WM function obtained from the dual n-back task is strongly correlated with inter-individual differences in broad cognitive functions (Jaeggi et al., 2010; Thompson et al., 2013). The dual n-back task has been most frequently used in cognitive training research and some of these attempts have demonstrated improvements in measures that share high variance with WM. For instance, training-related improvement has been reported in fluid intelligence and emotional cognitive control in healthy volunteers (Jaeggi et al., 2008a; Schweizer et al., 2013), as well as in untrained WM tasks in older adults (Salminen et al., 2016) and in individuals with dysphoria (Owens et al., 2013). These studies provide encouraging evidence suggesting that the dual n-back task may be an optimal training paradigm to improve WM efficiency and related cognitive functions in individuals with schizophrenia. However, to the best of our knowledge, no study has evaluated the clinical utility of the dual n-back task as a measure of WM function in patients with schizophrenia.

The present study aimed to investigate WM function with the dual n-back in patients with schizophrenia using functional Magnetic Resonance Imaging (fMRI). An *n*-level of 2 was used and a 0-back condition using identical stimuli served as the control condition. The main aim of this study was to explore the clinical utility of the dual n-back task as a measure of WM function. Validity of the result was examined in relation to the measures of WM capacity and intellectual functioning. We hypothesized that performance between the dual n-back task and these measures would be significantly correlated. Moreover, given that the dual n-back task has been shown to activate the DLPFC, the posterior parietal regions, the cerebellum and some subcortical regions in healthy volunteers (Jaeggi et al., 2003; Schweizer et al., 2013), we also aimed to examine whether such a relationship would also be found in patients with schizophrenia. We hypothesized that patients with schizophrenia would perform worse on the dual 2-back condition at the behavioral level and would exhibit hypoactivation in these brain regions during the dual n-back task compared with healthy controls. We also hypothesized that the reduced brain activity in schizophrenia patients would correlate with their WM performance.

2. Methods

2.1. Participants

Twenty-three schizophrenia patients were recruited from the Shanghai Mental Health Centre. All patients met the diagnostic criteria for schizophrenia according to the DSM-IV (American Psychiatric Association, 1994). Patients with a history of neurological disorder, substance abuse, or treatment with electroconvulsive therapy within the past three months were excluded from the study. Clinical symptoms were rated by experienced psychiatrists using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982). Medication dosage in chlorpromazine equivalence was recorded for all participants and side effects were evaluated using the Abnormal Involuntary Movements Scale (AIMS; Smith et al., 1979) and the Barnes Akathisia Rating Scale (BARS; Barnes, 1989).

Twenty-four healthy controls matched for age and sex ratio were recruited from the community through on-line advertising. No control participant had any personal or family history of psychiatric disorder, neurological disorder, or a history of substance abuse. All participants had normal or corrected-to-normal visual and auditory acuity, and their IQ were estimated with the four-subtest short form (information, arithmetic, similarity and digit span subscales) of the Chinese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Gong, 1992). The total number of items passed in the Letter Number Span task (LNS) (Chan et al., 2008; Gold et al., 1997) was used as the index of WM capacity.

2.2. Dual n-back task and procedure

The dual n-back task, adapted from Jaeggi et al. (2008a), was used for the experimental task. Chinese characters with one syllable and grey squares were used as stimuli. Participants were asked to decide whether the location of the square or the character they heard were the same as the one n back before with their left or right index finger respectively (Fig. 1). The task consisted of two conditions, 0-back and 2-back. In the 0-back condition, the stimulus was presented for 500ms, followed by an interval of 2000 ms. In the 2-back condition, the inter-stimulus interval was 2500 ms due to the highly demanding nature of the 2-back task. Each experimental condition was presented five times in the scanner in a block design with $10 + n$ trials in each block. Four trials in each block were "target trials" (two target trials per modality) presenting stimuli that matched the stimuli n positions back in the sequence. Each block was followed by a 12 s rest period.

