Traumatic brain injury impairs small-world topology

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ABSTRACT

Objective: We test the hypothesis that brain networks associated with cognitive function shift away from a “small-world” organization following traumatic brain injury (TBI).

Methods: We investigated 20 TBI patients and 21 age-matched controls. Resting-state functional MRI was used to study functional connectivity. Graph theoretical analysis was then applied to partial correlation matrices derived from these data. The presence of white matter damage was quantified using diffusion tensor imaging.

Results: Patients showed characteristic cognitive impairments as well as evidence of damage to white matter tracts. Compared to controls, the graph analysis showed reduced overall connectivity, longer average path lengths, and reduced network efficiency. A particular impact of TBI is seen on a major network hub, the posterior cingulate cortex. Taken together, these results confirm that a network critical to cognitive function shows a shift away from small-world characteristics.

Conclusions: We provide evidence that key brain networks involved in supporting cognitive function become less small-world in their organization after TBI. This is likely to be the result of diffuse white matter damage, and may be an important factor in producing cognitive impairment after TBI. *Neurology*® 2013;80:1826–1833

GLOSSARY

DMN = default mode network; **DTI** = diffusion tensor imaging; **EN** = executive network; **FA** = fractional anisotropy; **fMRI** = functional MRI; **ICA** = independent component analysis; **MD** = mean diffusivity; **PCC** = posterior cingulate cortex; **TAI** = traumatic axonal injury; **TBI** = traumatic brain injury.

Traumatic brain injury (TBI) frequently produces cognitive deficits.¹ Patients often show persistent impairments in information processing speed, memory, and executive function, which limit recovery.^{1–3} The pathophysiologic basis for these problems remain incompletely understood.⁴ However, the presence of traumatic axonal injury (TAI) appears to be particularly important in determining the pattern of cognitive problems.^{5–8} Cognitive functions are dependent on the efficient functioning of distributed brain networks, which consist of spatially separated brain regions connected by white matter tracts. TAI can disrupt these connections,^{9,10} and can impair network functioning.^{6,11} A detailed description of brain network function is likely to be important for understanding how TBI affects high-level cognitive processes.

Graph theory allows a quantitative analysis of network organization and has recently found application in the study of brain function.^{12,13} Graph theory describes brain networks as sets of interacting nodes (distinct brain regions or groups of neurons) connected by edges (white matter tracts). Networks with high levels of local node clustering and relatively few connecting edges strike an optimal balance between the demands of specialized processing in local modules and the need for integrated processing across the whole network, and are said to have a small-world architecture.¹³ The disruption of small-worldness has been observed in a number of neurologic conditions.^{14,15} As TAI disrupts the connections of distributed brain networks, graph theoretical analysis is likely to offer insights into the dysfunction of these networks following TBI.

Editorial, page 1822

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Our work examines the long-term effects of brain injury on measures of network organization using functional MRI (fMRI) in a group of patients with cognitive impairment after TBI. The extent of TAI is quantified using diffusion tensor imaging (DTI), and cognitive function assessed using standardized neuropsychological measures. We investigate the hypothesis that TBI results in a loss of small-world attributes within key cognitive networks, as measured by graph theoretical analysis of fMRI data. We go on to investigate whether the underlying cause for this network change is damage to long-distance white matter connections produced by TAI.

METHODS Subjects and clinical imaging. We recruited 21 patients with a history of TBI (7 women, ages 18–54 years, mean age $\pm$ S.D 37.8 ± 10.4 years). The patients were an average of 29 months since injury. Exclusion criteria included previous neurosurgery, a history of significant previous TBI or psychiatric or neurologic illness, antiepileptic medication, previous drug or alcohol abuse, or contraindication to MRI. All patients were assessed for structural damage and abnormalities using initial CT imaging and follow-up MRI (standard T1 and gradient echo). Pathologies present on initial CT imaging included cerebral contusions (53%), diffuse brain swelling (48%), skull fractures (33%), subdural or extradural hemorrhage (29%), and intraventricular or subarachnoid hemorrhage (29%). MRI at the time of the study showed residual evidence of contusions (33%) (figure e-1 on the *Neurology*® Web site at www.neurology.org) and diffuse axonal injury (52%) (table e-1). Three separate neurologically healthy control groups were used for different elements of the study (e-Methods).

