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ORIGINAL RESEARCH

Loss of white matter connections after severe traumatic brain injury (TBI) and its relationship to social cognition

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Abstract

Adults with severe traumatic brain injury (TBI) often suffer poor social cognition. Social cognition is complex, requiring verbal, non-verbal, auditory, visual and affective input and integration. While damage to focal temporal and frontal areas has been implicated in disorders of social cognition after TBI, the role of white matter pathology has not been examined. In this study 17 adults with chronic, severe TBI and 17 control participants underwent structural MRI scans and Diffusion Tensor Imaging. The Awareness of Social Inference Test (TASIT) was used to assess their ability to understand emotional states, thoughts, intentions and conversational meaning in everyday exchanges. Track-based spatial statistics were used to perform voxelwise analysis of Fractional Anisotropy (FA) and Mean Diffusivity (MD) of white matter tracts associated with poor social cognitive performance. FA suggested a wide range of tracts were implicated in poor TASIT performance including tracts known to mediate, auditory localisation (planum temporale) communication between nonverbal and verbal processes in general (corpus callosum) and in memory in particular (fornix) as well as tracts and structures associated with semantics and verbal recall (left temporal lobe and hippocampus), multimodal processing and integration (thalamus, external capsule, cerebellum) and with social cognition (orbitofrontal cortex, frontopolar cortex, right temporal lobe). Even when controlling for non-social cognition, the corpus callosum, fornix, bilateral thalamus, right external capsule and right temporal lobe remained significant contributors to social cognitive performance. This study highlights the importance of loss of white matter connectivity in producing complex social information processing deficits after TBI.

Keywords Traumatic brain injury · White matter · Diffuse axonal injury · Social cognition

Traumatic brain injury (TBI) is the most common cause of brain damage in the western world outside of war zones with incidence rates of severe TBI estimated between 12-14/100,000 population per annum (Kraus et al. 1984; Tate et al. 1998). TBI most commonly arises following motor vehicle accidents, work-related injuries, assaults and falls. Acceleration-deceleration forces during the trauma cause the ventromedial surfaces of the frontal and temporal lobes to scrape across the bony structures of the middle and anterior fossae of the skull. This combined with Wallerian degeneration leads to a preponderance of damage in the grey matter of the temporal and frontal lobes (Bigler 2007).

White matter pathology is also highly characteristic of severe TBI. During rapid acceleration-deceleration, white matter fibres are stretched, compressed and rotated. Axons enlarge and swell and structural damage leads to microlesions in white matter tracts and shearing at the white-grey matter juncture. Secondary deterioration of axons can occur months following the injury due to localized pathology and deterioration of neighbouring axons (Bigler and Maxwell 2011; Maas et al. 2008) The corpus callosum appears to be consistently vulnerable to diffuse axonal injury (Viano et al. 2005).

There is a high prevalence of social difficulties post TBI with changes to personality and behavior strongly related to poor social outcome (Bond 1976; Tate et al. 1991) and relative stress (Brooks et al. 1986; Kinsella et al. 1991).

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Many people with TBI have disorders of social cognition, affecting their ability to recognise and interpret emotional states in other people (Babbage et al. 2011; Croker and McDonald 2005; McDonald and Flanagan 2004) understand their intentions and beliefs (Bibby and McDonald 2005; Martin-Rodriguez and Leon-Carrion 2010) follow subtle inferences in normal conversation (McDonald et al. 2003) and experience empathy (de Sousa et al. 2010, 2011, 2012; Williams and Wood 2010; Wood and Williams 2008). Focal lesion research along with functional imaging in healthy adults suggests that social cognition is mediated by ventromedial grey matter structures that are vulnerable to TBI including the amygdala, striatum, anterior cingulate, orbitofrontal cortex and insula. (Adolphs 2001; Marsh and Cardinale 2014; Phillips et al. 2003; Shamay-Tsoory 2011). According to these authorities, lateral cortex is also implicated, entailing the superior temporal gyrus, anterior temporal pole, inferior parietal and inferior frontal gyrus and somatosensory cortex.

However, an important additional consideration is that social information is multi-modal involving auditory, visual, verbal and non-verbal processing. This paints a complex picture of neural activity within and across hemispheres, relying upon communication between disparate regions via major white matter tracts. White matter abnormalities in intrahemispheric tracts such as the inferior frontal occipital fasiculus have been associated with poor ability to recognise emotions and mental states in simple tasks using photographs across several clinical disorders including TBI (Genova et al. 2015) Parkinsons Disease (Baggio et al. 2012) and Multiple Sclerosis (Mike et al. 2013). Photos lack the complexity of real-life social encounters that place additional demands on cognitive processing and cerebral systems. For example, people with agenesis of the corpus callosum have been shown to perform poorly when assessed using complex naturalistic video stimuli from The Awareness of Social Inference Test (TASIT) (McDonald et al. 2003; Symington et al. 2010).

