Graph analysis of functional brain networks for cognitive control of action in traumatic brain injury

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Patients with traumatic brain injury show clear impairments in behavioural flexibility and inhibition that often persist beyond the time of injury, affecting independent living and psychosocial functioning. Functional magnetic resonance imaging studies have shown that patients with traumatic brain injury typically show increased and more broadly dispersed frontal and parietal activity during performance of cognitive control tasks. We constructed binary and weighted functional networks and calculated their topological properties using a graph theoretical approach. Twenty-three adults with traumatic brain injury and 26 age-matched controls were instructed to switch between coordination modes while making spatially and temporally coupled circular motions with joysticks during event-related functional magnetic resonance imaging. Results demonstrated that switching performance was significantly lower in patients with traumatic brain injury compared with control subjects. Furthermore, although brain networks of both groups exhibited economical small-world topology, altered functional connectivity was demonstrated in patients with traumatic brain injury. In particular, compared with controls, patients with traumatic brain injury showed increased connectivity degree and strength, and higher values of local efficiency, suggesting adaptive mechanisms in this group. Finally, the degree of increased connectivity was significantly correlated with poorer switching task performance and more severe brain injury. We conclude that analysing the functional brain network connectivity provides new insights into understanding cognitive control changes following brain injury.

Keywords: traumatic brain injury; cognitive control; functional MRI; task switching; functional network
Abbreviations: TBI = traumatic brain injury
Introduction

Many patients with traumatic brain injury (TBI) are faced with persistent cognitive deficits, including decreased mental flexibility, trouble with shifting sets, impaired attention, poor planning and organization, impaired judgement, deficits in verbal fluency, reduced working memory and increased impulsivity (Levin and Kraus, 1994; Miller, 2000; Godefroy, 2003), affecting independent living and psychosocial functioning (Garth et al., 1997). Hence, the burden on public health and social care is substantial (Thurman et al., 1999). The increased use of neuroimaging techniques has substantially enhanced our understanding of the underlying pathophysiology of these persistent impairments.

A number of recent diffusion tensor imaging studies in adults with TBI have demonstrated reduced white matter microstructural integrity, particularly in the cingulum fibre bundles, the corpus callosum, inferior fronto-occipital fasciculus and superior longitudinal fasciculus. In some cases, significant correlations between diffusion tensor imaging metrics and cognitive function have been identified, such that degree of white matter pathology predicts cognitive deficits (Salmond et al., 2006; Kraus et al., 2007; Kennedy et al., 2009; Kinnunen et al., 2010). Moreover, a voxel-based morphometry study has provided evidence for abnormal grey matter density decreases in frontal and temporal cortices, cingulate gyrus, subcortical grey matter and the cerebellum in patients with chronic TBI (Gale et al., 2005). This decreased grey matter concentration correlated with lower scores on tests of attention. Convergent evidence across various cognitive tasks also indicates abnormal functional MRI activation of frontal and parietal cortical regions (Perlstein et al., 2004; Scheibel et al., 2007; Newsome et al., 2008; Kim et al., 2009).

In the present study, we decided not to focus on these regional functional changes in specific areas but instead concentrate on the capacity of information flow within and between regions, which is equally crucial for behaviour. Indeed, TBI can be characterized as a ‘disconnection syndrome’ (Guye et al., 2010). TBI involves progressive biochemical and structural changes, including degradation of the myelin sheath and further degradation of the axonal membrane (Ewing-Cobbs et al., 2008; Sideros et al., 2008). It is therefore important to examine the characteristics of the brain network.

Although many studies have elucidated the pathophysiology of cognitive recovery after TBI by focusing on local changes in brain structure and function, little is known about the insult-induced alterations in the interactions among the nodes of task-related functional networks in patients with TBI. Within this perspective, the concept of functional connectivity has emerged, referring to the statistical association between spatially distributed brain activation time series (Lee et al., 2006). Graph theory is a powerful technique to map these relationships between spatially remote neurophysiological events in the brain. The area of graph theory is an established mathematical field and has proven a very effective and informative way to explore brain function and human behaviour (Bullmore and Sporns, 2009; Nakamura et al., 2009; Stam, 2010).

Graph theoretical measures have been applied previously to analyse functional brain connectivity in the context of TBI (Nakamura et al., 2009; Castellanos et al., 2010, 2011). However, although graph theory offers a broad selection of measures to examine and quantify relationships between activations in different brain regions, previous studies have frequently focused on only a few measures in each case, such as clustering coefficient, network path length, small worldness or connectivity degree. Here, we applied a number of graph theory measures to task-related functional MRI data.

Furthermore, previous functional connectivity studies in TBI have primarily been limited to task-free (resting state) EEG or magnetoencephalogram recordings, identifying alterations in network architecture (Cao and Slobounov, 2010; Tsirka et al., 2011). Although EEG and magnetoencephalogram signals supply a distinctly high temporal resolution, their limited spatial resolution hampers the detailed study of activity within distributed task-related (sub)cortical brain regions and their associated interactions. As a whole, these studies have mainly investigated abnormal networks based on the spontaneous activity in the resting brain. However, task-related functional connectivity is a useful tool for investigating a more specific interdependence between brain regions.

Moreover, previous studies commonly used methods such as coherence or synchronization likelihood rather than partial correlations to quantify the association in activation between brain regions, thereby not addressing the confounding effects of indirect connections between network nodes (Castellanos et al., 2011). Also a template-based a priori parcellation of the brain was used to define the network nodes, thereby including brain regions with little or no task-related activation (Nakamura et al., 2009). A recent study by Smith et al. (2011) provides strong indications that, in addition to using partial correlations to quantify unique functional associations between nodes, a data-driven approach by defining networks based only on areas showing clear task-related activation is preferable to template-based approaches in order to minimize confounds and obtain a better picture on functional connectivity within active neural networks. Therefore, we combined the partial correlation approach with a data-driven network definition, aiming to optimize the reliability of the results.

The present study was based on three main hypotheses:

(i) Based on previous studies of neural network functionality in TBI populations in a non-motor context (Nakamura et al., 2009; Castellanos et al., 2010, 2011), we expected an increase in functional connectivity in patients with TBI within the motor switching network. Behavioural studies have shown that switching between tasks and inhibition of responses are diminished in patients with TBI, reflecting impaired cognitive control of action (Mecklinger et al., 1999; Amos, 2002; Azouvi et al., 2004; Levin et al., 2004; Larson et al., 2006; Perlstein et al., 2006). Here, we studied impairments in task switching during bimanual coordination (Kelso, 1995). This form of switching temporarily dissociates the limbs from sharing an ongoing movement plan, requiring inhibition of a part of the existing plan and facilitation of an alternative plan (Wenderoth et al., 2009; Coxon et al., 2010).

