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Altered Cognitive Control Activations after Moderate-to-Severe Traumatic Brain Injury and Their Relationship to Injury Severity and Everyday-Life Function

Alexander Olsen[1,6], Jan Ferenc Brunner[2,6], Kari Anne Indredavik Evensen[3,4,11], Torun Gangaune Finnanger[5,7], Anne Vik[2,8], Toril Skandsen[2,6], Nils Inge Landrø[9,12] and Asta Kristine Håberg[2,10]

[1]MI-Lab and Department of Circulation and Medical Imaging, [2]Department of Neuroscience, [3]Department of Public Health and General Practice, [4]Department of Laboratory Medicine, Children's and Women's Health and [5]The Regional Centre for Child and Youth Mental Health and Child Welfare (RKBU) – Central Norway, Norwegian University of Science and Technology, Trondheim, Norway, [6]Department of Physical Medicine and Rehabilitation, [7]Children's Clinic, [8]Department of Neurosurgery, [9]National Competence Centre for Complex Symptom Disorders and [10]Department of Radiology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, [11]Department of Physiotherapy, Trondheim Municipality, Trondheim, Norway and [12]Clinical Neuroscience Research Group, Department of Psychology, University of Oslo, Oslo, Norway

Address correspondence to Alexander Olsen, MI-Lab and Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Postboks 8905, 7491 Trondheim, Norway. Email: alexander.olsen@ntnu.no

This study investigated how the neuronal underpinnings of both adaptive and stable cognitive control processes are affected by traumatic brain injury (TBI). Functional magnetic resonance imaging (fMRI) was undertaken in 62 survivors of moderate-to-severe TBI (>1 year after injury) and 68 healthy controls during performance of a continuous performance test adapted for use in a mixed block- and event-related design. Survivors of TBI demonstrated increased reliance on adaptive task control processes within an a priori core region for cognitive control in the medial frontal cortex. TBI survivors also had increased activations related to time-on-task effects during stable task-set maintenance in right inferior parietal and prefrontal cortices. Increased brain activations in TBI survivors had a dose-dependent linear positive relationship to injury severity and were negatively correlated with self-reported cognitive control problems in everyday-life situations. Results were adjusted for age, education, and fMRI task performance. In conclusion, evidence was provided that the neural underpinnings of adaptive and stable control processes are differently affected by TBI. Moreover, it was demonstrated that increased brain activations typically observed in survivors of TBI might represent injury-specific compensatory adaptations also utilized in everyday-life situations.

Keywords: cognitive control, compensation, continuous performance test, executive function, fMRI, time-on-task

Introduction

Moderate-to-severe traumatic brain injury (TBI) can cause varying degrees of cognitive control deficits, which in turn have negative impact on long-term functional outcome (Draper and Ponsford 2008; Ponsford et al. 2008). Cognitive control is supported by overlapping and distinct brain regions operating on different temporal scales (Dosenbach et al. 2006; Olsen et al. 2013). Processes such as response conflict- and error processing (Desmet et al. 2011; Nee et al. 2011) operate within a rapid reactive "adaptive" temporal scale, whereas sustained attention (Ogg et al. 2008) and stable task-set maintenance (Altmann and Gray 2002) are believed to be supported by proactive "stable" processes. The balance between adaptive and stable control processes has been shown to shift in aging (Paxton et al. 2008) and schizophrenia (Edwards et al. 2010) toward relying more on adaptive processes relative to stable. This emphasizes the dissociation between the different temporal systems and demonstrates their vulnerability to ageing and disease as well as indicates potential compensatory mechanisms (Braver 2012). Furthermore, only the stable control system seems to be altered as an effect of time-on-task (TOT) (Olsen et al. 2013), suggesting that this network may be particularly prone to the effects of cognitive fatigue (Cook et al. 2007). Cognitive fatigue is prevalent after TBI and has been related to the need for increased effort during task performance (Ponsford et al. 2012). It is still an open question whether adaptive and stable control systems are affected differently by TBI.

A region active during both adaptive and stable control processes has reliably been observed in the medial frontal cortex (MFC) in healthy participants (Dosenbach et al. 2006; Olsen et al. 2013). Interestingly, this brain region is also of particular interest after TBI, as demonstrated in several functional imaging studies (Scheibel et al. 2007; Hillary 2008; Rasmussen et al. 2008; Cazalis et al. 2011; Sozda et al. 2011). Indeed, the MFC is among the brain regions most consistently demonstrated to have altered blood oxygen level–dependent (BOLD) signal in several neurologic populations, including TBI (Hillary 2008). Accordingly, the core region for cognitive control within the MFC is potentially a key region for understanding how both adaptive and stable control processes are affected by TBI.

Previous functional magnetic resonance imaging (fMRI) studies have typically shown that survivors of moderate-to-severe TBI exhibit both increased and more widespread brain activations during performance of various cognitive tasks (Christodoulou et al. 2001; Scheibel et al. 2007; Rasmussen et al. 2008). It has been proposed that TBI survivors engage more neuronal resources to uphold adequate performance levels related to cognitive control (Turner and Levine 2008; Kohl et al. 2009; Turner et al. 2011). Increased BOLD activation after TBI has been positively correlated with both more severe injury and better fMRI task performance (Newsome et al. 2007; Scheibel et al. 2007, 2009), lending some support to its role as an injury-specific compensatory mechanism. However, whether increased activation after TBI represent true compensatory mechanisms

has yet to be elucidated (Hillary 2008, 2011). Moreover, the majority of previous fMRI studies on the effects of TBI have included relatively small heterogeneous samples, often reported imaging results uncorrected for multiple comparisons and/or failed to adjust for established outcome moderators such as age and education. It is therefore a need for further validation in sufficiently powered samples in order to establish the significance of previous findings.

Furthermore, a limitation when interpreting the functional role of BOLD activations in relation to task performance is that the 2 are inevitably related merely due to the way analyses are traditionally performed (Price et al. 2006; Hillary 2008). Consequently, it is considered crucial for the validity of BOLD activation differences between healthy controls and neurologically impaired participants that fMRI task performance is kept highly similar between groups and/or adjusted for (Price et al. 2006). Another implication of the tight coupling between fMRI task performance and brain activations is that validation of the functional significance of BOLD alterations should ideally rely on other measures than fMRI task performance (or highly similar neuropsychological tests) as such. Consequently, in contrast to previous studies, the present study implemented an alternative approach by utilizing the Behavioral Rating Inventory of Executive Function-Adult version (BRIEF-A) (Roth et al. 2005), which is a comprehensive and well-validated self-report measure of cognitive control function in everyday-life situations (Garcia-Molina et al. 2012; Lovstad et al. 2012; Waid-Ebbs et al. 2012).

In this study, the neuronal correlates of adaptive and stable control processes in moderate-to-severe TBI were investigated using a continuous performance test (Conners et al. 2003) adapted for use in a mixed block- and event-related fMRI design (Olsen et al. 2013). This particular test was chosen because of its extensive use in clinical settings (Rabin et al. 2005), well-described psychometric abilities (Riccio et al. 2002; Conners et al. 2003), capacity to measure both stable and adaptive control processes (Olsen et al. 2013), as well as having relatively simple task demands. The latter was important to ensure that both TBI survivors and healthy controls could perform the test accurately, which is a prerequisite for the validity of fMRI studies with neurological populations (Price et al. 2006).