Taking a region of interest approach we have found that there is a significant association between abnormalities of the corpus callosum and poor TASIT performance in people with severe TBI (McDonald et al. 2017). What remains unknown, however, is the extent to which abnormalities of other white matter tracts within and between hemispheres, contribute to impaired ability to process complex, dynamic social information after traumatic brain injury. Downey et al. (2015) reported that people with behavioral variant frontotemporal dementia who have poor social cognitive ability on TASIT have associated abnormalities in multiple white matter tracts including not only the corpus callosum but the fornix, uncinate fasiculus, thalamic radiation and other tracts in the temporal and frontal lobes. They concluded that white matter changes were predictive of social cognition impairments even more so than grey matter. White matter changes are particular relevant in TBI given that trauma may damage axons leaving the cell body (grey matter) preserved but disconnected and non-functional (Bigler et al. 2002). The following study aimed to examine the role of white matter abnormalities throughout the brain in poor social cognition post severe TBI using diffusion tensor imaging (DTI).

DTI measures water diffusion at specific points (voxels) along white matter tracts. Fractional anisotropy (FA) indexes the variability of diffusion in different directions at specified voxels with higher values (approaching 1) associated with intact white matter tracts and low values suggesting white matter anomalies (Pierpaoli and Basser 1996). Low FA has been reported following TBI of a range of severity (Sidaros et al. 2008; Xiong et al. 2014) and related to cognitive impairment (Kinnunen et al. 2011; Veeramuthu et al. 2015). Mean diffusivity (MD) indexes total diffusion within a given voxel, taken to reflect white matter lesions (Basser 1995). High mean diffusivity (MD) has also been reported following TBI (Kinnunen et al. 2011; Perez et al. 2014; Veeramuthu et al. 2015; Xiong et al. 2014).

Given the heterogeneity of neuropathology after TBI and the complexity of social cognition, we used track-based spatial statistics (TBSS) (Smith et al. 2006) to investigate WM contributions to social cognition impairments. TBSS is a multi-subject approach whereby the white matter of the whole brain is examined, using a representative white matter tract skeleton, which eliminates issues of spatial smoothing between participants. Using TBSS individual FA images are registered to a common skeleton using non-linear warping. Voxel-wise statistics are then conducted on FA and MD data that is aligned across participants. TBSS has been used in TBI to demonstrate relationships between white matter damage and impaired memory, attention, processing speed and executive function (Adamson et al. 2013; Kinnunen et al. 2011; Leunissen et al. 2014; Palacios et al. 2011; Veeramuthu et al. 2015; Xiong et al. 2014) as well as ability to recognise emotions in photos (Genova et al. 2015) but, to date, not in relation to ability to process naturalistic social stimuli. In the following study the white matter tracts of a group of adults with chronic severe TBI and a control group of adults without injuries were compared using TBSS. Voxel based correlations between white matter quality (FA and MD) and TASIT performance were examined to determine, in a data driven manner, which regions were associated with impaired social cognition broadly, and specifically once generic cognitive skills were accounted for. On the basis of prior research we hypothesised that, along with the corpus callosum, the fornix, thalamus, and tracts

running within frontal and temporal lobes would be implicated in complex social cognitive judgements.

Method

Participants

Seventeen participants with severe TBI (males n = 14) were sex and age matched (mean = 45.6 years, SD = 13.2, range 23 - 66) to healthy controls (mean = 44.3, SD = 14.6, range 23 - 67). Participants were recruited from three metropolitan brain injury units in Sydney. Participants with TBI were included if they had experienced a severe TBI resulting in a period of post-traumatic amnesia (PTA) for one day or longer (Russell and Smith 1961). The duration of PTA was estimated based upon hospital records or subjective, retrospective reporting from the patients and/or their relatives. All participants were discharged from hospital and living in the community, proficient in English. Participants were tested 2 to 35 years post-injury (mean 12.82, SD = 8.83), and had a period of Post Traumatic Amnesia (PTA) ranging from 5 to 137 days (mean = 49.9, SD = 35.0). Causes of injury were motor vehicle accidents (n= 10, 58.8%), falls (n= 5, 29.4%), and assaults (n= 2, 11.8%). Computerised tomography (CT) and MRI scans conducted for clinical purposes at the time of the injury showed injuries to be right hemisphere-focused (n = 8), left hemisphere-focused (n = 3), or bilateral (n = 4). For the remaining participants (n = 2), the injury site was not identified. See supplementary table 1 for detailed description of injuries.

