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# Functional connectivity reveals inefficient working memory systems in post-traumatic stress disorder

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ABSTRACT

We applied a covariance-based multivariate analysis to functional magnetic resonance imaging (fMRI) data to investigate abnormalities in working memory (WM) systems in patients with post-traumatic stress disorder (PTSD). Patients ($n=13$) and matched controls ($n=12$) were scanned with fMRI while updating or maintaining trauma-neutral verbal stimuli in WM. A multivariate statistical analysis was used to investigate large-scale brain networks associated with these experimental tasks. For the control group, the first network reflected brain activity associated with WM updating and principally involved bilateral prefrontal and bilateral parietal cortex. Controls' second network was associated with WM maintenance and involved regions typically activated during storage and rehearsal of verbal material, including lateral premotor and inferior parietal cortex. In contrast, PTSD patients appeared to activate a single fronto-parietal network for both updating and maintenance tasks. This is indicative of abnormally elevated activity during WM maintenance and suggests inefficient allocation of resources for differential task demands. A second network in PTSD, which was not activated in controls, showed regions differentially activated between WM tasks, including the anterior cingulate, medial prefrontal cortex, fusiform and supplementary motor area. These activations may be linked to hyperarousal and abnormal reactivity, which are characteristic of PTSD.


## 1. Introduction

The ability to hold and manipulate information in mind is a defining characteristic of human cognition. Working memory (WM) systems enable this process, subserving the maintenance and manipulation of information relevant to ongoing tasks and goals. WM abnormalities are associated with a range of psychiatric disorders including post-traumatic stress disorder (PTSD) (Yehuda et al., 1995; Vasterling et al., 1998; Samuelson et al., 2006). For patients with PTSD, difficulty holding information in mind causes frustration and distress and interferes with their ability to function effectively in employment or social situations.

This work uses functional neuroimaging to investigate brain activity in PTSD patients performing WM tasks. Previous neuroimaging studies of PTSD, using trauma-neutral stimuli, have shown abnormalities in several brain regions known to be implicated in the neurobiology of PTSD, including the prefrontal cortex, the anterior cingulate and the hippocampus. Within the prefrontal cortex, abnormal activity has been observed in the orbitofrontal cortex (Shaw et al., 2002; Bremner et al., 2003), medial prefrontal cortex (Bremner et al., 2003), dorsolateral prefrontal cortex (Clark et al., 2003; Bryant et al., 2005; Moores et al., 2008) and right middle frontal gyrus (Semple et al., 2000). Within the anterior cingulate, abnormal activity has been observed on both the dorsal (Bryant et al., 2005; Moores et al., 2008) and rostral aspects (Bryant et al., 2005). Abnormal anterior cingulate activity was observed by Semple et al., on the left side only (Semple et al., 2000).

Our recent fMRI experiment (Moores et al., 2008) extends previous neuroimaging studies of trauma-neutral information-processing abnormalities in PTSD, by specifically investigating WM maintenance and updating, considered an executive/manipulation process. Although similar studies of WM in healthy humans have determined that maintenance and manipulation processes differentially activate virtually identical neuronal systems, principally involving prefrontal and parietal regions (Veltman et al., 2003; Woodward et al., 2006), our previous work suggested that activity was abnormally elevated in these regions during WM maintenance in PTSD (Moores et al., 2008). The current work employed a covariance-

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based multivariate analysis of our fMRI data to investigate distributed neuronal systems in PTSD during trauma-neutral information processing. We were particularly interested in determining the degree of overlap between brain networks associated with WM maintenance and updating in PTSD.

Unlike standard univariate analyses, which focus on regionally specific brain activity, multivariate analyses are sensitive to interactions between brain regions and are therefore ideal to address questions about functional integration of brain processes and brain networks, termed "functional connectivity" (Friston et al., 1993). There is an established body of work demonstrating that multivariate analyses can reveal interesting effects in neuroimaging data, often un-detected with the standard univariate approach (Moeller and Strother, 1991; Friston et al., 1996; McIntosh et al., 1996; Worsley et al., 1997; Strother et al., 2002; Kriegeskorte et al., 2006). In addition, multivariate analyses may be of particular use for highlighting different patterns of activity between particular groups, due to its sensitivity to systematic differences in regional brain correlations. A further motivation to apply a multivariate analysis methodology to our fMRI data was the recent suggestion (Shin et al., 2006) that such methodologies would be useful to investigate the functional relationships between brain structures implicated in PTSD (e.g. amygdala, medial prefrontal cortex and hippocampus). We expected that the application of a multivariate analysis technique to our data would identify specific networks associated with WM maintenance and WM updating in healthy controls, and would reveal differences in these networks in PTSD.