Extending previous studies, both stable and adaptive control processes were investigated in order to delineate adaptations of these neural systems as a consequence of brain injury. First, 1) it was hypothesized that TBI survivors would demonstrate a shift toward relying more on adaptive task control processes (Paxton et al. 2008; Edwards et al. 2010; Braver 2012) within a predefined core region for cognitive control in the MFC (Olsen et al. 2013). Secondly, 2) it was predicted that TBI survivors would exhibit increased and more widespread BOLD activation (Christodoulou et al. 2001; Scheibel et al. 2007; Rasmussen et al. 2008) related to stable task-set maintenance TOT increases (Olsen et al. 2013), possibly in order to uphold adequate performance levels despite cognitive fatigue (Cook et al. 2007; Kohl et al. 2009). Finally, in order to explore the functional significance of possible BOLD alterations, 3) it was investigated whether such alterations would show a dose relationship with injury severity, and 4) if it was correlated with cognitive control function in everyday-life situations as measured with BRIEF-A (Roth et al. 2005), while controlling for fMRI task performance and the established outcome moderators age and education.

Materials and Methods

Participants

A total of 73 survivors with chronic moderate-to-severe TBI according to the criteria set by the Head Injury Severity Scale (HISS) (Stein and Spettell 1995) and 78 age-, sex-, and education-matched healthy controls were recruited for the present study. TBI survivors were recruited from a database of patients previously admitted to the Department of Neurosurgery, St. Olavs Hospital, Trondheim University Hospital, Norway. Details on how demographic and injury-related data were prospectively collected in the acute stage have been previously described (Skandsen et al. 2010). Glasgow outcome scale extended (GOSE) was administered at the time of fMRI. A self-report form and an interview were used to assess years of completed education. Healthy controls were recruited from friends and family of TBI patients, as well as from workplaces in Trondheim, Norway.

Inclusion criteria for both groups included being between 14- and 65-years old the year the testing was performed, fluency in the Norwegian language, ability to cooperate during fMRI testing, absence of previous moderate or severe head injury, diagnosed neurologic or psychiatric condition, as well as MRI incompatible implants. Eleven TBI survivors were excluded from further analysis: 3 due to missing fMRI data, 5 due to excessive movement (defined as relative displacement of >0.5 mm in any direction), 2 due to falling asleep during scanning, and 1 due to previously diagnosed psychiatric or neurologic disease that was not discovered before the day of scanning. This left 62 TBI survivors (17 women), for the full analyses in this study. Patient characteristics are presented in Table 1. Ten healthy controls were excluded: 3 because of missing data due to technical problems, 2 due to previously diagnosed psychiatric or neurologic conditions discovered at the day of testing, 4 due to excessive movement (defined as relative displacement of >0.5 mm in any direction), and 1 due to excessive fMRI artifacts. A total of 68 healthy controls (20 women) were hence included in the full analyses in this study. An independent t-test revealed no statistically significant age difference ($P = 0.86$) between TBI survivors (M = 32.4, SD = 14.2) and healthy controls (M = 33.8, SD = 13.6).

Table 1
Descriptive data characterizing TBI survivors

Variable	Total ($n = 62$)		Moderate ($n = 35$)		Severe ($n = 27$)	
	No.	Percent	No.	Percent	No.	Percent
Years since injury[a]	2.8	1.5–5.4	2.7	1.5–5.4	3	1.5–5.4
GCS score[a]	9	3–14	12	9–14	6	3–8
PTA duration						
Short (<7 days)	35	56.5	24	68.6	11	40.7
Long (≥7 days)	24	38.7	10	28.6	14	51.9
Missing data	3	4.8	1	2.9	2	7.4
Injury mechanism						
Vehicle accident	30	48.4	15	42.9	15	55.6
Falls	25	40.3	13	37.1	12	44.4
Skiing accident	3	4.8	3	8.6	0	0
Other/unknown	4	6.5	4	11.5	0	0
Early MRI: TAI grading						
No TAI	18	29.0	14	40.0	4	14.8
TAI 1	18	29.0	7	20.0	11	40.7
TAI 2	18	29.0	11	31.4	7	25.9
TAI 3	6	9.7	2	5.7	4	14.8
Missing data	2	3.2	1	2.9	1	3.7
Early MRI: cortical contusions						
No contusions	15	24.2	9	25.7	6	22.2
One	14	22.6	7	20	7	25.9
2 or more	31	50.0	18	51.4	13	48.1
Missing data	2	3.2	1	2.9	1	3.7
GOSE score at fMRI testing						
Moderate disability	25	40.3	13	37.1	12	44.4
Good recovery	37	59.7	22	62.9	15	55.6

Note: Descriptive data for the total TBI group, and moderate and severe TBI as defined by the Head Injury Severity Scale (HISS). TAI, traumatic axonal injury based on radiological evaluation of T2*, FLAIR and T2 images in the early phase (see Skandsen et al. 2010 for details).
GCS, Glasgow coma scale; PTA, post-traumatic amnesia; GOSE, Glasgow outcome scale extended; Good recovery, GOSE score 7–8; Moderate disability, GOSE score 5–6.
[a]Numbers representing GCS and years since injury are given as medians and ranges.

Neither was there a statistically significant difference in years of completed education ($P = 0.57$) between TBI survivors (M = 12.0, SD = 2.3) and healthy controls (M = 12.1, SD = 2.2). Written informed consent was obtained (also from parents if participants were under the age of 18). The study protocol adhered to the Helsinki Declaration and was approved by the Regional Committee for Medical Research Ethics.

Design of fMRI Task

An in-house-developed Not-X CPT (Olsen et al. 2013) inspired by the Conners' CPT (Conners et al. 2003) was presented to the participants in a mixed block- and event-related BOLD fMRI design (Petersen and Dubis 2012). The task consisted of a total of 480 stimuli, divided into 432 targets and 48 non-targets (10%). Targets consisted of randomly chosen letters (A–Z) other than "X," and non-targets were the letter X. Each stimulus was presented on the screen for 250 ms. The task was presented as 2 consecutive ~15-min runs, where each run consisted of 16 interleaving task blocks and 16 baseline (fixation cross) blocks. Each block contained 15 stimuli, and both inter-block intervals (IBIs) and inter-stimuli intervals (ISIs) were randomly scrambled within each block (with 6 IBIs of 14 s, 5 IBIs of 16 s, and 5 IBIs of 18 s and 5 ISIs of 1 s, 5 ISIs of 2 s, and 5 ISIs of 4 s). The jittered presentation of ISIs ensured sampling of different time points of the hemodynamic response curve, allowing for event-related fMRI analysis (Petersen and Dubis 2012). Counterbalancing was applied to eliminate systematic effects of ISI, IBI, or order of the different stimulus types (targets and non-targets). The task design was implemented using Matlab (The MathWorks, Inc., Natick, USA).

