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Default mode network functional and structural connectivity after traumatic brain injury

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Traumatic brain injury often results in cognitive impairments that limit recovery. The underlying pathophysiology of these impairments is uncertain, which restricts clinical assessment and management. Here, we use magnetic resonance imaging to test the hypotheses that: (i) traumatic brain injury results in abnormalities of functional connectivity within key cognitive networks; (ii) these changes are correlated with cognitive performance; and (iii) functional connectivity within these networks is influenced by underlying changes in structural connectivity produced by diffuse axonal injury. We studied 20 patients in the chronic phase after traumatic brain injury compared with age-matched controls. Network function was investigated in detail using functional magnetic resonance imaging to analyse both regional brain activation, and the interaction of brain regions within a network (functional connectivity). We studied patients during performance of a simple choice-reaction task and at 'rest'. Since functional connectivity reflects underlying structural connectivity, diffusion tensor imaging was used to quantify axonal injury, and test whether structural damage correlated with functional change. The patient group showed typical impairments in information processing and attention, when compared with age-matched controls. Patients were able to perform the task accurately, but showed slow and variable responses. Brain regions activated by the task were similar between the groups, but patients showed greater deactivation within the default mode network, in keeping with an increased cognitive load. A multivariate analysis of 'resting' state functional magnetic resonance imaging was then used to investigate whether changes in network function were present in the absence of explicit task performance. Overall, default mode network functional connectivity was increased in the patient group. Patients with the highest functional connectivity had the least cognitive

impairment. In addition, functional connectivity at rest also predicted patterns of brain activation during later performance of the task. As expected, patients showed widespread white matter damage compared with controls. Lower default mode network functional connectivity was seen in those patients with more evidence of diffuse axonal injury within the adjacent corpus callosum. Taken together, our results demonstrate altered patterns of functional connectivity in cognitive networks following injury. The results support a direct relationship between white matter organization within the brain's structural core, functional connectivity within the default mode network and cognitive function following brain injury. They can be explained by two related changes: a compensatory increase in functional connectivity within the default mode network; and a variable degree of structural disconnection that modulates this change in network function.

Introduction

Traumatic brain injury often results in persistent disability, particularly due to cognitive impairments (Whitnall *et al.*, 2006; Chen and D'Esposito, 2010). Patients typically show impairments of information processing speed, memory and attention (Stuss *et al.*, 1989, 2003), but there is a tremendous variability in how these impairments evolve after injury (Whitnall *et al.*, 2006). An important cause of brain injury is diffuse axonal injury, which is common after traumatic brain injury and damages the integrity of the white matter tracts that link connected brain regions (Povlishock and Katz, 2005). However, exactly how traumatic brain injury leads to persistent cognitive impairments remains difficult to understand, and this limits clinical assessment and restricts the ability to select homogenous groups for clinical trials (Lowenstein, 2009).

Cognitive functions depend on the integrated operation of large-scale distributed brain networks (Mesulam, 1998). The interaction between brain regions within a network (i.e. their functional connectivity), and the interactions between networks are both important for efficient cognitive function (Hampson *et al.*, 2006; Kelly *et al.*, 2008; Leech *et al.*, 2011). Recent methodological advances allow both structural and functional connectivity to be studied *in vivo* (e.g. Beckmann *et al.*, 2005; Jones, 2008). These approaches hold the promise of dramatically extending our understanding of the impact of brain injury on cognition, and the compensatory mechanisms that such injuries trigger (Greicius, 2008; Hagmann *et al.*, 2008; Zhang and Raichle, 2010). This is likely to be particularly important in understanding the cognitive effects of traumatic brain injury, because of the way in which diffuse axonal injury disconnects distributed brain networks.

Functional connectivity can be studied either during the performance of a specific task, or in the absence of an externally imposed task ('resting state' functional MRI). Abnormalities during task performance have been shown to correlate with cognitive impairments in a number of neurological conditions (Horwitz *et al.*, 1998; He *et al.*, 2007; Sharp *et al.*, 2010; Bonnelle *et al.*, in press). In addition, analysis of resting state data provides complementary information about network function in both the normal brain and in disease states (Beckmann *et al.*, 2005; Greicius, 2008; Smith *et al.*, 2009). In the absence of task performance, high-level cognitive networks important for controlling behaviour can be identified (Dosenbach *et al.*, 2007; Seeley *et al.*, 2007;

Smith *et al.*, 2009). These include networks activated by tasks requiring focused attention (task-positive networks), as well as the default mode network, which consists of a set of brain regions that show highly correlated brain activity during 'rest' and a reduced level of activation during most attentionally demanding tasks (Shulman *et al.*, 1997; Gusnard *et al.*, 2001; Raichle *et al.*, 2001; Buckner *et al.*, 2008).

It now appears that a detailed understanding of the effects of disease on the default mode network may be particularly important for understanding the impact of disease on the brain (Zhang and Raichle, 2010). Regions within the default mode network, including the posterior cingulate cortex, the retrosplenial cortex and parts of the ventromedial prefrontal cortex, have high metabolic demands at rest (Raichle *et al.*, 2001), and are densely interconnected by white matter tracts that form part of the brain's core structural network (Hagmann *et al.*, 2008). These regions are located at the centre of many distributed brain networks, suggesting that they have important cognitive functions (Gilbert *et al.*, 2007; Buckner *et al.*, 2008). One possibility is that the network supports mental activity that is internally directed (Gusnard *et al.*, 2001; Mason *et al.*, 2007). Alternatively, the default mode network is often thought of as a counterpoint to task positive networks that are engaged during focused attention (Seeley *et al.*, 2007), and the interaction between the default mode network and these task-positive networks appears important for cognitive function (Hampson *et al.*, 2006; Gilbert *et al.*, 2007).

Abnormalities of brain function following traumatic brain injury have previously been demonstrated using a range of techniques (Levine *et al.*, 2006; Dockree and Robertson, in press). Previous functional imaging studies of traumatic brain injury have often focused on differences in brain activity associated with the performance of attentionally demanding tasks (e.g. Christodoulou *et al.*, 2001; Levine *et al.*, 2006; Scheibel *et al.*, 2007; Rasmussen *et al.*, 2008; Bonnelle *et al.*, in press). Such tasks have generally been shown to be associated with greater and/or more extensive activation within frontal regions (Christodoulou *et al.*, 2001; Levine *et al.*, 2006; Scheibel *et al.*, 2007; Rasmussen *et al.*, 2008). As patients are often impaired on this type of task, the neural changes have generally been interpreted as representing an adaptive or compensatory response to the effects of brain injury (e.g. Rasmussen *et al.*, 2008), although an alternative explanation is that the activated networks may no

longer be operating efficiently (Scheibel et al., 2007). Functional connectivity changes after traumatic brain injury have been investigated less frequently (Nakamura et al., 2009; Kasahara et al., in press; Mayer et al., in press). Disrupted functional connectivity within the motor network has been shown in one study (Kasahara et al., in press), and acute abnormalities of default mode network functional connectivity after mild traumatic brain injury have recently been reported (Mayer et al., in press). The recovery of cognitive function after brain injury can be associated with increased coupling between nodes in control networks, a change we have previously shown in aphasic stroke patients (Sharp et al., 2010). Functional connectivity changes seen after traumatic brain injury may thus be the result of the combined effects of the initial injury, and the compensatory response to that injury.

Here, we employ recent advances in the assessment of functional connectivity (Beckmann et al., 2005; Filippini et al., 2009; Zuo et al., 2009) to investigate the impact of traumatic brain injury on brain network function and behaviour. We assume that functionally distinct networks show coherent and relatively stable brain activity, which in part reflects the underlying white matter connections. Behaviour is associated with rapid changes in brain activity, which occur in the context of this background activity. 'Resting' brain activity has been shown to influence behavioural responses and the associated task-evoked brain activity (Fox et al., 2006), as well as bias perceptual processing (Boly et al., 2007; Hesselmann et al., 2008). Therefore, investigating the structural and functional connectivity of large-scale cognitive networks, in addition to focusing on rapid changes in brain activity associated with abnormal behaviour, is likely to be important because relatively persistent changes in the connectivity of these networks are likely to influence a networks response to changing behavioural demands.

