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ORIGINAL ARTICLE

Changes in intrinsic functional brain networks following blast-induced mild traumatic brain injury

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Abstract

Objective: Blast-induced mild traumatic brain injuries (mTBI) commonly go undetected by computed tomography and conventional magnetic resonance imaging (MRI). This study was used to investigate functional brain network abnormalities in a group of blast-induced mTBI subjects using independent component analysis (ICA) of resting state functional MRI (fMRI) data.

Methods: Twenty-eight resting state networks of 13 veterans who sustained blast-induced mTBI were compared with healthy controls across three fMRI domains: blood oxygenation level-dependent spatial maps, time course spectra and functional connectivity.

Results: The mTBI group exhibited hyperactivity in the temporo-parietal junctions and hypoactivity in the left inferior temporal gyrus. Abnormal frequencies in default-mode (DMN), sensorimotor, attentional and frontal networks were detected. In addition, functional connectivity was disrupted in six network pairs: DMN–basal ganglia, attention–sensorimotor, frontal–DMN, attention–sensorimotor, attention–frontal and sensorimotor–sensorimotor.

Conclusions: The results suggest white matter disruption across certain attentional networks. Additionally, given their elevated activity relative to controls', the temporo-parietal junctions of blast mTBI subjects may be compensating for diffuse axonal injury in other cortical regions.

Keywords

Blast, cognition, functional magnetic resonance imaging (fMRI), independent component analysis (ICA), mild traumatic brain injury (mTBI), resting state networks (RSN)

History

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Introduction

The annual incidence of traumatic brain injury (TBI) in the US has been estimated at 1.7 million, accounting for one third of all injury-related deaths [1]. With two ongoing wars, the incidence of head injuries in the US armed forces has been on the rise. While US troops deployed in Iraq and Afghanistan today wear some of the most advanced armour in the world, improving their survivability dramatically, the rates of other non-fatal, yet debilitating, injuries have risen [2]. Due to the widespread use of improvized explosive devices by Iraqi and Afghani combatants, the rate of TBI has been especially elevated in US troops.

Most veterans who have come in close proximity to explosions report cognitive impairments that are similar to those caused by more direct mechanisms of TBI, such as difficulty with concentration, memory and mood [3, 4]. These symptoms collectively define post-concussive syndrome (PCS) [5], which in turn has been found to overlap significantly with post-traumatic stress disorder (PTSD) [6]. Post-concussive symptoms (e.g. cognitive, affective, physical, social) persist in over a third of veterans diagnosed with mild TBI (mTBI) [7]. Due to the high comorbidity of mTBI and PTSD and the similarity in certain of their clinical symptoms in the definition of PCS, it has been argued that PCS may not only be directly caused by mTBI, but sometimes misdiagnosed as PTSD resulting from the traumatic event of being near an explosion itself [8]. Meares et al. [9] suggested that PCS is not specific to head injury at all, but can occur following any traumatic injury. Consequently, soldiers who have sustained mTBI can sometimes be mistakenly diagnosed with PTSD and vice versa [6, 8]. Given their potential ability to discriminate between these two factors, neuroimaging studies on blast-induced trauma provide invaluable insight into understanding and diagnosing mTBI.

Advanced neuroimaging techniques have the potential to illuminate the structural and functional changes in the brain that contribute to mTBI symptoms. Mild TBI mainly disrupts the brain's neuronal cytoskeleton on a microscopic level, resulting in diffuse axonal injury (DAI) [10] and no large-scale tissue disruptions [11]. To date, however, DAI commonly goes undetected by computed tomography and conventional magnetic resonance imaging [12–14]. The damage to white matter neuronal fibres resulting from DAI can alter the tightly bundled tracts and decrease their ability to restrict water diffusion to the long axis of fibre track direction. Diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) techniques have

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been used to detect the fractional anisotropy decreases due to this loss of structural organization in DAI patients [11, 15–17]. However, the DTI findings on DAI are inconsistent, with some studies reporting fractional anisotropy changes long after injury [15] and others suggesting that the technique is most useful in detecting DAI in the first 24 hours following injury, with the diffusion anisotropy decreases becoming less apparent after just 1 month [18]. Additionally, while DTI can point to areas that have sustained structural damage, it is of little help in localizing regions of affected brain activity that suffered neuronal deafferentation. Thus, other sensitive imaging methods are needed to supplement DTI data in order to provide a more complete picture of mTBI's effect on brain structure and function.