## 2. Methods

### 2.1. Data

This study involved a post-hoc analysis of previously collected fMRI data and full details of this experiment can be found in Moores et al. (2008). Data were collected from 13 right-handed PTSD patients (8 M, 5F; mean age: 44.23; age range: 30–55 yrs) and 12 non-traumatised controls (7 M, 5F; mean age: 40.41; age range: 28–59 yrs; ($t$ (23) = 0.948, $P > 0.05$)). Exclusion criteria included head injury or loss of consciousness (> 1 h), epilepsy or other neurological conditions and learning or developmental disorders. Control subjects were matched to patients on years of education, occupational status and estimated verbal IQ. PTSD was diagnosed according to DSM-IV criteria (American Psychiatric Association, 1994) and symptomatology was assessed using the Clinician Administered PTSD Scale (CAPS, Blake et al., 1990) and the Impact of Event Scale (IES, Horowitz et al., 1979). The mean CAPS score (data unavailable for 2 patients) for the PTSD group was 73.82, indicating severe PTSD symptomatology (Weathers et al., 2001). Severity scores on CAPS item 15 (mean 5.00) indicated that patients subjectively experienced concentration and memory disturbances as an important source of difficulty. Similarly, the IES indicated that symptoms of intrusions and avoidance were severe (mean 59.90) in this sample (Hutchings and Devilly, 2001). Precipitating (sometimes multiple) traumas included: assault (5), witnessing people being injured or killed (7), and motor vehicle (2) or other (1) accidents. Comorbidity was diagnosed using the Composite International Diagnostic Interview (World Health Organization, 1990) with patients excluded for current panic disorder, bipolar disorder, lifetime psychotic disorder or alcohol abuse or dependence within the last year. Current comorbidities included major depressive disorder (3), phobias (2), nicotine dependence (3) and somatoform disorders (3). Six patients were taking selective serotonin reuptake inhibitors (SSRIs).

### 2.2. Experimental task

The study used a visuo-verbal target detection task, where target identity and related WM processes were experimentally manipulated. A similar paradigm has been previously employed in our laboratory (Clark et al., 2000; Clark et al., 2003). The WM task required participants to attend to a set of serially presented words (see Fig. 1)

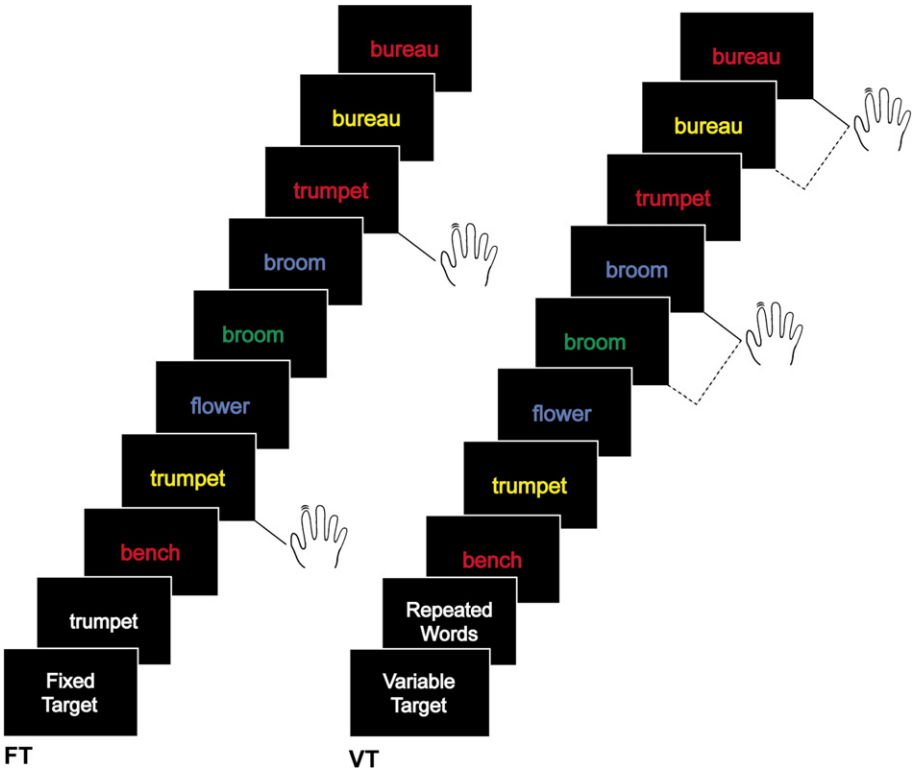


**Fig. 1.** Schematic representation of the Fixed Target (FT) and Variable Target (VT) conditions. For the FT condition, the target word was defined a priori at the beginning of the task block. In the VT condition, a target was defined as any consecutively repeated word, which required participants to continually update the target identity held in WM with the presentation of each new word.

on a computer monitor and to detect infrequent targets by making an appropriate finger response. There were four WM tasks that differed with regard to target definition (fixed or variable) and button-press response. For the Fixed Target (FT) condition, the target word was defined a priori at the beginning of the task block. In the Variable Target (VT) condition, a target was defined as any consecutively repeated word, which required participants to continually update the target identity held in WM with each new word. The reference baseline was a simple fixation (FIX) task, requiring attention to a line of five asterisks in the centre of the screen. Note that the two WM tasks involving varied button-press responses were not of interest for the current study and are not examined here.