Not-X CPT Paradigm Procedure

Participants were instructed to respond as fast and accurately as possible by pressing a response button whenever a target (A–Z) was presented on the screen, and to withhold their response whenever the letter X appeared. All participants went through a practice session using a desktop computer outside the scanner room together with an experimenter who ensured that each individual performed the task as intended before the actual fMRI session. E-prime 1.2 (Psychology Software Tools, Pittsburgh, USA) was used for stimulus presentation and timing of stimuli. MRI-compatible video-goggles (VisualSystem, Nordic NeuroLab, Bergen, Norway) were used for visual presentation during scanning for 95 subjects. Due to technical problems with the goggles, the remaining subjects had to use a head-coil–mounted mirror system and a MRI compatible monitor (Siemens AG, Erlangen, Germany). Using photo diodes and an oscilloscope, a difference of ~60-ms stimulus onset delay was detected for the monitor relative to the goggles, which was adjusted for during post-processing of response- and fMRI data. A fiber optic response grip (ResponseGrip, Nordic NeuroLab, Bergen, Norway) was used for registration of subject responses, and all behavioral data were stored in individual log files by utilizing a customized Python-based log-script interacting with E-prime.

Self-Report Measure of Cognitive Control

The BRIEF-A was used as a self-report measure of cognitive control (Roth et al. 2005). BRIEF-A is a 75-item self-report questionnaire that provides 9 subscales measuring different domains of cognitive control: 1) inhibit, 2) Shift, 3) Emotional Control, 4) Self-Monitor, 5) Initiate, 6) Working Memory, 7) Plan/Organize, 8) Task Monitor, and 9) Organization of Materials. Participants were asked to indicate the frequency of the statement belonging to each item on a 3-point Likert scale (1—never, 2—sometimes, and 3—often). Based on these subscales, a Behavioral Regulation Index (BRI, sum of subscales 1–4), Metacognition Index (MI, sum of subscales 5–9), and a Global Executive Composite score (GEC, sum of subscales 1–9) were calculated and used for further analyses in this study.

Three healthy controls had one missing single item score each. In these cases, missing scores were handled according to recommendations in the BRIEF-A manual, by replacing the missing value with the value 1 (never). One healthy control had 7 missing single item scores and was excluded from further analyses involving BRIEF-A. There was no missing data for BRIEF-A in the TBI group.

MRI Scanning

All MRI data were acquired on a Siemens Trio with a 12-channel Head Matrix Coil (Siemens AG). Head motion was reduced by the use of foam pads around the subjects' heads. During Not-X CPT performance ~380 T2* weighted, BOLD-sensitive volumes were acquired for each "run," using an echo-planar imaging pulse sequence with TR of 2400 ms, TE of 35 ms, FOV of 244 mm, matrix of 80 × 80, slice thickness of 3 mm, and a total of 40 slices, giving an in-plane resolution of 3 × 3 mm. Slices were positioned transversal along the A–P axis. Before each "run," 2 spin echo sequences (TR = 2010 ms, TE = 35 ms, FOV = 244 mm, slice thickness = 3 mm, and matrix 80 × 80, giving an in-plane resolution of 3 × 3 mm) with opposite phase encoding (A–P and P–A) were acquired for correction of static magnetic field-induced distortion (Holland et al. 2010). For anatomical reference, a T1-weighted 3D MPRAGE volume was acquired (TR = 2300 ms, TE = 30 ms, FOV = 256 mm, slice thickness = 1.2 mm, and matrix 256 × 256, giving an in-plane resolution of 1 × 1 mm).

Analysis of Behavioral Data

IBM SPSS 20.0 was used for statistical processing of behavioral data. Based on the behavioral raw data from the Not-X CPT task, the following CPT measures were calculated: "Hit Reaction Time," "Hit Reaction Time Standard Error," "Omission Errors," "Commission Errors," "Response style (β)," and "Detectability (d')" (Conners et al. 2003; Olsen et al. 2013). To investigate TOT effects, the Not-X CPT task was divided into 4 time epochs after collapsing "run 1" and "run 2." Each time epoch was of equal length and balanced with regard to all task demands. A previous study demonstrated that the majority of TOT-related brain activation changes could be detected by comparing time epoch 1 with time epoch 4 of the test (Olsen et al. 2013). The focus was therefore on the first and last quarter of the task when investigating TOT effects in this study. To get a representation of each individuals change in behavioral performance with TOT, difference scores (Δ) were computed for each Not-X CPT measure by subtracting the value from time epoch 1 from the value from time epoch 4: Δ = time epoch 4 − time epoch 1.

In order to assess group differences, separate (for Not-X CPT performance and Δ Not-X CPT performance) 2 × 6 multivariate analyses of variance (MANOVA) were applied, with group as a fixed factor (healthy controls, TBI survivors), and the 6 performance measures as dependent variables. As it is considered to be important for the validity of fMRI studies with neurological populations that performance is similar between the groups that are compared (Price et al. 2006), type II errors were a bigger concern than type I errors for these particular analyses. For exploratory and descriptive purposes, it was therefore decided to also assess and report univariate results and 95% CI for the difference of each single measure, even when the MANOVA did not reveal a statistically significant main effect. Partial ETA squared ($\eta\rho^2$) was calculated in order to investigate effect sizes.

A similar MANOVA as described earlier was applied for investigating between-group differences in self-reported (2 × 3 MANOVA, BRIEF-A) measures of cognitive control.

Analysis of MRI Data

Non-brain structures were removed with BET (Smith 2002) and motion correction done with MCFLIRT (Jenkinson et al. 2002). Correction of geometrical distortions was done as described by Holland et al. (2010). Then, the data were smoothed (Gaussian kernel FWHM 6 mm), grand mean intensity normalized, high pass temporal filtered (50 s for block analysis and 25 s for event-related analysis), before linear registration of fMRI data to native high-resolution space (T1 MPRAGE) using 7 degrees of freedom (Jenkinson and Smith 2001; Jenkinson et al. 2002), followed by nonlinear registration of individual high-resolution structural image to MNI152 1-mm standard template using 12 degrees of freedom and a 8-mm warp resolution (Anderson et al. 2007a, 2007b).

Whole-Brain and ROI Analyses

BOLD activity related to task blocks and individual trials was modeled using the general linear model. The hemodynamic response function

was convolved with a standard Gamma variate. Initially, all contrasts were computed for each of the 2 "runs" separately and then combined using a fixed-effects model. Finally, mixed-effects models were used to create group average statistical images as well as investigate group differences for each individual contrast. Both whole-brain and ROI-based analyses were performed. For all whole-brain analyses, SPMs were corrected for multiple comparisons by using a cluster threshold of $Z > 2.3$, and a corrected cluster significance threshold of $P < 0.05$. Main peak Z-values with up to 5 local maxima and size of clusters (number of voxels) in standard $1 \times 1 \times 1$ mm MNI space were extracted. For anatomical denotation of location of activation, visual inspection and the Harvard Oxford cortical and subcortical structural brain atlases as incorporated in the FSL software were applied.