In a case study of one blast mTBI subject, Huang et al. [19] used magnetoencephalographic imaging coupled with DTI to find abnormal low frequency delta wave activity in multiple regions of the left hemisphere: dorsolateral prefrontal cortex (DLPFC), middle frontal gyrus (MFG), orbital frontal cortex (OFC), anterior cingulate cortex (ACC) and temporo-parietal junction (TPJ) regions. In addition, the right hemisphere also exhibited delta wave activity in the MFG and the ventrolateral prefrontal cortex (VLPFC). The subject's DTI data showed a thinner bilateral superior longitudinal fasciculus (SLF) in the mTBI subjects relative to controls. These results provided insight into specific areas of neuronal deafferentation in the cortex due to the damage of white matter tracts caused by blast injury. In an attempt to detect such cortical abnormalities in a group of blast mTBI subjects, this study utilized independent component analysis (ICA) [20] of resting state fMRI data, which may be more sensitive to small individual differences than conventional fMRI analyses [21].

The aggregate blood oxygenation level-dependent (BOLD) signal observed by the functional magnetic resonance imaging (fMRI) technique is formed by a combination of multiple signals from their respective locations, with each location having a unique fluctuation in activity over time [22]. The temporal correlations between multiple regions can be examined using ICA, producing a set of independent components with high intrinsic temporal coherences. Independent component analysis separates the aggregate BOLD signal into its components using blind signal separation. One advantage of this method is that it is data-driven and an *a priori* behavioural model is not needed [23]. Three domains of fMRI data can be examined using ICA: spatial maps, functional network connectivity (FNC) and time course spectra. This study hypothesized abnormalities within intrinsic networks across all three domains in patients with blast mTBI compared to control subjects.

Methods

The experimental protocol was approved by the University of New Mexico Human Research Protections Office and the Veterans Affairs Hospital Office of Research and Development. Potential subjects who encountered blasts during deployment were referred to the researchers by the Veterans Affairs Hospital Department of Polytrauma. Study eligibility criteria included exposure to a blast, no neurological conditions (e.g. epilepsy), no substance abuse, no history of blunt head trauma and no PTSD diagnosis. The following criteria were used to classify the subjects as having sustained mTBI following blast exposure: minimal loss of consciousness (<30 minutes), minimal post-traumatic amnesia (<1 day), normal structural MR scans and mild-to-moderate post-concussive symptoms as determined by the Neurobehavioural Symptom Inventory. The Glasgow Coma Scale ratings were not available for most subjects and were not used as an eligibility criterion, as the injuries were usually sustained in the battlefield far from medical care facilities. Structural MR images were examined for abnormalities by an on-site radiologist. The above information was obtained from the subjects' Veterans Affairs Hospital medical records and supplemented with self-reports. Seventeen subjects were initially enrolled, with four being excluded from the study upon discovery of confounding blunt head injuries. Thirteen male veterans (age = 34.3 years, SD = 6.6 years) were included in the final dataset (Table I). The control group consisted of 50 healthy male subjects (age = 29.7 years, SD = 8.4 years) with no history of head injuries or substance abuse, whose fMRI data were obtained from the resting state ICA study by Allen et al. [24].

Table I. Blast-induced mTBI group summary. Blast directions were classified as roughly originating either from the front/back or left/right of the subjects' heads. Only three subjects reported the explosions at their sides. Loss of consciousness (LOC) occurred in all but three subjects. Five subjects have had more than one blast encounter throughout deployment.

Subject	Age	Direction	LOC	Blasts
1	53	Front/Back	No	1
2	30	Side	Yes	1
3	35	Front/Back	Yes	1
4	39	Front/Back	Yes	2
5	38	Front/Back	Yes	1
6	36	Side	Yes	3
7	32	Front/Back	Yes	1
8	33	Side	No	3
9	30	Front/Back	Yes	2
10	31	Front/Back	Yes	1
11	29	Front/Back	Yes	1
12	33	Front/Back	Yes	1
13	27	Front/Back	No	2

The following neuropsychological tests were administered to the TBI subjects by a trained neuropsychologist: California Verbal Learning Test II (CVLT-II) [25], Wisconsin Card Sorting Test (WCST) [26], Neurobehavioural Symptom Inventory (NSI) [27], Beck Depression Inventory II (BDI-II) [28], Digit Span (DS), Digit Symbol Test, Trail Making Test A (numbers only; TMT-A), Trail Making Test B (numbers and letters; TMT-B), Paced Auditory Serial Addition Test (PASAT), Wechsler Test of Adult Reading (WTAR), Controlled Oral Word Association Test (COWAT) and Stroop Test (ST) [29]. A one-sample t-test was used to compare the obtained t scores to the population estimated mean of 50.