Each imaging run (total duration = 256 s) consisted of one block of each of the four WM tasks (32 s each), each preceded by instructions (16 s) and interspersed with four fixation task blocks (16 s each). The WM tasks were balanced with respect to: (a) stimulus-target comparison demands, (b) number of task-related targets, (c) target rehearsal requirements, and (d) executive processes other than updating. Within each task block, four words were repeated four times, with the probability of any word, including targets, 25%. Words were displayed for 300 ms and stimulus onset asynchrony varied pseudo-randomly around 4 s (±0.2 s). Words comprised a master list of 338 concrete nouns obtained from the MRC Psycholinguistic Database (Version 2.00, Wilson, 1988), meeting the following criteria: (a) length of four to seven letters, (b) two to three syllables, (c) a written frequency between 20 and 50 (Kucera and Francis, 1967) and (d) no irregular plurals. Because we were investigating trauma-neutral information processing, words with emotive impact were excluded from the master list (128 words) and patients reviewed the reduced master list to exclude any words with idiosyncratic emotive impact. Words were presented in lowercase in colour (red, blue, green, yellow) at the centre of a black screen, though word colour was not relevant for the present study. Participants were trained on the WM tasks prior to scanning.

### 2.3. MRI data acquisition

MRI data were collected on a Siemens VISION (Magnotom, 4000) 1.5 Tesla MRI scanner with a CP Head Coil. Behavioural data were collected in a separate electroencephalography (EEG) session using precisely the same paradigm, with the order of fMRI/EEG sessions counterbalanced across participants. In addition to two high-resolution T1-weighted sagittal structural MRI volumes, fMRI data were acquired using a specialized gradient echo, echoplanar imaging (EPI) trapezoidal mosaic sequence developed in the Functional Imaging Laboratory (Wellcome Department of Imaging Neuroscience, University College