(ii) Furthermore, our previous functional MRI study has reported negative correlations specifically in patients with
Materials and methods

Participants

Forty-nine adults participated in the study, including 26 control subjects (mean age = 25 years 3 months; SD = 3 years; 13 males and 13 females) and 23 patients with moderate to severe TBI (mean age = 24 years 5 months; SD = 5 years 6 months; 16 males and 7 females), who had sustained closed head trauma due to traffic accident or sport injury. Time since injury averaged 4 years 10 months prior to the study (SD = 2 years 7 months, range = 1 year 6 months–9 years 8 months). Injury severity of the patients with TBI was based on post-resuscitation Glasgow Coma Scale (Teasdale and Jennett, 1974) when available (mean Glasgow Coma Scale score = 7, SD = 3, range = 3–13; data available for eight patients), initial neuropathology, or duration of loss of consciousness (> 30 min). The structural MRI scans (see below) were inspected and classified by an experienced neuroradiologist (S.S.) using the scheme of Adams et al. (1989), which allows the identification of three grades of diffuse axonal injury (Table 1). In Grade 1 there is histological evidence of axonal injury in the white matter of the cerebral hemispheres, the corpus callosum, the brainstem and, less commonly, the cerebellum; in Grade 2 there is also a focal lesion in the corpus callosum; and in Grade 3 there is additionally a focal lesion in the dorsolateral quadrant or quadrants of the rostral brainstem. The median severity score of the patients with TBI was 2 (range = 0–2.5). Demographic and neurological variables are provided in Table 1. The 26 control subjects had normal medical histories and MRI scans were rated as being ‘normal’ by a radiologist. All subjects were right-handed (laterality quotient: TBI: mean = 81, range = 22–100; control: mean = 92; range = 60–100) as verified by the Edinburgh Handedness Inventory (Oldfield, 1971). General motor performance was assessed using both bilateral items of the TEMPA (Desrosiers et al., 1995a) and the Purdue Pegboard Test (Desrosiers et al., 1995b). The study was approved by the local ethics committee for biomedical research. Informed consent was obtained from each patient or from the patient’s first degree relatives.

Behavioural testing

We used an established protocol applied previously in functional MRI studies assessing young and elderly healthy subjects (Coxon et al., 2010) and patients with TBI (Leunissen et al., 2012). In brief, participants were required to switch between coordination modes while making spatially and temporally coupled circular motions with joy-sticks. This task assesses cognitive control processes that are particularly affected in patients with TBI (Powell and Voeller, 2004; Cicerone et al., 2005; Rees et al., 2007). For each hand, the direction of circling could be either clockwise or counter-clockwise. An auditory metronome was used for pacing such that participants completed one circle per tone. Four possible bimanual movement patterns were introduced: inward circles, outward circles, clockwise circles and counter-clockwise circles. A constant visual display was shown comprising two white circles, each with a curved white bar immediately above, and a central fixation cross on a black background. Instruction cues were conveyed by arrows, visible for 800 ms (Fig. 1). Green arrows were used as imperative cues. The initial pattern to adopt was indicated by two green arrows. A single green arrow pointing opposite to the actual movement direction indicated that the right hand must change direction (Switch). This resulted in a change of movement pattern from asymmetric to symmetric circling or from symmetric to asymmetric circling. A single green arrow pointing in the same direction as the actual movement indicated that no change was necessary for the right hand (Continue). In both cases, the left hand was to maintain moving in the already established direction. White arrows indicated the correct movement pattern 4 s after the imperative cue (Confirm). For participants, this served as confirmation that they were performing the correct pattern or it provided an opportunity to correct their error.

Subjects performed five trial blocks, each 351 s in duration. A block comprised alternating movement (68 s) and rest (20 s) epochs to avoid fatigue. There were 14 switch trials, 14 continue trials, 4 reverse trials and 2 confirmation trials per block. Reverse trials were signalled by two green arrows, cueing a switch of both hands. They were included to change left hand direction within a movement epoch, but were of no interest for the analysis. One of the four possible movement patterns was used as an initial pattern for each movement epoch and the order was counterbalanced across runs. In total, there were 70 Switch trials of the right hand and 70 Continue trials.

MATLAB 7.7 (Mathworks) was used to analyse the kinematic data of the switching task. For each hand, a continuous estimate of angular velocity was determined by \( \omega = \frac{d\theta}{dt} \) with \( \theta = \arctan(x/y) \), where \( x \) and \( y \) describe the mean corrected values for vertical and horizontal joystick displacements, respectively. A second-order Butterworth low-pass filter (cut-off 5 Hz) was applied to \( \omega \). Two dependent variables were of primary interest. First, for trials where the right hand changed direction, switch response time was determined as the interval between stimulus onset and the first zero crossing of \( \omega \), indicating that cycling direction had reversed. This measure is an indication of the speed with which an ongoing coordination pattern is suppressed and a different coordination pattern is adopted. Second, the percentage of contralateral disruptions was recorded when left-hand direction reversed until the correct pattern was displayed. This measure reflects to what extent the performer is able to perform the switch selectively with the right hand while the left hand continues its motion (i.e. division of attention).