The mTBI group's fMRI data was acquired using a 3-Tesla Siemens Trio scanner at the Mind Research Network (MRN), Albuquerque, NM. T2*-weighed functional images were acquired using a gradient-echo echo planar imaging (EPI) sequence with the following parameters: echo time (TE) = 29 milliseconds (ms), repetition time (TR) = 2 seconds, flip angle = 75°, slice thickness = 3.5 millimetres (mm), distance factor = 30%, field of view = 240 mm, matrix size = 64 × 64 voxels, voxel size = 3.8 mm × 3.8 mm × 3.5 mm. Resting-state scans were 5 minutes, 34 seconds (167 volumes total). During the fMRI sequence, participants were instructed to fixate their eyes on the crosshairs presented on the screen in front of them, relax and think of nothing in particular while keeping their eyes open. Control subjects' T2*-weighted functional images were acquired using the same parameters as the TBI group, with the exception of more volumes being collected [24]. The first 150 volumes from both groups were analysed. Subjects' translation and rotation in the scanner were estimated by the motion correction algorithm and subjects whose average translation exceeded one voxel (3 mm) were to be excluded from the analysis.

Maximally independent whole-head spatial maps and time courses, which summarize the underlying BOLD signal, are the output of the multivariate ICA algorithm. The group ICA process produces single subject maps and time courses, which can then be tested for differences that exist between groups. The ICA package used here, called the Group ICA fMRI Toolbox (GIFT; http://mialab.mrn.org/software), examines three main aspects of the ICA components, including the voxel-wise weights for each component image, the spectral power of each ICA time course at a given frequency bin and the cross-correlation among ICA time courses (FNC). Comparison of spatial BOLD activation maps can reveal differences in the sizes of individual intrinsic networks. The time course spectra analysis allows examination of any differences in power of specific signal frequencies between groups. This has the potential to point toward abnormalities in certain ICs, as previous literature suggests that certain disorders, such as schizophrenia, have frequency patterns that are significantly different from those observed in healthy controls [30, 31]. Components' frequency ranges also serve as tools for distinguishing functional independent components of interest from those formed by noise, with large high–low frequency ratios and large dynamic ranges being present in functional ICs [24]. Differences in FNC are potentially of great importance as well, pointing to the connectivity between specific pairs of networks that may be functionally disrupted by injuries or disorders [32]. Any affected connections found by FNC analysis have the potential to explain certain cognitive impairments observed in TBI patients and warrant focused examinations of specific white matter tracts underlying these regions that may be compromised due to the injury using techniques such as DTI. ICA, therefore, has the potential to reveal information not previously detected by conventional fMRI analyses. Extensive information on group ICA has been presented in Calhoun et al. [33] and Erhardt et al. [34] and an application of group ICA to a large resting fMRI study is presented in Allen et al. [24].

The functional and structural data were pre-processed by an automated pipeline developed at MRN [35, 36], which was described in further detail in Allen et al. [24]. The fMRI data were then split into intrinsic networks using ICA with GIFT. Listed here are the parameters that were specified in GIFT to analyse the data. Seventy-five components were estimated from the data. Data were first scaled to a mean voxel value of 100 (intensity-normalized) and a two-stage principle component process was used to extract 100 principle components (PCs) from each subject and 75 PCs from the aggregate data. The Infomax ICA algorithm [20] was then run 10-times using the built-in ICASSO tool, which is used to estimate the reliability of ICs [37]. Resting state networks for multivariate analysis were qualitatively chosen out of the resulting components to match the networks identified using the GIFT software in Allen et al. [24].

Using the MANCOVAN tool in the GIFT software, multivariate analysis was performed on the isolated resting state networks to examine the effect of group (mTBI/Control) at a false discovery rate (FDR) corrected $p < 0.05$ on BOLD signal, time course spectra and FNC (see Allen et al. [24] for more details on the MANCOVAN approach). In addition to age, two variables of head motion in the scanner, translation in log (mm) and rotation log (degrees), were used as the covariates.

Results

The structural MR images did not show evidence of visible structural damage and were read as normal by a radiologist. Every effort was made to use subjects with blast-only injuries and eliminate any other confounding head injuries. The subjects, therefore, were representative of the target group of interest. The circumstances of each participant's injury are summarized in Table I. A trending difference in age between the mTBI and control groups was apparent upon completion of data collection. This difference did not reach statistical significance ($t(61) = 1.84$, $p = 0.07$). Due to this trend, however, age was used as a covariate in the fMRI data analysis.