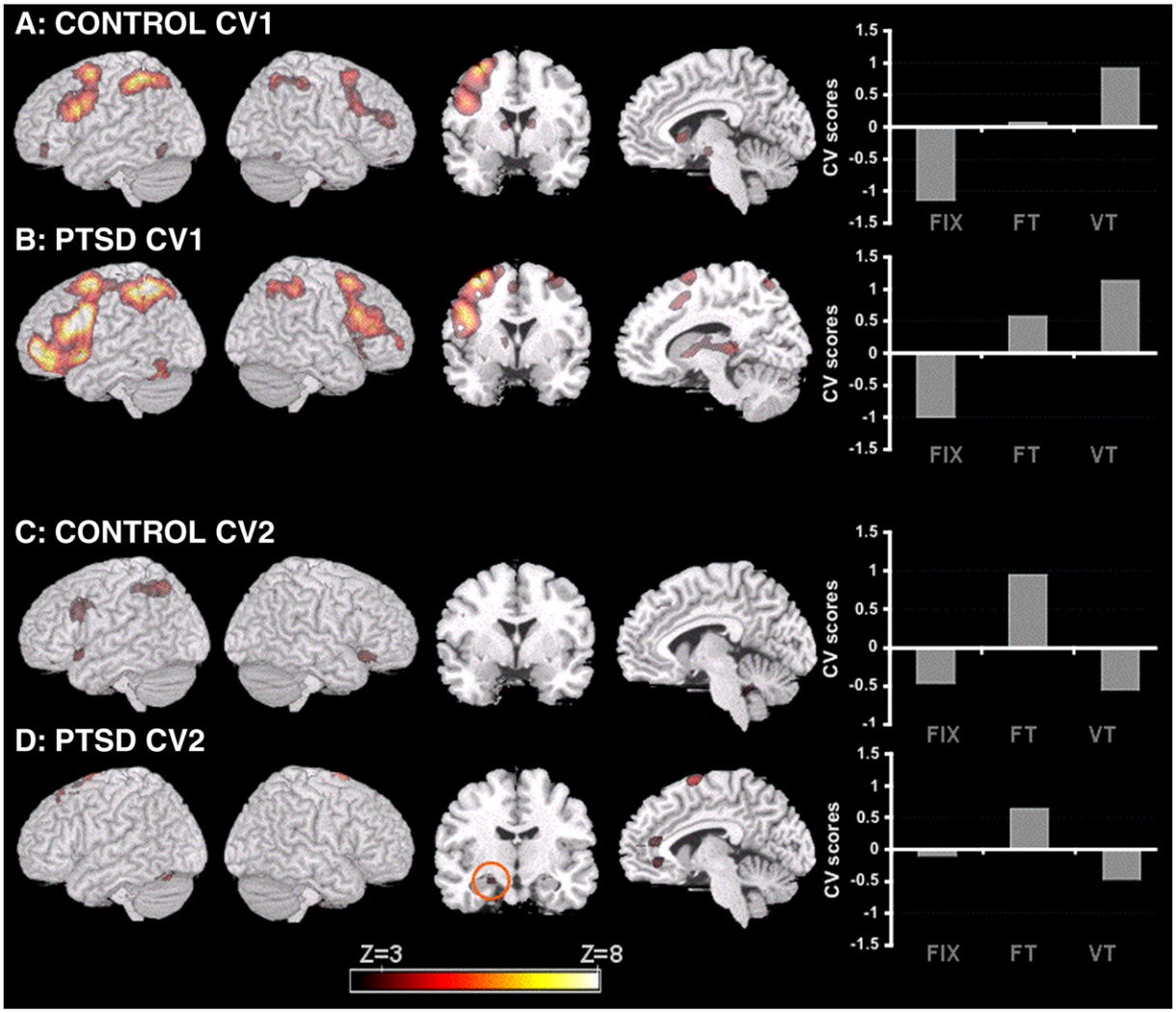


**Fig. 2.** SPM statistical maps and plots of the mean CV scores for the first and second CVs generated for each of the PTSD (rows B, D) and control (rows A, C) groups. SPM activations are shown on left and right rendered surface of the MNI standard brain (far left), as well as coronal and sagittal slices (middle). *Z*-scores ($2.33 < Z < 8$) are shown in red and yellow. The CV plots (right) show the mean CV score for each experimental condition, and show which conditions most strongly influence the neuronal system extracted by the first and second CVs for each of the control and PTSD groups.

London, UK) in collaboration with Siemens. Sixteen imaging runs were acquired per subject, with each imaging run comprising 80 axial fMRI volumes that were acquired every 3.494 s over the whole brain in 34 slices (TR = 0.76 ms, TE = 50 ms, TD1 = 20 ms, TD2 = 188.2 ms, flip angle = 90°, matrix = 64 × 64, FOV = 320 mm × 320 mm, pixel size = 5 mm × 5 mm, slice thickness = 4 mm with a 25% interslice gap. Only the first eight imaging runs were used for the current analysis, due to computational limitations (memory).

### 2.4. Data analysis

#### 2.4.1. Behavioural data

Full details concerning behavioural and neuropsychological data collection and analysis can be found in Moores et al. (2008). Briefly, mean reaction times and target detection rates were calculated for each subject for each experimental condition. Behavioural data were analysed using SPSS 11 (SPSS, 2002). Repeated measures analysis of covariance (ANCOVA) was used with medication as a covariate of no interest, to test the main effects of WM task and group on mean reaction times and target detection rates.

#### 2.4.2. fMRI preprocessing

EPI data were pre-processed using SPM2 (Wellcome Department of Cognitive Neurology; http://www.fil.ion.ucl.ac.uk/spm) with the following series of preprocessing steps: motion-detection, realignment, spatial normalisation and 3D Gaussian smoothing (10 mm). For spatial normalisation, the structural MRI was first co-registered to the mean EPI for each subject and then segmented. The gray matter component was then aligned to the gray matter MNI template.[1] The alignment matrices were combined and applied to the EPI data. Data were mean intensity normalised and high-pass-filtered (cut-off = 270 s). For all analyses, medication status of patients was included as a covariate of no interest.

#### 2.4.3. Canonical variates analysis (CVA) and interpretation of CVA results

CVA is a linear discriminant analysis that can be used to examine entire fMRI data sets (i.e. all voxels, scans, subjects) with the goal of identifying which brain regions co-activate in response to experimental tasks. We used the NPAIRS[2] software package to carry out this analysis and followed a similar method to that outlined in more detail in Shaw et al. (2002). For CVA (developed by Fisher, 1936), linear combinations of observed variables are found which maximise the mean difference between classes, with respect to within-class variance (Campbell and Atchley, 1981). "Classes" are chosen to partition observed data according to the experimental effect(s) of interest, in our case, the three experimental conditions of interest (FIX, FT, VT). The linear combinations are referred to as canonical variates (CVs) and are derived successively, until the full dimensionality of the between-class variance has been captured, up to $n - 1$, where $n$ is the number of classes. CV scores reflect the degree to which each fMRI scan is involved in each activation pattern, and they can therefore be used to determine which tasks are driving the activation covariance as captured by each dimension. An example of this can be seen in Fig. 2 (right panel), where a mean CV score was calculated for all scans corresponding to each of the three experimental tasks to determine which tasks are associated with each activation network.

Canonical eigenimages (CEs) show which brain regions contribute to the covariance captured by each dimension (for a detailed description of eigenimage determination, see: Friston et al., 1996). We used NPAIRS to convert CEs to statistical maps. The NPAIRS package is unique amongst image analysis software in that it incorporates cross-validation resampling as a way to generate statistical parametric maps (SPMs) for multivariate analyses (for full details, see Strother et al., 2002). As the SPMs are generated using cross-validation resampling, the analysis specifically identifies voxels showing *reproducible* activation across imaging runs and subjects. In this way, the approach is sensitive to random subject and imaging run effects (i.e. subject/run specific variations in the population from which the sample was drawn) (Strother et al., 2002). We report activations of the positive tail reaching (uncorrected) peak height probability of $P<0.0001$.