The stable task-set maintenance (task block > rest block) and adaptive task control (non-targets > targets) contrasts were created including data from the task as a whole (time epoch 1, 2, 3, and 4). First, an omnibus whole-brain analysis was performed in order to explore overall effects between healthy controls and TBI survivors. Second, according to the hypothesis regarding a shift toward more adaptive task control processing in TBI survivors, an ROI analysis was performed to specifically investigate differences in stable task-set maintenance and adaptive task control in an a priori chosen 10-mm sphere region in the MFC ($x = 5$, $y = 20$, $z = 41$). This region was chosen due to its role in a core network for cognitive control, which activates reliably in relation to both stable and adaptive cognitive control processes (Dosenbach et al. 2006; Olsen et al. 2013). Also, this particular brain region is among the brain regions that most reliably have shown increased task-related activation in TBI survivors as compared with healthy controls (Hillary 2008). For this analysis, parameter estimates for BOLD signal changes were extracted from each individual participant, compared between patients and controls, and finally also related to TBI injury severity as defined by HISS (Stein and Spettell 1995). As age and education was originally matched on the whole group level (TBI vs. healthy controls), a 3×2 multivariate analysis of covariance (MANCOVA) was used with group as a fixed factor (healthy controls, moderate TBI, and severe TBI), BOLD contrasts as dependent variables (stable task-set maintenance and adaptive task control), and age, years of completed education, and the 6 Not-X CPT performance measures as covariates.

In order to investigate TOT effects, the following contrasts were created: stable task-set maintenance TOT increase (task block time epoch 4 > task block time epoch 1), stable task-set maintenance TOT decrease (task block time epoch 1 > task block time epoch 4), adaptive task control TOT increase (non-targets time epoch 4 > non-targets time epoch 1), and adaptive task control TOT decrease (non-targets time epoch 1 > non-targets time epoch 4). In addition to the a priori MFC ROI also used for the previously described stable and adaptive contrasts, ad-hoc ROI analyses were performed to demonstrate the between-group effects with regard to injury severity as defined by HISS (Stein and Spettell 1995). Spherical ROIs (10 mm) were based on main peaks in the right inferior parietal lobe (IPL) ($x = 53$, $y = -43$, $z = 36$) and PFC ($x = 35$, $y = 27$, $z = 38$) demonstrating statistically significant differences between TBI survivors and healthy controls in the whole-brain analyses of the TOT effect contrast (Table 4). As for the main contrasts, a MANCOVA was used, with group as a fixed factor (healthy controls, moderate TBI, and severe TBI) and ROIs as dependent variables. Age, years of completed education, and Δ Not-X CPT measures (the relevant performance measure for these particular contrasts) were used as covariates.

Relationships between fMRI and BRIEF-A

In order to investigate the functional significance of the Not-X CPT fMRI results, findings were related to a self-report measure of cognitive control (BRIEF-A). Separate partial correlation models were applied for TBI survivors and healthy controls. First, parameter estimates extracted from the "core network" MFC ROI in both the overall stable task-set maintenance and adaptive task control contrasts and BRIEF-A measures were included in a partial correlation model. This model controlled for age, years of completed education, and Not-X CPT performance measures. For the TBI group, the model additionally controlled for GCS score, in order to adjust for general effects of injury severity. GCS was used as a covariate instead of HISS, as it is based on a continuous scale, which provided more variability in the scores, and hence represented a more appropriate and conservative approach for use in the partial correlation model. A similar partial correlation model was applied using the ad-hoc TOT stable task-set maintenance ROIs, controlling for Δ Not-X CPT measures in lieu of the overall Not-X CPT measures.

Results

Behavioral Results

Overall and Δ Not-X CPT performance was highly similar between TBI survivors and healthy controls, and no statistically significant differences were found between the groups (Table 2). However, TBI survivors reported significantly more everyday problems with cognitive control than healthy controls, on all 3 BRIEF-A measures (Table 3).

Imaging Results for Overall Stable Task-Set Maintenance and Adaptive Task Control

A MANCOVA was used to investigate differences across healthy controls and TBI survivors in BOLD activation in the a priori MFC ROI, related to stable task-set maintenance and adaptive task control during the whole task. The assumption of homogeneity of regression slopes was not violated, indicating that the relationship between the dependent variables (stable task-set maintenance and adaptive task control) did not vary as a function of group (healthy controls, moderate TBI, and severe TBI), $F_{6,\ 252} = 1.828$, $P = 0.094$, and $\eta\rho^2 = 0.42$. There was a statistically significant main effect of group, $F_{4,\ 238} = 2.591$, $P = 0.037$, and $\eta\rho^2 = 0.042$. Univariate analyses revealed that the main effect was driven by an effect for adaptive task control, $F_{10,\ 119} = 4.248$, $P < 0.001$, and $\eta\rho^2 = 0.263$. There was no statistically significant effect for stable task-set maintenance, $F_{10,\ 119} = 0.822$, $P = 0.608$, and $\eta\rho^2 = 0.065$. The planned polynomial contrast demonstrated a significant linear trend for adaptive task control, $P = 0.004$, indicating that BOLD activation increased proportionally with injury severity when adjusted for age, years of completed education, and Not-X CPT measures (Fig. 1). There were no statistically significant differences between TBI survivors and healthy controls for the 2 main contrasts, stable task-set maintenance (task block > rest block) and adaptive task control (non-targets > targets) in the omnibus whole-brain analyses.

Imaging Results for TOT Effects

TBI survivors had statistically significant larger increase in activation as an effect of TOT for the stable task-set maintenance contrast in right parietal and frontal areas, as compared with healthy controls (Table 4, Fig. 2). The assumption of homogeneity of regression slopes was met for the MANCOVA used for further investigation of stable task-set maintenance TOT effects within ROIs, $F_{9,\ 378} = 1.486$, $P = 0.151$, and $\eta\rho^2 = 0.034$. A significant main effect of group (healthy controls, moderate TBI, and severe TBI) was evident, $F_{6,\ 236} = 2.210$, $P = 0.043$, and $\eta\rho^2 = 0.053$. This effect was driven by the effects of the right PFC ROI, $F_{10,\ 119} = 2.523$, $P = 0.009$, and $\eta\rho^2 = 0.175$, as well as the right IPL ROI, $F_{10,\ 119} = 2.919$, $P = 0.003$, and $\eta\rho^2 = 0.197$, whereas no statistically significant effect was present for the a priori chosen MFC ROI. Planned polynomial contrasts demonstrated that BOLD activation in the right PFC ROI ($P = 0.002$) and the right IPL ($P = 0.001$) were both linearly related to injury severity when adjusted for age, years of completed education, and Δ Not-X CPT measures (Fig. 1).