Standard protocol approvals, registrations, and patient consents. All subjects gave written consent. The Hammersmith and Queen Charlotte's and Chelsea Research Ethics Committee approved the experiment.

Neuropsychological assessment. A comprehensive neuropsychological assessment was performed on all TBI subjects and on 20 age-matched controls of similar premorbid intellectual ability. The test battery used was designed to be sensitive to cognitive impairments commonly observed following TBI (e-Methods).

Volumetric, functional, and diffusion tensor MRI. Standard protocols were used for high-resolution T1, gradient-echo (T2*), and DTI to assess the extent of focal brain injury and white matter disruption. Fractional anisotropy (FA) and mean diffusivity (MD) were calculated in several regions of interest including the corpus callosum, corticospinal tract, and superior longitudinal fasciculus. These regions are frequently disrupted by TAI, and provide a representative measure of the degree of white matter tract damage.^{7,16} Resting-state fMRI was acquired for 10 minutes as part of a longer imaging session that also incorporated the collection of structural brain data including DTI and T1 structural whole-brain images. During the resting-state paradigm, subjects were asked to close their eyes and remain as still as possible. No specific cognitive task was given (see e-Methods for more details).

Defining the default mode and executive networks. A high-level description of the methods employed in assessing network topography is provided in figure 1. The first stage of our graph analysis involves definition of nodes in the networks of interest. We have previously shown that cognitive impairment after TBI is associated with abnormal network function within the default mode network (DMN) and an anticorrelated executive network (EN) involved in the control of attentionally demanding tasks.^{5,6} Therefore, we focused our graph theoretical analysis on these networks. As in our previous work, the networks were defined in a data-driven way using independent component analysis (ICA).^{6,16} To allow unbiased sampling of these networks, standard temporal concatenation–ICA was performed on a separate group of 19 young control subjects (7 women, ages 21–30 years, mean age $\pm$ SD 24.5 ± 2.75).^{17,18}

Figure 1 High-level description of the processing steps required for graph theoretical analysis of resting-state fMRI

Reference nodes are defined from a group independent component analysis (A), and are used to extract time-series from resting-state functional MRI data (B). Group-wise partial correlation analysis is used to construct functional connectivity adjacency matrices (B), from which network metrics can be calculated (C).

Table 1 Neuropsychological test results^a

Cognitive variables	TBI patients, mean ± SD	Normal controls, mean ± SD
WTAR raw score	41.5 ± 4.9	44.4 ± 5.5
Similarities raw score	39.3 ± 4.3 ^b	34.9 ± 5.6
Matrix reasoning raw score	28.7 ± 3.7	27.1 ± 4.5
Verbal fluency letter fluency (FAS)	40.2 ± 10.5 ^b	48.6 ± 13.0
Color-word color naming, s	36.5 ± 10.1 ^b	28.7 ± 6.2
Color-word word reading, s	25.0 ± 4.4	23.0 ± 4.7
Color-word inhibition, s	61.0 ± 24.9	52.8 ± 19.1
Color-word inhibition-switching, s	72.7 ± 27.7	61.0 ± 23.7
Trail-Making test A, s	30.0 ± 9.4 ^b	20.9 ± 6.4
Trail-Making test B, s	73.5 ± 43.4	50.5 ± 40.0
Digit span forward	10.3 ± 1.7 ^c	11.5 ± 2.0
Digit span backward	7.1 ± 2.4	7.6 ± 1.9
Logical memory I first recall total	29.1 ± 5.6	26.9 ± 8.5
Logical memory I recall total	47.6 ± 7.1	43.2 ± 13.1
Logical memory II recall total	30.0 ± 7.7	25.4 ± 8.4
People test immediate total	24.4 ± 5.0 ^c	28.1 ± 6.5
People test delayed total	9.5 ± 2.0	8.8 ± 3.6
Choice Reaction Time, ^d median RT (ms) ± SD	448 ± 96 ^c	380 ± 32
Choice Reaction Time, SD/RT	191 ± 42 ^c	158 ± 33
Choice Reaction Time, % accuracy ± SD	96.4 ± 4.0	97.1 ± 3.0

