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Aberrant modulation of brain activity underlies impaired working memory following traumatic brain injury

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ABSTRACT

Impaired working memory is a common and disabling consequence of traumatic brain injury (TBI) that is caused by aberrant brain processing. However, little is known about the extent to which deficits are perpetuated by specific working memory subprocesses. Using a combined functional magnetic resonance imaging (fMRI) and working memory paradigm, we tested the hypothesis that the pattern of brain activation subserving working memory following TBI would interact with both task demands and specific working memory subcomponents: encoding, maintenance, and retrieval. Forty-three patients with moderate-severe TBI, of whom 25 were in the acute phase of recovery ($M = 2.16$ months, $SD = 1.48$ months, range = 0.69 – 6.64 months) and 18 in the chronic phase of recovery ($M = 23.44$ months, $SD = 6.76$ months, range = 13.35 – 34.82 months), were compared with 38 demographically similar healthy controls. Behaviourally, we found that working memory deficits were confined to the high cognitive load trials in both acute ($P = 0.006$) and chronic ($P = 0.024$) cohorts. Furthermore, results for a subset of the sample (18 chronic TBI and 17 healthy controls) who underwent fMRI revealed that the TBI group showed reduced brain activation when simply averaged across all task trials (regardless of cognitive load or subcomponent). However, interrogation of the subcomponents of working memory revealed a more nuanced pattern of activation. When examined more closely, patterns of brain activity following TBI were found to interact with both task demands and the working memory subcomponent: increased activation was observed during encoding in the left inferior occipital gyrus whereas decreased activation was apparent during maintenance in the bilateral cerebellum and left calcarine sulcus. Taken together, findings indicate an inability to appropriately modulate brain activity according to task demand that is specific to working memory encoding and maintenance.

1. Introduction

Traumatic brain injury (TBI) is a debilitating condition that impairs a range of cognitive domains (Draper and Ponsford, 2008; Ponsford et al., 2014). Working memory is often affected, which comprises distinct cognitive subprocesses that integrate, store, and manipulate information online for temporary use (Baddeley, 2003; Baddeley and Hitch, 1974). Due to the inherent utility of these cognitive subprocesses for many of our everyday activities, impaired working memory following TBI significantly disrupts resumption of function (Avery et al., 2013; Baddeley, 2010; Burgess et al., 2011; McVay and Kane, 2012). Despite the relevance of intact working memory for adaptive function, little has been done to understand the role of the specific subprocesses in perpetuating these deficits.

In healthy individuals, functional magnetic resonance imaging (fMRI) studies have demonstrated that working memory is supported by a distributed network involving frontoparietal (Rottschy et al., 2012) and temporal regions (Lee and Rudebeck, 2010; Schon et al., 2009). These regions are critical for the integration of information necessary for decision-making (De Pisapia et al., 2007; Kim et al., 2015), updating of information (Murty et al., 2011), and coordinating attentional resources (Rossi et al., 2009).

Abbreviations: BOLD, blood oxygenation level-dependent; COPE, contrast of parameter estimates; DMN, default mode network; EPI, echo planar imaging; fMRI, functional magnetic resonance imaging; GCS, Glasgow Coma Scale; SDMT, Symbol Digit Modalities Test; SMS, simultaneous multi-slice; TMT, Trail Making Test; TE, echo time; TBI, traumatic brain injury; TR, repetition time WPTAS, Westmead Post Traumatic Amnesia Scale.

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The network of regions critical for working memory is also most susceptible to the direct physical forces and secondary pathology of TBI (Bigler, 2001). Functionally, this neural network displays aberrant brain activity following TBI, leading to impaired working memory capacity (Kasahara et al., 2011). These functional changes and behavioural deficits are particularly evident as task complexity and effort increases (Perlstein et al., 2004; Sanchez-Carrion et al., 2008a; Sanchez-Carrion et al., 2008b). Others, however, have demonstrated aberrant brain processes in this distributed network in the absence of significant working memory deficits (Christodoulou et al., 2001; McAllister et al., 2001), potentially highlighting longer-term restorative, compensatory, or neuroplastic processes (Hillary, 2008).

The field is also mixed with respect to the *direction* of aberrant brain processing during working memory performance; that is, whether working memory deficits are driven by hypo- (Sanchez-Carrion et al., 2008a; Sanchez-Carrion et al., 2008b) or hyper-activation (Christodoulou et al., 2001; McAllister et al., 2001; Perlstein et al., 2004), relative to healthy controls. These disparities likely reflect methodological differences across studies that are not taken into account when interpreting the results (Dunning et al., 2016). We proposed that a significant factor contributing to inconsistent findings in the field is the precision with which working memory is measured. Indeed, working memory can be parcellated into distinct temporal stages of 1) encoding – the initial intake of information, 2) maintenance – the rehearsal of information "online" over a brief period, and 3) retrieval – the recollection of information (Bedwell et al., 2005). However, although multiple subprocesses are known to support working memory capacity (Fletcher and Henson, 2001; Kim, 2019), working memory is generally measured using omnibus tests. For example, the n-back task, which has been used in several fMRI studies (McAllister et al., 2001; Perlstein et al., 2004; Sanchez-Carrion et al., 2008a; Sanchez-Carrion et al., 2008b), does not delineate specific subprocesses since the sequential nature of the task requires execution of these subprocesses simultaneously (Jaeggi et al., 2010). Studies in healthy individuals have shown the pattern of brain activation differs depending on the subprocesses of working memory (e.g. Narayanan et al., 2005). Despite this, there has been limited investigation of these specific subprocesses in individuals with TBI.

Delayed match-to-sample behavioural paradigms allow measurement and analysis of working memory subcomponents by demarcating stages of encoding, maintenance, and retrieval (Jensen et al., 2002). To our knowledge, only one previous study in paediatric TBI (Newsome et al., 2008) has combined this behavioural paradigm with fMRI to investigate the neural basis of working memory disruption in individuals with moderate-severe TBI. This single study highlights two key results: 1) hyperactivation, relative to controls, were apparent in frontal, temporal, and occipital regions as task demands increased, which was *specific* to encoding and retrieval subcomponents; 2) hypoactivation, relative to controls, were apparent in frontal and parietal regions, which was *specific* to the maintenance subcomponent of working memory. These findings have been interpreted as reflecting reduced capacity to differentially allocate neural resources during the maintenance phase, alongside compensatory over-activation during encoding and retrieval. However, as there are potential differences in pathophysiology, developmental, and psychosocial factors associated with paediatric TBI (Ponsford et al., 2012), it remains unclear whether these findings can be generalised to the adult TBI population.