The collected Neurobehavioural Symptom Inventory and Beck Depression Inventory II data classified the mTBI group as having moderate-to-severe post-concussive symptoms and moderate depression, respectively. The obtained scores are presented in Table II and were used to classify the levels of post-concussive symptoms and depression according to their manuals, respectively [27, 28]. Individual t-scaled performances across all of the neuropsychological tests in the mTBI group formed a normal distribution (mean = 44.1, SD = 6.5). TBI patient's averaged overall performance across all tests was significantly lower than the normal population's average performance of 50 on the t-scale ($t(12) = 2.64$, $p = 0.022$). mTBI subjects' scores across the neuropsychological battery revealed significant impairments in attention and processing speed (Table II). Specifically, performances on the symbol search, digit symbol test and trail making (numbers only) were significantly affected (Table II). Intelligence, verbal fluency, memory and executive function were not significantly different from the normal population's mean (Table II).

Subjects' average motion during imaging scans was within the acceptable range of less than 1 voxel (3 mm) of translation. No subjects were excluded for excessive motion in the MR scanner, with the largest average translation being 2.10 mm and the largest degree of rotation being 1.02°. Twenty-eight resting-state networks were identified in the 75 components produced by GIFT, all of which closely matched the reference networks found in Allen et al. [24] (http://mialab.mrn.org/data). The final set included six sensorimotor, six attention, six visual, four frontal, four default-mode

Table II. Neuropsychological examination summary for the mTBI group. The tests, along with the obtained *t*-scores, *t*-statistics and significance values, are organized according to the behavioural constructs measured. Mild TBI subjects as a group reported moderate depression and post-concussive symptoms. General intelligence, verbal fluency, memory function and executive function did not differ significantly from the expected population mean. The neuropsychological domains that were significantly impaired in the mTBI group were attention and processing speed.

Function	Test	Mean ± SE	*t*	*p*
PCS	NSI	2.42 ± 0.22	N/A Moderate	N/A
Depression	BDI-II	24.92 ± 3.73	N/A Moderate	N/A
Intelligence	WTAR	51.70 ± 2.50	0.68	0.511
Verbal Fluency	COWAT	45.39 ± 2.24	2.06	0.061
Memory	CVLT-II Short Delay	45.69 ± 4.27	1.01	0.333
Memory	CVLT-II Long Delay	46.00 ± 3.84	1.04	0.319
Executive	Digit Span Composite	47.00 ± 2.09	1.44	0.176
Executive	WCST	45.00 ± 2.89	1.73	0.109
Executive	Stroop	50.69 ± 1.69	0.41	0.688
Executive	TMT-B	44.85 ± 2.78	1.85	0.089
Attention	TMT-A	41.31 ± 2.83	3.07	0.010
Attention	PASAT	53.20 ± 2.41	1.33	0.209
Processing Speed	Digit Symbol	40.23 ± 1.94	5.03	< 0.001
Processing Speed	Symbol Search	42.39 ± 2.12	3.59	0.004

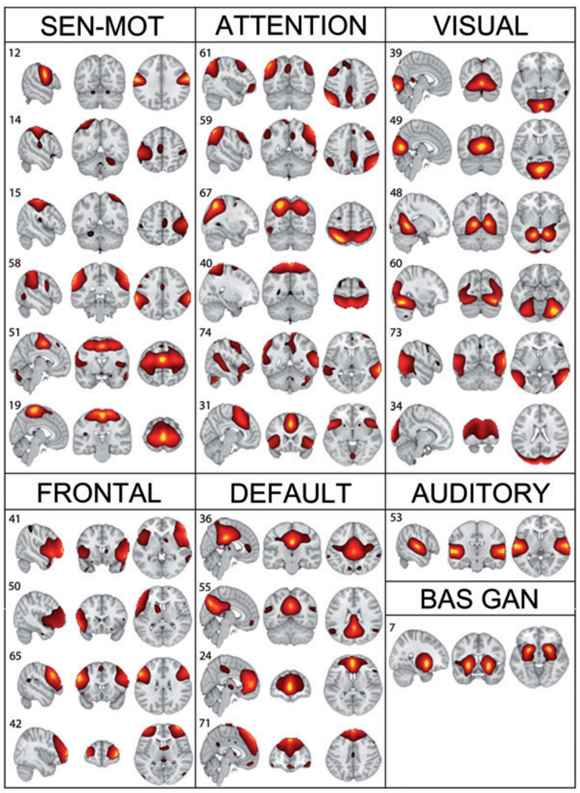

Figure 1. Identified Resting State Networks. A *t*-map covering the entire head was generated for every network. For illustration purposes, the above networks display the *t*-values of $t_{component} > \mu_{component} + 4\sigma_{component}$. Six sensorimotor (sen-mot), six attentional, six visual, four frontal, four default-mode, one auditory and the basal ganglia (bas gan) networks were identified using the networks identified in Allen et al. [24] as a reference. All further analyses were performed on the above resting state networks.