We specifically test the following hypotheses. First, in the chronic phase, traumatic brain injury is associated with abnormalities of regional brain activation and functional connectivity in brain networks that support high-level cognitive function. Secondly, changes in functional connectivity are correlated with impairments in cognitive function, and the task-evoked changes in brain activity associated with this behaviour. Last, functional connectivity is related to structural disconnection secondary to axonal injury, which we test by investigating whether functional connectivity correlates with abnormalities in adjacent white matter measured using diffusion tensor imaging. Taken together, our results for the first time link abnormalities in structural and functional brain connectivity after traumatic brain injury, and demonstrate how sustained changes in network function relate to patterns of evoked brain responses and the adaptive control of behaviour.

Materials and methods

Patients: demographic and clinical details

Twenty-one patients with traumatic brain injury (16 male) were recruited with a mean age of 37.57 ± 10.19 (see Supplementary Table 1

for individual clinical and demographic details). They were investigated at least 6 months after head injury to avoid the potential complication of rapidly changing functional connectivity in the acute or subacute period. The average time since injury was 964 days, with a range of 183–2437 days. All patients were recruited from traumatic brain injury follow-up clinics and had persistent cognitive or neuropsychiatric symptoms. All were initially cognitively impaired, but had made improvements in cognitive function since their injury. Patients were deliberately chosen with a range of injury severities to increase individual variability in cognitive function. To maximally use the positive evidence available for classifying severity, we used the Mayo Classification System (Malec et al., 2007). In this classification, 18/21 were classified as moderate/severe and the remainder as mild (probable) traumatic brain injury. The median admission Glasgow Coma Scale in the group (where available) was 9.5, and 16 had a documented period of post-traumatic amnesia (ranging in duration from 5 min to 3 months). Fifteen patients were not taking regular medication at the time of study. Two patients were taking anti-hypertensive medication (atenolol and ramipril/amlodipine), and another three patients were taking one of penicillin/thyroxine, ventolin or anti-TNF-α (as treatment for ankylosing spondylitis).

None of the patients had a formal psychiatric diagnosis at the time of testing. However, disturbances of mood are commonly seen after traumatic brain injury (Jorge and Robinson, 2003), and we were concerned that these might impact on our results. As a result, mood symptoms were assessed using the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983). At the time of testing, six patients had possible and five probable clinical anxiety, and five patients possible and four probable clinical depression, as measured using the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) (mean anxiety score = 8, range 2–14, mean depression score 7, range 2–15). Exclusion criteria were as follows: injury earlier than 6 months prior to scanning; neurosurgery, except for bolt intracranial pressure monitoring (one patient); a history of psychiatric or neurological illness prior to their head injury; a history of significant previous traumatic brain injury; anti-epileptic medication; current or previous drug or alcohol abuse; or contraindication to MRI. The experiment was approved by Hammersmith and Queen Charlotte's and Chelsea Research ethics committee, and all participants gave written informed consent according to the Declaration of Helsinki (World Medical Association, 2008).

Standard clinical imaging

All patients except one (who had no initial CT imaging) had abnormalities in keeping with traumatic brain injury either on initial CT imaging or follow-up MRI. Each patient had a standard T_1 to assess focal brain injury, and gradient echo imaging to provide evidence of microbleeds, a marker of diffuse axonal injury (Scheid et al., 2003). MRI scans were reviewed by a senior neuroradiologist. As is usually the case, many of the patients had a mixture of different types of injury. On initial CT imaging 11 patients had evidence of cerebral contusions, 10 had diffuse brain swelling, seven had skull fractures, six had either subdural or extradural haemorrhage, six had either intraventricular or subarachnoid haemorrhage and one patient had evidence of early hydrocephalus that was subsequently resolved. Individual structural MRI findings at the time of testing are summarized in Supplementary Table 1. Five patients had evidence of contusions. Eleven had evidence of microbleeds visible on gradient echo imaging, using standard criteria (Gregoire et al., 2009). This provides evidence of diffuse axonal injury (range of microbleed number 1–19, mean = 9). Structural lesions visible on T_1 were not extensive and the

lesions had a typical pattern of distribution for traumatic brain injury. The most common lesion load fell within the anterior temporal poles and orbitofrontal cortex. Lesion maps were generated (Supplementary material). There was little overlap between the patients' lesion locations (Supplementary Fig. 1), and no overlap in the location of the microbleeds.

Neuropsychological assessment

A battery of standardized neuropsychological tests was used, designed to be sensitive to cognitive impairments commonly observed following traumatic brain injury (Supplementary material). These tests included measures of information processing speed, executive functions and verbal memory.

Control groups

Four separate neurologically healthy control groups were used for different elements of the study (Supplementary material). Except for the young control group used for the generation of reference network maps, patient and control groups were matched for age at the group level. All patients and control subjects gave written consent.

Structural and functional magnetic resonance imaging

Anatomical, functional and diffusion tensor MRI data were acquired using standard procedures (Supplementary material). Patients had two sessions of imaging: one session consisted of resting state functional MRI plus structural brain imaging including diffusion tensor imaging; a second session consisted of task functional MRI. Resting state functional MRI was acquired for 10 min during which time subjects were instructed to relax and close their eyes. All patients and a control group performed the choice-reaction task in the scanner. This simple task involved rapid key presses to either left or right pointing arrows. In the scanner, subjects were presented with an initial fixation cross for 350 ms. This was followed by a response cue in the form of an arrow pointing left or right lasting 1400 ms in the direction of the required response. The interstimulus interval was 1750 ms. Finger press responses were made with the index finger of each hand. Subjects were instructed to respond as quickly and as accurately as possible. To maximize design efficiency stimulus presentation was blocked, with five repeated blocks of 14 response trials, 14 'rest' trials and four response trials at the start of the experiment, resulting in 74 response trials in total.

Data analysis

Standard functional MRI analysis of the choice-reaction task

A high-level description of how both the task and rest functional MRI data were analysed is presented in Fig. 1. Whole-brain functional MRI data from the choice-reaction task were analysed with standard random effects general linear models using the FMRIB Software Library (Supplementary material). To investigate the relationship between default mode network functional connectivity and task activation, a focused region of interest analysis was performed using Featquery. This technique allows the average brain activity from a region to be studied. The regions were defined based on the peaks of task activation in the control group. Within the default mode