Here, we used a delayed match-to-sample task combined with fMRI to investigate working memory deficits in adults with moderate-severe TBI. To first establish the sensitivity of our behavioural task, and ascertain the presence of chronic working memory deficits, we characterised behavioural performance across both acute and chronic TBI cohorts relative to healthy controls. We subsequently investigated *whether* and *how* observed behavioural deficits were associated with brain changes during specific working memory subcomponents using fMRI. Based on previous key studies (Perlstein et al., 2004; Sanchez-Carrion et al., 2008a; Sanchez-Carrion et al., 2008b), we hypothesised that participants with TBI would display working memory deficits that were conditional on task demands (i.e. greater deficits evident with increased task demands). Furthermore, based on the single previous study in adolescents (Newsome et al., 2008), we hypothesised that the *direction* of brain activation would depend on the working memory subcomponent: relative to healthy individuals, the TBI group were predicted to show increased activation during encoding and retrieval but decreased activation during maintenance.

2. Materials and methods

2.1. Participants

The study was approved by Monash Health/University Human Research Ethics Committee and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. Participants were recruited from the TBI rehabilitation program of Epworth Healthcare (Melbourne, Australia), either from successive admissions to the inpatient ward or via a longitudinal follow-up database. Exclusion criteria included age < 18 or > 75 years, prior history of TBI or other neurological conditions, significant psychiatric or substance abuse history, and MRI contraindication. Forty-three individuals with moderate-severe TBI participated in the study (see Table 1 and Supplementary Table 1 for participant details; see Supplementary Fig. 1 for TBI lesion overlay map). Of these, 25 were inpatients (17 males, 8 females) in the acute phase of recovery ($M = 2.16$ months, $SD = 1.48$ months, range = 0.69 – 6.64 months) and 18 individuals (14 males, 4 females) were in the chronic phase of recovery ($M = 23.44$ months, $SD = 6.76$ months, range = 13.35 – 34.82 months). TBI injury severity was defined by PTA duration (Arlinghaus et al., 2005; Corrigan et al., 2010) assessed prospectively using the Westmead Post Traumatic Amnesia Scale (WPTAS; Shores et al., 1986). Thirty-eight healthy controls (26 males, 12 females) of similar age, sex, and education were also recruited. There were no significant differences between the TBI groups and healthy controls on any of the demographic variables; nor were any significant difference between the two TBI groups on injury factors (all comparisons $P > 0.05$). All participants contributed to our first aim, characterising working memory behavioural performance (Fig. 1). However, only a subset of participants completed the fMRI working memory task (18 chronic TBI and 17 healthy controls), thus contributing to our second aim of linking brain activity with behaviour. Three participants (2 acute TBI and 1 healthy control) were excluded from the behavioural analysis due to technical errors with the response button and apparent poor effort on task (i.e. no variation in response).

2.2. Working memory paradigm

Working memory was examined using the Sternberg delayed match-to-sample task (Fig. 2; Sternberg, 1966). In this task, participants are

Table 1
Demographic and clinical information of participants.

Demographic variables	Acute TBI, *M* (*SD*)	Chronic TBI, *M* (*SD*)	Healthy controls,*M* (*SD*)
Age (years)	38.36 (16.82)	44.11 (15.79)	40.05 (17.14)
Gender (male/female)	17/8	14/4	26/12
Education (years)	13.82 (3.27)	14.81 (2.40)	14.68 (2.79)
Time since injury (months)	2.16 (1.51)	23.44 (6.96)	–
PTA (days)	22.46 (14.63)	33.12 (38.88)	–
GCS (lowest)	9 (4.37)	9.47 (4.14)	–

GSC = Glasgow Coma Scale; PTA = post-traumatic amnesia. Note: Acute GCS were available for $n = 42$ TBI participants; PTA duration were available for $n = 41$ TBI participants.

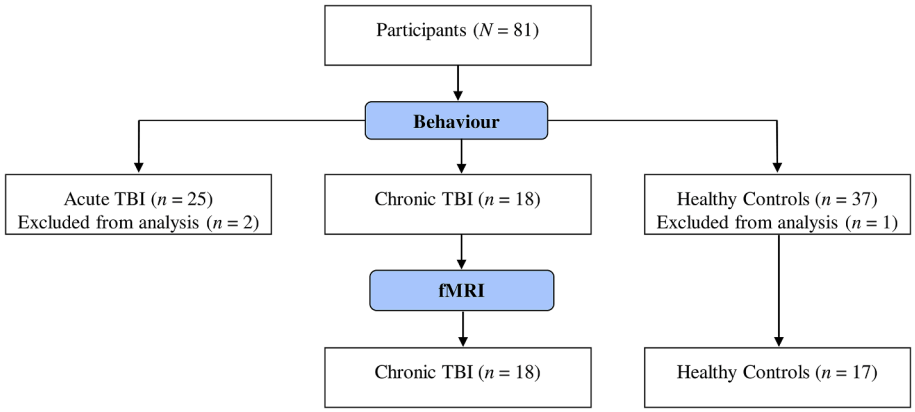

Fig. 1. Flowchart of participants involved with each component of the study. All participants completed in the behavioural working memory tasks (N = 81); however, only a subset of participants underwent fMRI scanning whilst completing this task (i.e. 18 chronic TBI and 17 healthy controls).

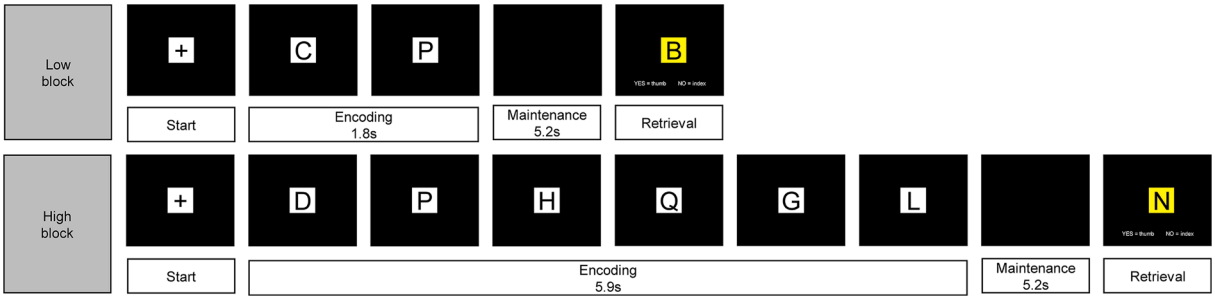

Fig. 2. Schematic diagram of low and high cognitive load trials of the Sternberg working memory task. Two (low cognitive load) or six (high cognitive load) letters were presented during the encoding phase, followed by a maintenance phase in which the screen was blank, and finally a probe was presented during retrieval phase. Low and high cognitive load conditions were presented alternately.