All participants underwent "offline" dual 0-back and 2-back practice sessions before fMRI data acquisition. Accuracy was calculated as the proportion of correct responses. Two patients could not complete the dual 2-back condition even after extensive practice, and one patient did not hear the auditory stimuli due to equipment failure. Thus the final sample included 20 schizophrenia patients and 24 healthy controls for whom complete data were available. To test for differences in performance accuracy, mixed ANOVA with WM load as the within-subject factor and diagnosis as the between-subject factor was conducted. *Post-hoc t* tests were performed to clarify the direction of the results.

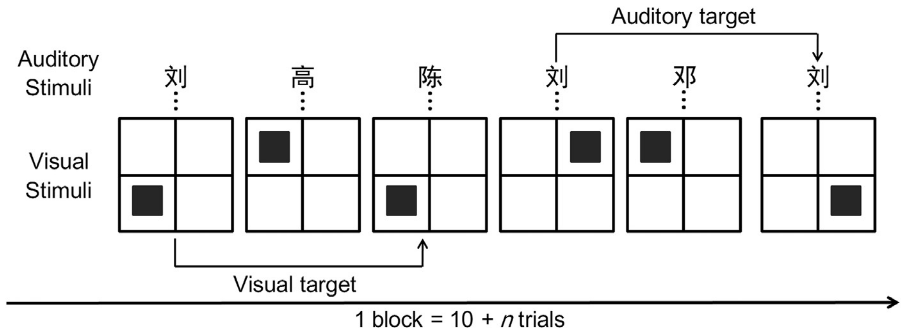

Fig. 1. Example of a 2-back condition in the dual n-back task.

Moreover, validity was assessed with bivariate correlations to examine the relationship between dual n-back performance and estimated IQ and score on the LNS task. Since we made an a-priori hypothesis that performances on these measures would be positively correlated with each other, one-tailed Pearson correlations were conducted to examine this relationship.

2.3. Imaging data acquisition

All imaging data were collected using a 3-Tesla Siemens Verio Magnetic Resonance Imaging (MRI) scanner at the Shanghai Mental Health Centre. The T1-weighted structural image was acquired with the following parameters: repetition time (TR) = 2,530 ms, echo time (TE) = 1.66 ms, field of view (FOV) = 256 mm, flip angle = 7°, image matrix = 256 × 256, and slice thickness = 1 mm. The fMRI data were acquired with a whole-brain echo planar imaging (EPI) sequence: TR = 2,000 ms, TE = 30 ms; field of view FOV = 210 mm, slices = 31, flip angle = 90°, image matrix = 64 × 64, and voxel dimensions = 3.3 mm × 3.3 mm × 4 mm. A T2-weighted image was also acquired to exclude participants with incidental brain lesions.

2.4. Image data analysis

Image preprocessing was performed using the Statistical Parametric Mapping software package (SPM8; Wellcome Department of Imaging Neuroscience, London, UK). The preprocessing steps included: (1) realignment to the first volume to correct for head motion; (2) co-registration to the structural image of each participant; (3) normalization to the Montreal Neurological Institute (MNI) stereotactic space with a 3 mm × 3 mm × 3 mm resolution; and (4) smoothing with 8-mm full-width at half-maximum (FWHM) Gaussian kernel. No participant had a head motion of more than 3-mm translation or 3° angular rotation.

Statistical analysis was performed using the General Linear Model (GLM). On the first level of analysis, condition blocks of 2-back and 0-back were modelled respectively with six head motion parameters entered as covariates of no interests. Contrast images were then constructed for each participant for 2-back minus 0-back to identify regions associated with WM ability and to exclude motor or attention effects associated with the task. Second level analysis was conducted with non-parametric permutation testing as implemented in the Statistical nonParametric Mapping package (SnPM, http://warwick.ac.uk/tenichols/snpm). One sample *t*-test were performed on the 2-back > 0-back contrast and the 0-back > 2-back contrast at the whole-brain level within the patient group and healthy controls respectively to identify activation patterns related to dual n-back performance. Schizophrenia patients and healthy controls were then compared using two-sample *t*-tests to examine the difference in activation (2-back > 0-back) between these two groups. To examine whether there was any difference in WM-related brain activations between schizophrenia patients and healthy controls, a two-sample *t*-test with accuracy of the dual 2-back condition as the covariate of interest was also conducted. A cluster-forming threshold of $p < 0.001$ with 10000 random permutations and a cluster-wise threshold of FWE-corrected $p < 0.05$ was employed.