## 3. Results

### 3.1. Behavioural results

Two-way repeated measures ANCOVAs indicated that reaction times for the PTSD group were significantly slower than for the control group for both WM tasks ($F(1,20) = 6.571$, $P<0.05$). However, across groups, the mean reaction time for the VT task (846 ms) was not significantly different than the FT task (778 ms) ($F(1,20) = 0.488$, $P > 0.05$), and there was no interaction between group and reaction time ($F(1,20) = 0.009$, $P > 0.05$). The mean target detection rate for the VT task did not differ significantly from the FT task ($F(1,20) = 3.580$, $P > 0.05$), there were no significant between-group differences ($F(1,20) = 1.526$, $P > 0.05$), and there was no interaction between group and target detection rate ($F(1,20) = 0.176$, $P > 0.05$).

### 3.2. CVA results

For the control group, the three-class CVA resulted in two CVs, which accounted for 59.1% and 40.9% of the covariance between classes, respectively. Fig. 2 shows statistical parametric maps (SPM) and plots of CV scores corresponding to this analysis for control subjects (rows A and C). Note that the plot of CV scores for the first CV (row A) shows a large difference between FIX and VT, indicating that this CV was associated with the VT (WM updating) task. The SPM corresponding to this CV shows an activation network with strong bilateral activations in the inferior parietal lobes (IPL; centred in the intraparietal sulcus and supramarginal gyrus) and PFC (centred in the inferior frontal gyrus, extending into the middle frontal gyrus), and lateral premotor area, as well as midline activity in the pre-supplementary motor area (pre-SMA). Subcortical activations were

**Table 1**
Component regions of the first working memory network in control subjects.

| Region | MNI coordinates | | | | | |
|---|---|---|---|---|---|---|
| | L/R | BA | *x* | *y* | *z* | *Z*-score |
| Parietal lobe | | | | | | |
| Intraparietal sulcus | L | 40/7 | −29 | −61 | 52 | 8.65 |
| | R | 40/7 | 31 | −59 | 52 | 5.10 |
| Supramarginal gyrus | L | 40 | −45 | −41 | 55 | 8.21 |
| | R | 40 | 50 | −33 | 55 | 3.85 |
| Frontal lobe | | | | | | |
| Middle frontal gyrus | R | 46 | 42 | 48 | 16 | 3.62 |
| Inferior frontal gyrus (opercularis) | L | 44 | −52 | 11 | 29 | 7.03 |
| | R | 44 | 48 | 15 | 29 | 4.52 |
| Precentral gyrus | L | 6 | −37 | 0 | 60 | 7.03 |
| | R | 6 | 33 | 7 | 60 | 5.01 |
| Supplementary motor area (pre-SMA) | L | 6 | −2 | 15 | 49 | 3.86 |
| Subcortical | | | | | | |
| Brainstem | L | | −1 | −7 | −14 | 5.49 |
| | L | | −5 | −37 | −16 | 3.18 |
| Striatum | L | | −2 | 15 | −1 | 4.58 |
| Thalamus | R | | 14 | −19 | 13 | 4.83 |

L/R indicates left/right hemisphere, BA = Brodmann area. All activations are $Z>3.1$, corresponding to an uncorrected probability value of $P<0.001$.

[1] The MNI template was developed by the Montreal Neurological Institute (MNI) for the International Consortium for Brain Mapping (ICBM) project.

[2] The Non-parametric, Prediction, Activation, Influence and Reproducibility resSampling (NPAIRS) package is fully described by Strother et al. (2002). For more details, see the NPAIRS website: http://www.neurovia.umn.edu/incweb/.

**Table 2**
Component regions of the second working memory network in control subjects.

| Region | MNI coordinates | | | | | |
|---|---|---|---|---|---|---|
| | L/R | BA | *x* | *y* | *z* | *Z*-score |
| Parietal lobe | | | | | | |
| Intraparietal sulcus | L | 40/7 | −34 | −61 | 57 | 3.77 |
| Frontal lobe | | | | | | |
| Supplementary motor area (pre-SMA) | L | 6 | −2 | 24 | 43 | 3.43 |
| Inferior frontal gyrus (orbitalis) | R | 47 | 48 | 25 | −12 | 3.34 |

L/R indicates left/right hemisphere, BA = Brodmann area. All activations are $Z>3.1$, corresponding to an uncorrected probability value of $P<0.001$.

present in the brainstem, striatum and right thalamus. Statistically significant activations within this SPM are summarised in Table 1.

Fig. 2, row C, shows the plot of CV scores and SPM for controls' second CV. Scores are uniformly higher in the FT versus both FIX and VT tasks, suggesting that this CV has extracted covariance associated with the FT (WM maintenance) task. As summarised in Table 2, the network corresponding to this covariance pattern involved activation in the left IPL, again centred in the intraparietal sulcus and extending into the supramarginal gyrus, the left pre-SMA and the right inferior frontal gyrus (pars orbitalis). There was sub-threshold activity in the left inferior frontal gyrus (pars opercularis) extending into lateral premotor cortex.