Abbreviations: TBI = traumatic brain injury; WTAR = Wechsler Test of Adult Reading.

^aNeuropsychological results for TBI patient and age-matched control group.

^bSignificant at $p < 0.01$.

^cSignificant at $p < 0.05$.

^dChoice Reaction Time performance includes reaction time (RT) and SD. SD/RT is standard deviation of the median RT divided by the median RT. It is reported as a measure of individual variability, which is less sensitive than SD to overall group differences in reaction time.

The DMN and EN components were selected from the components generated and used to define regions of interest (figure e-2). Using coordinates from previous work, additional regions of interest were placed in the hippocampi, which are highly connected to the DMN and often show dysfunction after TBI.¹⁹ Ten-millimeter sphere masks were generated around the peaks of activation. In this way,

Table 2 Global network properties of normal control and TBI patient groups^a

	Total connectivity <i>I</i>	Average clustering coefficient <i>C</i>	Average path length <i>L</i>	Efficiency <i>E</i>
Normal controls	0.333	0.898	0.977	1.008
TBI patients	0.276	1.008	1.040	0.981
Change, %	-17.117	12.249	6.448	-2.679
<i>p</i>	0.030 ^b	0.300	0.036 ^b	0.038 ^b

Abbreviation: TBI = traumatic brain injury.

^aTable 2 summarizes the global network properties of the normal controls and TBI patient groups. Patients show decreased total connectivity *I* and efficiency *E*. Patients demonstrate an increase in average path length *L* and average clustering coefficient *C*. Changes in total connectivity, efficiency, and average path length were shown to be significant ($p < 0.05$). Percent change taken as the difference between groups with respect to normal controls.

^bSignificant at $p < 0.05$.

the following nodes were defined: left parietal cortex, right parietal cortex, precuneus, and anterior prefrontal cortex in the DMN; superior frontal gyrus of the anterior prefrontal cortex, posterior prefrontal cortex, left inferior frontal gyrus, right inferior frontal gyrus, right inferior parietal, left inferior parietal, left superior temporal sulcus, right superior temporal sulcus, and posterior cingulate in the EN; and left hippocampal and right hippocampal formation (figure e-3, table e-2).

Functional connectivity analysis. The average time course of activity was then extracted from the regions of interest, and data from all regions were entered into the partial correlation analysis. This technique provides an accurate measure of the interaction between pairs of brain regions and has been shown to provide clinically useful information.^{20,21} Partial correlation controls for the effect of other nodes and nuisance factors such as the effects of movement and has shown to be robust to local noise.¹⁸ The output of this analysis is an adjacency matrix where values are specified as 1 or 0 depending on whether a significant correlation ($p < 0.05$, corrected for multiple comparisons) was present or absent between 2 nodes, i.e., $a_{ij} = 1$ or 0 (figure e-4).

Graph theory analysis. The connectivity matrix was used to test whether significant differences in network organization were present between the patients and controls. Networks can be defined by the organization of nodes and the edges (connections) between them. Total connectivity is the number of edges within the whole network. Path length is the number of edges required to go from one node to another and efficiency is related to the inverse of this value. Local measures include the number of connections one node has to other nodes (degree centrality) and the proportion of neighbors a node is connected to (clustering coefficient), which is a measure of the cliquishness of the node's neighborhood. A node's betweenness centrality measures how many of the shortest paths between all other node pairs pass through it. Nodes with high degree of betweenness centrality are considered hubs. The Brain Connectivity Toolbox²² was used to compute the different network metrics from each group's adjacency matrix within MATLAB. Permutation tests were used to assess the statistical significance of the variation of global measures and node properties between the 2 groups (see e-Methods for more information).