Control participants were recruited from the general community via advertisements. Controls and TBI participants were well matched for age and occupation, but controls were more highly educated (p = .03). All participants were excluded if they had: uncorrected hearing or vision loss, a current diagnosed alcohol or drug condition, active psychosis or were receiving treatment for a psychiatric condition, dementia or other neurodegenerative disease, aphasia, agnosia or profound amnesia. Ethics approval was obtained through the Human Research Ethics Advisory Panel (HREAP reference 103,049) at the University of New South Wales.

The study consisted of two separate testing sessions: a three hour session where written consent was obtained, information about the study was provided to the participant, and TASIT and other neuropsychological assessments were administered. The second session took place within two weeks of the first, where participants were taken to the Neuroscience Research Australia (NeuRa) research institute for a one hour MRI scan.

Cognitive assessments:

Social cognition: The Awareness of Social Inference Test (TASIT) (McDonald et al. 2003) uses audiovisual vignettes of actors engaged in everyday encounters. Multiple cues such as gesture, facial expression, prosody and context must be integrated in order to interpret social information. TASIT (version A) Part 1: Emotion Evaluation Test (EET) includes 28 vignettes and assesses seven basic emotions (happy, neutral, surprise, sad, anger, fear and disgust). After each clip, participants indicate what emotion the characters portrayed. Scores range from 0 to 28. Part 2: Social Inference Minimal (SI-M) includes 15 vignettes in which speakers are either being sincere or sarcastic. Following each vignette participants are required to answer four forced-choice questions (yes/no/don't know) regarding what the people in the scene were thinking, intending, felt and meant by what they said. Thus questions tapped knowledge of emotional states, beliefs and intentions of the characters, and the conversational meaning of the exchange. Scores on Part 2 range from 0 to 60.

Standard neuropsychological tests were also given to provide information about general cognitive ability in the participants with TBI. Information processing speed was assessed using the *Digit Symbol Coding (DSC)* subtest of the WAIS-III (Wechsler 1997). Working memory was assessed using *Digit Span (DS)* subtest of the WAIS-III (Wechsler 1997). Executive functioning was assessed via *Trails A and B* (Reitan 1992) (Ratio of time to complete B/A to index flexibility), and *Haylings Sentence Completion test* from the *Haylings and Brixton test* (Burgess and Shallice 1997) to index inhibition. This task requires participants to provide semantically-related or semantically-unrelated (inhibition condition) end words to complete aurally presented sentences (overall profile score, based on time to initiate response and errors made). A composite neuropsychological score was calculated, by averaging Z scores from Trails A, Trails B, Trails B/A, DS, DCS and Hayling Sentence Completion test.

Neuroimaging assessments

Image acquisition

Whole-brain diffusion-weighted images were obtained from a 3-Tesla scanner (Philips Achieva 3.0T TX) with a standard 8-channel head coil. For the diffusion-weighted sequence, two sets of whole-brain echo-planar images were acquired with 32 non-collinear gradient directions (repetition time /echo time /inversion time: 8400 /68 /90 ms; b-value = 1000 s/mm^2; 55 slices, horizontal slice thickness 2.5 mm, end resolution: 2.5 x 2.5 x 2.5 mm^3; field of view: 240 mm^2, 96 x 96 matrix).

Tract-based spatial statistics (TBSS)

DTI data were processed with Tract-based spatial statistics (TBSS v 1.2) (Smith et al. 2006) part of the Functional MRI of the Brain Software Library (FSL v 5.0.9).(Smith et al. 2004) Image pre-processing involved the following steps - Firstly, the

two DTI sequences were averaged to improve signal-to-noise ratio before being corrected for eddy current distortions and head movements using affine registration to the non-diffusion volumes (b0). Then, the Brain Extraction Tool was applied to both the b0 images and the diffusion-weighted images (Smith 2002). Each brain was visually checked to ensure the accurate removal of all non-brain tissues during the skull-stripping process. Finally, a tensor model was fitted into the diffusion images using FMRIB Diffusion Toolbox, and the primary, secondary and tertiary tensor eigenvalues (λ_1, λ_2 & λ_3) were generated.(Smith et al. 2004) The two DTI metrics obtained included fractional anisotropy (FA), which is the ratio of the above metrics, generating a value between 0 to 1 to show the overall magnitude and orientation of water diffusion in tissue and mean diffusivity (MD), the averaged diffusion coefficient along all axes.