(DMN), auditory and the basal ganglia networks. The resulting set of components averaged across all 63 subjects is presented in Figure 1. Figure 5 shows the FNC matrices of the 28 components for the mTBI and control groups separately, as well as the significant differences between the two.

Multivariate analysis revealed significant effects on spatial maps in multiple intrinsic networks (Figure 2). Effects on time course spectra and FNC were also detected. Univariate analysis identified significant spatial map differences between mTBI and control groups in components 50 (frontal) and 73 (visual), with specific locations and effect sizes presented in Figure 3. Mild TBI subjects had higher activity in bilateral temporo-parietal junctions and lower activity in the left inferior temporal lobe relative to controls. Time course spectra were significantly different between groups in components 31 (attention), 65 (frontal) and 71 (DMN; Figure 4). Functional connections in the mTBI group had significantly weaker connections than controls in the following network pairs: 36–7 (DMN–basal ganglia), 59–12 (attention–sensorimotor), 41–36 (frontal–DMN), 59–14 (attention–sensorimotor), 59–65 (attention–frontal), 58–15 (sensorimotor–sensorimotor; Figure 5).

Discussion

This study has identified multiple intrinsic networks that show significant differences between mTBI blast injury subjects and control groups across the three examined fMRI domains. The spatial map findings are interesting in demonstrating that the mTBI group exhibited hyperactivity in the temporo-parietal junctions. Previously published simulation studies by this group have shown that blast waves travelling through the cranium may create maximum shear stresses that tend to be diffusely elevated in the posterior section of the brain [38]. The cerebellum, vermis, pons and medial temporal lobe (MTL) have previously been shown to have decreased metabolic rates of glucose in blast-induced mTBI subjects [39]. In addition, as mentioned previously, the left DLPFC, MFG, OFC, TPJ and ACC regions, along with the right VLPFC and MFG areas, exhibited slow delta wave activity in one patient, possibly caused by neuronal deafferentation due to the damage of white matter fibre tracts in the SLF following blast exposure [19].

In these results, attentional network 59 had impaired connectivities with three of the other examined networks. The connectivities of two frontal networks 41 and 65, as well as DMN 36, were also negatively affected. Such disruptions in the DMN connectivities could potentially contribute to the observed attentional and processing speed deficits by not activating entirely or lagging in activation when required by

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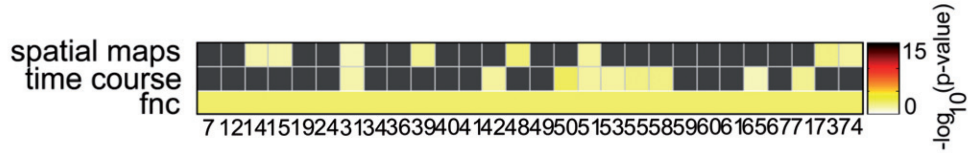

Figure 2. Multivariate Effects of Group. Group had an effect on all three of the examined domains: spatial maps, time course spectra and functional network connectivity (FNC). Multiple components were affected in each domain, with the yellow bins representing networks in which significant effects were observed at $\alpha = 0.05$. The observed widespread effect provided grounds to examine the univariate effects of group on each individual component in each examined domain.