Functional MRI data acquisition and pre-processing

A Siemens 3 T Magnetom Trio MRI scanner with standard head coil was used for image acquisition. For all subjects, a high resolution T1-weighted structural image was acquired using magnetization prepared...
<table>
<thead>
<tr>
<th>TBI Patient #</th>
<th>Age at injury (years, months)</th>
<th>Cause of injury</th>
<th>Acute scan within 24 h after injury, Lesion location/pathology</th>
<th>MRI scan at examination, Lesion location/pathology</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI 1 19.2/F</td>
<td>15.8</td>
<td>Traffic accident</td>
<td>(L) PL/OL contusion, subdural haematoma</td>
<td>(R) PL contusion, corpus callosum and OL shearing injuries, occipital horn lateral ventricle asymmetrical enlargement</td>
<td>2</td>
</tr>
<tr>
<td>TBI 2 27.6/F</td>
<td>25.2</td>
<td>Traffic accident</td>
<td>TL contusion, (R) PL haemorrhage, (L) FL intraparenchymatous haemorrhagic contusion, subdural haematoma</td>
<td>Drain tract (R), (L) FL and TL contusion</td>
<td>2</td>
</tr>
<tr>
<td>TBI 3 22.9/F</td>
<td>21.3</td>
<td>Traffic accident</td>
<td>(R) FL haemorrhage, (L) FL/TL and (L) PL and (R) orbito-frontal cortex contusion</td>
<td>Drain tract (R), haemosiderin deposits (R) PL and (R) orbito-frontal cortex (R) FL contusion</td>
<td>1.5</td>
</tr>
<tr>
<td>TBI 4 22.5/M</td>
<td>17.6</td>
<td>Traffic accident</td>
<td>(L) FL shearing injuries, splenium and body corpus callosum contusion</td>
<td>Drain tract (L), FL contusion</td>
<td>1</td>
</tr>
<tr>
<td>TBI 5 28.1/M</td>
<td>18.6</td>
<td>Traffic accident</td>
<td>FL contusion, (L) FL subdural haematoma, (L) TL and (R) PL haemorrhage</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>TBI 6 17.9/F</td>
<td>12.9</td>
<td>Traffic accident</td>
<td>Contusion (location not specified in available records)</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>TBI 7 16.1/F</td>
<td>8.2</td>
<td>Traffic accident</td>
<td>(R) FL Subdural haematoma</td>
<td>Drain tract (L and R), haemosiderin deposits thalamus and (L) OL</td>
<td>1</td>
</tr>
<tr>
<td>TBI 8 27.9/M</td>
<td>18.2</td>
<td>Traffic accident</td>
<td>(R) OL/TL contusion</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>TBI 9 27.2/M</td>
<td>20.9</td>
<td>Traffic accident</td>
<td>(L) FL contusion, subarachnoidal bleeding, epidural haematoma, FL volume loss</td>
<td>Drain tract (L), wide extended FL and (R) OL/PL contusion, corpus callosum degeneration (L) TL contusion</td>
<td>2.5</td>
</tr>
<tr>
<td>TBI 10 34.6/M</td>
<td>28.9</td>
<td>Traffic accident</td>
<td>(R) amygdala and basal ganglia and (R) PL haemorrhage, (L) FL inflammatory changes</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>TBI 11 16.8/M</td>
<td>9.1</td>
<td>Traffic accident</td>
<td>(L) TL and (L) FL punctiform and (R) mesencephalon contusion, (L) FL and (L) thalamus haemorrhagic injuries</td>
<td>Orbito-frontal cortex contusion, enlarged ventricles</td>
<td>1</td>
</tr>
<tr>
<td>TBI 12 33.8/M</td>
<td>27.9</td>
<td>Traffic accident</td>
<td>–</td>
<td>Drain tract (R), thalamus injury, corpus callosum shearing injuries, (R) FL and (L) inferior FL and (R) OL contusion</td>
<td>2.5</td>
</tr>
<tr>
<td>TBI 13 26.9/F</td>
<td>23.9</td>
<td>Traffic accident</td>
<td>FL injuries</td>
<td>Drain tract (L), PL and OL/PL and FL and (R) TL shearing injuries, slightly enlarged ventricles</td>
<td>1</td>
</tr>
<tr>
<td>TBI 14 21.9/M</td>
<td>15.2</td>
<td>Traffic accident</td>
<td>(L) FL contusion, (R) FL shearing injuries, bilateral haemosiderin deposits genu corpus callosum, diffuse axonal injuries</td>
<td>Superior and periventricular FL contusion, (R) orbito-frontal cortex and (R) OL shearing injuries</td>
<td>2.5</td>
</tr>
<tr>
<td>TBI 15 22.3/M</td>
<td>19.1</td>
<td>Traffic accident</td>
<td>Contusion and DAI (location not specified in available records)</td>
<td>(L) thalamus and (L) TL and (L) orbito-frontal cortex and (L) FL and (R) FL and central sulcus shearing injuries</td>
<td>2</td>
</tr>
<tr>
<td>TBI 16 31.7/M</td>
<td>29.6</td>
<td>Traffic accident</td>
<td>(L) FL/TL haemorrhage and DAI, FL and TL/OL shearing injuries</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>TBI 17 16.7/M</td>
<td>14.5</td>
<td>Fall</td>
<td>Enlarged (R) lateral ventricle, (R) haematoma occipital horn lateral ventricle, hyperdensity (L) thalamus and PL/TL, (LH) shearing injuries</td>
<td>Drain tract (R), (L) corpus callosum and thalamus and (R) PL and (L) FL and (R) TL shearing injuries, occipital horn lateral ventricle asymmetrical enlarged</td>
<td>2</td>
</tr>
<tr>
<td>TBI 18 28.1/M</td>
<td>18.4</td>
<td>Traffic accident</td>
<td>Hemosiderin deposits corpus callosum, DAI, ischaemic injury (L) occipital horn of lateral ventricle</td>
<td>Drain tract (R), (R) periventricular white matter FL and thalamus injuries, corpus callosum degeneration</td>
<td>1</td>
</tr>
<tr>
<td>TBI 19 27.9/M</td>
<td>24.9</td>
<td>Traffic accident</td>
<td>(L) thalamus and (L) periventricular and corpus callosum and brainstem and TL shearing injuries</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>TBI 20 30.9/M</td>
<td>28.3</td>
<td>Traffic accident</td>
<td>Lesion and location not specified in available records</td>
<td>Drain tract (R), (L) inferior TL contusion, (L) anterior cingulus and (R) FL and central sulcus shearing injuries</td>
<td>2</td>
</tr>
<tr>
<td>TBI 21 24.1/M</td>
<td>21.8</td>
<td>Traffic accident</td>
<td>(L) FL haemorrhage, FL parenchymal bleeding, subarachnoidal bleeding</td>
<td>Drain tract (R), orbito-frontal cortex and (L) cerebellum contusion</td>
<td>2</td>
</tr>
<tr>
<td>TBI 22 30.6/M</td>
<td>23.8</td>
<td>Traffic accident</td>
<td>(R) intrathalamic haemorrhage, bilateral frontal shearing haemorrhage, (R) subarachnoidal haemorrhage, (L) FL intracerebral haemorrhage</td>
<td>(L) inferior TL and wide extended FL contusion, thalamus injury</td>
<td>2.5</td>
</tr>
<tr>
<td>TBI 23 20.6/F</td>
<td>18.1</td>
<td>Traffic accident</td>
<td>Diffuse axonal injuries, (L) FL/TL/PL subdural haematoma, FL contusion, injuries corpus callosum</td>
<td>FL and (R) PL contusion, orbito-frontal cortex shearing injuries, enlarged ventricles</td>
<td>2</td>
</tr>
</tbody>
</table>

F = female; FL = frontal lobe; L = left; M = male; OL = occipital lobe; PL = parietal lobe; R = right; TL = temporal lobe.
rapid gradient echo (MPRAGE; repetition time = 2300 ms, echo time = 2.98 ms, 1.1 mm voxels, field of view: 240 x 256, 160 sagittal slices). Functional data (functional MRI) were acquired with a descending gradient echo planar imaging (EPI) pulse sequence for T2*-weighted images (repetition time = 3000 ms, echo time = 30 ms, flip angle = 90°, 50 oblique axial slices each 2.8 mm thick, inter-slice gap 0.028 mm, in-plane resolution 2.5 x 2.5 mm, 80 x 80 matrix).