3. Results

3.1. Basic information

The demographic information of these two groups and the clinical characteristics of the patient group are listed in Table 1. There was no significant difference between the two groups regarding age, sex and length of education. Schizophrenia patients had lower IQ ($p = 0.008$), and performed significantly worse on the LNS task ($p = 0.029$) than healthy controls.

3.2. Behavioral performance on the dual n-back task

Mixed ANOVA with accuracy as the dependent variable revealed a significant main effect of WM load (F (1, 42) = 119.679, $p < 0.001$), a significant main effect of diagnosis (F (1, 42) = 8.341, $p = 0.006$), and a significant WM load by diagnosis interaction (F (1, 42) = 7.705, $p = 0.008$). *Post-hoc t* test revealed that schizophrenia patients performed significantly worse than healthy controls on the 2-back task ($p = 0.002$), and no significant difference in accuracy on the 0-back task was found between these two groups ($p = 0.310$). Significant positive correlations were found between dual 2-back accuracy, performance on the LNS task ($r = 0.278$, $p = 0.034$) and estimated IQ ($r = 0.417$, $p = 0.002$). However, only marginally significant correlations were found between dual 0-back accuracy, performance on the LNS task and estimated IQ ($r = 0.248$, $p = 0.052$; $r = 0.214$, $p = 0.082$). There were no significant correlations between clinical symptoms and WM performance ($ps > 0$ .05).

3.3. Imaging results

3.3.1. Within-group effects

Both patients with schizophrenia and healthy controls showed significant within-group activations in the DLPFC, the inferior parietal lobule and the cerebellum (see Table 2 and Fig. 2) for the 2-back > 0-back contrast. For the 0-back > 2-back contrast, no significant activation was detected.

3.3.2. Comparison between schizophrenia patients and healthy controls

Group comparisons showed that significant hyperactivation was observed at the right hippocampus (adjacent to the superior temporal gyrus) in schizophrenia patients compared with healthy controls for the 2-back > 0-back contrast (see Table 3 and Fig. 3A). Signal changes at the peak hippocampal voxels (spherical ROI, radius 6 mm) were extracted and analyzed with 2 (WM load: 0-back, 2-back) x 2 (Diagnosis: schizophrenia, healthy controls) mixed ANOVA. We found a significant main effect of WM load (F (1, 42) = 8.511, $p = 0.006$) and a significant

Table 1
Demographic, clinical and cognitive function information for the participants

	Schizophrenia Patients		Healthy Controls		$t/\chi 2$	p
	Mean	SD	Mean	SD		
Sex(Male: Female)	13:7		16:8		0.013	0.908
Age	23.05	6.00	24.08	4.34	0.662	0.512
Education	13.00	2.64	14.21	1.93	1.752	0.087
IQ estimates	105.05	12.31	115.88	13.28	2.782	0.008
Duration of Illness (Year)	2.63	2.10				
CPZ equivalents [a] (mg/day)	194.99	106.76				
Other psychiatric medications [b]: mood stabilizers or antidepressants (n)	3					
PANSS	56.70	11.20				
Positive Symptoms	9.75	3.75				
Negative Symptoms	18.95	4.55				
General Psychopathology	28.00	6.94				
SANS	20.65	9.21				
AIMS	1.25	2.43				
BARS	0.4	1.1				
LNS	14.75	2.79	17.71	5.57	2.282	0.029
n-back performance (Accuracy)						
0-back (%)	87.75	11.29	90.63	7.12	1.027	0.310
2-back (%)	58.00	15.93	72.92	14.14	3.290	0.002

Abbreviations: CPZ, chlorpromazine; PANSS: Positive and Negative Syndrome Scale; SANS: the Scale for the Assessment of Negative Symptoms; AIMS: Abnormal Involuntary Movements Scale; BARS: Barnes Akathisia Rating Scale. LNS: the Letter Number Span task.