For the PTSD group, the first CV accounted for 83.9% and the second accounted for 16.1% of the covariance. Fig. 2 (row B) shows mean CV scores for each class for the first CV. Similar to controls, in PTSD the VT (WM updating) task had the highest score, but the mean score for the FT (WM maintenance) task also had a positive weighting, indicating that the CV has captured covariance induced by both experimental tasks. The statistical map corresponding to this dimension (Fig. 2, row B) shows similar activations to the control group, specifically in bilateral IPL and PFC, including extensive activation in the middle frontal gyrus, inferior frontal gyrus and premotor cortex

**Table 3**
Component regions of the first working memory network in PTSD subjects.

| Region | MNI coordinates | | | | | |
|---|---|---|---|---|---|---|
| | L/R | BA | *x* | *y* | *z* | *Z*-score |
| Parietal lobe | | | | | | |
| Intraparietal sulcus | L | 40/7 | −40 | −50 | 61 | 9.98 |
| | R | 40/7 | 35 | −54 | 52 | 5.63 |
| Supramarginal gyrus | R | 40 | 50 | −38 | 55 | 5.56 |
| Frontal lobe | | | | | | |
| Middle frontal gyrus | L | 46 | −38 | 54 | −1 | 10.97 |
| | R | 46 | 27 | 56 | 4 | 5.34 |
| Inferior orbital gyrus | L | 47/11 | −27 | 31 | −24 | 4.58 |
| Inferior frontal gyrus (orbitalis) | L | 47 | −38 | 41 | −20 | 6.88 |
| (opercularis) | L | 44 | −57 | 11 | 29 | 10.94 |
| | R | 44 | 48 | 20 | 29 | 6.91 |
| (triangularis) | R | 45 | 42 | 33 | 12 | 5.54 |
| Anterior insula | L | 48 | −37 | 18 | −7 | 5.83 |
| Fronto-temporal operculum | L | 38 | −57 | 12 | −7 | 8.78 |
| Superior frontal gyrus | L | 6 | −17 | 7 | 70 | 5.67 |
| | R | 6 | 13 | 17 | 64 | 3.52 |
| Precentral gyrus | L | 6 | −37 | 0 | 60 | 8.62 |
| | R | 6 | 33 | 7 | 60 | 6.53 |
| Supplementary motor area (pre-SMA) | L | 6 | −2 | 19 | 43 | 8.47 |
| Temporal lobe | | | | | | |
| Inferior temporal gyrus | L | 20 | −55 | −39 | −16 | 3.84 |
| Fusiform gyrus | L | 20/37 | −50 | −30 | −22 | 3.33 |
| Fusiform/Cerebellum | L | 37 | −44 | −65 | −23 | 5.67 |
| Subcortical | | | | | | |
| Cerebellum | R | | 12 | −78 | −26 | 4.78 |
| | R | | 32 | −70 | −47 | 3.90 |

L/R indicates left/right hemisphere, BA = Brodmann area. All activations are $Z>3.1$, corresponding to an uncorrected probability value of $P<0.001$.

**Table 4**
Component regions of the second working memory network in PTSD subjects.

| Region | MNI coordinates | | | | | |
|---|---|---|---|---|---|---|
| | L/R | BA | *x* | *y* | *z* | *Z*-score |
| Frontal lobe | | | | | | |
| Supplementary motor area | L | 6 | −2 | 2 | 70 | 7.51 |
| Supplementary motor area (pre-SMA) | L | 8 | −13 | 26 | 58 | 4.53 |
| Anterior cingulate gyrus (dorsal) | L | 24 | −3 | 32 | 17 | 3.71 |
| Anterior cingulate gyrus (ventral) | L | 24 | −3 | 39 | −4 | 4.03 |
| Medial prefrontal cortex | R | 10 | 17 | 57 | 9 | 3.28 |
| Temporal lobe | | | | | | |
| Fusiform/cerebellum | L | 37/19 | 49 | −70 | −23 | 4.62 |

L/R indicates left/right hemisphere, BA = Brodmann area. All activations are $Z>3.1$, corresponding to an uncorrected probability value of $P<0.001$.

(see Table 3 for summary). PTSD patients showed a much greater extent of activation than controls, particularly in PFC, and also showed activation in the left inferior temporal gyrus, left fusiform and cerebellum that did not reach significance in controls. In contrast, PTSD patients did not show activations in the right thalamus and brainstem as for controls.

Results for the second CV for the PTSD group are shown in Fig. 2 (row D). The CV plot shows that scores are uniformly higher in the FT versus the VT task, suggesting that this network corresponds to the difference between the WM maintenance and updating tasks. The statistical map corresponding to this CV shows activations in the ventral and dorsal AC, right medial prefrontal cortex (mPFC), left SMA and pre-SMA, and left fusiform region (see Table 4 for summary). Activation was also observed in the left anterior hippocampus, but this was just below statistical significance ($P<0.003$, uncorrected).