Then, imaging data were processed using the following methodology, which can be summarized in four steps - Firstly, each individual FA map was transformed to the FMRIB58 fractional anisotropy template using nonlinear registration. All aligned FA images were affine-registered into the Montreal Neurological Institute standard space (MNI-152). Secondly, the averaged FA data were thinned to create a skeleton of white matter that signified the centres of all white matter tracts (lines of maximum FA) common to the group. Thirdly, each individual FA data point was projected on the mean FA skeleton to correct residual misalignment and to line up the centres of individual tracts. The mean FA skeleton was thresholded at 0.2 to minimize partial volume effects and inter-subject variability. Lastly, MD was also mapped onto the skeleton using projection vectors from the FA-to-skeleton transformation for each individual (Smith et al. 2006).

A voxelwise general linear model was applied and clusters were generated from a permutation-based (5000 permutations performed), non-parametric test with the threshold-free cluster enhancement (TFCE) option (Winkler et al. 2014). The statistical threshold was set at $p < 0.01$ corrected for multiple comparisons (family-wise error) for all analyses.

Statistical analyses

Data were analysed with SPSS 23 (IBM Corp.). One-way analyses of variance, followed by post hoc tests where relevant were conducted to examine demographic and neuropsychological variables. Categorical variables (e.g., sex) were analysed using chi-square analyses.

Whole brain correlations between TASIT performance and white matter structure were modeled using FSL's general linear model. Analyses were conducted across both groups for FA and MD values against demeaned TASIT scores using Randomise in FSL. Part 1: EET and Part 2: SI-M were first run with FA and MD, separately, with age and years of education as covariates of no interest, and then repeated with the addition of the composite neuropsychological score as an additional covariate. All correlations were threshold at an α level of .05. Peak voxel values from significant clusters were then entered into SPSS to obtain Pearson's coefficient values and level of significance. For all analyses, the statistical threshold was set at $p < .05$.

Results

Demographic details for the two groups are provided in Table 1, and performance on neuropsychological tests and TASIT in Table 2.

Groups were well matched for sex, age and preinjury occupation (all values $p > .05$). Significant group differences were found in years of education, where TBI participants had significantly less years ($p = .03$) than healthy controls. Education was entered as a covariate in all subsequent analyses so this did not influence results. Participants with TBI, on average, had poorer performance on TASIT than controls, for both Part 1: EET and Part 2: SI-M (all p values < .05) (Table 2). Additionally, TBI participants performed significantly worse on the other neuropsychological measures (DSC, DS and Trails A) (all p values $\leq .05$), with the exception of Trails B, the flexibility measure (TMT B/A), and Hayling test (p values > .05).

White matter findings

White matter differences between TBI and healthy controls

People with TBI showed greater alterations (reduced FA and increased MD) than healthy controls in the following white matter tracts: fornix, corpus callosum, cingulum (excluding MD in the left anterior cingulum), anterior limb of the internal capsule, external capsule, brainstem, uncinate fasciculus, plantum temporale, forceps major, forceps minor, and both the inferior and superior longitudinal fasciculi. At the same significance level, areas that had reduced FA uniquely were the cerebellum, anterior fronto-occipital fasciculus, thalami, posterior internal capsules, and the right hippocampus. Conversely, the area uniquely significant to increased MD in people with TBI was the corticospinal tract. White matter regions that differed between groups are displayed figuratively in Fig. 1.

Correlations between white matter changes and neuropsychological scores

For MD, there were no significant clusters of white matter change that correlated with TASIT after correction for multiple comparisons. Decreased FA in widespread structures was

Table 1 Demographic information for control and TBI groups

Variable	Controls (n = 17)	TBI (n = 17)	p value
Sex (male/female)	14/3	14/3	-
[a]Age (years)	44.2 (14.6)	45.6 (13.2)	.75
[a]Education (years)	14.8 (2.9)	12.4 (3.3)	.03
Preinjury occupation			-
Student	4	4	-
Unskilled	3	5	-
Skilled trade	3	3	-
Professional	5	5	-
[a]Years since injury	NA	12.8 (8.8)	-
[a]PTA	NA	49.8 (35.0)	-

Abbreviations: PTA post traumatic amnesia

[a] Numerical values are illustrated in mean (standard deviation)

associated across both groups when including age and years of education as covariates of no interest. The corpus callosum, frontal and temporal regions were primarily correlated with part 1 with additional posterior white matter associated with Part 2 (Fig. 2). When the combined neuropsychological score was included as an additional covariate, there were no longer significant correlations between TASIT Part 1 and FA. However, significant clusters of decreased FA were still associated with TASIT Part 2 (Fig. 3). These focused on the body of the corpus callosum, fornix, thalami, right external capsule, and right mid-temporal gyrus. Pearson coefficients and p values for significant clusters, where FA showed a significant relationship with TASIT subscores across groups, are displayed in Table 3.