[a] CPZ equivalents were calculated for participants taking antipsychotic medications; one patient was unmedicated, and others were all medicated with second-generation antipsychotics.

[b] Three of the patients were additionally receiving mood stabilizer (magnesium valproate/sodium valproate) or antidepressant (fluvoxamine maleate).

WM load by diagnosis interaction ($F\,(1, 42) = 12.568, p = 0.001$). Post-hoc analysis revealed a significantly greater deactivation at the hippocampus for the 0-back condition in patients with schizophrenia ($p = 0.045$) and a significantly greater deactivation at the hippocampus for the 2-back condition in healthy controls ($p = 0.012$) (Fig. 3B). Additional analysis that included WM performance as a covariate of interest was conducted. Reduced performance-related brain activations were found at the right middle frontal gyrus and the right superior parietal lobule (extending to the inferior parietal lobule) in schizophrenia patients compared with healthy controls for the 2-back > 0-back contrast (Fig. 3C), suggesting that decreased activation at the DLPFC and the posterior parietal cortex (PPC) was associated with poor WM performance in schizophrenia patients.

Table 2
Significant brain activations of working memory (WM) in schizophrenia patients and healthy controls

Contrast	No. of sig. Clusters	Cluster Size (voxels)	x	y	z	T	Hemisphere	BA	Brain Regions
Healthy controls									
2-back > 0-back	3	10196	-30	24	3	12.45	L/R	6/8/9/44/47	SFG/MFG/IFG
			51	15	36	10.84			
			33	24	3	10.41			
		1737	-33	-45	42	7.77	L	7/39/40	IPL
			-45	-39	42	7.18			
			-39	-54	57	7.12			
		510	30	-60	-30	4.85	R/L		Cerebellum Posterior Lobe
			12	-72	-27	4.38			
			-9	-75	-27	4.31			
0-back > 2-back	0								
Schizophrenia Patients									
2-back > 0-back	8	1239	0	24	45	6.25		6/8/9	MeFG
			-30	3	63	5.46			
			-27	12	60	5.36			
		838	36	-42	39	6.16	R	40	IPL
			45	-48	54	5.3			
			27	-57	39	4.49			
		154	33	27	3	5.3	R	45/47	IFG
		146	-30	60	18	5.24	L	10	SFG
			-45	48	6	3.3			
		679	-33	-48	39	5.22	L	40	IPL
			-45	-48	54	4.71			
			-27	-66	42	4.52			
		211	42	39	30	5.2	R	9/10	MFG
			39	54	18	3.37			
		531	42	6	27	5.03	R	6	MFG
			33	6	63	4.99			
			27	6	51	4.36			
		105	-30	27	0	4.63	L	45/47	IFG
		88	-3	-39	-33	3.96	L		Cerebellum Anterior Lobe
0-back > 2-back	0								

BA: Brodmann Area; SFG: Superior Frontal Gyrus; MFG: Middle Frontal Gyrus; IFG: Inferior Frontal Gyrus; IPL: Inferior Parietal Lobule; MeFG: Medial Frontal Gyrus