In preparation for functional network analysis, the blood oxygen level-dependent time series were passed through several pre-processing steps using the SPM 5 software package (Wellcome Department of Imaging Neuroscience, University College, London) implemented in MATLAB 7.7 (Mathworks).

T1-weighted structural images were spatially normalized into standard Montreal Neurological Institute (MNI) space using the unified segmentation algorithm, which is less prone to normalization artefacts induced by changes in tissue signal (Ashburner and Friston, 2005; Crinion et al., 2007). The unified segmentation algorithm is a generative model that combines tissue segmentation, bias correction and spatial normalization in the inversion of a single unified model (Ashburner and Friston, 2005). To further refine the unified segmentation procedure for patients with clearly visible focal lesions (n = 9), a lesion mask was manually drawn in MRicro (Chris Rorden, University of South Carolina), smoothed with a Gaussian kernel of 6 mm full-width at half-maximum and used as a cost function mask. The registration process simply ignores the information within the mask and prevents contribution of lesion voxels to the normalization procedure. This combination of the unified segmentation procedure and cost function masking outperforms cost function masking alone (Crinion et al., 2007).

The first three functional images of each subject’s dataset were discarded to allow for T1 equilibration. The remaining images were spatially realigned to the first image in the time series, then corrected for differences in slice acquisition time by temporal interpolation to the middle slice (reference slice = 25). Functional images were spatially co-registered to the anatomical image, and normalized using the same transformation matrix applied to the anatomical image. Finally, the normalized functional images were smoothed with an isotropic 10 mm full-width at half-maximum Gaussian kernel.

The ensuing pre-processed functional MRI time series were analysed on a subject-by-subject basis using an event-related approach in the context of the General Linear Model (Friston et al., 1995). Events were specified at the time of cue onset and modelled as delta functions convolved with the canonical haemodynamic response function and its temporal derivative. Four conditions were specified: correct Switch trials, correct Continue trials, Confirmation, and Rest. Switch conditions were parametrically modulated by response time. An additional regressor modelled events of no interest such as Initiation trials, Reversals, Switch trials with complete contralateral disruptions, and...
studies (Coxon et al., 2010; Leunissen et al., 2012). Twenty-two 10-mm diameter spheres centred on peak coordinates from the activation data (clusters) from both Switch and Continue were created (by applying weights to the canonical haemodynamic response function for each condition). Both contrast Switch and contrast Continue were removed by scaling to the grand mean. For each subject, the mean time series of all voxels of a region of interest was element-wise averaged, so as to obtain a single average time series for each region of interest. Based on the average time series from all voxels within the node-sphere, the time series for each region of interest, the network connectivity was then determined by calculating undirected matrices of partial correlations between the regions of interest, quantifying the unique relationship between each pair of regions of interest. We used partial correlations to reduce indirect dependencies by other brain regions (Hampson et al., 2002; Liu et al., 2008). Amongst all methods of evaluating functional interdependencies between functional MRI time courses in different regions their subsequent correction on Confirmation trials. In addition, realignment parameters were included as covariates of no interest to correct for confounding effects of head movement. Translational motions did not exceed 1 voxel (TBI: mean = 0.55 mm, SD = 0.31; Controls: mean = 0.42, SD = 0.16). The intensity changes attributable to global signal noise due to changes in the magnetic field over time were accounted for by using the time series of the mean signal from the white matter, CSF and out of brain voxels (Verhagen et al., 2008). Data were filtered in the temporal domain using a high-pass cut-off of 1/128 Hz, and global differences in blood oxygen level-dependent signal were removed by scaling to the grand mean. For each subject, the contrast of Switch > Continue was created (by applying weights to the canonical haemodynamic response function for each condition). Both Switch and Continue conditions consisted of identical visual cues, but only the Switch trials required a change of movement plan.

Construction of functional networks
We constructed a functional network for each subject using the following multi-step procedure. First, we extracted the functional MRI time series. Second, we defined and calculated measures of connectivity. Next, a criterion was defined to select connections. Finally, graph measures were computed. These steps are described in detail in the following paragraphs.

The first step in all functional network analyses was to extract the blood oxygen level-dependent average time series for each region of interest in each subject for the contrast Switch > Continue for the runs. The average time series was taken as the first eigenvector from the singular value decomposition of a matrix composed of each time series from all voxels within the node-sphere, the time series of all voxels of a region of interest was element-wise averaged, so as to obtain a single average time series for each region of interest. Within each region of interest, voxels which showed insufficient activation to exceed a threshold of $P < 0.001$ (uncorrected) for the contrast Switch > Continue were not included in calculating the average time series for each region of interest. Based on the average time series data, the network connectivity was then determined by calculating undirected matrices of partial correlations between the regions of interest, quantifying the unique relationship between each pair of regions of interest. We used partial correlations to reduce indirect dependencies by other brain regions (Hampson et al., 2002; Liu et al., 2008). Amongst all methods of evaluating functional interdependencies between functional MRI time courses in different regions their subsequent correction on Confirmation trials. In addition, realignment parameters were included as covariates of no interest to correct for confounding effects of head movement. Translational motions did not exceed 1 voxel (TBI: mean = 0.55 mm, SD = 0.31; Controls: mean = 0.42, SD = 0.16). The intensity changes attributable to global signal noise due to changes in the magnetic field over time were accounted for by using the time series of the mean signal from the white matter, CSF and out of brain voxels (Verhagen et al., 2008). Data were filtered in the temporal domain using a high-pass cut-off of 1/128 Hz, and global differences in blood oxygen level-dependent signal were removed by scaling to the grand mean. For each subject, the contrast of Switch > Continue was created (by applying weights to the canonical haemodynamic response function for each condition). Both Switch and Continue conditions consisted of identical visual cues, but only the Switch trials required a change of movement plan.

Construction of regions of interest
Regions of interest were defined based on the previously published event-related functional MRI studies of young adults, elderly and patients with TBI performing the switching task (Coxon et al., 2010; Leunissen et al., 2012). Twenty-two 10-mm diameter spheres centred on peak coordinates from the activation data (clusters) from both studies (Coxon et al., 2010; Leunissen et al., 2012) were used to define the switching-related areas. The areas constituting this network included the medial frontal cortex (supplementary motor area: pre-supplementary motor area and supplementary motor area-proper), anterior cingulate cortex, bilateral dorso-lateral prefrontal cortex (DLPFC), inferior frontal cortex (Brodmann area 44), basal ganglia (globus pallidus, putamen, subthalamic nucleus region), bilateral cerebellum (lobe VI), right precuneus, left premotor cortex (dorsal and ventral), bilateral insula, and right superior and right inferior parietal lobules. The majority of these regions have been identified as reflecting a ‘core’ network for the implementation of task sets (Dosenbach et al., 2006). Thus, the switching motor network in the current study included 22 brain areas and is listed in Table 2.