required to remember a memory set consisting of items (letters) presented on a screen, which they are asked to encode into working memory (encoding). After a short delay (maintenance), a single item is presented, and participants respond by indicating whether the item was in the previous memory set (retrieval). To modulate cognitive load/task demands, participants were required to encode either a two-item (low cognitive load) or six-item (high cognitive load) memory set. This task consisted of 28 blocks, alternating between low and high cognitive load conditions. Each block comprised 2 trials. Items were presented for 0.8 s followed by a 0.2 s inter-stimulus interval. The duration of encoding was 1.8 s for the low cognitive load condition and 5.9 s for the high cognitive load condition. The duration of maintenance was 5.2 s across both load conditions. The duration of retrieval was modelled as the participant's reaction times. The total task duration was approximately 16 min.

2.3. Neuropsychological measures

A subset of participants who underwent fMRI also completed two cognitive tasks, which were administered upon the completion of the scan. The Symbol Digit Modalities Test (SDMT; Smith, 1973) was used to assess processing speed. This task involved decoding a set of symbols as quickly possible within 90 s. The Trail Making Test (TMT A and B; Reitan and Wolfson, 1985) was used to assess processing speed, complex attention (switching/shifting), and executive function (mental flexibility). In TMT A, participants were required to connect numbered circles in an ascending order. In TMT B, participants were required to alternate between connecting numbered and lettered circles in an ascending order. Both SDMT and TMT have strong reliability and has been validated in TBI population (Hanks et al., 2008).

2.4. MRI acquisition

Structural and functional MR images were acquired with a 3.0 Tesla Siemens Magnetom Skyra scanner (Monash Biomedical Imaging, Clayton, Australia) and 32-channel head coil. Functional images were obtained in a single run using single-shot gradient-echo planar imaging (EPI) with the following parameters: repetition time (TR) = 0.74 s; echo time (TE) = 39 ms; simultaneous multi-slice (SMS) acceleration factor = 8; flip angle = 52°; 210 × 210 matrix; voxel size = 2.4 × 2.4 × 2.4 mm. A single-band reference scan was also obtained for EPI registration purposes with the following parameters: TR = 6.37 s; TE = 39 ms; flip angle = 52°; 210 × 210 matrix; voxel size = 2.4 × 2.4 × 2.4 mm. To correct for B0 inhomogeneity in the EPI scans, a field map was acquired using a double-echo spoiled gradient echo sequence with the following parameters: TR = 0.68 s; TE = 4.92/7.38 ms, flip angle = 60°, 210 × 210 matrix, 3.3 × 3.3 × 2.4 mm. A high-resolution 3D T1-weighted image covering the entire brain was also acquired with the following parameters: TR = 2.0 s; TE = 2.03 ms; flip angle = 8°; 256 × 256 matrix; voxel size = 1.0 × 1.0 × 1.0 mm.

2.5. Statistical analysis

2.5.1. Behavioural and demographic data

Behavioural and demographic data were analysed using R version 3.6.0 (R Core Team, 2019). Two-tailed independent samples t-tests were used to assess group differences on the demographic variables (i.e. age, sex, and years of education) and performances on cognitive tasks (i.e. SDMT, TMT A and B). Behavioural data were screened and assessed for violation of statistical assumptions prior to analysis. Our behavioural measures of interest were accuracy and reaction time on the working memory task. Accuracy was determined using dprime, a sensitive index

which measures an individual's ability discriminate signal from noise. Reaction times were calculated using the average reaction time per load. Age and education were added as covariates in all models given they could affect working memory performance (Fitzpatrick et al., 2015; Mattay et al., 2006) and reaction time (Der and Deary, 2017; Tun and Lachman, 2008). Linear mixed models were used to analyse working memory accuracy and reaction time to better account for clustering and non-independence of measures within participants. In the first model, we used a linear mixed model to model group and load as fixed effects, and participant as a random effect. In a second model, we subsequently added a *group* × *load* interaction term to investigate whether cognitive load/task demands moderate accuracy and reaction time on the task. Given our a-priori hypothesis of a specific group difference for high cognitive load trials, we conducted linear regressions for each load condition (i.e. low and high) separately. As we expect lower performance for the TBI group, post-hoc analyses were followed up using one-tailed independent samples t-tests with multiple comparison correction.

2.5.2. MRI preprocessing

Lesions were manually segmented using MRIcron (http://www.mricro.com/mricron) and subsequently preprocessed using fMRIPrep 20.0.0 (Esteban et al., 2019). The following steps were applied: undistortion of EPI data, realignment, normalisation, and estimation of confounds. Further information about the MRI preprocessing can be found in the Supplementary (see "Detailed MRI Preprocessing").

2.5.3. fMRI analysis

Imaging data were analysed using FSL FEAT version 6.0.2 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Onset times for encoding were modelled as the first stimulus presentation of each load condition; low cognitive load trials were modelled as 1.8 s and high cognitive load trials modelled as 5.9 s in duration. Onset times for maintenance were modelled as the period immediately following the last stimulus presentation of each load; the maintenance period duration was 5.2 s regardless of load condition. Onset times for retrieval was modelled as the length of time of the probe stimulus presentation; this was equivalent to the participant's reaction/response times on the trial. In the first level FEAT model, we modelled the main effect of load (i.e. low and high), subcomponent (i.e. encoding, maintenance, and retrieval) and their interaction for each participant. To reduce motion-related artifact, additional anatomical CompCor regressions were also added at the first level (Muschelli et al., 2014). We investigated group-level differences using FLAME 1 + 2 mixed effects with automatic outlier de-weighting. Imaging findings are reported using a cluster level threshold of $Z > 3.1$ and a family wise error cluster correction of $P < 0.05$.