network, two regions were investigated: the ventromedial prefrontal cortex ($x = -10$, $y = 38$, $z = -2$) and the posterior cingulate cortex ($x = 10$, $y = -38$, $z = 40$). In the task-positive network, we focused our analysis on the supplementary motor area ($x = -2$, $y = 2$, $z = 62$). This is a key motor control region for this type of task. The mean percentage signal change associated with each contrast of interest was calculated for all voxels within a region of interest.
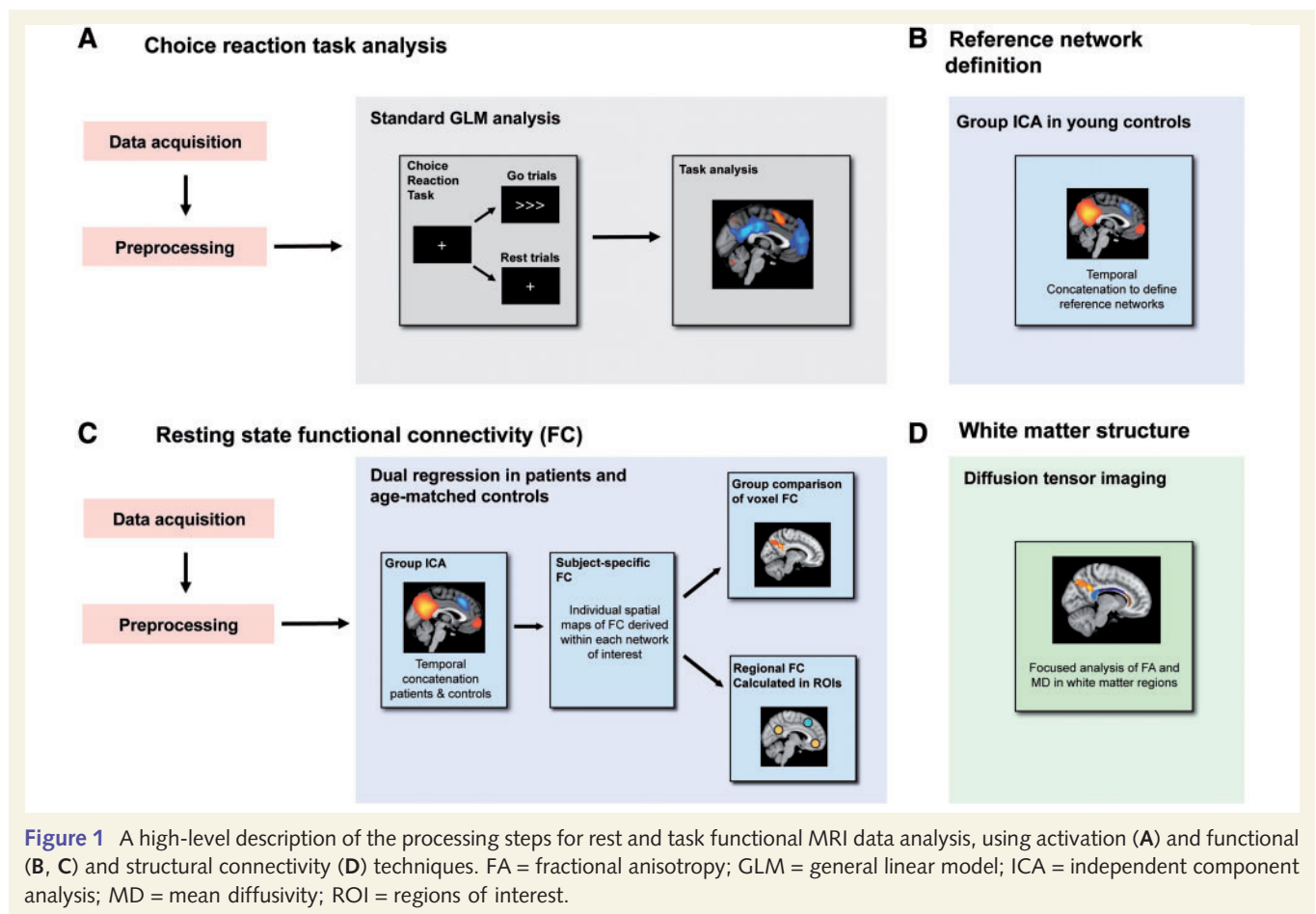
Functional connectivity analysis of 'resting' brain networks

We employed independent component analysis and dual-regression methodology to study functional connectivity in 'resting' state functional MRI (Filippini et al., 2009; Zuo et al., 2009; Leech et al., 2011). This approach has a number of advantages over the use of seed voxel-based approaches, which make it particularly useful in clinical studies (Zuo et al., 2009). It provides a voxelwise measure of functional connectivity that reflects the correlation between the activity of each voxel and the rest of the network being tested.

The first analysis step involved the generation of reference-independent component analysis components from 19 healthy control subjects. Standard temporal concatenation-independent component analysis was performed on the resting state data that resulted in 25 independent group components including 12 distributed brain networks, as well as physiological noise and movement artefacts (Beckmann et al., 2005; Smith et al., 2009). Guided by the results of the standard choice-reaction task functional MRI analysis, which showed group differences, we examined functional connectivity within the default mode network. In addition, we performed further functional connectivity analysis on a number of resting state networks likely to be affected by traumatic brain injury. These consisted of right and left frontoparietal networks, and an 'executive' network (Supplementary Fig. 2 and Supplementary material for further description). A visual network centred on primary occipital regions and a sensorimotor network were also investigated as examples of networks that we did not expect to be particularly vulnerable to the effects of traumatic brain injury.

Functional connectivity was compared in patient and control groups as follows: (i) reference networks were used to derive individual time courses for each component for each subject; and (ii) these subject- and network-specific time courses were then re-regressed onto each subject's data resulting in a subject-specific spatial map of functional connectivity. Spatial maps were tested for voxelwise between-group differences using non-parametric permutation testing (Smith et al., 2004). Voxelwise estimates of the probability of grey matter membership intensity were included as a covariate to control for the effects of atrophy and cortical damage associated with traumatic brain injury. To correct for multiple comparisons, results were cluster corrected using a nominal t-value of 1.68 ($P < 0.05$). To reduce loss of sensitivity associated with whole-brain multiple comparison corrections, analyses were constrained to those voxels most likely to be active for a given independent component (i.e. voxels > 0.5 threshold for the Gaussian mixture model). To avoid potential bias, the age-matched control group compared with the patients was completely separate to the control subjects used to define the reference networks.

In addition to the voxelwise analyses, a number of regions of interest were used to probe the relationship between functional connectivity and behaviour. To avoid bias, we initially investigated network functional connectivity using the reference default mode network-independent component analysis, defined from the young controls not included in other analyses. Peaks of the independent component analysis statistical maps for the default mode network component were used to define the centre of a 10-mm diameter spherical

Figure 1 A high-level description of the processing steps for rest and task functional MRI data analysis, using activation (**A**) and functional (**B**, **C**) and structural connectivity (**D**) techniques. FA = fractional anisotropy; GLM = general linear model; ICA = independent component analysis; MD = mean diffusivity; ROI = regions of interest.

region of interest (posterior cingulate cortex: $x = -2$, $y = -46$, $z = 20$; ventromedial prefrontal cortex: $x = 2$, $y = 54$, $z = 8$). Mean functional connectivity with the default mode network was subsequently extracted from this region of interest for each individual. In addition, as a check of the initial results, we also extracted functional connectivity data from regions of interest defined by the peaks of clusters of significant differences between patient and normal functional connectivity (posterior cingulate cortex: -14, -34, 36, and superior frontal gyrus; -2, 14, 53). Functional connectivity within these regions was correlated with behavioural measures on which the patients were impaired.

Structural connectivity: diffusion tensor imaging

Standard diffusion tensor imaging preprocessing methods were employed using the FMRIB software library (Smith et al., 2004). Sixty-four direction data were acquired (see Supplementary material for sequence details). A region of interest approach was then taken, focusing on white matter tracts commonly affected by traumatic brain injury. Three regions within the corpus callosum (the splenium, body and genu) were hand-drawn using the MNI-152 1 mm template. In addition, the left and right corticospinal tracts and superior longitudinal fasciculi were used, derived from the JHU White-Matter Tractography Atlas in the FMRIB software library (Wakana et al., 2007; Hua et al., 2008). Fractional anisotropy and mean diffusivity values for each region of interest were calculated using the mask images translated into each subject's brain space (Supplementary material).

Results

Neuropsychology

Compared with an age-matched control group, patients with traumatic brain injury demonstrated significantly slower reaction times and more intra-individual response variability across a range of cognitive tasks (Tables 1 and 2), a pattern consistent with impairments in speed of information processing and attentional deficits (Stuss et al., 1989a, b, 2003). This was a specific impairment limited to a subset of the behavioural measures, rather than a global impairment that spanned many domains of cognition. The patients were well matched with controls for estimates of pre-morbid IQ as measured by the Wechsler Test of Adult Reading, and most other cognitive variables. Indeed, the patients showed better performance on a test of verbal abstract reasoning.

