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The Nature of Processing Speed Deficits in Traumatic Brain Injury: is Less Brain More?

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Abstract The cognitive constructs working memory (WM) and processing speed are fundamental components to general intellectual functioning in humans and highly susceptible to disruption following neurological insult. Much of the work to date examining speeded working memory deficits in clinical samples using functional imaging has demonstrated recruitment of network areas including prefrontal cortex (PFC) and anterior cingulate cortex (ACC). What remains unclear is the nature of this neural recruitment. The goal of this study was to isolate the neural networks distinct from those evident in healthy adults and to determine if reaction time (RT) reliably predicts observable between-group differences. The current data indicate that much of the neural recruitment in TBI during a speeded visual scanning task is positively correlated with RT. These data indicate that recruitment in PFC during tasks of rapid information processing are at least partially attributable to normal recruitment of PFC support resources during slowed task processing.

Keywords TBI · fMRI · Reorganization · Working memory · Processing speed

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Background

While there are myriad cognitive deficits associated with traumatic brain injury (TBI), much work has focused on basic deficits in the areas of working memory and processing speed that are integral to a number of emergent cognitive processes (e.g., episodic memory, executive functioning). The cognitive constructs working memory (WM) and processing speed are fundamental components to general intellectual functioning in humans (Courtney 2004; Salthouse 1996; Salthouse and Coon 1993) and, critically, both WM and processing speed are highly susceptible to disruption following neurological insult. For example, deficits in WM and processing speed have been documented in TBI (McDowell et al. 1997; Stuss et al. 1985) multiple sclerosis (Demaree et al. 1999; Mostofsky et al. 2003; Rao et al. 1989a, b), schizophrenia (Cohen et al. 1997; Saykin et al. 1991, 1994), dementia (Bradley et al. 1989; Collette et al. 1999; Morris and Baddeley 1988) and normal aging (Salthouse 1992, 1996; Salthouse and Coon 1993).

Functional imaging and the study of WM and processing speed deficits

There is a growing literature using functional imaging to examine speeded WM deficits in cases of brain injury and disease including TBI (Christodoulou et al. 2001; Newsome et al. 2007; Perlstein et al. 2004; Sanchez-Carrion et al. 2008a, b; Scheibel et al. 2009; Turner and Levine 2008), human immunodeficiency virus (Chang et al. 2001, Ernst et al. 2002, 2003; Chang et al. 2004) and multiple sclerosis (Chiaravalloti et al. 2005; Forn et al. 2006, 2007; Hillary et al. 2003; Mainero et al. 2004; Penner et al. 2003). Because this literature has focused largely on speeded WM, the constructs of processing speed and WM have often been measured simultaneously. Thus, much of our understanding of the neural systems associated with rapid information processing in clinical samples has been inferred from functional neuroimaging studies using tasks with high WM demand.

With notable consistency, functional imaging studies of WM deficits have revealed increased involvement of prefrontal cortex (PFC) and anterior cingulate cortex (ACC) in clinical samples compared to healthy adults. In studies of TBI specifically, examiners using the n-back and speeded WM tasks such as the modified version of the paced serial addition task (mPASAT), or tasks of executive control, have documented increased involvement of dorsolateral and ventrolateral PFC and often ACC (Christodoulou et al. 2001; McAllister et al. 1999, 2001; Maruishi et al. 2007; Perlstein et al. 2004; Sanchez-Carrion' et al. 2008a, b; Turner and Levine 2008). Increased neural involvement paired with similar task accuracy between clinical and control groups has been interpreted as "neural compensation" or, alternatively, as "brain reorganization". While these two terms certainly have distinct implications for altered brain activation, (most notably its permanence), both are almost universally used to describe PFC involvement operating to bolster performance (for review see Hillary 2008). What remains a central dilemma in determining the nature of PFC recruitment in TBI (and in neurological insult more generally) is whether the recruitment of these neural resources: 1. occurs only in cases of injury and/or disruption or represents a latent support mechanism evoked during periods of cerebral challenge more generally; 2. serves to facilitate task performance or is associated with diminished performance. The meaning of PFC recruitment in the context of speeded WM deficits is a primary focus of the current study.

Processing efficiency and PFC recruitment

While the neural substrate(s) involved in tasks of speeded information processing are at least partially dependent upon the cognitive task used, several neuroanatomical regions have been shown with some consistency to play a critical role in rapid information processing. During delayed response tasks, examiners have demonstrated that, when compared to faster subjects, slower subjects show greater activation in dorsal PFC during working memory tasks (Rypma et al. 2002; Rypma et al. 1999; Rypma and D'Esposito 2000; Rypma et al. 2001) and this finding has been extended to tasks designed to eliminate WM demand (Rypma et al. 2006; Sweet et al. 2006). One potential role for PFC and ACC in tasks requiring rapid information processing (with and without significant WM component) would be the allocation of attentional (or cognitive control) resources and this assignment should be related to the on-task "cycle time", or the amount of time taken to process individual components of the task. The notion of task cycle time has been used in explanations of "neural efficiency" models (see Rypma et al. 2006) and in the aging literature to describe how diminished speed accounts for more general cognitive decline observed in normal aging (see Kail and Salthouse 1994). This established relationship between information processing speed and prefrontal networks has important implications for understanding the meaning of neural recruitment and the information processing deficits commonly observed in TBI.

Clinical imaging studies of WM have not included a behavioral index for processing speed (e.g., RT) or isolated the fundamental relationship between regions of neural recruitment (commonly in PFC) and task performance. Occasionally, when such direct examination of performance-activation relationships has been conducted using block designs, no relationship has been observed in PFC (Newsome et al. 2007; Sanchez-Carrion et al. 2008a, b), potentially due to methodological limitations (e.g., diminished sensitivity due to block designs, "over-subtraction"). Work by Perlstein et al. (2004) offers one of the few WM studies to successfully isolate these effects using an event-related (ER) design to examine the relationship between task load and PFC activation in cases of head injury. These data demonstrate that the neural recruitment observed in PFC following brain injury may be at least partially attributable to task load/difficulty and thus performance decrements, but these findings have not been well integrated into compensatory/brain reorganization explanations. That is, these findings are not consistent with the position that recruitment of PFC facilitates performance and is a prerequisite or marker for recovery.