3. Results

3.1. Working memory deficits in TBI are conditional on task demands

We used mixed linear models to investigate the association between group (healthy controls vs acute TBI; healthy controls vs chronic TBI), load (low vs high), and working memory performance (accuracy and reaction time). Overall, both the *acute* ($t(148) = -2.37$, 95% CI [-0.66 – -0.06], $P = 0.009$) and *chronic* cohorts ($t(148) = -1.97$, 95% CI [-0.64 – 0.001], $P = 0.025$) were significantly less accurate than healthy controls. *Acute* TBI participants were significantly slower to respond during trials, compared to healthy controls ($t(148) = 3.89$, 95% CI [0.13 – 0.40], $P < 0.001$). No reaction time difference was apparent between *chronic* TBI participants and healthy controls ($t(148) = -0.50$, 95% CI [-0.18 – 0.11], $P = 0.309$). As expected, task accuracy was significantly higher in low cognitive load condition, compared to high cognitive load condition, regardless of group ($t(148) = 13.37$, 95% CI [0.94 – 1.27], $P < 0.001$). Reaction time was significantly faster in the low cognitive load condition, compared to the high cognitive load ($t(148) = -9.60$, 95% CI [-0.31 – -0.20], $P < 0.001$).

To examine whether cognitive load moderated the relationship between group and task performance (accuracy and reaction time), we subsequently added a *group* × *load* interaction into the model. Cognitive load moderated the relationship between group and task accuracy for the *acute* TBI cohort ($t(146) = -1.83$, 95% CI [-0.72 – 0.03], $P = 0.034$). Cognitive load did not moderate the relationship between group and task accuracy for the *chronic* TBI cohort, though this was trending towards significance ($t(146) = -1.27$, 95% CI [-0.66 – 0.14], $P = 0.102$). Similarly, cognitive load did not moderate the relationship between group and reaction time for both *acute* ($t(146) = -0.79$, 95% CI [-0.17 – 0.07], $P = 0.214$) and *chronic* TBI cohorts ($t(146) = -0.36$, 95% CI [-0.16 – 0.11], $P = 0.361$).

Given the significant interaction effect observed for the *acute* TBI group, we used linear regression to further examine the relationship between load and group. In addition, we also conducted post-hoc analyses for the *chronic* TBI group despite not finding a significant interaction due to our a-priori hypothesis and the smaller sub-sample size for this group may have not been sufficiently powered to detect this effect. In line with our predicted hypothesis, task accuracy did not differ between groups in the low load condition (*acute* TBI vs healthy controls: $t(73) = -1.21$, 95% CI [-0.52 – 0.13], $P = 0.116$; *chronic* TBI vs healthy controls: $t(73) = -1.15$, 95% CI [-0.55 – 0.15], $P = 0.126$; Fig. 3A). However, both the *acute* ($t(73) = -2.57$, 95% CI [-0.93 – -0.12], $P = 0.006$) and *chronic* TBI cohorts ($t(73) = -2.01$, 95% CI [-0.88 – 0.004], $P = 0.024$; Fig. 3B) were significantly less accurate in the high load condition. *Acute* TBI participants were significantly slower to respond, compared to healthy controls, during both the low ($t(73) = 3.73$, 95% CI [0.13 – 0.44], $P < 0.001$; Fig. 3C) and high cognitive load conditions ($t(73) = 3.13$, 95% CI [0.09 – 0.39], $P = 0.001$; Fig. 3D). However, no reaction time differences were apparent between *chronic* TBI participants and healthy controls in both the low ($t(73) = -0.23$, 95% CI, −0.19 – 0.15, $P = 0.411$; Fig. 3C) and high cognitive load conditions ($t(73) = -0.66$, 95% CI, −0.22 – 0.11, $P = 0.257$; Fig. 3D). To determine whether performance in the high cognitive load condition was due to a speed-accuracy trade-off, reaction time was included as a covariate in the regression model. Results indicated that both TBI groups still performed significantly poorer than healthy controls (*acute* TBI vs healthy controls: $t(72) = -2.32$, 95% CI [-0.94 – -0.07], $P = 0.012$; *chronic* TBI vs healthy controls: $t(72) = -2.01$, 95% CI [-0.89 – -0.004], $P = 0.024$), thereby indicating that impaired performance was not due solely to a speed-accuracy trade-off.

3.2. TBI participants performed comparably to healthy controls on measures of processing speed and attention

Results of independent samples t-tests indicated that there were no significant differences between groups on the SDMT ($t(32.99) = 1.16$, $P = 0.256$), TMT A ($t(30.79) = 0.82$, $P = 0.419$), or TMT B ($t(32.51) = -0.57$, $P = 0.573$).

3.3. Sternberg task activates the expected brain network associated with working memory

Prior to testing our key fMRI analyses, we first assessed whether our Sternberg memory task activated the expected 'working memory' brain network in our study sample (i.e. 18 chronic TBI participants and 17 healthy controls; Fig. 4A and Supplementary Table 2). There were areas of overlap between the various subcomponents in frontal and occipital areas, the insula, and cerebellum. Encoding was associated with increased activation in temporal areas (e.g. left middle temporal gyrus, right superior temporal gyrus). Retrieval was associated with increased activation in the left angular gyrus. In general, these results overlap with *meta*-analytic working memory mask derived from neurosynth (https://www.neurosynth.org/; Fig. 4B). However, consistent with the visual nature of our task, we found more activation in occipital areas