RESULTS Neuropsychological assessment. TBI patients showed significant impairment in cognitive function, compared to an age-matched control group. Patients had significantly slower and more variable reaction times across a range of cognitive tasks, demonstrating a pattern consistent with impairments in information processing speed and attentional deficits^{23,24} (table 1). Significant differences between groups were also apparent in the Trail-Making and Stroop tests, also demonstrating impairments of speed and attention. Patients also displayed significant impairments in associative and working memory. In other tests, the patient group performed similarly to controls and actually demonstrated a significantly better performance on an IQ test of verbal reasoning (table 1).

TBI patients show a shift away from a small-world network profile. Graph theoretical analysis provided evidence for a shift away from an optimal network organization following TBI. A number of global measures of network function were abnormal (table 2). As expected, patients

Figure 2 Topographic connectivity maps in normal control and traumatic brain injury patient groups

Network connectivity in (A) normal controls and (B) traumatic brain injury patients. Node outline color indicates individual networks: Red = default mode network, blue = executive network, green = hippocampi. Each link represents a significant positive functional connection between node pairs. The area of each node is directly proportional to the normalized betweenness centrality of that node. The nodes are presented to maximize visualization and are not in exact anatomical location. 1 = Left parietal cortex, 2 = right parietal cortex, 3 = precuneus, 4 = anterior prefrontal cortex, 5 = anterior prefrontal cortex (superior frontal gyrus), 6 = posterior prefrontal cortex, 7 = left inferior frontal gyrus, 8 = right inferior frontal gyrus, 9 = right inferior parietal, 10 = left inferior parietal, 11 = left superior temporal sulcus, 12 = right superior temporal sulcus, 13 = posterior cingulate cortex, 14 = left hippocampal formation, 15 = right hippocampal formation. Node outline color indicates individual networks: red = default mode network, blue = executive network, green = hippocampi.

exhibited a significant reduction in total functional connectivity compared to normal controls. This is defined as the number of connections present within the whole network, illustrated in figure 2 as a reduced number of edges between nodes in the patient group. There was also an associated increase in average path length and a reduction in the network efficiency. These abnormalities suggest a reduction in global network integration following TBI. There were no significant group differences in average clustering coefficient, a measure of network segregation. Taken together, these results demonstrate that TBI patients shift away from an efficient, small-world profile. As the average path length increased while the average clustering coefficient showed no significant change, one can conclude that the reduction in connectivity in the patient group is due to the loss of long-range connections, which are particularly affected by TBI (see below).

TBI patients show reduced integration of the posterior cingulate cortex. Graph theoretical analysis also allows the contribution of individual nodes in the network to be investigated. A number of local measures were abnormal in the TBI group (figure 3, A and B). Changes were particularly prominent in the posterior cingulate cortex (PCC). This region has dense white matter connections to many cortical regions, suggesting it forms part of the brain's structural core.²⁵ In keeping with this observation, our network analysis of the PCC from control data demonstrated high degree and betweenness centrality (18.36% share of the network) suggests its role as a hub.^{25,26} Following TBI, the PCC was the only part of the network to show a significant reduction in degree centrality (change = -28.57% , $p < 0.05$) (figure 3A). Similarly, a dramatic and unique reduction in betweenness centrality was also observed (change = -73.10% , $p < 0.01$) (figure 3B). These results suggest that TBI impacts on the PCC's role as a cortical hub, which is likely to be important for integrating brain activity across the DMN, EN, and hippocampi. As these networks support the cognitive functions frequently affected by TBI, this may be a critical change in network organization.