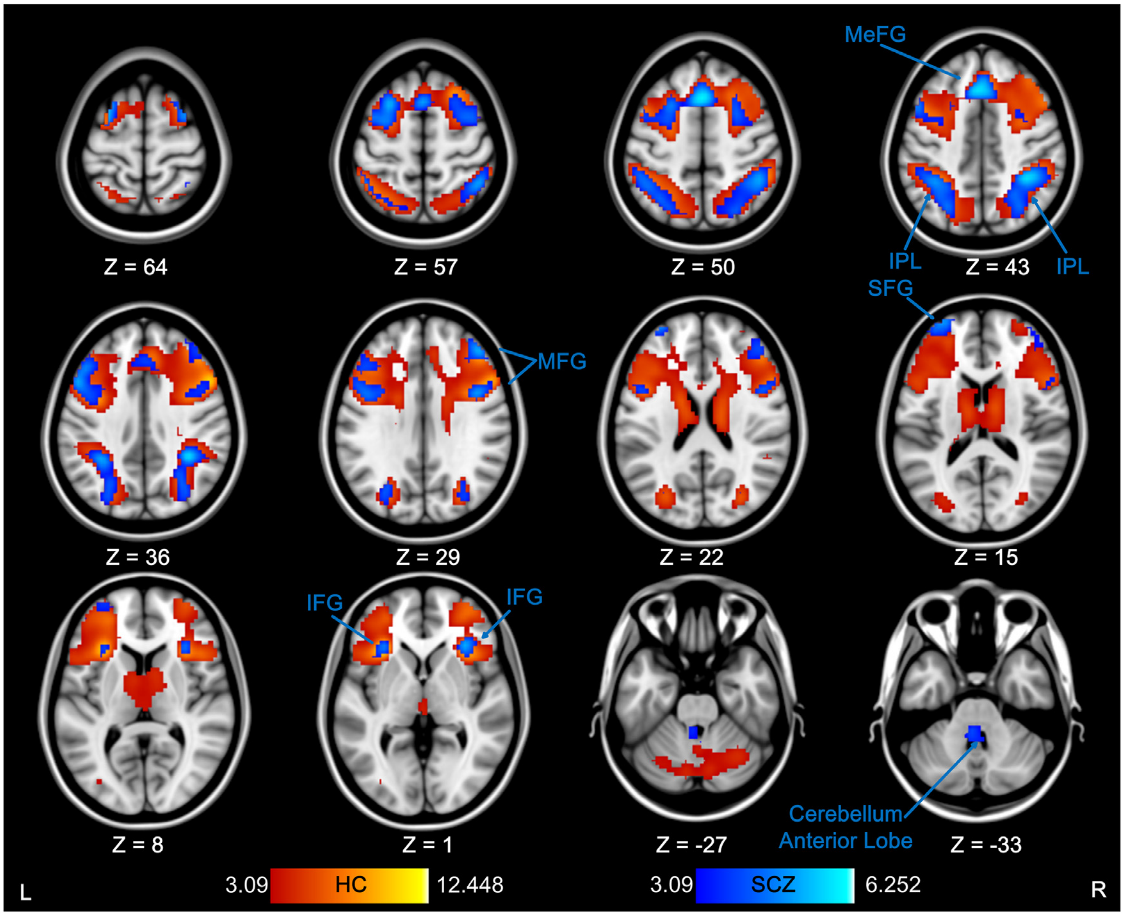

Fig. 2. Brain activations for the 2-back > 0-back contrast in patients with schizophrenia and healthy controls respectively. MFG = Middle Frontal Gyrus; IFG = Inferior Frontal Gyrus; SFG = Superior Frontal Gyrus; MeFG = Medial Frontal Gyrus; IPL = Inferior Parietal Lobule.

4. Discussion

The present study provides important insights into WM dysfunction in patients with schizophrenia using a dual version of the n-back task. Our behavioral results indicate that patients with schizophrenia exhibited substantial impairment in WM capacity under higher WM load. Imaging results of healthy controls are consistent with those reported in previous studies (Jaeggi et al., 2003; Schweizer et al., 2013). The comparison between schizophrenia patients and healthy controls indicates a focused functional insufficiency at the right DLPFC and the right PPC in patients with schizophrenia. This further confirms the central role of WM in the general cognitive system and highlights impairments in regions which exert control on other subsystems.