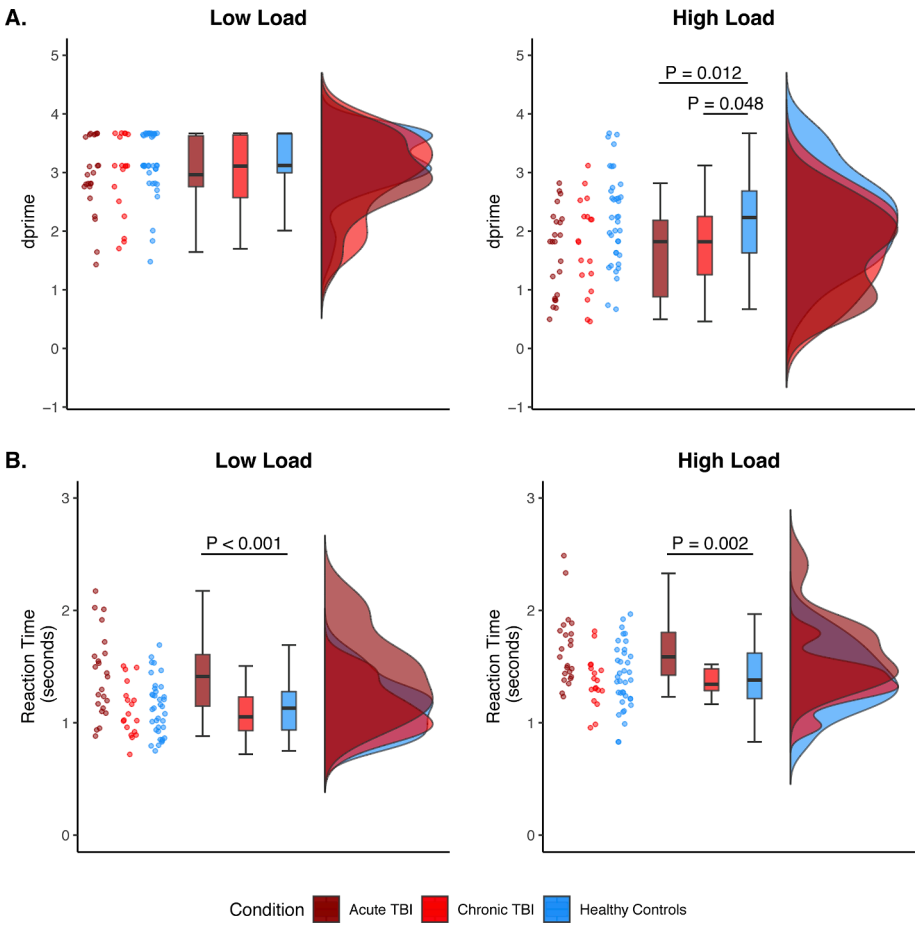

Fig. 3. Behavioural results for the Sternberg working memory task. (A) Plots depicting accuracy, as measured using dprime (higher values denote better performance). Individual datapoints are displayed along with violin plots and boxplots showing distribution. Performances were comparable across groups in the low cognitive load condition ($P > 0.05$; panel A, left). In the high cognitive load condition, however, performance was significantly impaired for both the acute ($P = 0.006$) and chronic TBI groups ($P = 0.024$; panel A, right). (B) Plots representing reaction time (higher values denote slower performance). The acute TBI group was significantly slower than healthy controls in both the low ($P < 0.001$; panel B, left) and high cognitive load condition ($P = 0.001$; panel B, right). There were no significant differences in reaction time between the chronic TBI group and healthy controls in both load conditions ($P > 0.05$; panel B, left and right). Note: *P*-values were adjusted for multiple comparisons.

compared to the *meta*-analytic mask (which includes results from working memory studies of various modalities).

3.4. Working memory following TBI is characterised by reduced brain activation when disregarding cognitive load and working memory subcomponent

TBI participants showed reduced activation in comparison to healthy controls when brain activation was averaged across all trials, regardless of load or working memory subcomponent. This 'hypoactivation' was present in three clusters: left cerebellum (crus I), left middle frontal gyrus, and left superior temporal gyrus (Fig. 5A and Supplementary Table 3). Healthy controls did not show reduced patterns of activation in comparison to the TBI group.

3.5. Individuals with TBI show aberrant modulation of brain activity with increased task demands

During low cognitive load trials, TBI participants showed reduced activity compared to healthy controls in several brain regions. This 'hypoactivation' was found in the left cerebellum (crus I), right middle frontal gyrus, left superior temporal gyrus, and left superior frontal gyrus (Fig. 5B and Supplementary Table 4). Interestingly, no group difference was found for high cognitive load trials. However, relative to healthy controls, TBI participants showed attenuated reduction in activity with increased working memory load in four brain regions: right superior parietal gyrus, right inferior temporal gyrus, right middle frontal gyrus, and left inferior occipital gyrus (Fig. 5C and Supplementary Table 5).

3.6. Patterns of aberrant brain activation following TBI were apparent during encoding and maintenance

As predicted, the *direction* of aberrant brain activation following TBI were dependent on the working memory subcomponent and cognitive load. TBI participants showed 'hypoactivation' during working memory maintenance, relative to healthy controls, regardless of load condition. This reduction in activation was present in the right dorsolateral prefrontal cortex (Fig. 5D and Supplementary Table 6). However, no significant group differences were apparent during working memory encoding or retrieval.

In addition, activation of working memory subcomponents differed as cognitive load increased. With increased cognitive load, TBI participants showed relatively greater activation in the left inferior occipital gyrus, that was specific to the encoding subcomponent (Fig. 5E and Supplementary Table 7). In addition, as cognitive load increased, TBI participants showed relatively reduced activation during maintenance, relative to healthy controls, in two clusters: bilateral cerebellum (crus I) and left calcarine sulcus (Fig. 5F and Supplementary Table 8).

3.7. Motion

Motion was minimal across all participants (average framewise displacement = 0.22 mm) and the average framewise displacement did not exceed 0.5 mm for any participant. There was no significant difference in framewise displacement between groups ($t(30.63) = 0.31$, $P = 0.758$).