Table 2
Not-X CPT and Δ Not-X CPT measures across TBI survivors and healthy controls

Variable	MANOVA	Group	*n*	Mean	95% CI of means	95% CI of difference	*P*	$\eta\rho^2$
Not-X CPT								
Hit RT (ms)	$F(6, 123) = 1.09$, $P = 0.373$, and $\eta\rho^2 = 0.050$	TBI	62	416.73	402.21, 431.24	−25.80, 14.35	<0.573	0.002
		Control	68	422.45	408.59, 436.31			
Hit RT SEM		TBI	62	6.16	5.61, 6.72	−0.92, 0.61	<0.692	0.001
		Control	68	6.32	5.79, 6.85			
Omissions		TBI	62	9.18	6.18, 12.18	−0.55, 7.76	<0.088	0.023
		Control	68	5.57	2.71, 8.44			
Commissions		TBI	62	16.90	14.68, 19.13	−1.78, 4.38	<0.405	0.005
		Control	68	15.60	13.48, 17.73			
Response style (β)		TBI	62	0.14	0.11, 0.18	−0.01, 0.92	<0.098	0.021
		Control	68	0.10	0.06, 0.13			
Detectability (*d′*)		TBI	62	2.75	2.54, 2.96	−0.522, 0.06	<0.123	0.018
		Control	68	2.98	2.78, 3.18			
Δ Not-X CPT								
Δ Hit RT (ms)	$F(6, 123) = 0.421$, $P = 0.864$, and $\eta\rho^2 = 0.020$	TBI	62	8.25	0.77, 15.73[a]	−17.17, 3.51	<0.194	0.013
		Control	68	15.08	7.94, 22.24[a]			
Δ Hit RT SEM		TBI	62	0.59	−0.90, 2.09	−1.91, 2.22	<0.884	<0.001
		Control	68	0.44	−0.99, 1.87			
Δ Omissions		TBI	62	1.90	0.69, 3.12[a]	−1.31, 2.06	<0.661	0.002
		Control	68	1.53	0.37, 2.69[a]			
Δ Commissions		TBI	62	0.19	−0.40, 0.79	−0.65, 0.98	<0.692	0.001
		Control	68	0.03	−0.54, 0.59			
Δ Response style (β)		TBI	62	0.08	0.03, 0.12[a]	−0.05, 0.08	<0.697	0.001
		Control	68	0.06	0.02, 0.11[a]			
Δ Detectability (*d′*)		TBI	62	−0.21	−0.38, −0.03[a]	−0.32, 0.17	<0.527	0.003
		Control	68	−0.13	−0.30, 0.04			

Note: The table presents multi- and uni-variate results from a comparison of Not-X CPT and Δ Not-X CPT performance measures across TBI survivors and healthy controls.
MANOVA, multivariate analysis of variance; Δ, difference score (time epoch 4 − time epoch 1); SEM, standard error of the mean; TBI, traumatic brain injury; CI, confidence interval; $\eta\rho^2$, partial ETA squared.
[a]Within-group univariate TOT effects for Δ Not-X CPT performance measures at the $P < 0.05$ level.

Table 3
Self-report measures of cognitive control across TBI survivors and healthy controls

Variable	MANOVA	Group	*n*	Mean	95% CI of means	95% CI of difference	*P*	$\eta\rho^2$
BRIEF-A								
BRI	$F(3,125) = 4.89$, $P = 0.003$, and $\eta\rho^2 = 0.11$	TBI	62	43.82	41.77, 45.88	2.57, 8.27	<0.001	0.100
		Control	67	38.40	36.43, 40.38			
MI		TBI	62	60.55	57.36, 63.74	0.49, 9.33	<0.030	0.037
		Control	67	55.64	52.58, 58.71			
GEC		TBI	62	104.37	99.49, 109.25	3.57, 17.10	<0.003	0.067
		Control	67	94.05	88.35, 98.74			

Note: The table presents multi- and uni-variate results from comparisons of BRIEF-A measures across TBI survivors and healthy controls. One healthy control was excluded from the analyses involving BRIEF-A due to too many missing item scores (see Methods).
MANOVA, multivariate analysis of variance; BRI, Behavioral Regulation Index; MI, Metacognition Index; GEC, Global Executive Composite; TBI, traumatic brain injury; CI, confidence interval; $\eta\rho^2$, partial ETA squared.

There were also noteworthy within-group effects for stable task-set maintenance TOT effects in the explorative whole-brain analysis. Healthy controls had large clusters of significant activations related to stable task-set maintenance TOT increase in midline posterior and anterior regions, including the precuneus, posterior cingulate cortex, ventromedial prefrontal cortex, and frontal poles (Fig. 2). Parallel to this, healthy controls had significant decreases of activation as an effect of TOT in the right anterior insula/frontal operculum, as well as in frontal midline regions encompassing the anterior cingulate-, paracingulate-, and supplementary motor cortices. TBI survivors also had stable task-set maintenance TOT increase of activation in midline posterior and anterior regions (e.g., in the precuneus, posterior cingulate cortex, ventromedial prefrontal cortex, and frontal poles), however far more extensive and widespread than for the healthy controls (Fig. 2). In addition to the midline regions also activated in the healthy controls, TBI survivors had particularly pronounced additional areas of increased activation bilaterally in the inferior parietal lobules, as well as bilaterally in dorso-lateral regions of the frontal cortex, in addition to several subcortical regions. Contrary to healthy controls, TBI survivors had no statistically significant decreases in activation as a function of TOT. There were no within- or between-group TOT effects for adaptive task control.

Relationships between BOLD Activation and BRIEF-A Scores

The partial correlation model revealed several statistically significant findings for the TBI group. The general finding was that BOLD signal increases in several ROIs were related to lower levels of self-reported problems associated with cognitive control (Table 5). There were no statistically significant relationships between the BOLD signal in any of the ROIs and BRIEF-A scores for healthy controls (Table 5).

Discussion

The present study revealed 4 main findings with importance to understanding alterations of neuronal correlates to cognitive