TBI patients show evidence of traumatic axonal injury. DTI provides a validated measure of white matter disruption following TBI,¹⁶ which is predictive of clinical outcome.²⁷ FA and MD are sensitive markers of white matter damage after TBI.⁷ Our TBI patients have previously shown abnormality in DTI measures of white matter structure.¹¹ Evidence of axonal damage was present in all regions examined including the corpus callosum (genu, body, and splenium), left and right corticospinal tracts, and superior longitudinal fasciculi (figures e-5 and e-6). Hence, the results suggest that significant traumatic axonal injury was present in our patient group.

Figure 3 Comparison of local network characteristics between normal control and traumatic brain injury patient groups

Local node features compare (A) degree centrality, k , and (B) betweenness centrality, b , between normal controls and traumatic brain injury (TBI) patients. *Significant difference between controls and patients ($p < 0.05$). aPFC = anterior prefrontal cortex; aPFC-sfg = superior frontal gyrus of the anterior prefrontal cortex; IHF = left hippocampal formation; IIFG = left inferior frontal gyrus; IIP = left inferior parietal; IPC = left parietal cortex; ISTS = left superior temporal sulcus; pC = precuneus; pCC = posterior cingulate; pPFC = posterior prefrontal cortex; rHF = right hippocampal formation; rIFG = right inferior frontal gyrus; rIP = right inferior parietal; rPC = right parietal cortex; rSTS = right superior temporal sulcus.

Damage to long-distance structural connections is associated with disruption of network function and cognitive outcome. A small-world architecture is dependent upon intact long-distance connections, as well as local interactions.²⁸ To directly test whether TAI to large white matter tracts is associated with a shift away from small-world architecture, we split the TBI patient group into subgroups with low and high levels of structural integrity based on an average of MD and FA measures across the aforementioned regions. The low TBI group constitutes those patients who, on average, have low levels of FA and high levels of MD, whereas patients in the high TBI group showed high levels of FA and reduced MD. In keeping with a role for TAI in disrupting small-worldness, total functional connectivity (change = -24.98% , $p < 0.05$) and network efficiency (change = -4.09% , $p < 0.05$) were both reduced in the low group. Average path length also

showed a marginally significant reduction in the low group (change = -10.35% , $p < 0.1$), although there was no difference in average clustering coefficient. Importantly, there were no significant differences between the high TBI group and controls across all measures (figure e-7).

The low and high groups, defined by DTI measures, showed distinct relationships to the control group in terms of cognitive function. We focused this analysis on the 6 measures showing where the TBI group showed abnormal cognitive function. These measures were used as outcome variables in a multivariate analysis of variance, which demonstrated a significant overall difference among the 3 groups (controls, low, and high patient DTI groups): Wilks $\lambda = 0.4998$, $\chi^2(2,12) = 23.9$, $p < 0.05$ (e-Results). Further one-way analysis of variance testing and post hoc analyses revealed that the low TBI patients

showed abnormalities on Trail-Making A ($F_{2,37} = 6.60$, $p < 0.005$) and Color-Word Color-Naming ($F_{2,37} = 6.37$, $p < 0.005$), whereas the high TBI group were not different from controls (e-Results).

We also dichotomized the TBI patient group according to cognitive function and compared measures between subgroups and controls (e-Results). No network differences were found between groups. Finally, we removed the single patient classified as symptomatic (possible), who had no evidence of brain injury. Significant network changes between the TBI group and controls were maintained, with total connectivity showing a greater degree of abnormality (table e-3).

DISCUSSION Large-scale brain networks normally show small-world organization, with few long-range connections and dense local connectivity.^{12,22} We tested whether TBI disrupts this organization using a graph theoretical approach. Patients showed a significant reduction in total connectivity, accompanied by a longer average path length and a reduction in overall network efficiency, indicating a shift away from small-world network organization.