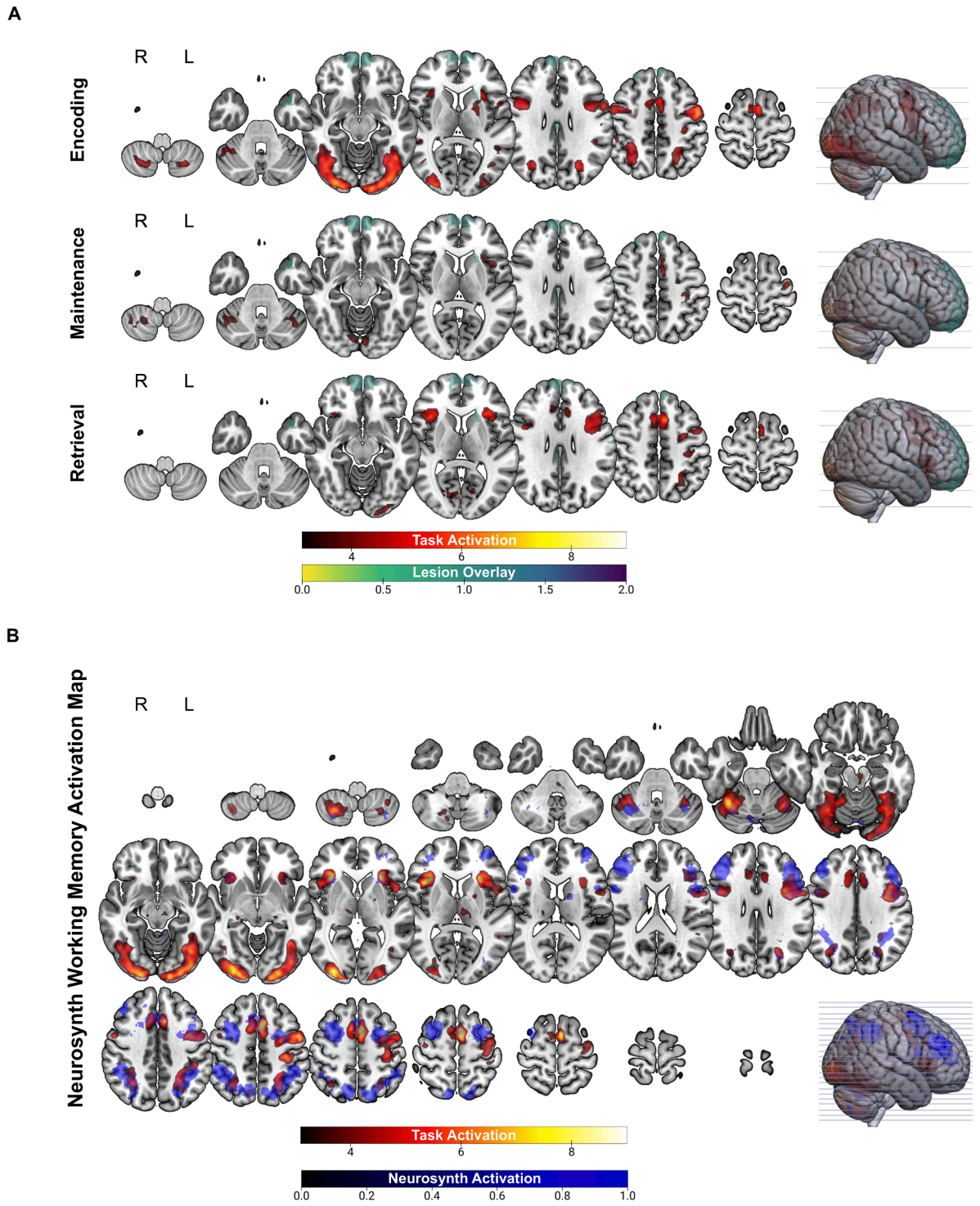

Fig. 4. Activation during the Sternberg working memory task for the fMRI cohort (18 chronic TBI, 17 healthy controls). (A) Pattern of activation segregated according to encoding, maintenance, and retrieval stages (red/yellow). There was minimal overlap between these clusters and TBI lesions (green). All subcomponents were associated with increased activation in frontal and occipital areas, the insula, and cerebellum. Encoding was associated with increased activation in temporal areas (e.g. left middle temporal gyrus, right superior temporal gyrus). Retrieval was associated with increased activation in the left angular gyrus. (B) Overall activation during the Sternberg working memory task (red/yellow) overlaid on a working memory *meta*-analytic mask (blue) derived from neurosynth. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

This study tested the hypothesis that changes in working memory following TBI would be dependent on task demands and specific working memory subcomponents. We used a combined fMRI and a delayed match-to-sample behavioural task to probe working memory encoding, maintenance, and retrieval. Behaviourally, we showed that individuals with TBI displayed impaired working memory deficits that were confined to the high cognitive load condition, for both the acute and chronic cohorts. Furthermore, we showed that aberrant brain activation during working memory may be characterised as hypo- or hyperactivation, depending on both task demands and the working memory