Previously, we have argued that, in studies measuring task accuracy alone, the resultant between group differences are at least partially attributable to unrecognized processing speed decrements (Hillary et al. 2006; Hillary 2008). If the regions of neural recruitment commonly observed in TBI are coupled with task performance (as will be directly measured here), it will be important to reframe brain reorganization hypotheses as they are currently posed. The

current study is designed to examine rapid decision making in order to isolate processing speed decrements and to determine if on-task "cycle time" can account for the neural recruitment commonly observed in clinical WM studies. To do so, we employed a relatively simple task providing ample time to respond in order to demonstrate that basic information processing differences can account for the neural recruitment consistently observed in studies of basic information processing in clinical samples. To date, there has been no direct examination of these factors and we anticipate that because of this, studies interpreting between group differences in brain activation as "brain reorganization" overestimate the permanent changes to baseline neural networks in clinical samples.

Primary study aim

The functional imaging literature to date examining speeded information processing has consistently demonstrated recruitment of PFC in neurological populations, including TBI. What remains undetermined is if this neural recruitment represents permanent change in PFC networks, or if increased involvement of PFC is at least partially attributable to slowed response time. Thus, there are two important aims for this event-related BOLD fMRI study: 1. to determine if engaging in a task of basic information processing speed results in neural recruitment in PFC regions in TBI; 2. to determine the nature of PFC recruitment by establishing performance-activation relationships in those regions of increased neural involvement. Based upon these goals, the study hypotheses are:

Hypothesis 1: Similar to previous studies of WM deficits, the current task examining speeded information processing will elicit greater PFC involvement in individuals with TBI compared to a control group.

Hypothesis 2: Similar to previous findings in WM, increased involvement of PFC occurring in TBI will appear differentially greater in right PFC compared to left PFC.

Hypothesis 3: Contrary to prior hypotheses, increased PFC involvement observed in TBI can be accounted for by differences in RT and does not represent permanent brain changes secondary to injury.

Methods

Participants

Demographic characteristics of the sample are presented in Table 1. The final study sample included 24 right-handed participants aged 21–55 years. There were 12 healthy control participants (HCs) between the ages of 27 and 55 (M=38.9, SD=10.2) without any reported medical disabilities, and 12 participants diagnosed with moderate and severe traumatic brain injury between the ages of 21 and 54 (M=38.4, SD=11.7). The mean education for HCs was 15.0 years (SD=1.8) and the mean education for the TBI sample was 14.75 years (SD=2.6).

Defining the TBI sample

Individuals with TBI had a definitive diagnosis, defined by the CDC as: "damage to brain tissue caused by an external mechanical force, as evidenced by loss of consciousness due to brain trauma, post-traumatic amnesia, skull fracture, or objective neurological findings that can be reasonably attributed to TBI on physical examination or mental status examination." TBI severity was defined using the Glasgow

Table 1 Demographic and cognitive testing results for TBI and HC samples

Demographic variables	TBI (mean, SD)	HC (mean, SD)	Group comparison
Age	38.42 (11.6)	38.92 (10.2)	p=0.892
Education	14.75 (2.6)	15.00 (1.7)	p=0.785
Gender	10 m, 2 f	5 m, 7f	p=0.035*
Neuropsychological results			
SDMT	45.55 (6.40)	60.42 (13.40)	p=0.003*
Forward Digit Span	8.83 (3.00)	8.42 (2.46)	p=0.717
Backward Digit Span	6.67 (2.42)	7.92 (2.50)	p=0.227
Total Digit Span	15.5 (4.90)	16.33 (4.18)	p=0.659
Trail Making Test A	41.21 (18.10)	24.05 (5.15)	p=0.005*
Trail Making Test B	77.17 (30.10)	58.97 (22.70)	p=0.115
Cancellation Test	116.0 (34.00)	74.07 (15.20)	p=0.001*
Hopkins Verbal Learning Test	25.17 (5.18)	28.50 (3.45)	p=0.077
Matrix Reasoning	14.33 (4.79)	18.17 (4.84)	p=0.064

Coma Scale in the first 24 h after injury (Teasdale and Jennett 1974) and GCS scores from 3–8 were considered "severe" and scores from 9–12, or individuals with significant neuroimaging findings, were considered "moderate." All individuals with TBI had an initial GCS score between 3 and 12, had at least one identifiable brain lesion site confirmed by CT/MRI results identified in their medical records, and were at least 1 year post injury (range 1–31 yrs, M=9.2, SD=2.7). Candidates for the study were excluded if they had a history of previous neurological disorder such as seizure disorder, or significant neurodevelopmental psychiatric history (such as schizophrenia or bipolar disorder). These exclusions were covered in the IRB approved consent form and were discussed with the family members of each study participant.

Heterogeneity in TBI and focal lesions

Examination of traumatic brain injury is complicated by the nature of the injury process which is most appropriately described as both focal and diffuse. Recent work has demonstrated that even in cases where one observes focal lesions in "isolation", there are commonly whole-brain consequences (Bigler 2001; Fujiwara et al. 2008; Buki and Povlishock 2006; Levine et al. 2008; Merkley et al. 2008) and that diffuse injury to white matter is nearly ubiquitous (Levine et al. 2008; Wu et al. 2004). One method for homogenizing study samples has been to eliminate any cases where focal lesions occur, focusing specifically on diffuse axonal injury (DAI). These methods have provided insight into the effects of DAI (if cases of isolated DAI can be successfully isolated), but by eliminating focal regions of injury, they also eliminate pathophysiology endemic in TBI and reduce the ability to generalize findings to clinical samples. For this reason, existence of focal contusions and hemorrhagic injuries were not reason for exclusion unless these injuries were so severe so as to require neurosurgical intervention (i.e., craniectomy) or removal of tissue resulting in gross derangement of neuroanatomy. In doing so, the current study permits the generalization of these findings to what is observed in TBI as it occurs and allows for the examination of neural recruitment, even in brain regions directly influenced by injury (e.g., PFC). Ultimately, lesion-specific effects adds "noise" and not signal to the measurement, but we remain confident that the phenomenon of interest here is robust enough so as to curtail the influence of focal pathology. Indeed, the PFC recruitment that is of primary interest in this study, has been repeatedly observed in mild, moderate and severe TBI with and without conspicuous brain lesions.