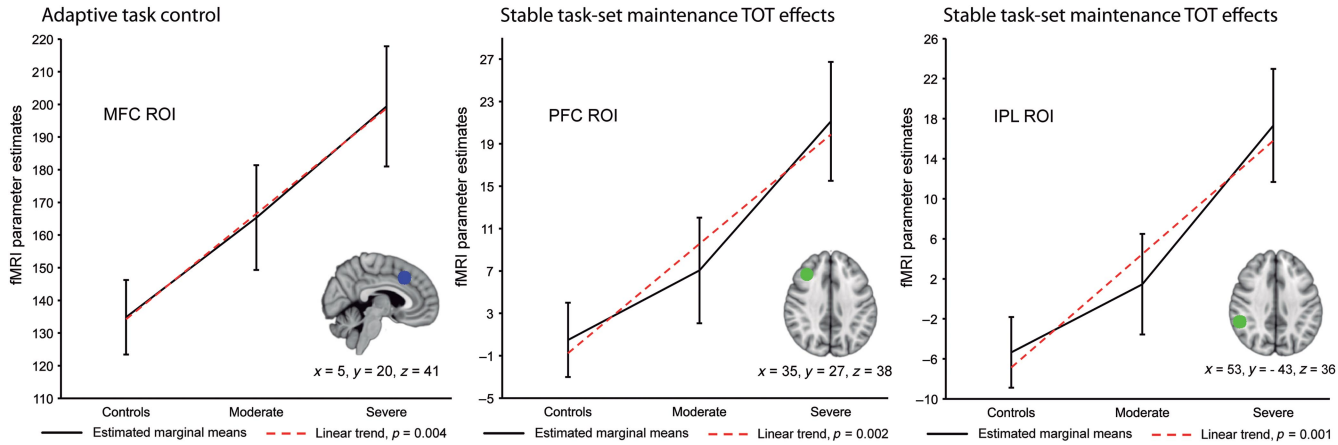

Figure 1. ROI analyses across healthy controls, moderate- and severe TBI survivors. The figure shows the results of planned polynomial contrasts following statistically significant MANCOVAs. Only statistically significant results are shown. Results are adjusted for age, education, and Not-X CPT performance (Δ Not-X CPT performance for TOT effects). TOT, time-on-task; ROI, region of interest; MFC, medial frontal cortex; IPL, inferior parietal cortex; PFC, prefrontal cortex. Error bars represent ± standard error of estimated marginal means.

Table 4

Differences between TBI survivors and healthy controls on TOT activations related to stable task-set maintenance (Δ stable task-set maintenance)

Anatomical region	R/L	Size (number of voxels)	Z	Coordinates for peak activation (MNI)		
				X	Y	Z
TBI survivors > healthy controls (Δ stable task-set maintenance)						
Supramarginal gyrus, posterior division	R	24 769	4.21	53	−43	36
Supramarginal gyrus, posterior division	R	lm	4.1	50	−43	36
Angular gyrus	R	lm	4.05	47	−45	29
Angular gyrus	R	lm	3.78	56	−54	49
Angular gyrus	R	lm	3.76	49	−49	47
Angular gyrus	R	lm	3.63	54	−55	49
Middle frontal gyrus	R	16 777	3.98	35	27	38
Frontal pole	R	lm	3.87	34	46	5
Frontal pole	R	lm	3.80	37	45	6
Middle frontal gyrus	R	lm	3.73	54	15	44
Middle frontal gyrus	R	lm	3.72	56	15	41
Frontal pole	R	lm	3.58	16	53	14

Note: Results were corrected for multiple comparisons by using a cluster threshold of $Z > 2.3$, and a corrected cluster significance threshold of $P = 0.05$. Main peak Z-values (and up to 5 local maxima within each cluster) and size of clusters (number of voxels) in standard $1 \times 1 \times 1$ mm MNI space were extracted and presented in the table. For anatomical denotation, visual inspection, and the Harvard Oxford cortical and subcortical structural brain atlases as incorporated in the FSL software were applied.

lm, local maxima; R/L, right/left; Δ stable task-set maintenance, stable task-set maintenance time epoch 1 vs. stable task-set maintenance time epoch 4.

control after TBI: 1) during Not-X CPT performance, TBI survivors demonstrated an overall shift toward utilizing more adaptive task control processes in a core region for cognitive control in the MFC, 2) accompanied by increased stable task-set maintenance BOLD activations as an effect of TOT in the right IPL and PFC, as compared with healthy controls. Increases in BOLD activation were related to 3) injury severity in a linear dose-dependent fashion and 4) to lower levels of self-reported problems with cognitive control, a relationship only present in TBI survivors, and not in healthy controls.

Increased Reliance on Adaptive Task Control in the MFC After TBI

In the context of no general whole-brain differences and highly similar performance, TBI survivors had increased activation related to adaptive task control in an a priori chosen ROI in the MFC known to be extremely reliably activated during both adaptive and stable control processes (Dosenbach et al. 2006; Olsen et al. 2013). Interestingly, this increase in activation had a linear dose relationship to injury severity, with stronger activation with more severe TBI, when adjusted for age, education, and fMRI task performance. Moreover, there was no difference in activation between healthy controls and TBI survivors for the overall stable task-set maintenance contrast in the same MFC ROI.

Increased activations after TBI within the MFC have been found in several other studies using other cognitive tasks (Christodoulou et al. 2001; Scheibel et al. 2007; Rasmussen et al. 2008) and been related to injury severity in a study that included 30 patients with sub-acute (3 months after injury) TBI (Scheibel et al. 2009). Our study extends previous findings by showing that adaptive and stable control processes are affected differently by injury severity and that these changes are persisting into the chronic stage. More specifically, in a task where TBI survivors could uphold similar performance to healthy controls, they recruited more neuronal resources related to adaptive task control. This can be interpreted as a compensatory mechanism, similar to findings in other populations (Paxton et al. 2008; Edwards et al. 2010; Braver 2012). It should, however, be noted that in these previous studies, both increased probe related, and at the same time reduced cue related, PFC activation was observed. This was not the case in the present study, as there was no significant group difference for the stable task-set maintenance contrast. One possible explanation for this result could be that it was partially influenced by increased variability, in particular in the TBI group, due to TOT-related changes in this contrast.

Increased TOT Effects for Stable Task-Set Maintenance in TBI Survivors

A whole-brain exploratory analysis investigating differences between healthy controls and TBI survivors revealed differences in TOT effects for stable task-set maintenance, but not for adaptive task control. This supports that stable task-set maintenance is particularly susceptible to cognitive fatigue as a