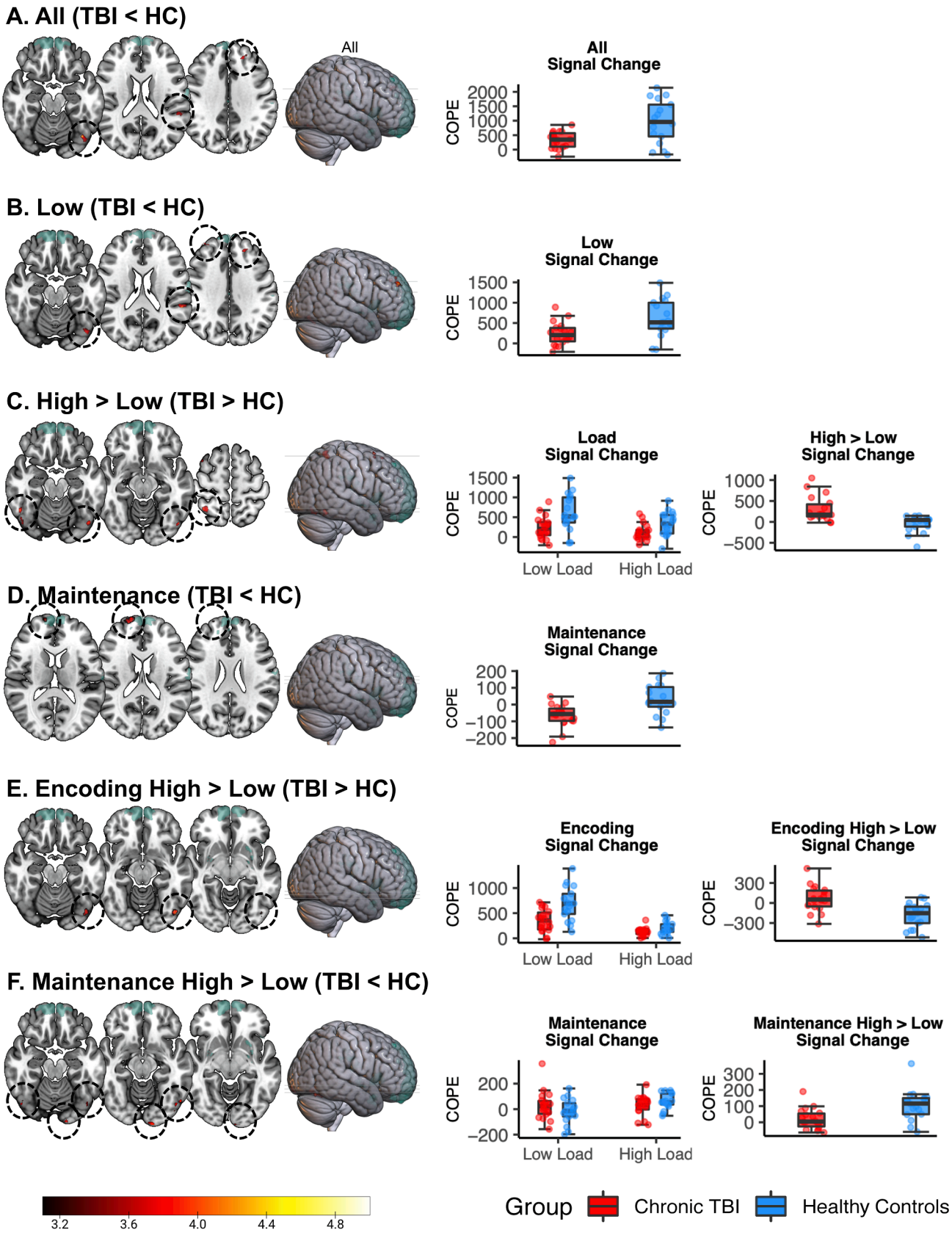

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Fig. 5. fMRI group differences on the Sternberg working memory task. There was minimal overlap between significant clusters (red/yellow) and TBI lesions (green). (A) Average across all trials (i.e. regardless load and subcomponent), the TBI group showed reduced activation in the left cerebellum, left middle frontal gyrus, and left superior temporal gyrus. Panel A right, boxplot overlaid with individual datapoints comparing signal change when averaged across all trials between the TBI group and healthy controls. (B) The TBI group showed reduced activation in the low cognitive load condition in the left cerebellum, right middle frontal gyrus, left superior temporal gyrus, and left superior frontal gyrus. Panel B right, comparison of signal change during the low cognitive load condition between the TBI group and healthy controls. (C) With increased cognitive load, the TBI group showed attenuated reduction in activity in the right superior parietal gyrus, right inferior temporal gyrus, right middle frontal gyrus, and left inferior occipital gyrus. Panel C middle, comparison of signal change in the low and high cognitive load conditions between the TBI group and healthy controls. Panel C right, comparison of signal change with increased cognitive load (i.e. high > low) between the TBI group and healthy controls. (D) During maintenance, the TBI group showed reduced activation in the right dorsolateral prefrontal cortex. Panel D right, comparison of signal change during maintenance between the TBI group and healthy controls. (E) With increased cognitive load, the TBI group showed increased activation during encoding in the left inferior occipital gyrus. Panel E middle, comparison of signal change during encoding of low and high load conditions between the TBI group and healthy controls. Panel E right, comparison of signal change during encoding with increased cognitive load (i.e. encoding high > encoding low) between the TBI group and healthy controls. (F) In contrast, the TBI group displayed decreased activation during maintenance in bilateral cerebellum and left calcarine sulcus. Panel F middle, comparison of signal change during maintenance of low and high conditions between the TBI group and healthy controls. Panel F right, comparison of signal change during maintenance with increased cognitive load (i.e. maintenance high > maintenance low) between the TBI group and healthy controls.

subcomponent: TBI participants demonstrated increased activation in the left occipital gyrus during encoding whereas decreased activation was observed in the bilateral cerebellum and left calcarine sulcus during maintenance. The present results suggest that individuals with TBI have impaired capacity to appropriately modulate brain activity with increased task demands specific to encoding and maintenance stages.

Our behavioural results are consistent with past studies that have observed greater difficulties with working memory as task demands increased (Perlstein et al., 2004; Sanchez-Carrion et al., 2008a; Sanchez-Carrion et al., 2008b). In the current study, this was apparent for both acute and chronic TBI participants and thus indicates the persistence of working memory deficits after TBI. Interestingly, we found that effects on reaction time varied according to recovery phase. That is, acute TBI participants were significantly slower in both load conditions whereas chronic TBI participants performed comparably to healthy controls on reaction time regardless of load conditions. One possibility is that slowed processing speed may contribute to working memory deficits initially whilst other mechanisms may be responsible for maintaining working memory dysfunction in the longer term. However, the inclusion of reaction time as a covariate in follow up analyses did not change our results and therefore slowed processing speed is unlikely to explain for poorer performance in both TBI cohorts. Rather, the observed slower reaction times may represent generalised impairment in processing speed during early recovery that is unrelated to the presentation of working memory difficulties (Felmingham et al., 2004).

The neural underpinning of working memory has been previously explored in TBI (Perlstein et al., 2004; Sanchez-Carrion et al., 2008a; Sanchez-Carrion et al., 2008b). Our results align with these prior studies by demonstrating that impaired working memory following TBI involves aberrant activation in a distributed network of brain regions. Evaluation of task load revealed greater brain activation with increased task demands following TBI, relative to healthy controls. Similar findings have been reported in other clinical populations including schizophrenia (Guerrero-Pedraza et al., 2012; Pomarol-Clotet et al., 2008) and mild cognitive impairments (Migo et al., 2015). In contrast, studies in healthy individuals have shown reduced brain activation with increased working memory demands, particularly in regions of the default mode network (DMN; Chee and Choo, 2004; McKiernan et al., 2003; Pyka et al., 2009; Tomasi et al., 2006). The DMN is a network that demonstrates increased activation during rest but disengages during task performance (Raichle et al., 2001). Indeed, greater suppression of the DMN has been found to predict better working memory performance (Sambataro et al., 2010). This finding has often been interpreted as reallocation of limited cognitive resources of irrelevant processes to task-relevant processes during task performance (Mayer et al., 2010). Key structures of the DMN include the medial prefrontal cortex, posterior cingulate cortex/precuneus, and lateral parietal and temporal cortices (Mak et al., 2017; Raichle et al., 2001). The middle frontal gyrus has also been implicated (Demertzi et al., 2011; McGeown et al., 2009), albeit less consistently. The regions implicated in the present study that showed increased activation with greater working memory load (i.e. right superior parietal gyrus, right inferior temporal gyrus, and right middle frontal gyrus) can be considered broadly falling within the DMN. Thus, greater brain activity of this network of regions as working memory demands increased – evident in the TBI group – suggest an impaired capacity to effectively reallocate neural resources with this increased task demand.

We demonstrated that patterns of brain activity following TBI not only depends on task demands, but appear to be specific to working memory subprocesses. In line with our predicted hypothesis, the TBI group showed greater activation in the left inferior occipital gyrus with increased cognitive load during encoding. Interestingly, the inferior occipital gyrus has rarely been implicated in working memory, but rather in processing of faces (Jacques et al., 2019) as well as emotionally relevant stimuli (Geday et al., 2003). Despite this, similar findings were reported by Newsome et al. (2008) who found that adolescents with TBI had increased activation in occipital lobe regions (i.e. cuneus, middle occipital gyrus, and lingual gyrus). As interpreted by Newsome et al. (2008), increased activation in these regions may represent a compensatory response for diminished connectivity with key structures (e.g. frontoparietal structures) involved with working memory. However, in addition to occipital regions, Newsome et al. (2008) also reported aberrant activation in frontal, temporal, and parietal regions, which did not differentiate between the TBI group and healthy controls in the present study. This indicates that TBI participants are recruiting similar areas during encoding but require additional activation to support working memory function. Thus, greater recruitment of the inferior occipital gyrus may reflect brain reorganisation, but the extent to which this is adaptative is unclear. An alternative but not mutually exclusive hypothesis is that this increased occipital activation may represent increased reliance on visualisation strategies (Gerton et al., 2004).