### Table 2 Cortical and subcortical regions defined as core switching network

<table>
<thead>
<tr>
<th>Region name</th>
<th>Hemisphere</th>
<th>MNI coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Anterior rostral cingulate cortex</td>
<td>Right</td>
<td>8 18 35</td>
</tr>
<tr>
<td>2 Inferior frontal gyrus: pars opercularis (BA44)</td>
<td>Left</td>
<td>−48 5 25</td>
</tr>
<tr>
<td>3 Inferior frontal gyrus: pars opercularis (BA44)</td>
<td>Right</td>
<td>53 10 20</td>
</tr>
<tr>
<td>4 Cerebellum (VI)</td>
<td>Left</td>
<td>−33 −40 −38</td>
</tr>
<tr>
<td>5 Cerebellum (VI)</td>
<td>Right</td>
<td>35 −53 −30</td>
</tr>
<tr>
<td>6 Middle frontal gyrus: Dorsolateral prefrontal cortex</td>
<td>Right</td>
<td>35 43 30</td>
</tr>
<tr>
<td>7 Middle frontal gyrus: Dorsolateral prefrontal cortex</td>
<td>Left</td>
<td>−38 35 28</td>
</tr>
<tr>
<td>8 Insula lobe</td>
<td>Left</td>
<td>−40 13 3</td>
</tr>
<tr>
<td>9 Insula lobe</td>
<td>Right</td>
<td>45 18 0</td>
</tr>
<tr>
<td>10 Inferior parietal lobule</td>
<td>Right</td>
<td>45 −35 48</td>
</tr>
<tr>
<td>11 Pallidum</td>
<td>Left</td>
<td>−18 5 0</td>
</tr>
<tr>
<td>12 Pallidum</td>
<td>Right</td>
<td>18 10 0</td>
</tr>
<tr>
<td>13 Precuneus</td>
<td>Left</td>
<td>−53 3 40</td>
</tr>
<tr>
<td>14 Precuneus</td>
<td>Right</td>
<td>13 −60 55</td>
</tr>
<tr>
<td>15 Putamen</td>
<td>Right</td>
<td>18 8 5</td>
</tr>
<tr>
<td>16 Putamen</td>
<td>Left</td>
<td>−18 8 5</td>
</tr>
<tr>
<td>17 Superior frontal gyrus: Dorsal premotor cortex</td>
<td>Left</td>
<td>−28 −8 58</td>
</tr>
<tr>
<td>18 Medial superior frontal gyrus: preSMA (Supplementary motor area) (BA6)</td>
<td>Right</td>
<td>0 10 53</td>
</tr>
<tr>
<td>19 Medial superior frontal gyrus: SMA proper (BA6)</td>
<td>Left</td>
<td>−3 −10 55</td>
</tr>
<tr>
<td>20 Superior parietal lobule</td>
<td>Right</td>
<td>40 −45 60</td>
</tr>
<tr>
<td>21 Subthalamic nucleus</td>
<td>Left</td>
<td>−8 −13 −8</td>
</tr>
<tr>
<td>22 Subthalamic nucleus</td>
<td>Right</td>
<td>10 −13 −10</td>
</tr>
</tbody>
</table>

**BA = Brodmann area.**
of interest, partial correlations have been found to provide the most reliable approaches (Smith et al., 2011). The calculation of the matrix of partial correlations makes use of the inverse of the sample covariance matrix. Specifically, the partial correlation matrix is a symmetric matrix in which each off-diagonal element is the correlation coefficient between a pair of variables after filtering out the contributions of all other variables included in the dataset. In the present study, therefore, the partial correlation between any pair of regions filters out the effects of the remaining 20 brain regions. The procedure for obtaining partial correlation values here is consistent with other work (Salvador et al., 2005; Liu et al., 2008; Nakamura et al., 2009).

Graph theoretical analysis
A binary graph (i.e. network), consisting of 22 nodes (brain regions) and undirected edges (functional connectivity) between nodes, was achieved by testing the null hypothesis that the partial correlation coefficient was significantly different from zero between any region pairs. Two regions were considered functionally connected if their partial correlation coefficient was significant at $P = 0.0001, 0.0005, 0.001, 0.005$ and $0.01$, respectively, to ensure that the statistical results with regard to group effects between patients with TBI and controls were stable and reliable at different connection densities. It has been shown that manipulating the connection density in a network by varying the number of valid network connections can have a noticeable impact on graph theoretical metrics (Van Wijk et al., 2010). Hence, rather than thresholding the connectivity matrices at only one arbitrary $P$-threshold, we repeated the graph theoretical analyses across five threshold values. In each case, the thresholding of the connectivity matrices resulted in binary matrices where existing (valid) connections carried a value of $1$ while the absence of a functional connection between network nodes was designated by a value of $0$. Self-connections of nodes were not included in the analyses.

In addition to the binary matrices, we also calculated weighted matrices, where for each valid functional connection between a pair of nodes, the value of $1$ in the binary matrix was replaced by the value of the partial correlation for this node-pair, with the partial correlation then representing a proxy measure for the weight/strength in connection between this pair of nodes. This approach allowed us to examine connection strength between node-pairs and to calculate a mean connection strength for each node defined as the sum of its connection weights (i.e. the sum of partial correlations for valid connections) with other nodes in the network. Subsequently, the mean connection strength of a network was then defined as the mean connection strength across all its network nodes.

We investigated the topological properties of the functional network at the global and regional (nodal) levels using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010), quantifying the global network architecture in terms of the small-worldness, normalized clustering coefficient, normalized path length, density, and global efficiency. We described the regional properties in terms of degree, strength, clustering coefficient, path length and betweenness centrality. Based on the constructed functional network, we looked for significant differences in global and nodal properties between the patients with TBI and controls. We only provide brief, formal definitions of each of the network properties used in this study in the Supplementary material.

Statistical analysis
For the outcome measures of the switching task and the clinical tests of bimanual coordination (TEMPA, Purdue Pegboard Task), two-sample $t$-tests were conducted for comparing the TBI with the control group.