Discussion

Diffuse axonal injury is almost ubiquitous in severe traumatic brain injury. This study, focused on a convenience sample of 17 adults with severe TBI, confirmed that white matter pathology is widespread with significant group differences in FA in numerous tracts. The corpus callosum, providing major inter-hemispheric connection extending anteriorly into the forceps minor and posteriorly into the forceps major was significantly damaged as was the fornix. Longitudinal fasiculi providing anterior-posterior connections were also compromised as were the uncinate fasiculus and cingulum disrupting fronto-temporal communication. Corticospinal, brain stem and cerebellar tracts were also affected. Disorders of social communication are common following severe TBI and this group was no exception. They were impaired when asked to identify emotional states, make judgements about feelings, beliefs, intentions and determine the meaning of conversational remarks.

We surmised that loss of connections would disrupt understanding of naturalistic social stimuli that required multimodal processing, including verbal and non-verbal cues, e.g. facial and body cues, auditory and emotional parameters and broader appreciation of context. The correlations between white matter voxels and TASIT performance bore this out. Accurate identification of emotional state was associated with better directional diffusivity of inter-hemispheric (corpus callosum and fornix) connections. The corpus callosum enables communication between verbal processes which are predominantly mediated by the left hemisphere (Price 2012) and vocal and facial processes supported by the right hemisphere (Charbonneau et al. 2003). The fornix is critical to memory recall (Tsivilis et al. 2008) transmitting both verbal and non-verbal information from the hippocampus to the thalamus. The cerebellar peduncles providing connection with the cerebellum were also implicated. While traditionally associated with motor coordination, the cerebellum also plays a role in synthesising somatosensory input, emotion and motor regulation (Sacchetti et al. 2009; Timmann et al. 2010).

White matter in the region of the left thalamus was also significantly associated with TASIT 1 (and 2). Damage to

Table 2 Group averages (and standard deviations) for TASIT performance and neuropsychological assessment, adjusted for years of education

	Controls (n = 17)	TBI (n = 17)	p value	Effect size η^2p
TASIT				
Part 1: Emotion Evaluation Test	25.2 (2.0)	22.3 (3.5)	.021	.22
Part 2: Social Inference - Minimal	55.8 (3.3)	49.1 (5.6)	.001	.36
Neuropsychological assessment				
Digit Symbol Coding (standard score: SS)	10.8 (2.1)	7.4 (2.3)	< .001	.43
Digit Span SS	12.0 (3.3)	9.4 (2.5)	.012	.25
Trails A (secs)	26.4 (6.6)	35.2 (11.8)	.042	.18
Trails B (secs)	58.8 (16.5)	84.1 (36.3)	.051	.18
Trails B/A	2.3 (0.5)	2.4 (0.9)	.741	.02
Haylings Sentence Completion: SS	5.8 (1.9)	5.2 (2.1)	.723	.02
Composite neuropsychology score (mean Z score)	0.1 (0.3)	-0.2 (0.4)	.003	.31