General procedure

All subjects signed informed consent forms approved by the Institutional Review Boards of Kessler Medical Research Rehabilitation and Education Corporation and the University of Medicine and Dentistry of New Jersey prior to final enrollment in the study and all study procedures complied with HIPAA standards. Consistent with the policy of the University Heights Center for Advanced Imaging at the University of Medicine and Dentistry of New Jersey, subjects were excluded if they had any metal in their bodies (e.g., cochlear implants, pace-makers), determined by a metal screening form and metal detector, or if they were pregnant determined via a urine pregnancy test. Subject participation in the study lasted approximately 3 h and each subject received $50 for participating.

Neuropsychological testing procedure

On the same day as the MRI scanning, a battery of neuropsychological tests was administered to each participant to assess neuropsychological functioning. The battery assessed common cognitive functions known to be impaired in individuals in TBI, such as processing speed, working memory, and new learning. Processing Speed tasks included *Symbol Digit Modalities Test (SDMT)—oral version* (Smith 1997) (which was always administered following the fMRI session), *Trail-Making Test (TMT) A and B* (Reitan 1958), *the Visual Search and Attention Test* (VSAT, Trenerry et al. 1990). To assess higher cognitive processing, the *Matrix Reasoning subtest* from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler 1997) was administered. Working memory was assessed with the *Digit Span subtest of the* WAIS-III, including simple attention/rehearsal (digits forward) and rehearsal/manipulation (digits backward) (Wechsler 1997). Verbal memory and new learning was assessed using the *Hopkins Verbal Learning Task (HVLT)* (Brandt 1991).

Behavioral task in the scanner

The cognitive paradigm used to assess processing speed during fMRI activation was a modification of the Symbol Digit Modalities Task (mSDMT) (Smith 1973, 1997), which has been modified for usage in fMRI in order to examine processing speed and efficiency (DeLuca et al. 2008; Genova et al. 2009; Rypma et al. 2006). In the current design, the mSDMT requires the participant to respond via left and right thumb key-press to minimize head movement. To familiarize each subject with the task, all subjects underwent task training of four practice runs and were required to accurately perform the task at greater than 90% hit rate prior to entering the scanner. During these practice sessions and while in the MRI environment, subjects were instructed to "respond as quickly as possible without making mistakes".

Positioned supine in the scanner, the subjects viewed a panel of 9-paired stimulus boxes projected onto a screen. In

the stimulus boxes, the upper row each contained a symbol and its matching lower box contained a digit (1 through 9). Below the panel of boxes were two paired "probe" boxes containing a digit and a symbol. The subject was required to determine if the probe pair matched any of the corresponding pairs of stimulus boxes and then respond "match" or "no match" by making a right or left thumb key-press, respectively. Each subject was permitted up to 6 s to respond to each stimulus and the stimulus remained on the screen for this duration in order to maximize task accuracy. The 9 symbol-digit pairings were altered with each presentation, thus minimizing new learning and working memory load. All subjects completed three runs, each with a duration of 7 mins 48 s. Each run contained 225 TRs, for a total task time of 31.2 min. In sum, there were a total of 256 "events" where responses were collected. Following each event there was a variable interstimulus interval lasting either 0, 4, 8 or 12 s during which the subjects were required to focus on a crosshair in the center of the screen which served as the implicit "control" for this ER design. There were two reasons for not including a formal control task or additional contrast in this study. First, it was not a goal in the current study to isolate specific cognitive mechanisms (e.g., separate visual processing from decision making); the goal here was to examine rapid information processing deficit (broadly defined) associated with a rapid visual scanning task and with focus on PFC. Second, there are a number of methodological pitfalls associated with using complex subtraction scenarios in clinical samples (Price and Friston 1999; Price and Friston 2002), including differential subtraction between subjects due to performance decrements (Hillary 2008). Reaction time (RT) was recorded for all subjects, but due to a software programming error, task accuracy was not collected in 6/12 subjects with TBI. The results throughout this manuscript focus on RT values as the critical behavioral variable. Even so, individuals with missing accuracy values also met the training requirement of 90% accuracy prior to entering the MRI environment, did not differ significantly in reaction time or omitted responses from the 6 subjects for whom accuracy data were available, and were neuropsychologically similar. Because of the desire to replicate prior findings in block design studies where all trials are included and the interest in examining "processing speed deficit" broadly defined, trials for both correct and incorrect responses were included in the analysis. This approach also permitted examination of greater variance in RT.

Magnetic resonance imaging procedure

Neuroimaging was performed at UMDNJ on the Siemens Allegra 3T MRI. Sagittal T1-weighted images were obtained before fMRI. Whole brain axial T1-weighted conventional spin-echo images (in-plane resolution= 0.859×0.859 mm^2) for anatomic underlays (TR/TE=450/14 ms, contiguous 5 mm, 256×256 matrix, FOV=24×24 cm^2, NEX=1) were then obtained. Functional imaging consisted of multislice gradient echo, T2*-weighted images acquired with echoplanar imaging (EPI) method (TE=30 ms; TR=2,000 ms; FOV=24×24 cm^2; flip angle=90°; slice thickness=5 mm contiguous), yielding a 64×64 matrix with an in-plane resolution of 3.75×3.75 mm^2.

Data analysis

Preprocessing of the fMRI data and all subsequent image analyses were performed using SPM5 software (http://www.fil.ion.ucl.ac.uk/spm5). The first nine volumes were removed from analyses in order to control for initial signal instability. Preprocessing steps included realignment of functional data of each run to the first functional image of that run using affine transformation (Ashburner et al. 1997). Functional images were then co-registered to the individual's T1 MPRAGE and all data were normalized using a standardized T1 template from the Montreal Neurological Institute, MNI, using a 12 parameter affine approach and bilinear interpolation. Normalized time series data were smoothed with a Gaussian kernel of $8 \times 8 \times 10$ mm^3 in order to minimize anatomical differences and increase signal to noise ratio.