Statistical comparisons of all network measures (i.e. normalized clustering coefficient, normalized path length, degree, strength, density and local efficiency) between the two groups were performed by using two-sample $t$-tests. Network measures were confirmed to have a normal distribution using the Shapiro–Wilk Normality Test. If any change in the local topological properties was found between the two groups, we investigated the regions that showed significant differences in these topological properties. Bonferroni corrections for multiple comparisons were made, hence $P_{corr} < 0.002$ was considered significant following correction for the node-specific analyses regarding the 22 regions of interest. To determine whether the network topology in TBI was correlated with performance on the switching task, we calculated Pearson’s correlation coefficients of the network parameters against Switch response time and percentage of contralateral disruptions. The grades of diffuse axonal injury were also used to assess relationships between the topological properties and severity score. To this end, we applied the Spearman’s rank correlation within the TBI group. Finally, to point out whether correlations between blood oxygen level-dependent response and switching performance are mirrored in similar associations between the graph theoretical network measures and switching task performance on one hand and injury severity on the other hand, correlation analyses were conducted, in which the degree of two regions (pre-supplementary motor area and left inferior frontal gyrus) of the overactivation network was correlated with the behavioural parameters separately. Due to the number of correlations examined, only correlations below a statistical significance level of $P < 0.01$ were considered significant. All statistical analyses were performed with the Statistica software (StatSoft, Inc).

Results
Bimanual switching task performance
The kinematic results of the cognitive control task showed that the patient group took longer to implement pattern change via the right hand ($t(47) = 4.35, P < 0.001$; patients with TBI $764 \pm 27$ ms, controls $645 \pm 29$ ms), and resulted in more complete contralateral disruptions than the control subjects ($t(47) = 2.53, P < 0.01$; patients with TBI $6.29 \pm 5.96\%$, controls $2.93 \pm 3.03\%$). Moreover, baseline motor differences between patients with TBI and controls were measured, using both bilateral items of the TEMPA and the Purdue Pegboard Test. The TBI group scored on average worse than the control group on the number of pegs in the bimanual condition of the Purdue Pegboard Test ($t(41) = -4.17, P < 0.001$; mean for controls: 13 pegs; mean for patients with TBI: 11 pegs), and on the summary score for the TEMPA bimanual tasks ($t(41) = 5.56, P < 0.001$; mean for controls: 9.89 s; mean for patients with TBI: 13.03 s), confirming the TBI group lower mean motor performance levels. However, no effect of these variables (as potential confounding factors) was found on the switch cost in our group analyses (all $P$-values $> 0.05$). Therefore, we suggest that these switching problems in our patients with TBI rather reflect cognitive control deficits than merely being an expression of baseline motor differences.
Graph theory analyses at different connectivity thresholds

The graph theory analyses were repeated across five connectivity threshold levels, i.e. for each subject, graph theory analyses were calculated based on connectivity matrices thresholded at $P = 0.0001$, $0.0005$, $0.001$, $0.005$ and $0.01$ to define valid functional connections. This revealed that the statistical results of topological changes between patients with TBI and controls were stable and essentially unaffected by manipulating the network density, reinforcing the robustness of the obtained findings (see Supplementary material). Overall, the results showed that the topological architecture of the functional networks was significantly altered in patients with TBI. These changes in patients with TBI included higher connectivity degree and strength, and higher values of network density and local efficiency. Similarly, the ‘small-world’ nature remained stable in both groups across all assessment points. Because the statistical results were equivalent across all network densities, we chose to report the data based on the $P = 0.001$ threshold (i.e. the threshold in the centre of the examined threshold range) as representative description of TBI-induced changes in functional connectivity in the assessed network.

Also, no significant effect of gender was found in our analyses (all $P$-values $> 0.05$). Therefore, the graph theory analyses were conducted without this variable as a potential confounding factor.

Between-group differences in functional connectivity

Group comparisons revealed an increased level of connectivity degree $[t(47) = 2.40, P < 0.05]$ in patients with TBI. Specifically, patients showed higher connectivity degree in left ventral pre-motor cortex ($P_{corr} < 0.002$). Node specific values of connectivity degree are presented in Fig. 2A and B. A significant effect for group was also seen on density, representing the total ‘wiring cost’ of the network. Density showed significantly higher values in patients with TBI (mean = 0.28, SD = 0.03) compared with controls (mean = 0.26, SD = 0.04) $[t(47) = 2.40, P < 0.05]$.

A significant effect for group was also seen on the weighted connectivity strength, calculated as the sum of connection weights (i.e. the sum of partial correlations for valid connections) of a node with other nodes in the network. Connection strength showed significantly higher values in the TBI group (mean = 1.60, SD = 0.16) compared with controls (mean = 1.46, SD = 0.17) $[t(47) = 3.11, P < 0.01]$. Compared with controls, TBI children showed significantly higher connectivity strength in the left ventral premotor cortex ($P_{corr} < 0.002$).

Overall topology of the functional brain network

Both patients and healthy controls showed a small-world organization of the functional brain network expressed by a $\gamma > 1$ (TBI group: mean = 1.43, SD = 0.30; control group: mean = 1.42, SD = 0.26) and $\lambda \sim 1$ (TBI group: mean = 1.00, SD = 0.04; control group: mean = 1.01, SD = 0.04). Furthermore, the normalized clustering coefficient $\gamma$ did not differ between the patients with TBI and healthy controls, nor did the overall normalized path length $\lambda$ ($P = 0.90$ for $\gamma$, $P = 0.74$ for $\lambda$). In other words, patients with TBI displayed $\gamma$- and $\lambda$-values close to the values of the brain networks of healthy controls, suggesting an intact overall organization of the functional brain network in patients with TBI.
Identification of hubs

To identify the hub regions, we calculated the betweenness centrality for each node of each subject’s functional network. Then we calculated the mean betweenness centrality of each node by averaging across subjects for each group. For the TBI group, the identified hub nodes included right dorsolateral prefrontal cortex, right insula lobe, and left dorsal premotor cortex (Fig. 3B). The hubs for the control group included only the right insula (Fig. 3A).

Between-group differences in measures of functional segregation

Results revealed higher values of local efficiency between the TBI and control group \( t(47) = 2.29, P < 0.05 \).

Relationship between cognitive control of action and network properties in patients with traumatic brain injury

We considered only degree as network property in these analyses because it has been suggested to be the most important measure of network analysis and it has a straightforward neurobiological interpretation (Rubinov and Sporns, 2010): nodes with a high degree are functionally interacting with many other nodes in the network.

A significant positive correlation was found between mean connectivity degree of the network in the TBI group and percentage of contralateral disruptions \( r = 0.42, P < 0.05 \) (Fig. 4). In other words, increase in connectivity degree was associated with poorer switching task performance (i.e. more contralateral disruptions). Percentage of contralateral disruptions is a measure of generalized and undifferentiated responding, reflecting a lack of focal switching with irradiation of the response to the contralateral hand. No significant results were obtained with the other dependent variable, i.e. Switch response time. Moreover, no significant results were obtained within the control group. Similar results were obtained using different graph organizational measures, for example increased efficiency was associated with lower performance on the switching task.