Greater deactivation of the default mode network following traumatic brain injury during accurate behaviour

The patients' main cognitive impairments (slow and variable reaction times) were identifiable during performance of the choice-reaction task. Therefore, we first investigated brain

Table 1 Neuropsychological test results

Cognitive variable	Traumatic brain injury, mean ± SD	Control, mean ± SD
WTAR raw score	41.5 ± 4.9	44.4 ± 5.5
Similarities raw score	39.3 ± 4.3**	34.9 ± 5.6
Matrix Reasoning raw score	28.7 ± 3.7	27.1 ± 4.5
Verbal Fluency Letter Fluency (fractional anisotropy)	40.2 ± 10.5**	48.6 ± 13.0
Colour-Word (Stroop) Colour Naming (s)	36.5 ± 10.1**	28.7 ± 6.2
Colour-Word (Stroop) Word Reading (s)	25.0 ± 4.4	23.0 ± 4.7
Colour-Word (Stroop) Inhibition (s)	61.0 ± 24.9	52.8 ± 19.1
Colour-Word (Stroop) Inhibition-Switching (s)	72.7 ± 27.7	61.0 ± 23.7
Trail Making Test A (s)	30.0 ± 9.4**	20.9 ± 6.4
Trail Making Test B (s)	73.5 ± 43.4	50.5 ± 40.0
Digit span forward	10.3 ± 1.7*	11.5 ± 2.0
Digit span backward	7.1 ± 2.4	7.6 ± 1.9
Logical memory I 1st 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 delayed recall total	30.0 ± 7.7	25.4 ± 8.4
People Test immediate total	24.4 ± 5.0*	28.1 ± 6.5
People Test delayed total	9.5 ± 2.0	8.8 ± 3.6

Neuropsychological results for the traumatic brain injury group ($n = 21$) and an age-matched control group ($n = 20$). Significant group differences shown by *$P < 0.05$ and **$P < 0.01$. Units vary across tests based on the dependent variable used.
WTAR = Wechsler Test of Adult Reading.

Table 2 Choice-reaction task performance

	Traumatic brain injury	Control
Median reaction time (ms) ± SD	448 ± 96*	380 ± 32
SD/reaction time	191 ± 42*	158 ± 33
Accuracy ± SD (%)	96.4 ± 4.0	97.1 ± 3.0

Behavioural performance for choice-reaction time functional MRI. SD/reaction time is the standard deviation of the median reaction time divided by the median reaction time. It is reported as a measure of individual variability, which is less sensitive than SD to overall group differences in reaction time. Significant group differences shown by *$P < 0.05$.

activation evoked by the choice-reaction task using standard functional MRI analysis. This task minimizes cognitive load, and patients performed with the same level of accuracy as controls, although with slower reaction times and more intra-individual variability (Table 2). A predictable pattern of activation was observed within bilateral sensory, motor and superior parietal regions, as well as in the supplementary motor area, the thalami and the putamen (Fig. 2). Activation was similar for patients and controls, suggesting an absence of general, non-specific changes in brain physiology following traumatic brain injury. As expected, the default mode network showed deactivation during task performance in the posterior cingulate cortex, ventromedial prefrontal cortex, precuneus and bilateral parietal lobes (Fig. 2 and Supplementary Tables 2–5). Patients showed a greater difference in activation between 'rest' and task than controls within the ventromedial prefrontal cortex (Fig. 2 and Supplementary Table 6), a difference consistent with the patients finding the task more cognitively demanding (Singh and Fawcett, 2008).

Default mode network functional connectivity correlates with behaviour

Next, we investigated patterns of functional connectivity following traumatic brain injury in specific resting state networks. Informed by the results of the choice-reaction task analysis, we first investigated the functional connectivity of the default mode network. Patients showed greater posterior cingulate cortex and precuneus functional connectivity to the rest of the default mode network than controls (Fig. 3 and Supplementary Table 7). We reasoned that this might directly reflect the effect of brain injury. Alternatively, as our patients had in general made a good cognitive recovery, the abnormal default mode network functional connectivity could also represent an adaptive response to cognitive impairment.

To distinguish between these possible explanations, we investigated the relationship between default mode network functional connectivity and behaviour. To avoid bias, we initially sampled activity in the posterior cingulate cortex based on the pattern of functional connectivity observed in a separate group of young controls. In keeping with a role for the default mode network in a compensatory neural response, both patients and age-matched controls showed a negative relationship between default mode network functional connectivity and information processing speed, as measured by median reaction time for accurate responses on the choice-reaction task. This was assessed using an ANOVA with reaction time as the dependent variable and posterior cingulate cortex functional connectivity and group as independent variables. This revealed a significant effect of posterior cingulate cortex functional connectivity [$F(1,39) = 6.312$, $P < 0.05$], due to greater default mode network functional connectivity being associated with faster reaction times (Fig. 3C).
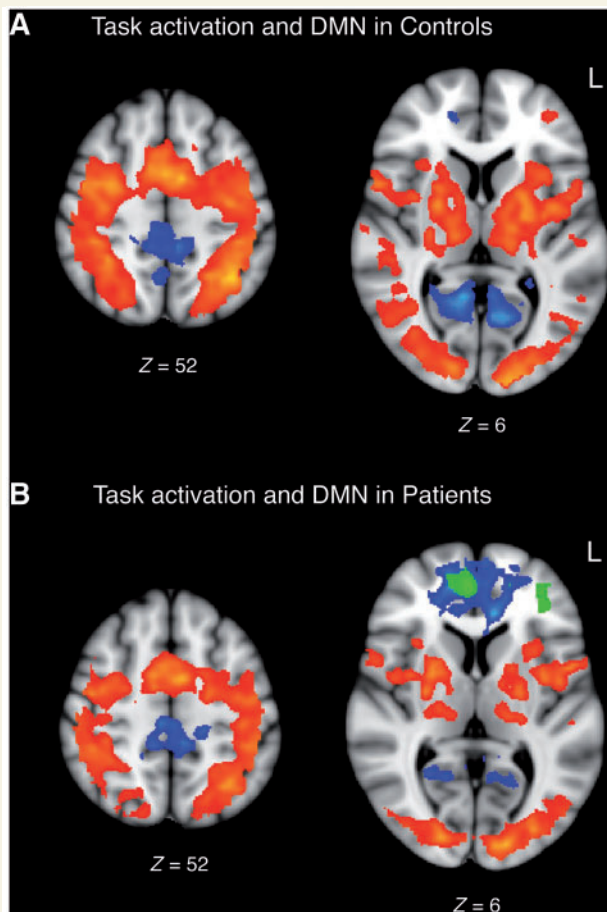
Figure 2 Task-induced activation differences within the default mode network (DMN) following traumatic brain injury. Voxels showing significant brain activation during the simple choice-reaction task for the contrast of choice-reaction task versus 'rest' shown in red–yellow. Voxels showing significantly reduced activation for the same contrast shown in blue-light blue. Results are for: (**A**) age-matched controls and (**B**) patients with traumatic brain injury. Voxels showing significantly greater deactivation in patients versus controls, for the contrast of choice-reaction task versus 'rest', are shown in green. Greater deactivation is observed in the ventromedial prefrontal cortex. A standard Z-statistic threshold of 2.3 was employed combined with a corrected cluster significance threshold probability of $P < 0.05$. Results are shown superimposed on sagittal and axial slices of the MNI 152 T_1 1-mm brain template. MNI coordinates for brain slices are shown. L = left.

There was also a significant group effect [$F(1,39) = 9.06$, $P < 0.01$], as patients were slower on the task, but there was no group × posterior cingulate cortex connectivity interaction. Although this part of the posterior cingulate cortex did not show a group difference in the level of functional connectivity, a similar relationship between reaction time and functional connectivity was observed when we directly sampled the posterior cingulate cortex region showing the group difference in our whole-brain analysis ($\rho = -0.38$, $P < 0.05$). In the patients only, this relationship generalized to other measures of processing speed (Stroop

Colour-Word, $\rho = -0.48$, $P < 0.05$; Trail Making A, $\rho = -0.52$, $P < 0.05$). The relationship was specific to the posterior cingulate cortex, as the ventromedial prefrontal cortex did not show a significant correlation with behaviour.