## 4. Discussion

This study used a multivariate analysis to retrospectively analyse an fMRI experiment probing WM function in PTSD. The experiment was designed to investigate whether WM abnormalities in PTSD are related to the *updating* or to the underlying *maintenance* of information in WM. A multivariate analysis was utilised to specifically investigate the degree of overlap between brain networks subserving these processes in PTSD.

We found two distributed brain networks activated for both PTSD and control groups. In controls, the first network identified brain activity associated with WM updating (VT task) and the second, activity associated with WM maintenance (FT task). The two networks reflected the differential task demands, and consistent with previous literature (e.g., Veltman et al., 2003), the updating task (first network) activated bilateral IPL, bilateral PFC (including both dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC)), as well as lateral and medial premotor regions. As expected, the maintenance task (second network) generated less extensive activations, which were largely a subset of those identified for the WM updating network. This result is in line with other studies demonstrating that WM maintenance and WM manipulation activate virtually identical neuronal systems (Veltman et al., 2003; Woodward et al., 2006). Regions included the left IPL, pre-SMA and inferior frontal gyrus, and represent the typical pattern associated with storage and rehearsal of verbal material in WM (Paulesu et al., 1993; Fiebach et al., 2006).

The patterns of CV scores and SPMs were different for PTSD patients. As shown in Fig. 2, row B, the FT task had a positive weighting for the first CV in PTSD patients, whereas controls showed no weighting for this task, indicating that for patients, the first network is associated with both the WM updating *and* maintenance tasks, whereas for controls it was specific to updating. Thus, controls recruited overlapping, but distinct brain activation networks for WM updating and maintenance processes, respectively, whereas PTSD

patients largely activated a single fronto-parietal network during updating *and* maintenance processes. The single fronto-parietal network engaged by PTSD patients for both WM tasks is suggestive of an inability to efficiently modulate brain processes according to differential task demands. This finding accords precisely with our earlier (univariate) analysis of these data (Moores et al., 2008), which found that PTSD patients activated regions (e.g., DLPFC) during WM maintenance processes that were normally only activated during WM updating.

This single fronto-parietal network activated during both updating and maintenance processes in PTSD was highly similar to the updating network in controls, and involved extensive bilateral activation of parietal and prefrontal (again including both DLPFC and VLPFC), and premotor cortices. This network showed more extensive activation in PTSD than for controls, particularly in both DLPFC and VLPFC regions. A similar finding has been observed in a previous study (Bryant et al., 2005), where a trauma-neutral auditory Oddball task generated increased activity in PTSD relative to controls in the IPL, inferior frontal gyrus, middle frontal gyrus, and dorsal and rostral anterior cingulate (AC). Results suggested that PTSD may be characterised by elevated processing of salient trauma-neutral stimuli, and the authors linked excessive activation of cognitive-attention networks to hyperarousal in PTSD (Bryant et al., 2005).

We have previously suggested (Moores et al., 2008) that elevated DLPFC activity observed during WM processing in PTSD may reflect compensatory recruitment of this region, indicative of increased dependence on the executive role of the DLPFC to control WM contents, perhaps serving to counteract distractibility from hyperarousal, which results in reduced discrimination of task-relevant stimuli (Aston-Jones et al., 1999). Elevated activation of these networks may therefore reflect increased effort required in PTSD to maintain an appropriate motivational state toward the WM tasks, particularly in the face of distraction associated with the characteristic hyperarousal of the disorder (Moores et al., 2008). This suggestion is supported by the behavioural data, indicating that although PTSD patients were as accurate as controls, they were slower to respond, a pattern which is associated with increased activation power in posterior parietal cortex (Honey et al., 2000), supporting the suggested inefficient allocation of resources in PTSD.

The first network in PTSD also showed activation of the left inferior temporal gyrus, left fusiform and cerebellum, which did not reach significance in controls. Activity in the left fusiform can be interpreted in light of recent discussion by Fiebach et al., who demonstrated inferotemporal activity to be functionally connected to activity in the left PFC, and which was thought to reflect a semantic contribution to word maintenance (Fiebach et al., 2006). In combination with the substantially more extensive recruitment of the inferior frontal cortex (including Broca's area) and inferior parietal lobe, we interpreted these findings to reflect compensatory involvement of these regions to cope with diminished linguistic processing in PTSD (Bremner et al., 1999), suggesting it is somehow more difficult for language structures to maintain verbal material on-line.