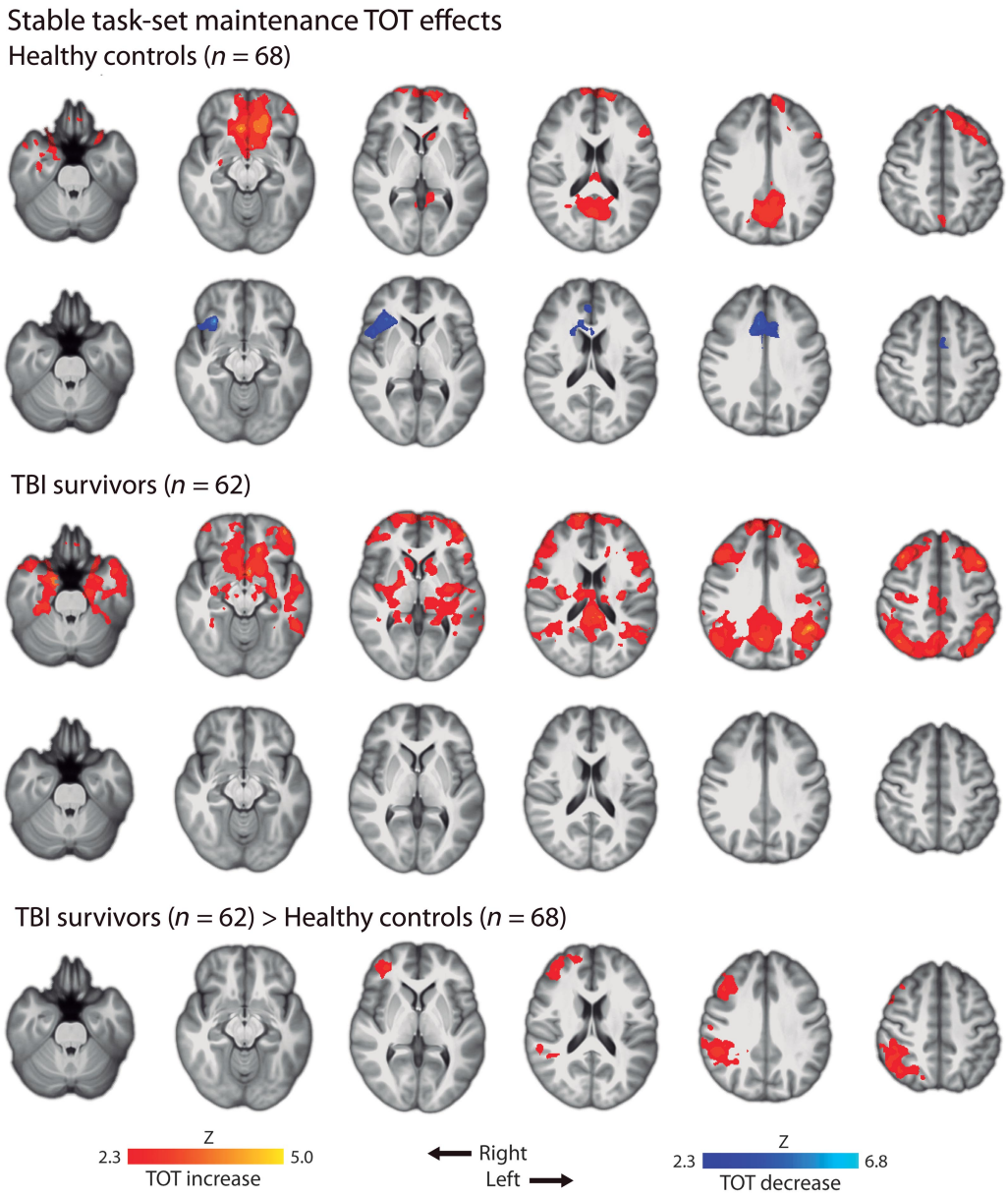

Figure 2. Whole-brain TOT effects for stable task-set maintenance. SPMs are corrected for multiple comparisons using a cluster threshold of $Z > 2.3$, $P = 0.05$. Results are presented on a 1-mm MNI standard space template. SPM, Statistical Parametric Mapping; MNI, Montreal Neurological Institute.

function of TOT (Olsen et al. 2013). Clusters of increased BOLD activation as a function of TOT were found in TBI survivors, as compared with healthy controls, with main peaks in the IPL and PFC in the right hemisphere. The IPL and PFC have been suggested to play a crucial role in a right lateralized attention control network (Corbetta and Shulman 2002). The right IPL has also previously been related to Not-X CPT performance (Ogg et al. 2008; Tana et al. 2010) and suggested to be part of the core network for cognitive control (Olsen et al. 2013). Moreover, in addition to PFC regions, a region just posterior to this right IPL region has previously been related to cognitive fatigue after TBI (Kohl et al. 2009).

The right PFC in particular is more extensively recruited in response to increased task demands in several neurological populations, including TBI (Hillary 2008). This recruitment may indicate that increased cognitive control resources are allocated. It has also been observed that PFC activations in TBI increase from the early stage after TBI until 6 months later (Sanchez-Carrion et al. 2008), suggesting that such increases represent an adaptive change in this region developing in the rehabilitation phase after injury.

In TBI survivors, the TOT effect was shown to be linearly related to injury severity, after adjusting for age, education, and fMRI task performance. This implies underlying injury-specific changes involved in the stable task-set maintenance TOT increase differences. Both in this and in a previous study (Olsen et al. 2013), there were no within-group changes in commission errors as an effect of TOT. There were, however, changes in response time, omission errors, and response style, suggesting that the threshold for Not-X responses was

Table 5
Correlations between BOLD activation and self-report measures of cognitive control for TBI survivors and healthy controls

	BRIEF-A		
	BRI	MI	GEC
TBI survivors ($n = 62$)			
Overall main contrasts[ab]			
Stable task-set maintenance MFC	−0.177	−0.363**	−0.305*
Adaptive task control MFC	−0.077	−0.058	−0.069
Stable task-set maintenance TOT effects[bc]			
MFC	−0.346*	−0.281*	−0.322*
Right IPL	−0.423**	−0.400**	−0.431**
Right PFC	−0.369**	−0.317*	−0.355**
Healthy controls ($n = 67$)			
Overall main contrasts[a]			
Stable task-set maintenance MFC	−0.091	0.009	−0.048
Adaptive task control MFC	−0.078	−0.062	−0.077
Stable task-set maintenance TOT effects[c]			
MFC	−0.081	−0.074	−0.085
Right IPL	−0.222	−0.067	−0.145
Right PFC	0.100	0.089	0.103

Note: Partial correlations (r) between NOT-X CPT fMRI ROI parameter estimates and BRIEF-A measures. One healthy control was excluded from the analyses involving BRIEF-A due to several missing item scores (see Methods).
[a]Controlled for age, education, and Not-X CPT performance measures. [b]Additionally controlled for GCS score. [c]Controlled for age, education, and Δ Not-X CPT performance measures.
*$P < 0.05$ (two-tailed). **$P < 0.01$ (two-tailed).

increased, implying a top-down regulation through strategy change. It makes sense that compensatory mechanisms are more readily implemented in a top-down fashion, rather than in a system relying on reactive bottom-up processes. A disadvantage of proactive- (stable) as opposed to reactive (adaptive) control is that it is computationally more demanding and thereby uses more neural resources (Braver 2012). By engaging the stable task-set maintenance network, there are fewer resources available for other tasks over a prolonged period of time. It is therefore plausible that an increased reliance on stable task-set maintenance relative to adaptive task control may lead to increased fatigue after TBI (Kohl et al. 2009; Ponsford et al. 2012), despite partially compensating for some of the cognitive deficits after injury (Braver 2012). However, this needs to be further investigated as the present study was limited by the lack of an independent measure of fatigue to specifically evaluate this interpretation.

In order to activate the bottom-up adaptive system, particularly salient stimuli are needed (Seeley et al. 2007; Menon and Uddin 2010). In light of this, it can be speculated whether the shift toward increased adaptive processing within the MFC as found in the overall adaptive task control contrast represents an increased burden on the adaptive system due to insufficient compensation (preparation) by the use of stable task-set maintenance (Jahfari et al. 2012). Since the number of commission errors was stable throughout the task and TOT effects were not seen for BOLD activation related to adaptive task control in this study, future studies should aim to investigate nonlinear relationships or functional connectivity interactions between the 2 networks in order to test this hypothesis (Dosenbach et al. 2007; Hillary et al. 2011; Bonnelle et al. 2012; Gratton et al. 2012).