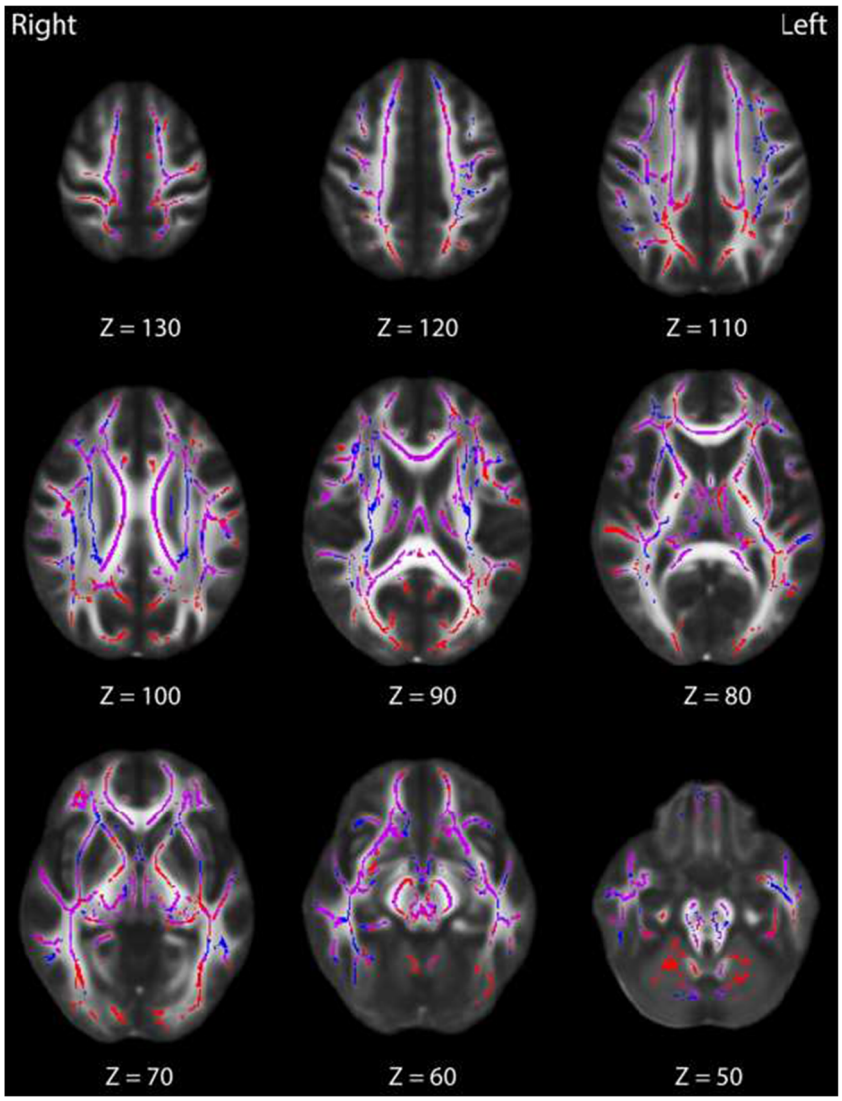

Fig. 1 White matter tracts showing greater white matter deficits in TBI participants versus healthy controls. Voxelwise changes are shown for FA and MD ($p < .01$, TFCE corrected for multiple comparisons). Significant voxels common to both FA and MD (purple), unique to FA (red), and unique to MD (blue), are overlaid on the FMRIB58 FA brain template

connections within the thalamus are increasingly considered to be a major consequence of TBI possibly due to the vulnerability of deep corticospinal fibre tracts during mechanical distortion associated with the forces of trauma (Little et al. 2010) as well as secondary effects from raised intracranial pressure, vascular changes and Wallerian degeneration (Bigler and Maxwell 2011). Thalamic nuclei play specific roles in the integration and relay of complex sensory, motor, cognitive and affective information. Thus, thalamic disruption has the potential to cause broad network disturbance manifesting in a variety of ways depending on the sub-thalamic nuclei affected. Posterior (left) thalamic lesions are commonly associated with language disorders while more anterior and medial lesions have been associated with changes to personality, affect and behavior (Carrera and Bogousslavsky 2006). Thalamic nuclei have been attributed with a role in mediating affective prosody (Leigh et al. 2013), empathy (Bzdok et al. 2012) and autonomic arousal (Rushby et al. 2016) and have been shown to mediate between prefrontal processing of emotional experience and hypothalamic processes (Kober et al. 2008). Thalamic regions have also been surmised to play a pivotal role in producing executive dysfunction after TBI (Little et al. 2010).

Abnormalities in white matter within the planum temporale (right), a region associated with spatial auditory location and visuo-auditory integration (Alho et al. 2014; Alink et al. 2012; Lewis and Noppeney 2010; Zundorf et al. 2014) were also implicated in poor TASIT 1 scores. So too, were bilateral external capsules. The external capsule is a cortico-striatal fibre system that helps integrate information, carrying fibres from prefrontal, premotor, precentral, temporal and preoccipital cortical regions to the claustrum, putamen and caudate nucleus (Schmahmann and Pandya 2006). Finally, poor emotion perception was associated with damaged connections bordering the anterior temporal horn deep within the temporal lobe. The right temporal lobe, especially the pole is surmised