In addition to correlating with neuropsychological measures of processing speed, posterior cingulate cortex functional connectivity with the default mode network also correlated with patient anxiety, with more anxious patients showing greater network functional connectivity ($\rho = 0.614$, $P < 0.01$). Importantly, anxiety ratings showed no relationship to processing speed ($P > 0.6$), and controlling for anxiety alone or in combination with depression ratings strengthened the correlation between reaction time and functional connectivity in the patient group ($\rho = -0.687$, $P < 0.01$ controlling for both anxiety and depression, and multiple comparisons). Thus, the relationship between posterior cingulate cortex functional connectivity with the default mode network and processing speed is independent of the mood symptoms that are frequently present following traumatic brain injury, and survives multiple comparison.

The default mode network is often thought of as the counterpoint to a flexible executive network that is highly active during tasks that require cognitive control (Duncan *et al.*, 2010). Our patients with traumatic brain injury also showed greater executive network functional connectivity than age-matched controls (Fig. 4 and Supplementary Table 8). Specifically, an extensive region within the medial prefrontal cortex including the supplementary motor area showed greater functional connectivity, echoing our previous findings in stroke (Sharp *et al.*, 2010). In contrast to the default mode network, functional connectivity within this region did not show a significant relationship with information processing speed and was not correlated with anxiety or depression scores.

No other networks investigated showed group differences in functional connectivity, and no brain areas showed lower functional connectivity in patients than controls in either the default mode network or executive network.

Default mode network functional connectivity correlates with task activation

Greater functional connectivity within the default mode network may allow more efficient network function (Kelly *et al.*, 2008). To investigate this possibility, we tested whether variability in default mode network functional connectivity at 'rest' predicted later regional brain activation during performance of the choice-reaction task. Comparing functional connectivity and task activation can be done many ways, and the approach taken here was hypothesis driven and highly constrained by the previous findings to a number of theoretically interesting regions of interest. Default mode network function was studied in the posterior cingulate cortex and ventromedial prefrontal cortex using the regions of interest defined from the unbiased young control group (as above). This information was correlated with the patterns of brain activation or deactivation associated with choice-reaction task performance from the posterior cingulate cortex,
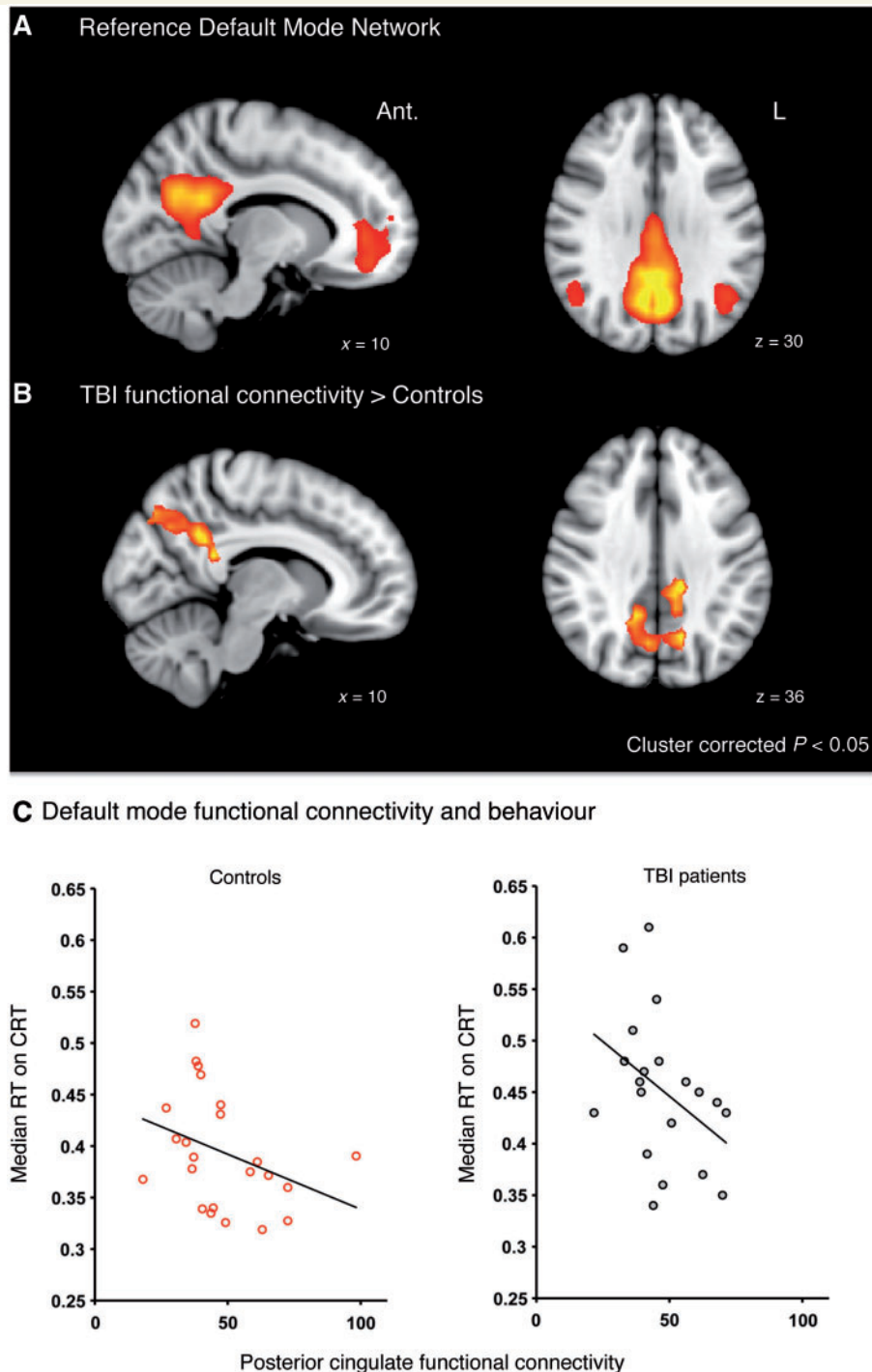
Figure 3 Functional connectivity within the default mode network correlates with information processing speed following traumatic brain injury. (**A**) The resting state default mode network identified in control subjects using independent component analysis. Voxels showing significant functional connectivity are shown in red–yellow. (**B**) Voxels showing greater correlation with the network-specific time course of the default mode network for patients with traumatic brain injury than age-matched control patients are shown in red–yellow. Results are cluster corrected $P < 0.05$ significance and shown superimposed on sagittal and axial slices of the MNI 152 T_1 1-mm brain template. Anterior (Ant.) MNI coordinates for brain slices are shown. (**C**) Posterior cingulate cortex functional connectivity within the default mode network is correlated with the speed of responses on the choice-reaction task performed at a different time. Posterior cingulate cortex functional connectivity is plotted against median reaction time (RT) on the choice-reaction time (CRT) task. To avoid bias, the posterior cingulate cortex was sampled from the peak of the default mode network in the reference independent component analysis component ($x = -2$, $y = -46$, $z = 20$). Patients and controls are plotted separately. Controls are plotted with red and patients with grey circles. L = left; TBI = traumatic brain injury.
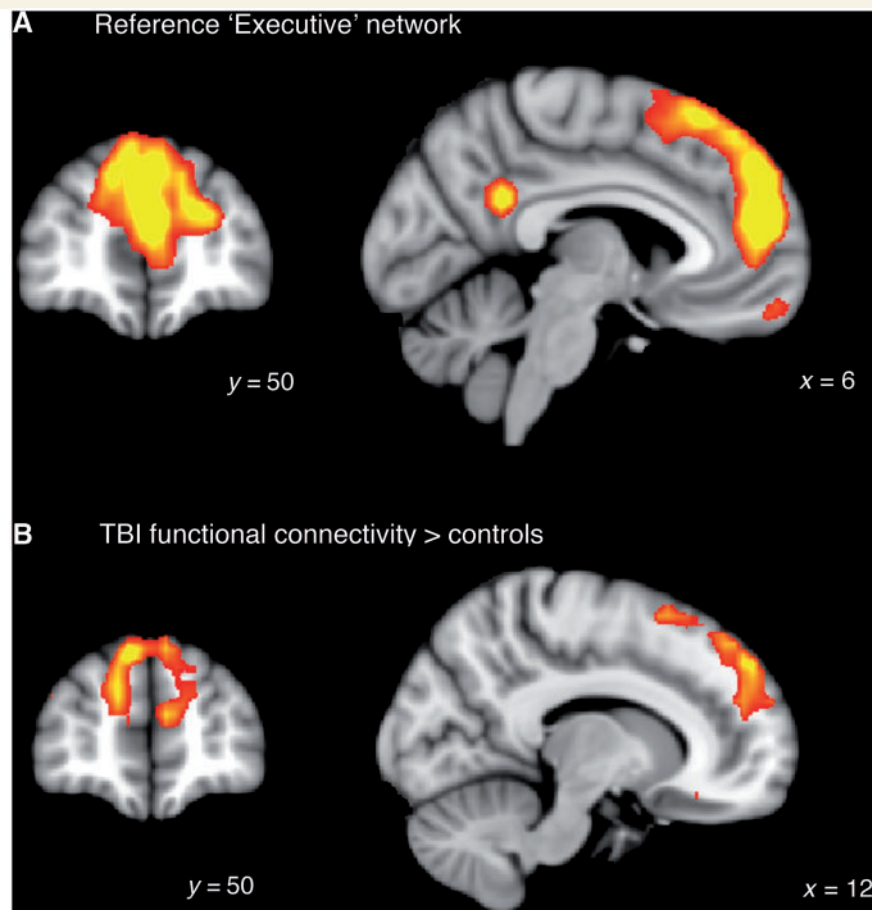
Figure 4 Increased functional connectivity within an executive network following traumatic brain injury (TBI). (**A**) The 'resting' state executive network was identified in control subjects using independent component analysis. Regions showing significant functional connectivity are shown in red–yellow. (**B**) Voxels showing greater correlation with the network-specific time course of the executive network for patients with traumatic brain injury than age-matched control patients are shown in red–yellow. Results are cluster corrected $P < 0.05$ significance and shown superimposed on sagittal and axial slices of the MNI 152 T_1 1-mm brain template. MNI coordinates for brain slices are shown.