The WM capacity estimated in the present study is consistent with studies using other WM paradigms (Johnson et al., 2013) and the extent of impairment in our sample resembles those documented in a meta-analysis that examined a wide range of verbal and visuospatial WM measures in patients with schizophrenia (Lee and Park, 2005). The present study also provides some evidence supporting the validity of the dual n-back task as a clinically meaningful measure of WM, as performance on the dual 2-back task correlated with performance on the LNS task and IQ scores of the participants. In the dual n-back task, participants have to coordinate and combine the encoding, storage and retrieval of two modality streams presented simultaneously. Previous studies have consistently shown that WM function is strongly associated with performance across general cognitive functions and WM capacity

Table 3
Comparison between schizophrenia patients (SCZ) and healthy controls (HC) for the 2-back > 0-back contrast

Contrast	No. of sig. Clusters	Cluster Size (voxels)	*x*	*y*	*z*	*T*	Hemisphere	BA	Brain Regions
No covariates									
SCZ > HC	1	73	36	-6	-27	4.06	R		Hippocampus Gyrus
			39	15	-27	3.63			
			33	-15	-21	3.41			
SCZ < HC	0								
WM performance as the covariate of interest									
SCZ > HC	0								
SCZ < HC	2	93	48	15	36	4.67	R	8/9	MFG
		113	18	-54	69	4.47	R	7/40	SPL/IPL
			30	-45	69	4.12			
			57	-36	51	3.83			

BA: Brodmann Area; MFG: Middle Frontal Gyrus; SPL: Superior Parietal Lobule; IPL: Inferior Parietal Lobule

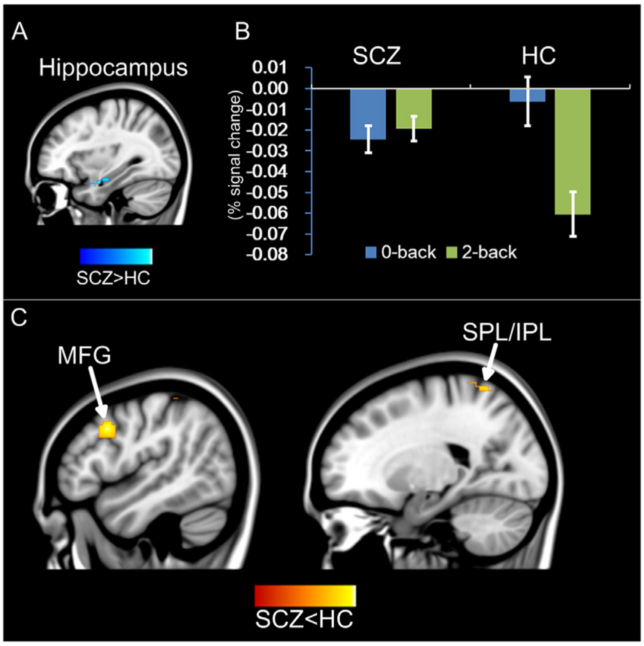

Fig. 3. **A**, hyperactivation in schizophrenia patients compared with healthy controls for the 2-back > 0-back contrast. **B**, percent signal change at the right hippocampus evoked by 0-back and 2-back conditions in patients with schizophrenia and healthy controls. Error bars indicate SE. **C**, hypoactivation in schizophrenia patients compared with healthy controls for the 2-back > 0-back contrast. MFG = Middle Frontal Gyrus; SPL = Superior Parietal Lobule; IPL= inferior Parietal Lobule.

reduction have been identified as a critical determinant of general cognitive impairment in patients with schizophrenia (Gold et al., 2010; Johnson et al., 2013). Behavioral performance difference was observed in the 2-back condition only in the present study, while studies with single n-back tasks reported reduction of performance both in the 0-back control condition and 2-back WM conditions in schizophrenia (Callicott et al., 1998; Deserno et al., 2012). It is noteworthy that a study examining differential age effects on n-back task performance revealed a reliable interaction between age and task performance only if the n-back task was performed as a dual task (Jaeggi et al., 2008b). Thus, although the single version n-back task was not tested in this study and the evidence is indirect, there are good reasons for assuming that the dual n-back task may be a more sensitive measure for individual differences in WM capacity in patients with schizophrenia.