Functional imaging contrasts

In order to test the study hypotheses, we employed four specific analyses. First, for each group a vector of interest was used to create contrast maps based upon the modeled BOLD signal at the onset of each stimulus presentation. "Activation" was first determined using a time-shifted BOLD response with SPM's standard canonical reference function modeling the BOLD response at each event of interest in the design. Second, to test Hypotheses 1 and 2, these two vector-based contrast images from the two study groups were statistically compared to determine between-group differences (e.g., TBI>HC and HC>TBI). The goal of this initial analysis was to replicate between-group differences commonly observed between TBI and HC samples during tasks of rapid information processing. Third, within-group comparisons were made between Run 1 and Run 2 in both samples to examine the influence of task learning on regions recruited in the TBI>HC contrast. Fourth, to test Hypothesis 3, each event of interest was replaced with the RT value for that response and used as a regressor to predict the BOLD signal in TBI. This analysis included the use of the canonical reference function and a temporally flexible reference function (i.e., time derivative) to permit inclusion of BOLD response occurring within

Table 2 HC and TBI accuracy for runs 1-3

	TBI (mean, SD) n=6	HC (mean, SD) n=12
Run 1	90.8 (SD=2.4)	91.8 (SD=4.7)
Run 2	94.8 (SD=2.0)	93.0 (SD=3.5)
Run 3	97.7 (SD=2.3)	97.4 (SD=4.6)

1,000 ms immediately prior to or immediately following the conventional canonical HRF. This step to include the time derivative was to account for the potential influence of injury on blood flow and, consequently, onset of the HRF which might account for between group differences observed in the literature to date (see Hillary and Biswal 2007). In order to examine both positive and negative relationships with the BOLD response, TBI>HC and RT-regression contrasts were created using the canonical and temporally flexible reference functions using an "IMcalc" command to implement the procedure developed in Calhoun et al. (2004). This procedure permits two-tailed observation of the combined effects of time-shifted canonical and time-derivative hemodynamic response functions. For our purposes, the time derivative was treated as "of interest" variance in the BOLD signal as opposed to a nuisance variable or confound. These data revealed change in the BOLD response as a function of RT and contrasts were created based upon both positive and negative correlation with BOLD signal change. Based on these findings, we determined if the BOLD response in those regions that differentiated the two groups (e.g., TBI>HC) were anatomically similar to those regions predicted by RT. This last analysis was designed to aid in interpreting the meaning of neural recruitment commonly observed in studies of rapid information processing in TBI.

Results

Demographic and behavioral results

Independent samples t-tests revealed no significant between-groups differences with respect to age (t(22)= −.11, p=0.91), or education (t(22)=−0.28, p=0.79). Chi-square analysis revealed that the percentage of females was significantly higher in the HC group (58%) compared to the TBI group (17%) (χ^2(1)=4.44; p=0.035). Table 1 provides the cognitive testing results for the neuropsychological assessment outside the MRI environment and results of independent samples t-tests. On average, the group of individuals diagnosed with TBI demonstrated mild to moderate deficits in the areas of processing speed and higher order cognitive functioning. These data are consistent with the deficits commonly observed in moderate and severe TBI.

Functional imaging results

mSDMT results Both groups were able to complete the task with a high degree of accuracy prior to MRI scanning and, for available data (HC=12, TBI=6), during three separate runs of the task. Tables 2 and 3 demonstrate HC and TBI accuracies and reaction times for DSST runs 1–3.

When the groups were considered together, repeat measures ANOVA revealed a significant influence of Run number on accuracy [F(1,16)=28.46, p<.001, η_p^2=.626] and RT [F(1,22)=27.36, p<.001, η_p^2=.543], with RTs decreasing and accuracy increasing from Run 1 to Run 3. That is, performance improved for both groups across runs.

When examining specific between-group effects, there was no significant effect of group membership on task accuracy for Runs 1–3 [F(1,16)=.23, p=0.638, η_p^2=.014]. There were, however, significant between group differences in RT for this task. Analysis of variance revealed a main effect of group membership on RT [F(1,22)=4.21, p=.045, η_p^2=.17].

fMRI results

The results of the dichotomous ER analyses examining "events-of-interest" are presented in Fig. 1a and b for the TBI and HC groups. These data represent change in the BOLD response at each event of interest using a temporally flexible canonical HRF to model the data. The Brodmann's areas of peaks of activation and surrounding regions of activation are represented in these contrasts as an independent anatomical reference. Supplementary Tables S1 and S2 outline the MNI coordinates and Brodmann's areas for regions determined to be "active" in each group. Brodmann's areas were estimated by converting MNI coordinates to

Table 3 HC and TBI reaction time for runs 1–3

	HC mean (SD); median	Range (ms)	TBI mean (SD); median	Range (ms)	Group Comparison
Run 1	1949.9 (389); 1829.5	1474.8–2944.5	2376.3 (575.7); 2291	1526.4–3497.6	F(1)=4.51, p=0.045*
Run 2	1719.9 (425.5), 1596	1205.0–2865.9	2117.5 (495.2), 2025	1283.4–3064.81	F(1)=4.47, p=0.046*
Run 3	1757.4 (463), 1619	1325.4–3073.1	2202.4 (511), 2099	1364.8–3238.1	F(1)=4.99, p=0.036*

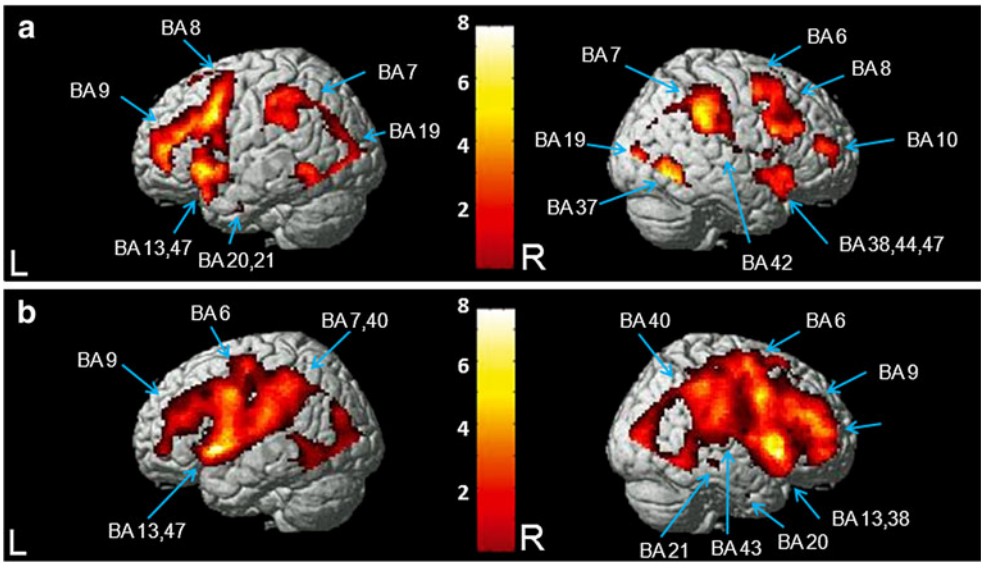

Fig. 1 **a**,**b**: Regions determined to be "active" based upon a dichotomous analysis of the standard canonical HRF in SPM5. The colorbar represents t values from 0 to 8. Note: for an exhaustive list of peak areas of activation visible here, see Supplementary Tables S1 and S2. Note: contrast created using FDR correction $p<.05$

Talaraich space using the calculations described by Rorden and Brett (2000) and submitting the new coordinates to the Talaraich daemon (Lancaster et al. 2000).