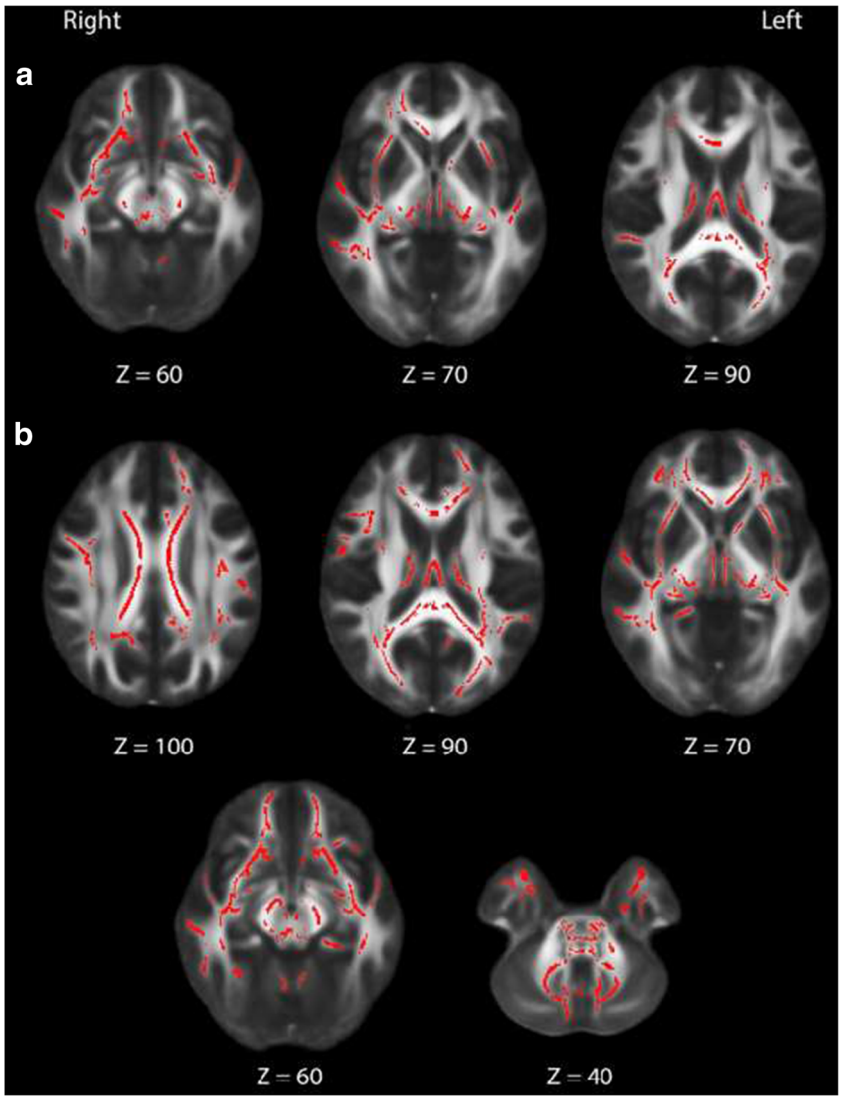

Fig. 2 Significant correlations across groups between emotional evaluation performance and decreased FA (**a**) (3 images) and social inference minimal performance and decreased FA (**b**) (5 images) adjusted for age. Significant voxels ($p <$ .05, TFCE corrected for multiple comparisons) (red) are overlaid on the FMRIB58 FA brain

to combine highly processed perceptual inputs with emotional responses (Olson et al. 2007).

Poorer performance on more complex social inference making (TASIT Part 2) involved additional tracts, notably, connections to the left mid temporal gyrus and left hippocampus highlighting the importance of semantic memory and verbal recall in making such judgements. Also, poorer connections within the bilateral orbito-frontal cortex and (left) frontal pole were associated with poorer scores. The orbitofrontal and frontopolar cortex are closely associated

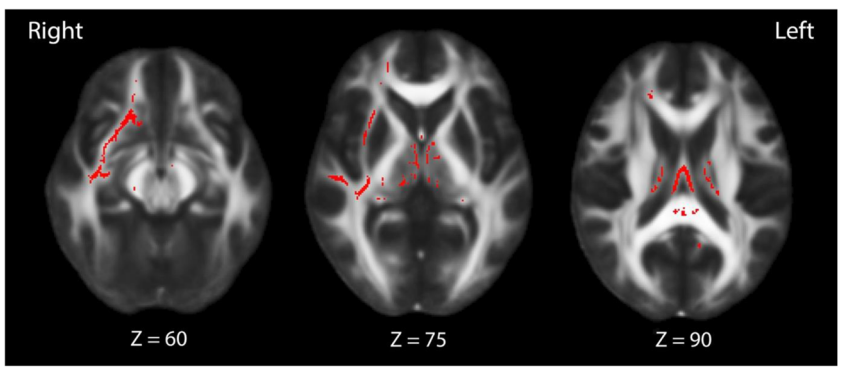

Fig. 3 Significant correlations across groups between social inference-minimal performance and decreased FA, adjusted for age and composite neuropsychological score. Significant voxels ($p <$ .05, TFCE corrected for multiple comparisons) (red), are overlaid on the FMRIB58 FA brain

Table 3 FA Regions of significant clusters correlated with either TASIT part 1 or 2 (with covariate) for central, left and right brain regions (α = .05)

	Central			Left			Right		
		R^2	*p* value		R^2	*p* value		R^2	*p* value
TASIT 1 (age and education)	Fornix	0.53	.002	Thalamus	0.54	.001	Plantum temporal	0.49	.005
	CC body	0.54	.001	External capsule	0.51	.003	External capsule	0.50	.004
	Cerebellar peduncle	0.46	.009				Anterior temporal horn	0.38	.034
TASIT 2 (age and education)	Fornix	0.43	.013	Orbital prefrontal cortex	0.47	.007	Orbital prefrontal cortex	0.37	.036
	CC splenium	0.48	.006	Thalamus	0.50	.004	External capsule	0.52	.002
	Cerebellar peduncle	0.49	.004	Superior frontal pole	0.49	.004			
				Hippocampus	0.42	.018			
				Mid-temporal gyrus	0.44	.012			
TASIT 2 (age, education and composite NP score)	Fornix	0.48	.006	Thalamus	0.40	.026	Thalamus	0.37	.043
	CC body	0.47	.007				External capsule	0.54	.002
							Mid-temporal gyrus	0.44	.014

Abbreviations: CC corpus callosum, *NP* neuropsychology

with emotion and flexible perspective taking respectively (Adolphs 2001; D'Argembeau et al. 2007; Ruby and Decety 2004).