Disruption of small-world network structure has been observed in other conditions such as Alzheimer disease,²⁹ schizophrenia,¹⁵ and aging,³⁰ and is believed to be functionally important. The change in network organization following TBI is also likely to be significant. Our patients show a pattern of cognitive problems typical of TBI, with particular problems of attention and memory function.²⁴ These high-level cognitive functions require the efficient and integrated functioning of distributed brain networks, which is likely to be disrupted by a shift away from small-world network organization. In keeping with a relationship between white matter damage and network dysfunction, we found evidence for widespread traumatic axonal injury in the patient group using DTI. Patients with greater white matter damage showed more abnormal graph theoretical measures, as well as more abnormal cognitive function. This supports the importance of traumatic axonal injury as a proximal cause for loss of small-world connectivity.

In line with previous work, our graph theoretical analysis demonstrated the presence of highly connected cortical hubs.³¹ Damage to these focal regions is likely to have a detrimental effect on wider network function.³² In graph theoretical terms, hubs enable a shorter average path length, which increases network efficiency. In cognitive terms, this may provide the neural architecture necessary for the integration of information processing across modules with a highly interconnected local structure. Consistent with previous studies,^{33,34} our analysis supports a role for the PCC as a key hub region due to its high connectivity. Following TBI, local reductions of both degree and

betweenness centrality were uniquely seen in the PCC. We have previously shown that the PCC shows highly complex patterns of interaction with many other brain regions, and displays a pattern of activity suggesting an active role in the control of attention.^{35,36} After TBI, we have also demonstrated that PCC abnormalities predict cognitive impairments.^{5,6,11} The graph analysis we report extends this work by providing evidence that the PCC becomes less of a cortical hub following TBI, which is likely to affect the efficient functioning of processes that are particularly dependent on the integration of brain activity across large-scale neurocognitive networks.³⁷

Our results are consistent with other studies, which report decreases in connectivity after brain injury.^{38,39} A recent study using EEG investigated patients shortly after mild TBI and observed consistent decreases of functional connectivity (increased path length and reduced clustering coefficient).³⁹ Another fMRI study examined both weighted and unweighted networks during a 6-month recovery period following TBI.³⁸ The unweighted network analysis revealed no significant changes, possibly because only 6 patients were included. In contrast, the weighted network analysis demonstrated initial decreases in global efficiency and path length after injury, which normalized during the recovery period. Although this work fails to demonstrate consistent network dysfunction after TBI, our results suggest that TBI can lead to permanent changes in the organization of networks important for cognition.

Our approach has some limitations. We focused on a restricted set of nodes within networks vulnerable to TBI. Future work could be more anatomically detailed and more closely investigate the relationship between structural and functional connectivity. As is common after TBI, our patients were quite heterogeneous, which could affect our results. Our subsidiary analyses showed the change in small-worldness in a subgroup of patients with definite evidence of TBI. Furthermore, by stratifying our analysis on the basis of white matter structure, we provide evidence that the presence of traumatic axonal injury is likely to be an important factor in determining the amount of network dysfunction and cognitive impairment. Finally, although focal lesions were present in some of our patients (figure e-1), there was little overlap in their location.

In summary, white matter microstructural damage following TBI is likely to affect the functioning of distributed networks subserving cognitive function. Graph theoretical analysis provides a novel way of describing the impact of TBI brain network organization. Our results provide evidence for a shift away from small-world network organization following TBI, coupled with a reduction in the extent to which the PCC acts as a cortical hub.

AUTHOR CONTRIBUTIONS

A.S.P., F.E.T., R. Leech, and D.J.S. designed and conceptualized the study. A.S.P., P.E., V.B., R. Lambiotte, R. Leech, F.E.T., and D.J.S. were involved in analysis or interpretation of the data (including contribution of tools and reagents). A.S.P., F.E.T., and D.J.S. were involved in drafting and revising the manuscript for intellectual content.

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