Between-group comparisons

In order to determine differences in the task-induced BOLD response between the two groups, contrast images were created using SPM5. Because we were interested in gathering all potential sites for neural recruitment, we set the minimum cluster size to 0 and the minimum threshold at $p<.001$ (Note: our primary concern was threshold consistency between contrasts, even so, the results of this analysis were also examined using FDR correction in SPM5 and the current results were slightly more conservative). The results of these contrasts are presented in Fig. 2a and b. The data here demonstrate significant between-group differences with the TBI sample demonstrating greater involvement of PFC, temporal, and insular regions (see Table 4). Additional comparison revealed that there were no regions of activation in the healthy adult sample not evident in the TBI sample (i.e., HC>TBI revealed no significant activation).

Predicting BOLD with RT: regression analyses

Individuals with TBI in this sample demonstrated recruitment of bilateral Broca's area and right DLPFC and pre-scan training operated to maximize accuracy during this task, but during scanning they were significantly slower than the healthy control sample. In order to test the hypothesis that areas of increased involvement in PFC (e.g., TBI>HC) are due to on-task cycle time, independent whole-brain analyses using RT to predict the fMRI signal were conducted. Results

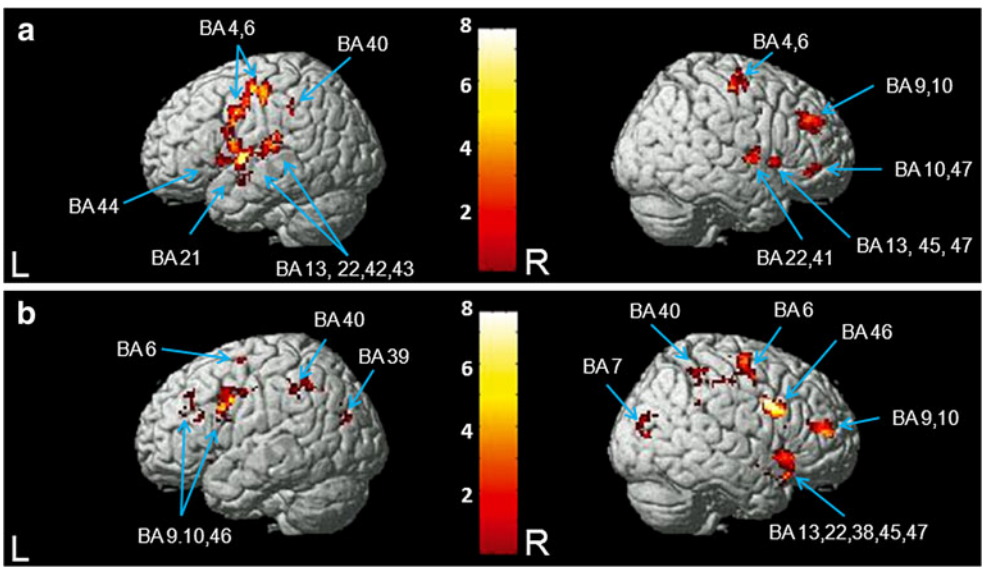

Fig. 2 **a** illustrates those regions exhibiting greater task-induced BOLD response in the TBI sample compared to the HC sample. The colorbar represents t values from 0 to 8. **b** is the result of a whole-brain analysis using RT as a regressor to predict a time-shifted BOLD response (i.e., canonical+time derivative). NOTE: For Fig. 2b, left BA 44 is suprathreshold, but not evident on the image rendering (see Table 6). Note: contrast created using FDR correction $p<.05$

Table 4 Data for the TBI>HC (*FDR*<.*05*) contrast presented in Fig. 2a. Note: "Region" indicates peak activation for Brodmann's areas. For Regions where more than one peak was present in any specific Brodmann's area and gyrus, only the most significant peak is reported

	Region	BA	X	Y	Z	T-Value
Right hemisphere	Precentral Gyrus	4	32	−18	52	4.98
	Precentral Gyrus	6	58	0	12	3.82
	Medial Frontal Gyrus	6	8	2	60	3.59
	Middle Frontal Gyrus	9	26	38	30	4.50
	Superior Frontal Gyrus	9	28	46	34	5.83
	Precentral Gyrus	9	38	4	38	4.04
	Inferior Frontal Gyrus	10	46	46	−2	3.92
	Middle Frontal Gyrus	10	28	40	20	4.05
	Superior Frontal Gyrus	10	38	48	22	3.58
	Insula	13	42	−26	16	4.53
	Parahippocampal Gyrus	19	26	−54	−10	3.66
	Superior Temporal Gyrus	22	55	0	4	5.54
	Cingulate Gyrus	24	12	−2	36	4.50
	Cingulate Gyrus	31	16	−30	40	4.30
	Cingulate Gyrus	32	12	30	32	3.72
	Superior Temporal Gyrus	41	44	−40	10	3.72
	Middle Frontal Gyrus	47	42	40	−8	4.21
Left hemisphere	Precentral Gyrus	4	−20	−26	66	3.68
	Precentral Gyrus	6	−58	4	10	5.81
	Medial Gyrus	6	4	−8	56	5.18
	Cuneus	7	−18	−78	30	3.68
	Precuneus	7	−18	−70	40	4.15
	Insula	13	−42	−16	−4	4.16
	Parahippocampal Gyrus	19	−28	−44	−10	3.59
	Middle Temporal Gyrus	21	−50	0	−16	4.52
	Superior Temporal Gyrus	22	−48	8	0	3.59
	Cingulate Gyrus	24	−6	8	38	4.17
	Precuneus	31	−24	−72	24	4.95
	Anterior Cingulate Gyrus	33	−8	22	18	3.65
	Fusiform Gyrus	37	−30	−52	−12	4.15
	Supramarginal Gyrus	40	−44	−40	36	3.91
	Transverse Temporal Gyrus	42	−58	−14	8	3.60
	Superior Temporal Gyrus	42	−58	−28	16	3.60
	Postcentral Gyrus	43	−50	−20	16	6.19
	Inferior Frontal Gyrus	44	−56	6	16	5.49
	Inferior Frontal Gyrus	45	−58	10	20	5.13
	Inferior Frontal Gyrus	47	−30	20	−12	3.86