ventromedial prefrontal cortex and supplementary motor area, as described in the 'Materials and methods' section. These regions were chosen based on the peaks of default mode network deactivation as well as task-related activation. Functional connectivity within the ventromedial prefrontal cortex at 'rest' predicted brain activation associated with choice-reaction task performance. Higher functional connectivity of the ventromedial prefrontal cortex predicted lower activation of the supplementary motor area ($\rho = -0.438$ $P < 0.01$). Similarly, ventromedial prefrontal cortex functional connectivity showed a borderline relationship with lower activation of the ventromedial prefrontal cortex ($\rho = -0.307$ $P = 0.073$). These relationships were due to the presence of strong correlations in the patients (Fig. 5) (patient supplementary motor area correlation $\rho = -0.629$ $P < 0.01$, and ventromedial prefrontal cortex correlation $\rho = -0.588$ $P < 0.01$, both significant with outliers removed and multiple comparison adjustment). In contrast, posterior cingulate cortex functional connectivity was not correlated with patterns of activation during task performance in either patients or controls.

White matter structure correlates with default mode network functional connectivity

We predicted that greater white matter disruption after traumatic brain injury (as measured by diffusion tensor imaging) would disrupt functional connectivity. Our patient group had evidence of axonal damage in all regions examined (Fig. 6 and Supplementary Table 9). Diffusion tensor imaging provides a validated measure of white matter disruption following traumatic brain injury (Mac Donald et al., 2007), that is predictive of clinical outcome (Sidaros et al., 2008). We have previously shown mean diffusivity to be a sensitive measure of white matter abnormality following traumatic brain injury (Kinnunen et al., 2010). Here, mean diffusivity in the splenium of the corpus callosum was negatively correlated with posterior cingulate cortex functional connectivity, corrected for multiple comparisons ($\rho = -0.68$ $P = 0.001$), with a borderline relationship in the body of the corpus callosum
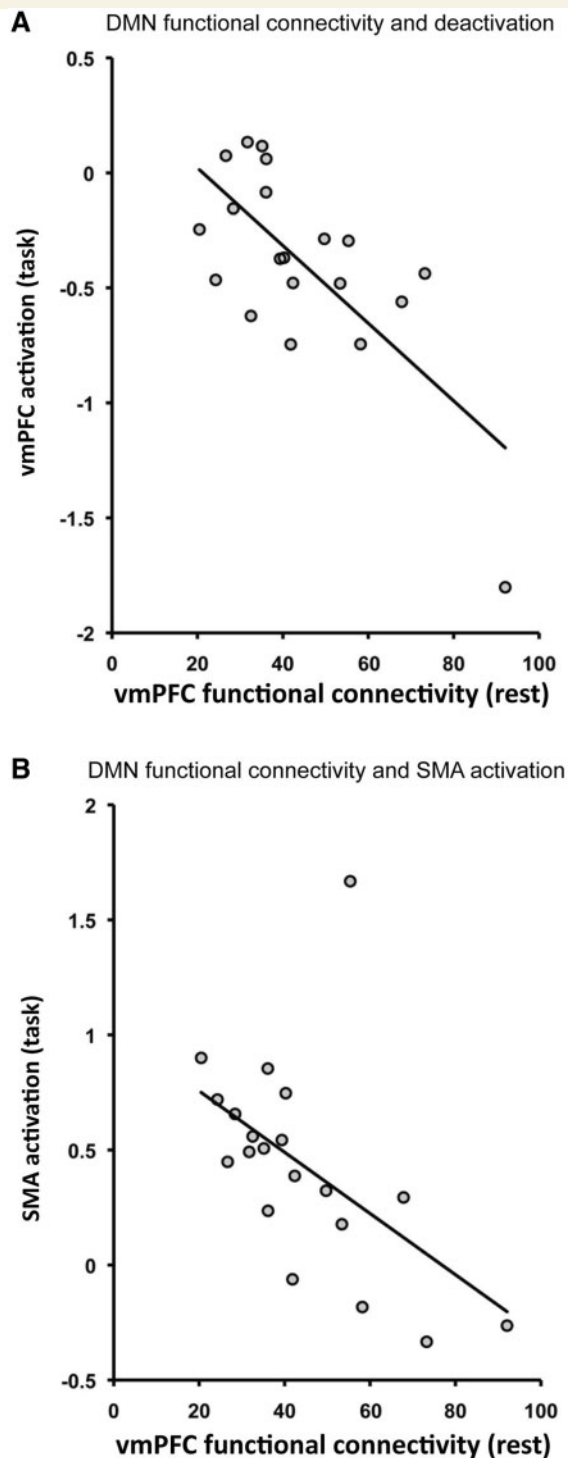
Figure 5 Default mode network functional connectivity correlates with task activation. Functional connectivity of the ventromedial prefrontal cortex (vmPFC) within the default mode network (DMN) at 'rest' correlates with: (**A**) activation within the ventromedial prefrontal cortex and (**B**) activation within the supplementary motor area (SMA) during task performance. Measurements of network functional connectivity were calculated from resting state functional MRI, acquired in a separate scan session from the task scanning. To avoid bias, the ventromedial prefrontal cortex was sampled from the peak of node in the default mode network reference component ($x = 2$, $y = 54$, $z = 8$).

($\rho = -0.52$ $P = 0.02$). Therefore patients with more abnormal white matter showed less functional connectivity within the default mode network. Fractional anisotropy in these regions was not correlated with functional connectivity, and there was no significant correlation in any of the other regions examined.

Controlling for medication use and structural brain damage

Five of our subjects were taking regular medication. Although no single drug was taken by more than one subject, we performed an additional control analysis excluding these patients. This had no impact on our main findings (Supplementary material). We also controlled for the impact of structural brain damage by limiting the analysis to 11 patients with either normal conventional structural MRI imaging or white matter microbleeds only (Supplementary Table 1). This removed any potential effect of focal cortical brain injury and superficial siderosis. Our results remained largely unchanged within this smaller group. The region of interest analyses showed significant correlations between posterior cingulate cortex functional connectivity and behaviour, task activation change and a borderline significant relationship with white matter structure (Supplementary material).