The second network in the PTSD group was entirely different from that observed for controls — which was specific to WM maintenance processes and showed the typical network associated with the storage and rehearsal of verbal material. In PTSD, the pattern of CV scores indicated that this network reflects what *is* differentially activated between the WM maintenance and updating tasks (Fig. 2, row D). This result is an extension of our previous univariate analysis of these data (Moores et al., 2008), which failed to find any differential activity between maintenance and updating conditions in PTSD (due to elevated activity during WM maintenance), highlighting an advantage of using a functional connectivity approach. The network identified here included activity in the dorsal and ventral AC, medial prefrontal cortex (mPFC), supplementary motor area (SMA), and left fusiform gyrus, as well as weak activation in the left hippocampus ($P<0.003$, uncorrected). These findings inform our previous work (Moores et al., 2008), which suggested abnormal activity in the AC, hippocampus and brainstem, but did not allow conclusions to be drawn about the nature of the abnormalities in these regions. Increased activation in the dorsal anterior cingulate (AC) during trauma-neutral information processing has been observed in one other study (Bryant et al., 2005). Bryant et al. (2005) discussed the role of the AC in attention and vigilance processing, and suggested that AC activation may therefore be associated with increased hypervigilance, characteristic of PTSD.

It is noteworthy that this second network involves two of the three key regions (ventral AC/mPFC and hippocampus) consistently implicated in the neurobiology of PTSD, and which according to current models (Rauch et al., 2006), make up a neuronal circuit that has etiological significance for the phenomenology of PTSD. Rauch et al., for example, propose that the ventral AC/mPFC fails to exert adequate modulatory top-down control over the hyper-responsive amygdala, mediating symptoms of hyperarousal and the diminished capacity to suppress attention and responsivity to trauma-related stimuli (Rauch et al., 2006). Others have observed increased activation for trauma-related stimuli in the AC/mPFC (Shin et al., 1997; Zubieta et al., 1999; Morey et al., 2008). Our observation of increased activation of the ventral AC in the context of WM processing in PTSD informs the current neurocircuitry model of PTSD, by also implicating these regions in trauma-neutral information processing. Perhaps in the context of trauma-neutral information processing, ventral AC/mPFC activity is up-regulated to over-ride the hyper-responsive amygdala in order to perform the task effectively, which may in turn decrease the efficiency of brain networks subserving WM function. This explanation, however, is purely speculative and requires further investigation. One approach might be to employ both trauma-neutral and trauma-related stimuli in the same patients and monitor the time course of haemodynamic AC/mPFC activity in this region between trauma-related modalities.

Similarly, although we found weak activation of the left anterior hippocampus in the second network in PTSD, and although elevations of hippocampal activity have been previously observed in PTSD during a word-stem completion task (Shin et al., 2004), the role of the hippocampus in the neurocircuitry model of PTSD remains unclear (Rauch et al., 2006). Lastly, abnormal activation of the SMA in this second network, consistent with results we have observed previously in PTSD during WM function (Clark et al., 2003), may be linked to the idea that PTSD is a disorder of abnormal reactivity, with the exaggerated startle response[3] a defining characteristic.

One limitation of this study is the lack of a direct between-group CVA analysis. A between-group analysis was carried out on these data and significant between-group differences were observed. However, none of the five dimensions (resulting from six classes) provided a clear and interpretable comparison of the within-group results reported here. It is anticipated that methodological developments to improve and increase the use of multivariate analyses will continue, as the potential utility of these methods becomes clear, particularly for the study of psychiatric disorders such as PTSD, as recently discussed by Shin et al. (Shin et al., 2006). Results of this study also need to be interpreted with consideration of the small sample sizes, the absence of a trauma-exposed control group, and the use of medication in some patients. Sample size may be particularly relevant for the study of disorders such as PTSD, where symptoms can be highly heterogeneous (Lanius et al., 2006). Although we used a covariate to control for the effects of medication use in some patients, these medications could increase the heterogeneity of activations in the patient group and thus may reduce statistical power of the study. Also, because subjects in our control group were not trauma-exposed, it is possible that results could

[3] Note that exaggerated startle refers to specific psychophysiological measures in response to unexpected alerting stimuli (as outlined in Pole et al., 2003).

be driven by trauma-exposure, rather than PTSD. We believe this is unlikely, particularly given results of a recent meta-analysis of *emotionally neutral* information processing in PTSD, which found that the effect of control group (trauma-exposed or not) was not a significant factor (Brewin et al., 2007). Nevertheless, to discount this possibility, further work in this should include a trauma-exposed control group.

Overall, this study provides converging evidence that PTSD is characterised by elevated processing of trauma-neutral stimuli (Bryant et al., 2005; Moores et al., 2008), and an inability to efficiently modulate brain processes according to differential task demands, as indicated by the single fronto-parietal network engaged by patients for both WM maintenance and updating tasks. Indeed we found that for those with PTSD, there was activation not only of regions normally associated with maintenance but also areas that were normally associated with updating of newly relevant information, implying that those with PTSD were repeatedly updating ongoing information in a way that healthy controls did not need to do. Thus, if this interpretation is correct, it accords well with subjective reports from those with PTSD of a failure to retain goal-relevant information on-line for any period of time. This pattern might reflect compensatory recruitment of brain networks subserving WM updating to counteract distractibility from hyperarousal (Moores et al., 2008), possibly including involvement of the AC/mPFC. These findings are directly relevant to difficulties with concentration and memory in PTSD, which are both important components of the clinical manifestations of this disorder.

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