from this whole-brain analysis revealed that the BOLD signal in Brodmann's areas of increased PFC involvement in TBI overlaps with those regions significantly predicted by RT (see Fig. 2b, Tables 5 & 6). These data demonstrate that RT was an important predictor of the BOLD response in PFC in both groups and that the regions observed to be recruited in the TBI sample (TBI>HC) were similar to those regions reliably predicted by RT during regression analysis. By contrast, a whole-brain analysis investigating negative correlations between change in the BOLD response and reaction time revealed no small significant peaks.

Between-run task acquisition

One final analysis for examining the influence of RT and task acquisition on the BOLD signal was to determine the change in the BOLD response between runs in those brain regions recruited in TBI (TBI>HC). As noted above, performance improved significantly from Run 1 to Run 3 for both groups, but the greatest improvement was from Run 1 to Run 2. For this reason, change in the BOLD response from Run 1 to Run 2 was examined in the ROIs recruited in the TBI sample (e.g., right PFC, right Broca's

Table 5 Data for TBI>HC (FDR<.05) contrast presented in Fig. 2b. Note: "Region" indicates peak activation for Brodmann's areas. For Regions where more than one peak was present in any specific Brodmann's area and gyrus, only the most significant peak is reported

	Region	BA	X	Y	Z	T-Value
Right Hemisphere	Middle Frontal Gyrus	6	40	−2	50	7.15
	Paracentral Lobule	6	8	−30	48	4.21
	Precuneus	7	26	−70	34	13.90
	Superior Parietal Lobule	7	24	−66	42	8.49
	Inferior Frontal Gyrus	9	54	6	34	12.77
	Middle Frontal Gyrus	10	44	48	12	9.62
	Subgyral Temporal Lobe	13	42	0	−12	4.30
	Superior Temporal Gyrus	22	50	12	−6	6.20
	Medial Frontal Gyrus	32	2	8	48	5.17
	Superior Temporal Gyrus	38	40	10	−20	4.98
	Inferior Parietal Lobe	40	34	−44	46	5.42
	Inferior Frontal Gyrus	45	46	20	16	4.10
	Middle Frontal Gyrus	46	44	48	10	7.54
	Inferior Frontal Gyrus	47	36	22	−18	7.41
Left Hemisphere	Precentral Gyrus	6	−50	2	36	9.77
	Superior Frontal Gyrus	6	−2	8	56	4.69
	Inferior Frontal Gyrus	9	−54	8	30	11.81
	Middle Frontal Gyrus	9	−40	32	36	7.41
	Superior Frontal Gyrus	9	−36	36	30	4.12
	Middle Frontal Gyrus	10	−38	40	26	4.46
	Insula	13	−44	6	20	4.21
	Anterior Cingulate	24	−8	22	28	5.27
	Cingulate Gyrus	32	−6	16	34	5.42
	Middle Temporal Gyrus	39	−26	−70	26	5.67
	Inferior Parietal Lobule	40	−34	−50	44	6.18
	Inferior Frontal Gyrus	45	−52	26	22	6.25
	Middle Frontal Gyrus	46	−40	38	24	6.74

area, left Broca's area, and left insular area) as well as peak areas of activation in the same regions (e.g., left Broca's area/insula, right Broca's area, right BA 9, right BA 10). Paired sample one-tailed t-tests revealed significant change from Run 1 to Run 2 when considering the average change in the four PFC peak regions of activation collapsed $t(22)=1.89$, $p=0.042$, Cohen's $d=0.70$] and non-significant change in the three PFC ROIs collapsed $F(1)=1.43$, $p=0.085$; Cohen's $d=0.56$]. Separately, when examining mean ROI and peak values individually, with the exception of BA 9, which showed significant decline in activation between Run 1 and Run 2 [$F(1)=2.68$, $p=.021$, Cohen's $d=0.88$], the between-run differences showed consistent but statistically non-significant decline. Overall, the direction of change in the BOLD signal between Run 1 to Run 2 in TBI was consistent with what was observed in HCs (see Fig. 3).

When examining the inter-relationships in the BOLD response between these regions of neural recruitment, correlational analyses revealed greater relationships between bilateral Broca's area (including the left insular region) compared to right dorsal PFC regions (BAs 9 and 10). Change in the BOLD response in Run 1 to Run 2 revealed significant correlations between left Broca's/insula and right Broca's regions ($r=0.639$, $p=0.025$) but no significant relationship between either of these regions and right dorsal lateral PFC (left Broca's/insular area: $r=0.053$, $p=0.871$, and right Broca's area: $r=0.352$, $p=0.262$). Due to the focus on right dorsolateral PFC (Hypothesis 2), change in the BOLD response in this ROI, partial correlations were conducted between change in RT from Run 1 to Run 2 and right PFC while controlling for change in the BOLD signal in bilateral Broca's regions. Analysis revealed a significant positive correlation ($r=548$, $p=.032$; one-tailed test). Thus, distinct components recruited in PFC may be differentially involved during acquisition of this speeded visual scanning task.