In contrast, TBI participants demonstrated reduced activation of the dorsolateral prefrontal cortex during working memory maintenance. The dorsolateral prefrontal cortex has been established as a critical structure involved in executive aspects of working memory, including maintenance and manipulation of information (D'Esposito et al., 2000) and strategic control (Bor et al., 2004; Bor et al., 2003). Furthermore, this region is actively engaged during retention intervals of delayed response tasks (Curtis and D'Esposito, 2003). Reduced activation in this structure therefore suggests that individuals with TBI may have broad difficulty in maintaining strategic task representation. Interestingly, we also found that as task demands increased during maintenance, TBI participants demonstrated reduced activation in the left calcarine sulcus and bilateral cerebellum maintenance. The calcarine sulcus has been implicated in maintaining persistent visual representations observed during short-term maintenance (Tallon-Baudry et al., 2001). Therefore, reduced activation apparent for the TBI group suggests impaired ability to hold visual representation in mind. With increased task demands, increased activity in this region is even more critical since more information must be temporarily maintained in working memory. In

addition, accumulating evidence suggests the cerebellum supports higher cognitive functions (Hayter et al., 2007; Ramnani, 2006), including working memory (Emch et al., 2019; Owen et al., 2005; Tomlinson et al., 2014). The cerebellum has closed-loop projections to cortical regions including areas of the prefrontal cortex via the cortico-cerebellar circuit (Ramnani, 2006). The role of the cerebellum in working memory, in particular the superior regions of the cerebellum (crus I), specifically appears to be related to articulatory or subvocal rehearsal (Chen and Desmond, 2005; Emch et al., 2019; Kirschen et al., 2005). This indicates that TBI participants, in comparison with healthy controls, may have used fewer rehearsal strategies to help retain information in mind as working memory demands increased. This further supports the interpretation that individuals with TBI have impaired strategy use.

Although our findings are largely consistent with those of Newsome et al. (2008), one key distinction was that we failed to find differences in activation between the TBI group and healthy controls during retrieval. One reason for this difference may be due to the slight variations in tasks used in the two studies. The task used by Newsome et al. (2008) differed in that stimuli were presented simultaneously during encoding and for shorter durations (1.7 s for both low and high load conditions). It is possible that participants in this previous study found the task more difficult, consequently influencing uncertainty during working memory retrieval. An alternative explanation may be that brain activation during working memory differs between children and adults. Previous work in typically developing children and adolescents has found similar, albeit more widespread, patterns of brain activity compared to adults (Klingberg et al., 2002; Scherf et al., 2006). The more extensive recruitment is thought to reflect neural inefficiencies in developing brain networks (Bathelt et al., 2018). Thus, while aberrant brain activation during retrieval may manifest in paediatric TBI, our results suggest this is not the case for adults.

Our study has several important implications. By characterising working memory performance across different recovery periods, we showed that deficits manifest at across the acute and chronic phases of recovery. As working memory integrity is critical to support adaptive functioning, this further highlights the importance of ongoing rehabilitation to optimise working memory function following TBI. We also replicated past studies by showing that these behavioural deficits are associated with aberrant brain processing. However, here we also extended the field by demonstrating that deficits manifest due to disruption of specific working memory subcomponents (i.e. encoding and maintenance). This points to the potential for interventions aiming to improve working memory, for example, by providing specific strategies to improve efficiency of encoding or by extending memory representation in mind. Lastly, we demonstrated that conclusions about the neural underpinning of impaired working memory may vary as a function of level of analysis and the extent to which general cognitive domains are parcellated into finer subprocesses. In the current study, we showed that systematic interrogation of task demands and working memory subcomponents is necessary to unpack the patterns of findings and discern whether brain changes are driven by hypo- or hyperactivation. As an example, we may have been unable to uncover differences during encoding if load effects were not considered. More generally, our findings have important theoretical and clinical implications for the relevant wider field with respect to how we use and interpret our measures for diagnosis and prognosis of cognitive impairment.

Despite these important implications, our study findings should be considered in the context of various limitations. One potential confound related to the task was that duration times differed for the various load conditions and subcomponents. It is possible, for example, that another reason why we failed to find significant group differences during the retrieval phase is because it was shorter in duration. However, the fact that we found significant differences between TBI participants and healthy controls during the low encoding load condition despite it also having a short duration suggest that this was not the case. An important consideration that could affect the interpretation of our findings is presence of other cognitive deficits (e.g. attention, processing speed) that could secondary impact working memory. For example, poor attention during the task may have also led to reduced BOLD signal. However, the fact that TBI participants did not show deficits on measures of attention and processing speed provides confidence that results were not simply to due inattentiveness or slowed reaction times. Of note, the lack of significant differences on these measures contrasts with prior studies (Draper and Ponsford, 2008; Spitz et al., 2013). This may reflect the fact that our chronic TBI participants had high levels of education ($M = 14.8$ years) and thus had more cognitive reserve to negate some of the deleterious impact on attention and processing speed (Leary et al., 2018). Another limitation was that acute and chronic TBI participants were not matched. For example, compared to the acute cohort, the chronic TBI group were older, slightly more educated, and had longer duration of PTA. Despite this, it is reassuring that both TBI groups cohorts did not significantly differ overall with respect to demographic and injury factors. In the context of these limitations, future research may consider conducting a longitudinal study to investigate the association between behaviour and brain activation. This approach could provide further insights by clarifying whether the neural mechanisms underpinning working memory evolve over time, what neural reorganisation takes place at different recovery timepoints, and whether changes in behavioural performance are associated with specific brain patterns.

In conclusion, our findings indicated that both acute and chronic TBI cohorts had impaired working memory for that were confined to the high cognitive load condition. Moreover, our key fMRI finding showed that TBI participants displayed patterns of brain activation that interacted with both task demands and working memory subcomponents: increased activation was observed during encoding whereas decreased activation was apparent during maintenance. Taken together, findings indicate an inability to appropriately modulate brain activity according to task demand that is specific to working memory encoding and maintenance.

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CRediT authorship contribution statement

Abbie S. Taing: Investigation, Methodology, Writing - original draft. **Matthew E. Mundy:** Conceptualization, Methodology, Writing - review & editing. **Jennie L. Ponsford:** Conceptualization, Writing - review & editing. **Gershon Spitz:** Conceptualization, Methodology, Investigation, Writing - review & editing.

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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Appendix A. Supplementary data

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