In the primary functional MRI analysis, two regions (pre-supplementary motor area and left inferior frontal gyrus) of the overactivation network showed a significant correlation between blood oxygen level-dependent activation and switching performance (Leunissen et al., 2012). The associations between switching performance and graph measures in these two areas revealed that percentage of contralateral disruptions was positively correlated to connectivity degree of left inferior frontal gyrus \( r = 0.55, P < 0.01 \) (Fig. 5). No correlations with switching performance were found in the pre-supplementary motor area.

Relationship between injury severity and network properties in patients with traumatic brain injury

Regarding the injury severity (according to Adams et al., 1989), we observed a significant positive correlation between the severity score and connectivity degree \( r = 0.50, P < 0.01 \). Thus, the patients with more severe TBI showed a higher connectivity degree.
Discussion

This is the first time that graph theoretical approaches reveal unique associations between network properties and behavioural functions in patients with TBI. Our results show altered functional connectivity in the networks of patients with TBI. In particular, compared with controls, patients with TBI show increased functional connectivity, and higher values of local efficiency, representing adaptive mechanisms. Furthermore, the increased connectivity degree is significantly correlated with poorer switching task performance and more severe brain injury. It is clear from the present results that assessment of the functional brain networks provides new insights into the mechanism underlying cognitive control deficits after brain injury.

Behavioural switching deficits in patients with traumatic brain injury

Patients with TBI demonstrated difficulties with cognitive control, presenting slower response times and more disruptions during the switching task. There is only limited previous evidence of impaired switching performance during bimanual coordination following TBI, despite the fact that slowing of motor functions is a frequent clinical outcome in these patients (Levin et al., 1990). More specifically, the patients took longer to implement pattern change via the right hand and showed more left-hand reversals than the control subjects. These results are consistent with previous studies using different cognitive task-switching paradigms in TBI (Larson et al. 2006; Schroeter et al. 2007). These switching deficits in patients with TBI may be related to attentional problems when transferring between different motor tasks (Park et al., 2009). In other words, patients with TBI have difficulty shifting attention in order to perform on-line modification of motor patterns during the execution of complex movements.

Group differences in functional brain networks

The human brain is a large, dynamic system with an optimal balance between local specialization and global integration. Although small-world properties were present for both the normal control and TBI groups, the topological architecture of the functional networks was significantly altered in patients with TBI.

First, an increase in connectivity degree and strength was consistently observed in patients with TBI, implying that their network connections were relatively denser than in controls. Connectivity degree increase has also been reported in studies of brain tumours (Bartolomei et al., 2006a, b; Bosma et al., 2008). Node-specific analyses showed increased degree and strength of functional connectivity in the left ventral premotor cortex, suggesting that this area may play an important role in the switching network in patients with TBI compared with controls. The premotor cortex is composed of multiple areas, including the dorsal premotor area and ventral premotor area (Dum and Strick, 1991). The increase in connectivity degree was located within the ventral premotor area close to the M1 hand area. The ventral premotor area is densely interconnected with primary motor cortex and is involved in coordination (Sadato et al., 1997; Stephan et al., 1999; Debaere et al., 2001; Ehrsson et al., 2002). The strengthened connectivity degree in this region may reflect a functional compensation. However, a higher degree can also point to high levels of energetic cost indicative of an overcharged network that is unbalanced in the transmission versus energy consumption trade-off, as recently observed in a longitudinal study in patients with TBI using resting-state magnetoencephalogram recordings (Castellanos et al., 2011). Examination of the density values indeed revealed an increase in total ‘wiring cost’ of the network for the TBI group.

Second, our patients with TBI showed strong increases in local efficiency. The local efficiency is predominantly related to short-range connections between neighbouring nodes. The underlying mechanisms of increased local efficiency of a network have
been widely discussed in various studies. For example, De Vico Fallani et al. (2007) reported that increased local efficiency in spinal cord injured patients could be attributable to functional reorganization. Latora and Marchiorio (2001) indicated that higher values of local efficiency suggest a larger level of internal organization and fault tolerance in the face of external attack. Similarly, the higher local efficiency observed in TBI may imply that the network tends to form clusters of regions of interest which preserve efficient communication and this may be indicative of compensatory mechanisms.

The increased functional connectivity of the patients with TBI appears consistent with previous studies of brain injury. For example, Nakamura and colleagues (2009) showed comparable topological changes in six patients with severe TBI using weighted networks from resting state functional MRI. Specifically, they observed higher efficiency, lower path length, higher strength and a lower small-worldness in patients with TBI compared with control subjects. Similarly, analysis of weighted networks derived from resting-state magnetoencephalogram data revealed that patients with TBI (n = 15) showed increased connectivity as shown by increased strength, decreased path length, increased efficiency and an increased clustering coefficient (Castellanos et al., 2011). Furthermore, several studies in patients with TBI have examined already how network connectivity progresses over time using a longitudinal design, showing connectivity increases shortly after traumatic injury followed by decreases during recovery (even restoring towards control values) (Nakamura et al., 2009; Castellanos et al., 2010, 2011). One piece of information missing from these previous studies is how the brain network metrics relate to cognitive and motor task performance to assess their associations with behaviour (Bullmore and Sporns, 2009). Here, we were able to correlate network parameters with switching behaviour in patients with TBI for the first time.

### Importance of specific brain regions for network functionality

Functional network analysis estimated for TBI and controls revealed that both groups exhibit hubs. In particular, insular lobe acted as ‘hub’ in both groups, implying that removal of insula from the estimated patterns will cause a collapse of the whole functional network. The insula is situated within the lateral sulcus. This area is involved in discerning external from internal bodily signals (Platel et al., 1997; Bamiou et al., 2003; Thaut, 2003; Lewis et al., 2004; Heuninckx et al., 2005; Goble et al., 2011). Accordingly, the observed increased normalized betweenness in the insula may suggest that both groups relied heavily on the external visual signal to trigger coordination changes. The insula has also been identified as hub in a previous study using structural networks (Iturria-Medina et al., 2008). In the latter study, anatomical connection probabilities were estimated from diffusion tensor imaging techniques. A similar betweenness centrality analysis allowed identifying the most indispensable and critical anatomical areas: putamen, precuneus, insula, superior frontal and superior parietal region. These structural findings complement our functional findings and support the notion of the insula as being one of the most vulnerable focal areas.