A secondary goal was to determine whether there were any specific tracts that may be implicated in social cognition, over and above those involved in generic non-social processes such as attention, information processing efficiency and executive function. When a covariate indexing such skills was included no tracts remained significantly associated with Part 1 of TASIT. However, the corpus callosum, fornix, bilateral thalamus, right external capsule and right mid-temporal gyrus remained significantly associated with Part 2. The small battery of neuropsychological tests employed were all verbally mediated, thus, the corpus callosum may have continued to emerge due to the importance of non-verbal cues mediated by the right hemisphere in social cognition. The continued significant association with the right external capsule is consistent with this explanation as is the emergence of the right mid-temporal gyrus as a significant predictor. This latter finding is also consistent with research into patients with right lateralised semantic dementia. In this group problems with face perception and emotion perception are specifically associated with right anterior temporal lobe thinning (Kumfor et al. 2016). Indeed, there is a substantial literature that suggests that right hemisphere processes play a dominant role in socio-emotional processes (e.g. Adolphs et al. 2000; Champagne-Lavau and Joanette 2009; Charbonneau et al. 2003; Saldert and Ahlsen 2007).

It may be also concluded that the fornix has a role in social cognition that is over and above its involvement in the more generic neuropsychological tests given. Finally, the continued emergence of connections with the thalamus, highlights the importance of this system of nuclei in complex social information processing. As argued by Little et al. (2010), thalamic injury may play a greater role in producing cognitive impairment following TBI than previously thought. Little found that reduced FA in ventral and anterior thalamic structures was significantly associated with loss of attention, executive function and memory. In our study, even when controlling for other cognitive abilities, the thalamic regions remained important in social cognition. Clearly, these subcortical structures have a pivotal role in complex multimodal processing and integration for both social and non-social information.

This study is not without limitations. Our sample size was relatively small which limits generalisation. Further, the group was highly variable with respect to time since injury. Thus, it is difficult to know what role chronicity of injury may have played in the findings. Despite this, the pattern of findings is consistent with expectations. The fibre tracts identified as playing a role in social cognition include those that are known to mediate auditory localisation (planum temporale) communication between nonverbal and verbal processes in general (corpus callosum) and in memory in particular (fornix) as well as tracts and structures associated with semantic processing (left temporal lobe), multimodal processing and integration (thalamus, external capsule, cerebellum) and with social cognition specifically (orbitofrontal cortex, frontopolar cortex, right temporal lobe).

As an exploratory study, we cannot conclude that these structures play a unique role in mediating social cognitive performance. Although structures have been identified using the TBSS method, caution must be taken when making inferences about the overall diffusion properties in the individual structures. Our methods are consistent with others published using TBSS to examine white matter tracts in people with TBI (Adamson et al. 2013; Genova et al. 2015; Kinnunen et al. 2011; Leunissen et al. 2014; Palacios et al. 2011; Veeramuthu et al. 2015; Xiong et al. 2014) representing a standard, well

accepted approach. However, the present findings are based on the selected set of voxels that are constrained to the skeletonised template, which may not be representative of whole white matter regions. Therefore, a further region of interest approach may yield more information regarding individual structures. A further limitation is that shared with all neuroimaging studies of this nature, that is, the correlation between white matter changes and poor social cognitive performance cannot be interpreted as evidence of a causal relationship. However, the pattern of results is consistent with expectations, i.e. those with greater abnormalities in regions presumed to support social cognition, had poorer social cognitive performance. The patterns suggest that social cognition is not simply mediated by specific frontal and temporal cortical regions, but by a complex interplay of functions made possible through white matter connections within and between the hemispheres. They also highlight the importance on understanding loss of white matter connectivity in producing complex impairments following severe TBI.

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Compliance with ethical standard

Conflict of interest SM receives royalties for The Awareness of Social Inference Test. There are no other conflicts to declare.

Ethical approval All procedures performed were in accordance with the ethical standards of the Human Research Ethics Advisory Panel (HREAP approval reference 103,049) at the University of New South Wales and complied with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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