Working Memory Load-Related Brain Activity in Drug-Naïve, First-Episode Schizophrenia Patients

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Introduction

Working memory (WM) deficits in schizophrenia are well-documented[1]. Functional MRI studies show abnormal activations of especially the prefrontal cortex (PFC) in schizophrenia patients performing WM tasks[2]. According to the inverted U-function theory, participants exhibit a hyperfrontal response before WM capacity is exceeded whilst the response becomes hypofrontal after exceeding WM capacity. Purportedly, this pattern occurs at lower WM loads in schizophrenia patients than healthy participants[3,4]. The present study explores whether this relationship is present in antipsychotic drug-naïve, first-episode schizophrenia patients using a verbal N-back task with two WM loads. We hypothesised that patients will exhibit a hyperfrontal response at the higher WM load when performance levels are comparable to that of control subjects.

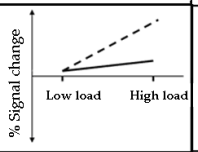
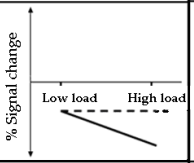
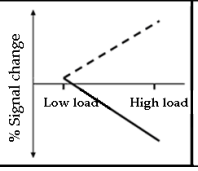
Method

Twenty-three (18M; mean age of 26 years, SD=5.0) antipsychotic drug-naïve, first-episode schizophrenia patients and thirty-five (24M; mean age of 27 years, SD=5.8) healthy controls were scanned on a 3T Siemens Trio scanner. A WM task consisting of pseudo-randomised blocks of rest, 0-back, 1-back, and 2-back was presented to participants during whole-brain BOLD-sensitive EPI acquisition (3.8×3.8×3.8mm voxels) followed by a B0 field map scan. A 3D, T1-weighted structural image was acquired using a MPRAGE sequence of the whole head (1×1×1mm voxels). The structural image was unwarped for gradient non-linearity distortions and normalised into MNI space. EPI images were unwarped for gradient non-linearity and B0 distortions, and coregistered to the mean EPI image. As the mean image was coregistered to the T1 image, EPI images were normalised using the T1 spatial normalisation transformation matrix. Resulting images were smoothed with an 8mm FWHM Gaussian kernel. Movement parameters were entered as nuisance regressors for each subject. The data were analysed in a Group-by-WM load factorial design based on first level contrasts where 0-back was entered as a control task and subtracted from the 1-back (low load) and 2-back (high load) conditions.

Results

Groups did not differ in performance at the high WM load condition but patients did perform significantly worse at the low WM load condition. Both groups activated expected WM areas with increased WM load to similar extents. However, we observed a significant Group-by-WM load interaction effect (p= 0.05, FDR corrected). We identified three different types of interaction (Table 1). Type I: areas where activity increased with WM load in both patients and controls but steeper so for the patient group. Type 2: areas which show more deactivation at high load in controls, while patients maintained a similar deactivation level as in the low WM load. Type 3: areas where control subjects showed a deactivation at high load, while patients, in contrast, showed an increased activation. Above results remained unchanged when using performance (measured in discrimination index, *d'*) as a covariant.

Table 1. Areas conforming to three Group-by-WM load interaction effect types

	Patients / Controls	Left hemisphere	Right hemisphere
Interaction 1		Middle frontal gyrus, fusiform gyrus	Superior parietal gyrus
Interaction 2		Subcentral gyrus, supramarginal gyrus, insula lobe, precentral gyrus, central sulcus, parietal operculum, posterior cingulate gyrus	Subcentral gyrus, superior temporal gyrus, insula lobe, precentral gyrus, central sulcus, amygdala
Interaction 3		Posterior cingulate gyrus, superior frontal gyrus (medial aspect), lingual gyrus, superior parietal gyrus	Middle cingulate gyrus, central sulcus/precentral gyrus, lingual sulcus

Discussion/Conclusion

Our finding that left dorsolateral PFC activity increased significantly more from low to high WM load in schizophrenia patients as compared to controls supports the inverted U-function theory of PFC activation in WM (interaction type 1). The other two types of Group-by-WM load interaction effects were observed in areas previously reported as activated in the resting state and normally deactivated during task-related cognitive processing. Task-induced deactivations have been found to increase with task difficulty[5,6], a finding which has been replicated in our cohort of healthy control participants. The failure of the patient group to deactivate specific brain regions with increasing WM load can be explained as an inability to efficiently allocate resources from task-irrelevant areas to areas necessary for task execution. This inability could eventually lead to poor performance and underlie the WM deficits that have been observed in schizophrenia. A previous study with a graded N-back task also found schizophrenia patients to have abnormal frontoparietal activations in concordance with decreased temporocingulate deactivations[7]. There is also some evidence suggesting that task-induced deactivated regions and task-induced activated regions are negatively coupled in healthy subjects[8]. Hence our findings might point to a possible disconnection between the two systems in schizophrenia.

References

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