Our neuroimaging results revealed widespread activation of the lateral prefrontal cortex and parietal regions in healthy volunteers in the 2-back > 0-back contrast, indicating a WM load effect on the prefrontal-parietal network. This is consistent with results reported in healthy populations in previous studies using the dual n-back task (Jaeggi et al., 2003; Schweizer et al., 2013). The prefrontal and parietal regions are the most widely reported brain areas associated with WM performance. They serve to retain and update task-relevant information and expel irrelevant contents from WM (Nee et al., 2013). There is no doubt that various WM paradigms address different WM functions and activation probability for a given brain area may vary due to experimental implementations. However, the bilateral prefrontal and parietal regions have been shown to be engaged by WM tasks independent of the type of stimuli, tasks or contrasts as a highly stable “core” network for WM processing (Rottschy et al., 2012). These results corroborate the utility and validity of our paradigm in assessing various processes involved in WM.

For patients with schizophrenia, the effect of WM load was also observed at the bilateral prefrontal gyrus and the inferior parietal lobule. It appears that fewer brain regions are involved in schizophrenia patients to complete this demanding task, resulting in poorer behavioral performance. A direct comparison between patients with schizophrenia and healthy controls further confirmed the presence of hypofrontality in schizophrenia. Greater performance-dependent activation of the right DLPFC has been demonstrated in healthy participants during successful encoding in WM task (D'Esposito et al., 2000), which could potentially reflect task failure in schizophrenia patients, as they are unable to sufficiently activate the DLPFC when performing WM tasks. Other studies have also observed similar patterns of difference in accuracy and reduced brain activation at the DLPFC when schizophrenia patients performed emotional 2-back tasks (Guimond et al., 2018; Kim et al., 2015). It is possible that when the task is cognitively demanding, such as when there is a need to maintain various modalities in WM as in the present study or when there is a need to discriminate emotional stimuli, greater differences were observed between patients and healthy controls. Unaffected relatives of patients with schizophrenia have also been shown to exhibit decrease in activation at the right middle frontal gyrus (Zhang et al., 2016). Despite tremendous interest in DLPFC dysfunction as the neurobiological substrate of WM deficits in schizophrenia, clear evidence for direct connection between functional abnormality in this region and individual differences in WM capacity is still lacking. Some studies did not find any significant effect of WM performance on brain activities in either schizophrenia patients or healthy controls (Quide et al., 2013), while a recent study demonstrated that the association between left DLPFC activation and WM capacity is diminished in patients with schizophrenia (Van Snellenberg et al., 2016).

WM performance-related hypoactivation were also observed at the PPC in patients with schizophrenia in our study. The PPC is critical for the manipulation and rearrangement of information in WM (Koenigs et al., 2009). Previous studies have shown that there is reduced task-related activation at the PPC during the encoding and maintenance of the association between verbal and spatial information in WM in patients with schizophrenia (Grot et al., 2017). The active binding task used in that study requires additional cognitive effort than passive binding conditions, and schizophrenia patients only exhibited poorer behavioral performances in the active binding condition. Taken together with our findings, PPC hypoactivation may reflect difficulties in maintaining and manipulating information in WM in schizophrenia patients. On the other hand, a recent study utilizing WM paradigms emphasizing storage rather than executive control demonstrated a crucial role of PPC dysfunction in WM storage deficits in schizophrenia (Hahn et al., 2018). These findings are not mutually exclusive, but indicate that schizophrenia patients have difficulty in encoding and maintaining WM contents efficiently. Moreover, several white matter tracts connect the PPC to the prefrontal cortex, and these tracts contribute significantly to the important role of the prefrontal-parietal network in WM (Olson and Berryhill, 2009). With dynamic causal modelling, it has been reported that WM-dependent connectivity from the DLPFC to the PPC is reduced in schizophrenia (Deserno et al., 2012). The identification of altered functional coupling of the DLPFC and the PPC highlights the particular relevance of brain systems implicated in WM performance for pathological brain changes associated with schizophrenia. The altered activation pattern revealed in our study therefore may have important implications for future studies.