Discussion

Our results show for the first time a relationship between changes in functional connectivity after traumatic brain injury, cognitive impairment and white matter damage. This is particularly important for understanding the pathophysiology of traumatic brain injury because diffuse axonal injury is a common mechanism of injury, which disrupts the large-scale distributed brain networks that support cognition. We use a novel approach to study functional connectivity (Zuo *et al.*, 2009), which builds on recent work showing that distributed brain networks are identifiable at rest (Beckmann *et al.*, 2005; Smith *et al.*, 2009). This approach provides a way of probing the function of cognitive networks without many of the difficulties associated with variable patient performance on tasks (Price *et al.*, 2006). We demonstrate abnormal patterns of functional connectivity after traumatic brain injury, and investigate the cognitive significance of these changes by relating network dynamics to impairments of information processing speed. Within the default mode network, 'resting' functional connectivity correlated with subsequent behaviour, as well as with the patterns of brain activity associated with that behaviour. After controlling for important potential confounds such as cortical volume and psychiatric state, abnormally high posterior cingulate cortex connectivity correlated with more efficient response speeds, suggesting that the changes observed within the default mode network may be a novel mechanism for cognitive recovery after brain injury.

Our analysis of the regional brain activation associated with a simple choice-reaction task also suggests that changes in default mode network activity may be an important influence on behaviour after traumatic brain injury. Impairments in the speed of information processing are a core cognitive deficit following
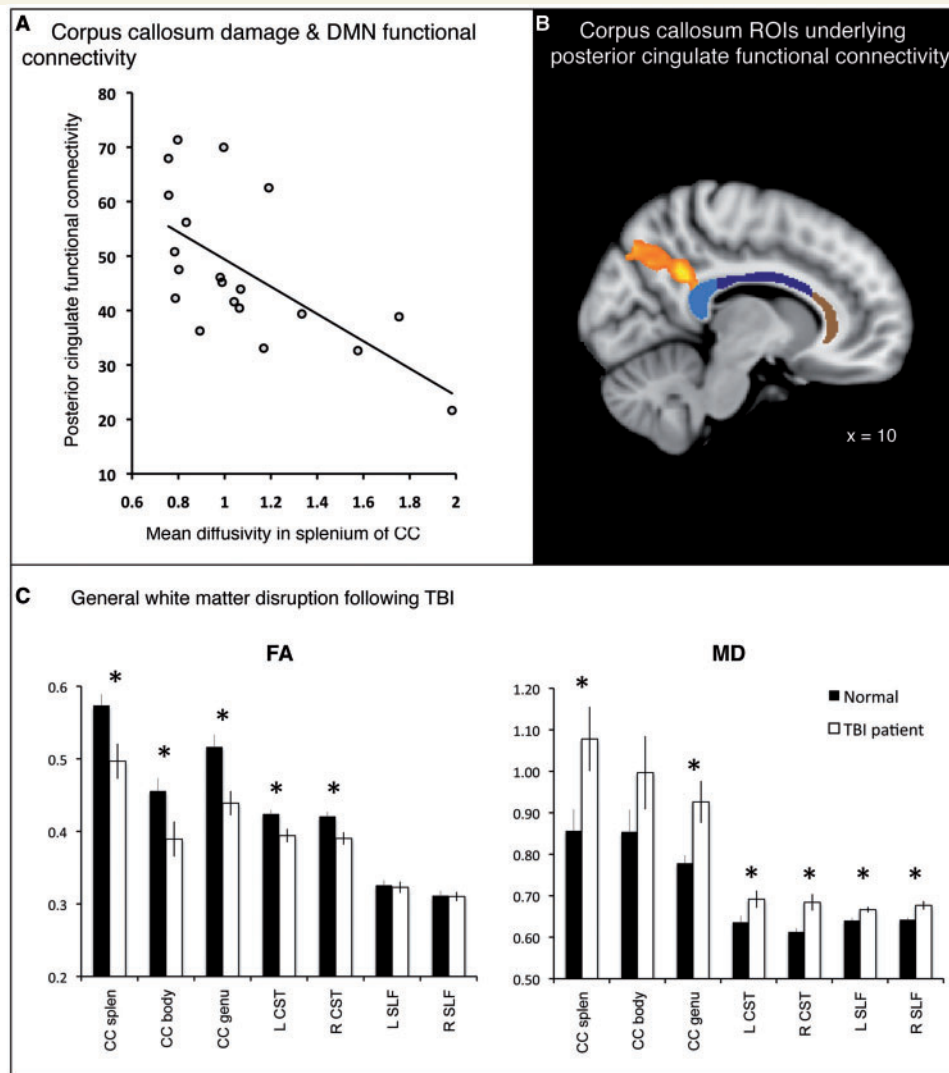
Figure 6 Disruption of the brain's structural core is correlated with default mode network functional connectivity. (**A**) The correlation of white matter integrity in the splenium of the corpus callosum (CC), as measured by mean diffusivity, and posterior cingulate cortex (PCC) functional connectivity with the rest of the default mode network (DMN). Increasing mean diffusivity is associated with more disrupted white matter following traumatic brain injury. (**B**) Corpus callosum regions of interest overlaid on a MNI 152 1-mm brain template. The splenium of the corpus callosum is highlighted in light blue, the body in dark blue and the genu in brown. Increased functional connectivity within the posterior cingulate cortex is demonstrated in red–yellow, overlying the splenium of the corpus callosum. (**C**) General white matter disruption following traumatic brain injury (TBI). Diffusion tensor imaging of the splenium, body and genu of the corpus callosum (CC splen, CC body and CC genu), the left and right corticospinal tracts (L CST and R CST) and superior longitudinal fasciculi (L SLF and R SLF). Fractional anisotropy (FA) and mean diffusivity (MD). *$P < 0.05$ between traumatic brain injury patient and control groups.

traumatic brain injury (Stuss *et al.*, 1989), which can impact widely on cognitive function by limiting the speed with which individual processing operations can be performed (Salthouse, 1996). Our patients were slower and more variable in their responses on the task, but importantly were able to perform it accurately. In contrast to much previous work, we observed a similar pattern of frontoparietal activation during task performance in patients compared with controls, but greater deactivation within the default mode network. Rapid and highly reactive changes in activation are observed within the default mode network during behaviour, with greater deactivation seen during more cognitively demanding

tasks (Singh and Fawcett, 2008; Pyka *et al.*, 2009). This suggests that the increased deactivation within the default mode network in patients with traumatic brain injury is likely to be associated with a requirement for greater cognitive effort to maintain accurate task performance. We also observed an interesting relationship between functional connectivity at rest and the patterns of brain activation associated with later task performance. Functional connectivity of the ventromedial prefrontal cortex correlated with brain activation evoked by performance of the choice-reaction task. Together our results show that high 'resting' functional connectivity within the default mode network after traumatic brain

injury is associated with less impairment in information processing speed, and suggests that sustained changes in default mode network connectivity (observed at 'rest') might influence behaviour by modulating the responsiveness of networks engaged by task performance.

As expected, we found evidence for white matter disruption in our patients (Kinnunen *et al.*, 2010). Recent work shows that structural and functional connectivity are closely related (Hagmann *et al.*, 2008; Greicius *et al.*, 2009). A key question for traumatic brain injury research is how physiological abnormalities relate to underlying structural disconnection produced by diffuse axonal injury (Dockree and Robertson, in press), and we predicted that white matter damage would impact on patterns of functional connectivity. We found that as white matter disruption within the splenium of the corpus callosum increased (as indicated by mean diffusivity), posterior cingulate cortex functional connectivity decreased. This appeared to be a relatively specific relationship. However, in most situations, the cumulative effect of widespread white matter tract damage across many tracts is likely to be a key factor affecting brain network function, rather than focal damage in a particular location. We performed a focused analysis of white matter structure motivated by our interest in the default mode network, and we may have observed this particular relationship because: (i) the splenium of the corpus callosum is adjacent to the posterior cingulate cortex; (ii) mean diffusivity is a more sensitive marker of white matter damage than fractional anisotropy in this patient group (Kinnunen *et al.*, 2010); and (iii) diffuse axonal injury frequently affects this anatomical location making it easily identifiable (Adams *et al.*, 2000) across patients. It is important that future work uses more sophisticated methods to study the integration of structural and functional connectivity across the whole brain.