Discussion

To our knowledge the current study is the first to examine the neural networks associated with processing speed deficits in TBI. Previous imaging research examining these

Table 6 Suprathreshold regions of activation for the two primary analyses in the TBI sample. The table indicates regions of suprathreshold activation presented in Fig. 2a and b. These data demonstrate consistency between those regions recruited in TBI (Fig. 2a) and the results of whole-brain analysis examining the BOLD response as a function of RT (Fig. 2b). The bottom row provides results for positive regression analysis with RT in the HC sample, demonstrating significant overlap between groups for the RT-regression analysis

	Pre-motor						Insula		Anterior Cingulate						Dorsolateral PFC						Ventrolateral PFC					
BA	4		6		8		13		24		32		33		9		10		46		44		45		47	
Hemisphere	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
TBI > HC	X	X	X	X			X	X	X	X		X	X		X	X		X			X	X	X	X	X	X
TBI Regression		X	X	X			X	X	X		X	X			X	X	X	X	X	X	X	X	X	X		X
HC Regression			X	X	X	X	X	X			X				X	X	X	X	X	X		x			X	X

basic decrements in information processing has focused largely on speeded WM and the most consistent finding across studies in neurologically impaired samples to date has been increased involvement of PFC. In this literature, recruitment of PFC has been interpreted as neural compensation and/or brain reorganization operating to bolster performance (see Maruishi et al. 2007; McAllister et al. 1999, 2001; Sanchez-Carrion' et al. 2008a, b) or alternatively, as an indication of neural inefficiency and poorer performance (Christodoulou et al. 2001; Perlstein et al. 2004). It was a primary goal to clarify the role of PFC recruitment in modulating basic information processing in a disrupted neural system (i.e., brain injury).

The current findings offer some insight into the nature of PFC recruitment in TBI. Figure 2a illustrates the between group differences in activation during the task. Consistent with Hypothesis one, the current data are similar to other studies of speeded information processing (e.g., WM) in TBI, demonstrating increased involvement of PFC regions (Christodoulou et al. 2001; Maruishi et al. 2007; Perlstein et al. 2004; Scheibel et al. 2007; Sanchez-Carrion et al. 2008a, b) and even one study examining PFC changes after treatment/intervention (Kim et al. 2009). The findings also support the second hypothesis and are consistent with prior work revealing differentially greater recruitment in the right versus left hemisphere (elaborated upon below) (e.g., Christodoulou et al. 2001; Perlstein et al. 2004; Sanchez-Carrion et al. 2008a, b). Without the additional analyses conducted here, the neural recruitment observed in the current data might be interpreted as a response attributable to injury (e.g., brain reorganization) operating to facilitate performance.

When conducting whole-brain analyses using RT as a regressor, RT was positively correlated with the BOLD signal in several overlapping regions demonstrated to be recruited in TBI during the initial between group comparison (e.g., TBI>HC) (see Fig. 2b; Table 6). In particular, Brodmann's area 44 (which likely subserve subvocalization and rehearsal during task performance) maintained significant correlation with RT and have been consistently observed to be recruited in clinical WM studies. In general, there was good overlap between those regions recruited in the TBI sample (TBI>HC) and those regions predicted by RT (see Fig. 2a and b). These effects were also corroborated by examining within-subject change; as RT diminished across Runs (presumably due to acquisition of task demands and shorter rehearsal times), the BOLD response in regions recruited in TBI mirrored this effect (see Fig. 3).

Taken together, the current data demonstrate that neural recruitment of PFC in TBI may be at least partially dependent upon RT. We have previously argued that recruitment of PFC (often right PFC) in clinical samples demonstrating WM dysfunction represents a "latent support mechanism" that is transient and performance dependent (Hillary et al. 2006; Hillary 2008). In fact, recruitment of these resources is an indication of reduced processing efficiency and may represent recruitment of attentional control resources as the task is more slowly processed (Rypma et al. 2006). If this interpretation is correct, then the increased PFC involvement observed here is neither abnormal, nor injury specific, but the result of latent support mechanism(s) brought online to tolerate novel task demands during skill acquisition. In fact, there was significant overlap in the neural substrates showing positive correlation between RT and the BOLD response between the TBI and HC samples, demonstrating that these neural resources are similarly allocated irrespective of injury.

One important finding emerging from these data is the differentially greater role of right PFC (compared to left hemisphere regions) in modulating task performance. For example, there was a greater relationship between RT and the BOLD response in regions in right compared to left PFC (e.g., dorsal PFC). These data are consistent with what has been observed in prior functional imaging studies of speeded WM deficits whereby right PFC has been a primary site for neural

recruitment (Christodoulou et al. 2001; McAllister et al. 1999, 2001; Perlstein et al. 2004; Sanchez-Carrion et al. 2008a, b). Moreover, for the current data, right dorsal PFC recruitment maintained little correlation with recruitment in left and right Broca's area (while recruitment in the latter two was significantly correlated). Thus, when considering those brain regions brought online during slowed task processing, right PFC may be differentially contributing to sustained attention and providing scaffolding to permit new learning in the injured brain.

Early work examining inter-hemisphere specialization noted a greater role of the right hemisphere in processing novel features to tasks during the development of subroutines that allow for greater task efficiency (see Gazzaniga 2000) and others have noted that the right hemisphere is differentially involved in the processing of novel sensory stimuli and that attentional control resources may be lateralized to the right hemisphere (Pardo et al. 1991). In the context of these results, increased right PFC involvement in TBI may be at least partially attributed to increased demand on cognitive control mechanisms in order to process novel features in the task and develop "subroutines" to handle task demands (Hillary et al. 2003; Hillary et al. 2006). Again as RT diminishes from Run 1 to Run 2, peak activation in right PFC originally recruited in TBI mirrors this behavioral change (see Fig. 3).