Two hub regions, the right dorsolateral prefrontal cortex and the left dorsal premotor cortex, presented as hubs in the TBI group only and support the increased penetration of cognition into action control. The dorsolateral prefrontal cortex receives visual, somatosensory and auditory information from the occipital, temporal and parietal cortices (Goldman-Rakic and Schwartz, 1982; Barbas and Pandya, 1989; Seltzer and Pandya, 1989; Pandya and Yeterian, 1990; Petrides and Pandya, 1999) and has preferential connections with the motor system structures (Miller and Cohen, 2001). Accordingly, the dorsolateral prefrontal cortex is hypothesized to play a central role in the cognitive control of motor behaviour (Miller and Cohen, 2001). The dorsolateral prefrontal cortex is involved in replanning and generation of new movements, in task rehearsal, and in attention to action (Deiber et al., 1991; Debaere et al., 2004; Puttemans et al., 2005). Therefore, assigning an increased importance to the dorsolateral prefrontal cortex in the functional network in patients with TBI may allude to less automatized movement generation. TBI most commonly disrupts frontal systems and therefore executive control processes (Hillary et al., 2002). Moreover, Alstott and colleagues (2009) demonstrated that the target attack over the frontal lobes induces a severe disruption of the network.

The other hub region, the dorsal premotor cortex has been divided into a rostral and caudal part, i.e. the pre-dorsal premotor cortex and dorsal premotor cortex proper (Picard and Strick, 2001). In the present study, the region of interest was located within the caudal part of the dorsal premotor cortex. The dorsal premotor cortex proper, known to have direct projections to the spinal cord and primary motor cortex (Dum and Strick, 1991), is mainly involved in movement preparation and execution (Toni et al., 1999; Picard and Strick, 2001; Thoenissen et al., 2002). Although no study has investigated structural or functional changes in the premotor cortex in patients with TBI, we speculate that the increased betweenness centrality of the dorsal premotor cortex in the functional network demonstrates the functional importance of higher control of bimanual coordination for the patients with TBI. Overall, the emergence of dorsal premotor cortex and dorsolateral prefrontal cortex as hub regions in the TBI but not in the control group suggests that the patients with TBI relied on increased cognitive control and performance monitoring. This analysis of the hub-status of the brain regions in the switching network reveals new insights on the potential importance of certain brain regions that go beyond mere identification of functional activation afforded by standard functional MRI.

### Network properties and its relation to cognitive control and traumatic brain injury severity

To our knowledge, this is the first time that associations between cognitive control disabilities and functional reorganization in patients with TBI from a network perspective have been reported. Increased connectivity degree was significantly correlated with percentage of contralateral disruptions, indicating that those
patients with TBI who showed higher connectivity degree displayed lower switching task performance. Moreover, the patients’ severity score was also correlated with the connectivity degree, suggesting that more severe head injury was associated with a more profound change in network topology. As discussed above, the increase in connectivity degree might have a hidden cost, to the extent that higher connectivity degree is partly non-functional, reflecting difficulties in recruiting specialized neural mechanisms and, as a result, may be associated with lower task performance (Hillary, 2008). Although an adaptation interpretation of higher connectivity degree in TBI adults is appealing, it is clearly not the whole story. Subjects with TBI rely more on ‘cognitive reserve’ (as shown by the hub regions) and are thus more likely to reach a limit on the resources that can be brought to bear on task performance. We suggest that the better functional network cohesion in the TBI group may be an effect directly related to a poorer neurobiological substrate, i.e. structural disconnection between brain areas. The increased functional connectivity in patients with TBI suggests a simplified functional system adjusting to a disrupted neurobiological substrate. If the integrity of the neurobiological system is disrupted, it is less versatile in coping with diversity in the activity levels among its network nodes. In other words, to manage decreased structural resources, the brain resorts to a simplified functional architecture characterized by increased functional coherence between network areas. As a result, this increased functional connectivity constrains the brain areas into synchronized activity. This may hamper behavioural flexibility, i.e. flexible coupling and decoupling between brain areas to produce goal-directed behaviour and adjustments to environmental contingencies. This interpretation is consistent with previous research showing a reduced ability in patients with TBI to explore different functional states across brain regions (Hillary et al., 2011; Medaglia et al., 2011). It would be intriguing in future studies to test directly how the structural network changes in TBI are associated with the alteration of functional brain networks, by combining diffusion tensor imaging with functional MRI data.

Our focused correlation analyses showed that increase in connectivity degree in the left inferior frontal gyrus was associated with poorer switching performance, i.e. more contralateral dysfunctions. The inferior frontal cortex is a critical node in the response inhibition network (Duann et al., 2009). It is part of the ventral attention system, which features in the detection of salient, behaviourally relevant targets (Corbetta and Shulman, 2002; Corbetta et al., 2008). For instance, in a stop signal task, the right inferior frontal cortex activates to a higher extent during stop (or no-go) trials compared with go trials, because the stop signal is both salient, less frequent and behaviourally relevant, and it demands a change of response. Leunissen and colleagues (2012) found that right inferior frontal cortex activation was common in both controls and patients with TBI during successful motor switching. More importantly, functional MRI overactivation in the left inferior frontal gyrus was observed only in the patients with TBI, reflecting stimulus driven attention and inhibition of the ongoing movement. We suggest that the left inferior frontal cortex, in addition to manifesting increases in intensity of activation after brain injury, also shows changes in the nature and strength of its functional interdependence. However, further studies are required to confirm this suggestion. There are some limitations to this study. First, changes of functional network topology in the switching network focused on 22 predefined regions of interest. This selection may have resulted in the omission of some switching-related regions or the inclusion of some regions that were no longer switching-related following TBI. However, a recent study by Smith et al. (2011) provides strong indications that an elaborate functional MRI-based functional protocol is preferable to template-based approaches in order to minimize confounds and obtain a better picture on functional connectivity within active neural networks. Second, Pearson’s correlations were employed to estimate the relationship between switching performance and connectivity degree of the brain regions. Correction for multiple comparisons was used, but future studies are needed to determine the optimal methodology to control for multiple testing in a network setting. Alternative correction methods have been suggested (Zalesky et al., 2010).

Even though our results should be interpreted with caution, to our knowledge, this is the first report providing new evidence for cognitive control deficits in patients with TBI from a network perspective. Although small-world properties were present for both patient and control networks, the topological architecture of the functional networks was significantly altered in patients with TBI. Specifically, patients with TBI showed increased connectivity degree, increased density, and higher values of local efficiency, possibly representing an adaptive strategy. Furthermore, connectivity degree was significantly correlated with switching performance and severity score. These brain-behaviour relations pave the way for topology-based brain network analyses that may ultimately serve as biomarkers to improve TBI diagnostics/prognosis and for follow-up of cognitive deficits.

Supplementary material

Supplementary material is available at Brain online.

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