Both TBI survivors and healthy controls had pronounced within-group increases of activation in areas of the DMN as an effect of TOT. Activations in DMN regions have been linked to prospective planning (Buckner et al. 2008), hence suggesting a possible role in a proactive compensatory control system (Braver 2012). However, increased activity in DMN areas such as the precuneus and posterior cingulate cortex has previously also been related to impairments of sustained attention in TBI patients (Bonnelle et al. 2011), possibly due to a failure in successfully deactivating these regions (Weissman et al. 2006). Moreover, disrupted structural white-matter integrity between typical task-positive regions, such as anterior insula and pre-supplementary motor cortex/anterior cingulate gyrus, may be related to this failure (Bonnelle et al. 2012). TBI survivors in our study also seemed to recruit more pronounced DMN node activation; however, despite the already mentioned findings in the right IPL, no other DMN regions survived the statistical threshold in a direct comparison between the groups.

According to the within-group analysis of TOT effects, TBI subjects also recruited additional subcortical regions, including the basal ganglia. Previous fMRI studies have highlighted the role of the interaction between the basal ganglia and frontal cortex for proactive selective response suppression (Majid et al. 2013), as well as decision-making under time pressure (Forstmann et al. 2008). Moreover, in their model of central fatigue, Chaudhuri and Behan (2000) proposed that fatigue observed in a range of patient groups might be caused by a failure of the non-motor function of the basal ganglia, which in turn may affect the striatal–thalamic–frontal cortical system. Particularly interesting in this context is that increased activation in the basal ganglia related to cognitive fatigue in TBI survivors was observed in a study utilizing an ROI analysis specifically aimed at investigating this model (Kohl et al. 2009). Furthermore, an interesting line of very recent TBI research demonstrated that reduced fronto-striatal white-matter integrity (Leunissen et al. 2013a) and possibly related subcortical atrophy changes (Leunissen et al. 2013b) were associated with task-switching impairments.

Another interesting within-group observation was that healthy controls demonstrated a stable task-set maintenance TOT decrease in the MFC and right insula, which are part of the core network for cognitive control (Dosenbach et al. 2006; Olsen et al. 2013), whereas no such effect was apparent within the TBI group. Such a TOT decrease can be interpreted as a habituation effect or reduced processing needs due to a practice effect. An important factor to consider is that compensation and/or habituation may be displayed differently in healthy controls and TBI survivors. In accordance with the compensation hypothesis, it has been found that TBI survivors exhibit increased TOT-related activation during performance of a modified coding task, both within-group and as compared with healthy controls (Kohl et al. 2009). However, healthy controls in the same study demonstrated decreased TOT-related activation on a within-group level, which is better accommodated by a habituation hypothesis (Kohl et al. 2009). The finding that compensation/habituation mechanisms may be different in injured- as compared with healthy-brains was also supported by our study. This was demonstrated by the fact that stable task-set maintenance TOT activity increase during Not-X CPT was functionally related to BRIEF-A only in TBI survivors and not in healthy controls.

In mixed fMRI designs, there is generally a tendency for lower statistical power for event-related, relative to block-related, contrasts (Miezin et al. 2000; Petersen and Dubis 2012). Additionally, in the present study, there were relatively few non-targets as compared with targets in the Not-X CPT (48 vs. 432), potentially introducing additional concerns regarding the sensitivity and precision of this contrast. However, as

demonstrated in our previous study in healthy participants (Olsen et al. 2013) as well as the ROI analysis in the present study, this contrast yielded extremely robust results on a within-group level. It is therefore highly unlikely that the observation of less between-group differences related to adaptive task control, as compared with stable task-set maintenance, was merely caused by a lack of statistical power. An alternative explanation for more general TBI-related increases in the BOLD signal without presence of differences in task performance may be that they are driven by permanent functional brain reorganization (Hillary 2008), or physiological and structural factors not related to function as such (Hillary and Biswal 2007). However, the finding of significant between-group TOT effects makes this explanation unlikely, as these are within-task transient changes, more likely to be related to compensation (Hillary 2008). Another potentially confounding factor is that the presence of global signal change may introduce noise in the data when investigating the BOLD signal over an extended time period. We used a well-balanced task design and analysis approach (e.g., by combining 2 runs) in addition to conventional filtering to minimize this effect. Furthermore, the fact that TOT effects were present in typical task-positive regions for this task, and that they were different between groups, also gives a strong indication that our results were not due to such effects (Fox et al. 2009).

TBI-Related BOLD Increases Might Play a Compensatory Role for Everyday Cognitive Control Function

Stable task-set maintenance BOLD signal increases during the task as a whole and in particular as an effect of TOT were related to experiencing less everyday problems with cognitive control as measured with BRIEF-A. This was only evident in TBI survivors, and not healthy controls, suggesting that the increased BOLD activations may represent injury-specific compensatory mechanisms successfully applied in unrestricted everyday-life situations after injury. Considering the underlying positive linear association between BOLD increase and injury severity, it is noteworthy that the association between self-reported cognitive control function and increased activation was present after adjusting for injury severity. Consequently, the increased BOLD activation appears to represent both injury severity mechanisms and compensatory mechanisms associated with improved self-reported cognitive control function.

An important implication from these findings is that caution should be applied when generalizing relationships between cognitive control and BOLD activation in healthy controls to those of neurological populations such as TBI (Hillary and Biswal 2007), also due to the fact that differences in signal changes appear to be multifactorial. As discussed earlier, differences with regard to habituation and compensatory mechanisms in the healthy and injured brain (Kohl et al. 2009) may further complicate the interpretation of differences in neuronal activation between healthy controls and neurological populations such as TBI.

An alternative explanation of our results may be that TBI survivors who exhibit BOLD increases underreport their cognitive deficits, due to impaired self-awareness, which may be present in some TBI survivors (Hart et al. 2005). This is, however, rather unlikely, given the temporally dynamic TOT effects, and that impaired self-awareness in chronic TBI usually is considered a more stable trait. Also, previous studies have demonstrated relatively strong agreement on the magnitude of cognitive deficits between family informants and TBI survivors (Lannoo et al. 1998; Lovstad et al. 2012). However, future studies should aim to investigate this aspect more directly, for example by relating BOLD increases after moderate-to-severe TBI to scores on the informant version of the BRIEF-A.

Summary and Conclusions

This study demonstrated that the neural underpinnings of adaptive and stable task control processes are differently affected by injury and that increased BOLD activations observed in moderate-to-severe TBI survivors might represent injury-specific compensatory mechanisms also utilized in everyday-life situations. A particular strength of this study was that results were adjusted for the effects of fMRI task performance, as well as the established outcome moderators, age and education.

To this date, this is the largest fMRI study in survivors of moderate-to-severe TBI. New knowledge was provided utilizing a validated fMRI-adapted version of a commonly administered clinical continuous performance test, carefully integrated within an innovative neurocognitive theoretical framework. By relating fMRI findings to the most comprehensive and increasingly popular self-report form for cognitive control function (BRIEF-A), this knowledge has the potential for giving rise to valuable new questions within basic and clinical TBI research, as well as new perspectives for interpretation of clinical test results.

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Notes

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