As is common after traumatic brain injury, a proportion of our patients also had evidence of contusions. In general, these were seen in a typical frontotemporal distribution, and are also likely to impact on brain function. However, previous work has demonstrated that the contusion load is often a poor predictor of cognitive deficit (Bigler, 2001), and in the case of our patients, there was very little overlap in the location of the contusions (Supplementary Fig. 1). Removing patients with focal brain injury from our analysis did not affect the results in a major way, suggesting that there was no consistent relationship between contusion location and either information processing speed or functional connectivity.

Although the findings of structural disconnection and increased default mode network functional connectivity at first glance appear to be contradictory, these two findings could be explained by the presence of two interrelated processes. First, a compensatory increase in functional connectivity within the default mode network, seen on average across the whole patient group. Secondly, a variable degree of structural disconnection that modulates functional connectivity within the default mode network. We suggest that the interaction between these factors means that patients with high levels of diffuse axonal injury would be unable to maintain increased default mode network functional connectivity, either because of damage to the internal connections of the default mode network, or to its connections with other networks. Abnormalities of default mode network functional connectivity using a seed voxel-based methodology have also been shown recently following mild traumatic brain injury (Mayer *et al.*, in press). In this study, patients were initially studied in the acute setting and showed a complex pattern of functional connectivity, with reductions within the default mode network but increases between the default mode network and other networks. These changes also appeared functionally important as they correlated with subjective symptom scores, although the group as a whole had normal neuropsychological function. The differences with our work might be explained by the fact that our patients had more severe initial injuries and were studied in the chronic phase when adaptive changes will have had a chance to develop. Below we consider possible interpretations of these findings, both for understanding the recovery from traumatic brain injury and the functioning of the default mode network.

Converging evidence that the posterior cingulate cortex is important for the control of information processing is provided by the observations in humans that a failure to deactivate the posterior cingulate cortex during task performance is associated with behavioural impairment (Weissman *et al.*, 2006), and in non-human primates that the firing of cells in the posterior cingulate cortex prior to a response correlates with the speed of that response (Pearson *et al.*, 2009). We extend these results by showing that increased posterior cingulate cortex functional connectivity to the rest of the default mode network is associated with more efficient behavioural responses, a relationship observed across patients and controls. Our results suggest that default mode network deactivation does not necessarily signify disengagement during cognitive processing (Greicius *et al.*, 2004; Hampson *et al.*, 2006). Instead, dynamic changes in default mode network function may be made more efficient by greater functional connectivity at 'rest' (Kelly *et al.*, 2008), in which case an increase in default mode network functional connectivity could promote the appropriate and sustained deactivation necessary for focused goal-directed behaviour.

Varying the functional connectivity within resting state networks might therefore 'tune' the responsiveness of a network, and influence the efficiency of the behaviour supported by that network. Some evidence for this hypothesis is provided by the relationship we report between resting state default mode network functional connectivity and task-induced activation. Higher functional connectivity within the ventromedial prefrontal cortex was associated with greater deactivation of the same region during the choice-reaction task. As consistent deactivation of the ventromedial prefrontal cortex is associated with the ability to sustain attention on a task (Weissman *et al.*, 2006), this result suggests that a sustained increase in the functional connectivity of the default mode network might support a more pronounced deactivation during focused task performance, thereby improving the efficiency of behaviour. The functional connectivity of the ventromedial prefrontal cortex was also correlated with activation within a key motor control node, the supplementary motor area, providing further evidence of a potential role for the default mode network in modulating task activation. This relationship was only present in patients, and so one must interpret its relevance for normal brain function with caution. However, its absence in

control subjects could relate to the low cognitive load involved in the task we used. Further work will be needed to clarify whether variability in default mode network functional connectivity is an important factor in determining the pattern of task-evoked brain activation.

We also observed increased functional connectivity for patients within an executive network commonly activated during cognitive control. This builds on our previous work demonstrating that the recovery of language function after aphasic stroke is associated with increased connectivity within a similar executive network (Sharp *et al.*, 2010). A recent computational model of network dynamics provides a mechanism by which the default mode network might be coupled to networks such as the executive network that are engaged during demanding task performance (Deco *et al.*, 2009). In the model, coupled anti-phase network oscillations emerge as a result of interactions between the networks. This pattern has been observed during many types of externally directed behaviour (Kelly *et al.*, 2008), and greater anti-correlation is associated with less variable task performance (Kelly *et al.*, 2008). Therefore, the responsiveness of a network might be influenced through the modulation of anti-correlations that emerge as the result of local changes in default mode network functional connectivity. Our observation of increased functional connectivity in patients in two networks that are anti-correlated during task performance, the default mode network and executive network, is compatible with this mechanism of behavioural control.

The default mode network has previously been thought of as having a unitary function. However, our results and other recent work suggest that this is an over-simplification (Uddin *et al.*, 2009; Andrews-Hanna *et al.*, 2010; Leech *et al.*, 2011). Although the posterior cingulate cortex and ventromedial prefrontal cortex show high functional connectivity at rest, and highly correlated changes in activation during task performance, recent work demonstrates that these two regions exhibit distinct functional connectivity (Uddin *et al.*, 2009), and even within the posterior cingulate cortex distinct patterns of functional connectivity are observed (Margulies *et al.*, 2009; Leech *et al.*, 2011). Our results support distinct yet complementary functions for the posterior cingulate cortex and ventromedial prefrontal cortex in the adaptive control of behaviour, and show that although the default mode network is involved in internally directed thought, this is unlikely to be its sole function.

One limitation of our study is its cross-sectional design. We studied patients with traumatic brain injury in the chronic phase after their injury, so that relatively stable network function could be investigated. Changes in default mode network functional connectivity may facilitate the recovery of cognitive function after traumatic brain injury, but because of our study design we are unable to comment on this. Further studies, similar for example to Mayer and colleagues (in press) should focus on the acute or subacute effects of traumatic brain injury on default mode network function, and investigate longitudinally whether these predict long-term cognitive function. Although we investigate cross-sectional correlations across patients these constitute necessary first steps in developing rich hypotheses about the complex interactions between structural, functional and behavioural levels of description occurring following traumatic brain injury. A second

potential limitation is that our patient population is not representative of the whole traumatic brain injury population. We were interested in studying patients with a range of cognitive function, which led us to recruit more patients with a greater severity of injury than is representative. It is possible that patients with varying clinical severities of traumatic brain injury would show differential patterns of functional connectivity change, and further studies with larger sample sizes will need to address this question. This might be an issue at both ends of the severity spectrum, with severely injured patients being unable to produce adaptive changes in the default mode network and very mildly injured patients having no motivational drive to do so.

In summary, our results provide evidence for cognitively important changes in the default mode network after traumatic brain injury. We show that functional connectivity within the default mode network changes after traumatic brain injury, and provide evidence that this change may be adaptive, perhaps through an influence on the responsiveness of networks engaged during focused task performance. As predicted, white matter disruption to the 'structural core' of the brain was associated with lower functional connectivity within the default mode network, providing evidence that axonal injury disrupts functional connectivity following traumatic brain injury. More generally our results emphasize the importance of studying changes in the default mode network following brain injury, and suggest that the phasic changes in brain activation evoked by task performance should be studied in the context of more sustained changes in network dynamics that are revealed through the study of resting state networks.

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Supplementary material

Supplementary material is available at *Brain* online.

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