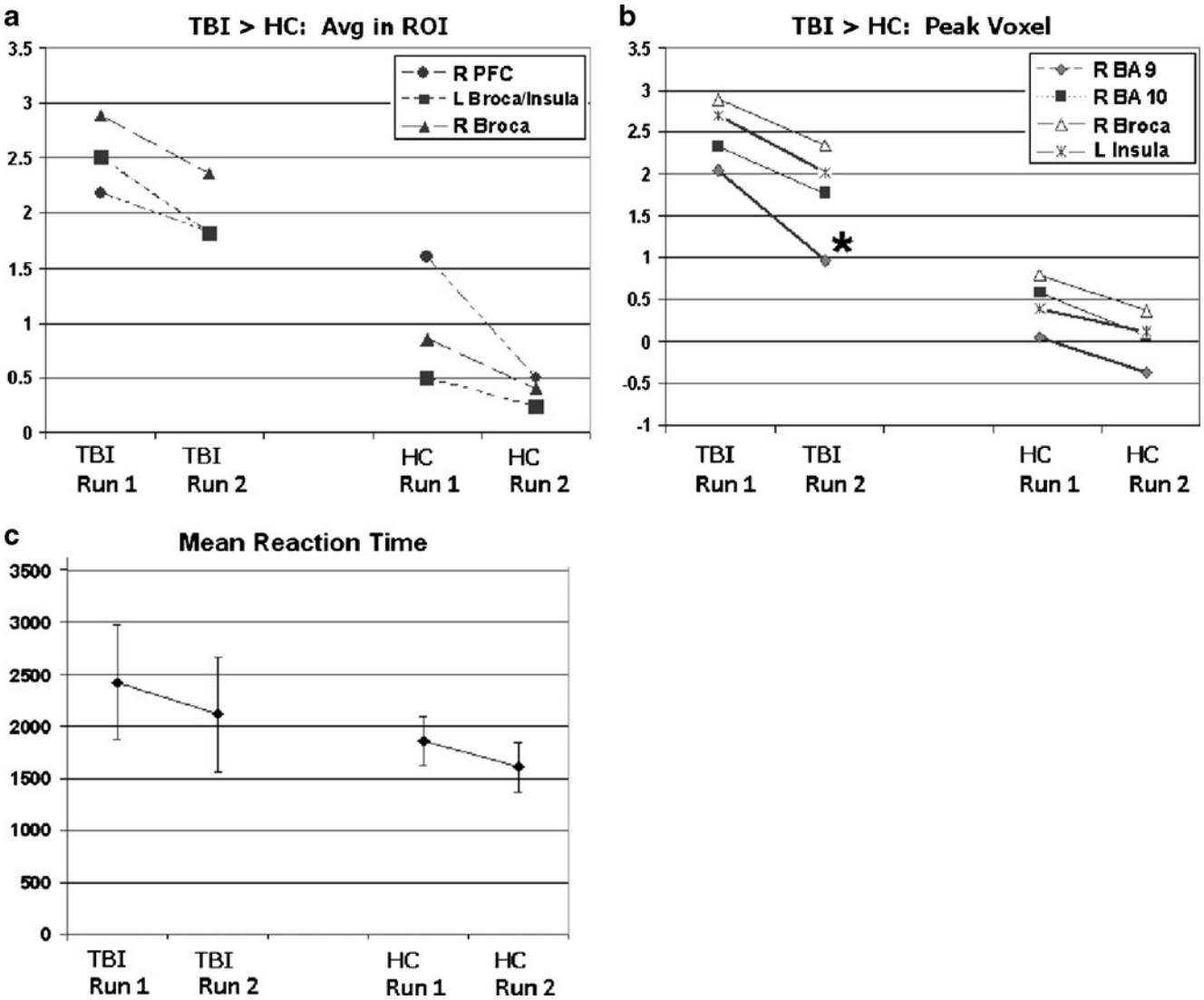

Fig. 3 **a**-**c**. Examining change in the BOLD response and RT between Run 1 and Run 2 in each group. BOLD signal change measured using canonical hemodynamic response function in SPM5. In a, data demonstrate the direction of change between Run 1 and Run 2 in the average BOLD response in those regions where TBI>HC (Fig. 2a) with focus on anterior networks. **b** illustrates change in the primary peak voxels in the same regions. **c** reflects the change in RT between Run 1 and Run 2. Note: *=$p<0.05$; PFC=prefrontal cortex, L=left, R=right, BA=Brodmann's area, HC=healthy control, TBI=traumatic brain injury

Of note, the cognitive paradigm used in this study reduces WM demand in order to examine rapid decision making in TBI; the primary task demands are visual scanning and stimulus-to-target matching. Because of this, the current data are not expected to map directly onto the WM findings to date, but to demonstrate the role of common neural substrates (e.g., PFC) in rapid information processing. The current data provide evidence that on-task cycle time may have important implications for PFC recruitment during this task in individuals with TBI.

Study limitations

While the current study may have important implications for understanding the role of PFC recruitment in processing speed deficits, it is not without limitations. First, the sample size is relatively small and there were several missing data cells within the behavioral data. In the case of the latter, we anticipate that task accuracy was consistent across the sample given the nature of the task which was designed to maximize accuracy, the out-of-scanner task performance, and the consistency across the sample with respect to the number of omissions, RT, and the standard deviation of RT. More importantly, if RT values were meaningless in a subsample of the TBI cases presented here, it would make it more and not less difficult to predict the BOLD response during the regression analysis. Even so, to be certain that potential accuracy effects did not influence the functional imaging findings, a fixed-effects analysis was conducted comparing the two TBI subsamples. The results were comparable and cannot account for the right PFC recruitment observed here in the TBI sample.[1]

Separately, while education and age were nearly identical between groups, there was greater number of women in the HC group. Again, we conducted post-hoc analyses, splitting the HCs into subgroups (7 men, 5 women) and there were few observable differences between these subgroups, with only small distinguishing features in occipital and temporal regions in the Women>Men contrast. For these reasons, we do not believe that sampling or poor performance in a subset of the TBI sample can account for the current data.

[0] Fixed-effects analyses were conducted in SPM5 comparing the TBI subsamples (n=6, n=6) using FDR, p<.05 and no differences were noted. When using a liberal threshold to increase sensitivity to possible differences (p<.001, uncorrected, no cluster threshold), this analysis revealed only small differences between TBI subgroups including clusters in: 1) left middle frontal gyrus (BA9) at −34 42 34 (cluster extent 2 voxels), and right supplementary motor cortex (BA 8) at 32 32 48 (cluster extent 67 voxels), and a cluster of 17 voxels in the left medial inferior parietal lobule (BA 31) at −2 −54 32. These subtle differences do not account for the between-group differences observed here when comparing TBI and HC samples.

Conclusion

Ultimately, if the PFC recruitment that has been observed in a number of clinical WM studies to date is indicative of brain reorganization, then recruitment of this substrate should not be coupled with performance and functionally similar to that observed in healthy adults. The relationship between performance and activation observed in this TBI sample, however, is similar to what is observed in healthy adults (e.g., PFC involvement is negatively correlated with performance, see Table 6), thus indicating that the disrupted neural system operates to use similar auxiliary systems to tolerate slowed processing and longer cycle time. This common neural response to cerebral challenge has been observed across studies and across samples, including healthy adults. These data demonstrate that at least part of the neural recruitment observed in TBI (and potentially other samples showing similar effects, e.g., multiple sclerosis): 1.) may not be an effect specific to neural disruption, 2.) does not facilitate task performance, and/or 3.) is not indicative of permanent change in the network. We conclude that the altered neural response observed in clinical studies of WM deficit is at least partially attributable to a transient, normal response in PFC during slowed information processing.

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