We also found that the right hippocampus was more activated in patients with schizophrenia. Although activity in the hippocampus was not found to correlate with WM capacity directly in the present study, the importance of this region to WM should not be neglected. Further investigation of the signal changes of the hippocampus indicated increased deactivation during 0-back condition and reduced deactivation during 2-back condition in patients with schizophrenia compared with healthy controls. Task-related deactivations are indicative of brain activity suppression and imply disengagement of the region. The inverted-U shape pattern of neural activation associated with WM suggests that brain activities of schizophrenia patients reached a peak at lower WM load, while healthy controls reached a peak at higher WM load. In the dual 0-back condition of the present study, schizophrenia patients experienced a higher cognitive load and more deactivation at the hippocampus was observed. While their behavioral performance did not differ from healthy controls, greater hippocampus deactivation may suggest a compensatory response to the increased cognitive demand. However, the dual 2-back condition might have exceeded the limits of their WM capacity, resulting in a failure to deactivate the hippocampus. Indeed, decreased efficiency of WM-irrelevant networks has been observed under high WM load conditions in schizophrenia patients (Metzak et al., 2012) and a more deactivated hippocampus have been found to be associated with better WM performance in a visual-spatial *n*-back task in healthy individuals (Stretton et al., 2012).

Progress in understanding the neural basis and cognitive mechanism underlying WM impairment in schizophrenia may offer viable targets for psychological and pharmacological treatment development as any improvement in this area will likely have a positive impact on broad aspects of cognitive performance (Shipstead et al., 2012). In fact, the dual n-back paradigm has been used as a training task to generate improvement beyond the WM domain, such as fluid intelligence (Jaeggi et al., 2008a), affective cognitive control (Schweizer et al., 2013) and episodic memory (Rudebeck et al., 2012). Moreover, dual n-back training has been utilized to alleviate hedonic deficits in individuals with social anhedonia. It was found that their reduced anticipatory sensitivity towards rewards was alleviated to the same extent as individuals with intact hedonic processing ability (Li et al., 2016b). Brain activations related to anticipation were enhanced after dual n-back training in these high risk individuals at the anterior cingulate cortex, the left dorsal striatum and the left precuneus when processing anticipatory affective cues, and at the DLPFC and the supramarginal gyrus when processing anticipatory monetary cues (Li et al., 2016a). It remains unclear whether this dual version n-back task could be utilized in clinical samples as few studies have investigated the remediation effect of dual n-back training in patients with schizophrenia.

This study has several limitations. First, the sample size of the patients group was relatively small, which might limit the interpretability of the results. Secondly, only 0-back and 2-back conditions of the dual n-back task were utilized in the present study, which is consistent with the majority of previous studies utilizing single version n-back tasks (Deserno et al., 2012; Quide et al., 2013). Parametric manipulation of WM load across a wide range of task difficulties, for example from zero to 3 or even more memory items, might provide more valuable information for the temporal dynamic of brain activations when performing WM tasks. Lastly, the dual n-back task used in this study only recorded accuracy. However the participants' response times may provide additional valuable information to our understanding of WM functions in schizophrenia.

In summary, using a dual version n-back paradigm allowing for the direct estimation of WM function, we demonstrated a pattern of reduced activation at the DLPFC and the PPC in schizophrenia patients. Moreover, the hippocampus of patients with schizophrenia was less deactivated than healthy controls when performing the demanding dual 2-back task. More research is warranted to characterize WM cortical-subcortical functional organization and connectivity in schizophrenia for a better understanding of the nature of individual differences in WM processes. Our findings could also contribute to the development of WM training paradigms aiming at ameliorating general cognitive deficits in schizophrenia.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.01.002.

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