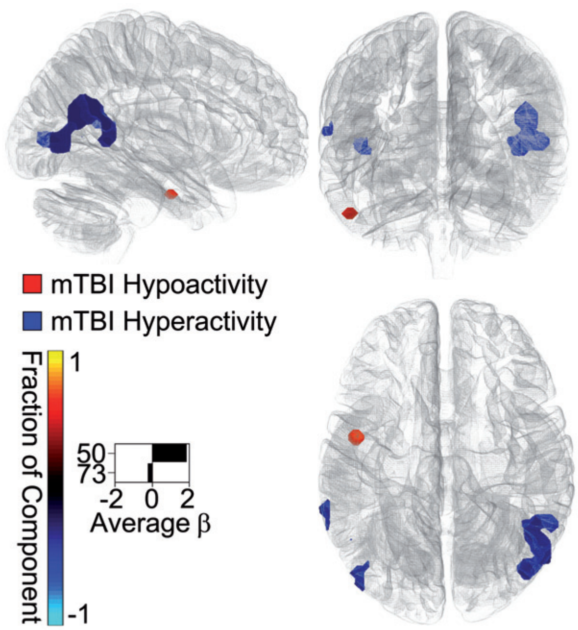

Figure 3. Spatial Map Results. The significant BOLD signal differences ($p < 0.05$ FDR corrected) between the mTBI and control groups (control − mTBI) are plotted on the Montreal Neurological Institute brain in blue (mTBI > Control) and red (Control > mTBI). The mTBI group displayed a higher activity in the temporo-parietal junctions, while the control group had elevated activity in the left inferior temporal lobe. The effect sizes (betas) are indicated by the lengths of the bars on the bottom left. The directions of the bars indicate which group had higher activity (control − mTBI). The colours of the bars indicate the fractions of the total respective component volumes that were affected. The areas affected by group, therefore, were small fractions of visual network 73 and frontal network 50.

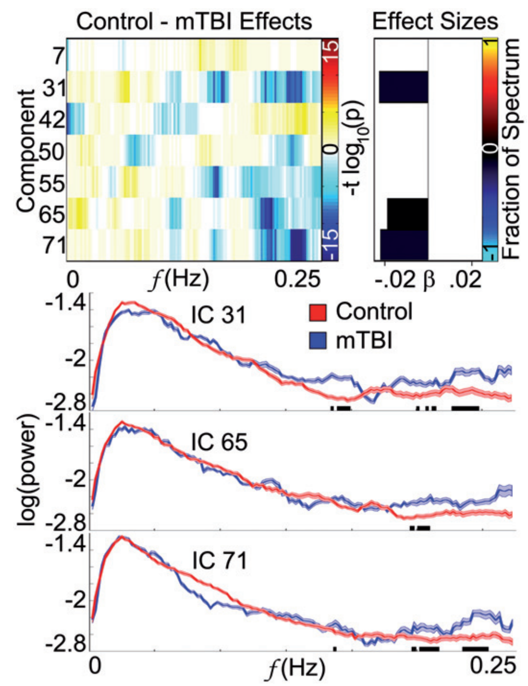

Figure 4. Time Course Spectra Results. The figure on the top-left shows the frequencies in components that were affected by group according to multivariate results. The bars to the right represent the effect sizes via their length and the colours of the bars indicate the fraction of each spectrum that was affected. Univariate results found only three components that were affected by group, with the mTBI group having significantly elevated high frequency activities in components 31, 65 and 71 ($p < 0.05$ FDR corrected). The time course spectra for each individual affected network are plotted on the lower half of the figure. The black bars at the bottom of the plots indicate the frequency bins in which the difference between the two groups reached statistical significance.

other cortical areas. While The FNC results are consistent with the cognitive impairments in attention and processing speed revealed by neuropsychological testing, the authors are cautious to suggest the direct translation of the neuroimaging results to the neuropsychological data, as no neuropsychological results from the neuroimaging control group were available and a 1-sample *t*-test was conducted instead.

The regions of increased activity within bilateral TPJ in subjects with mTBI are of interest, given the well-established role of these regions in sustained attention and vigilance [40]. More specifically, the right TPJ has been implicated in the salience of external stimuli, with those events with high behavioural relevance being able to interrupt ongoing cognition to actuate behavioural responses accordingly [41]. This ‘circuit breaking’ characteristic of the TPJ could be seen as an adaptive response to situations where environmental threats might be high. As exposure to trauma of any sort is associated with behavioural symptoms of increased vigilance, the extreme manifestation of which can be found in PTSD [9], it is plausible that upregulation of this ‘vigilance network’ in the brain would occur in patients exposed to unexpected blast injury. Previous studies have shown positive coupling between right TPJ and other brain regions including left TPJ, bilateral inferior frontal lobe and precuneus during attention-grabbing events presented in virtual environmental videos [42]. While speculative, it is possible that increased activation of right hemisphere vigilance networks in this cohort was associated with a corresponding decrease in left ventral pathways associated with object identification. The authors are unaware of corresponding studies showing inverse coupling of regions within dorsal and ventral pathways during such realistic visual processing scenarios.

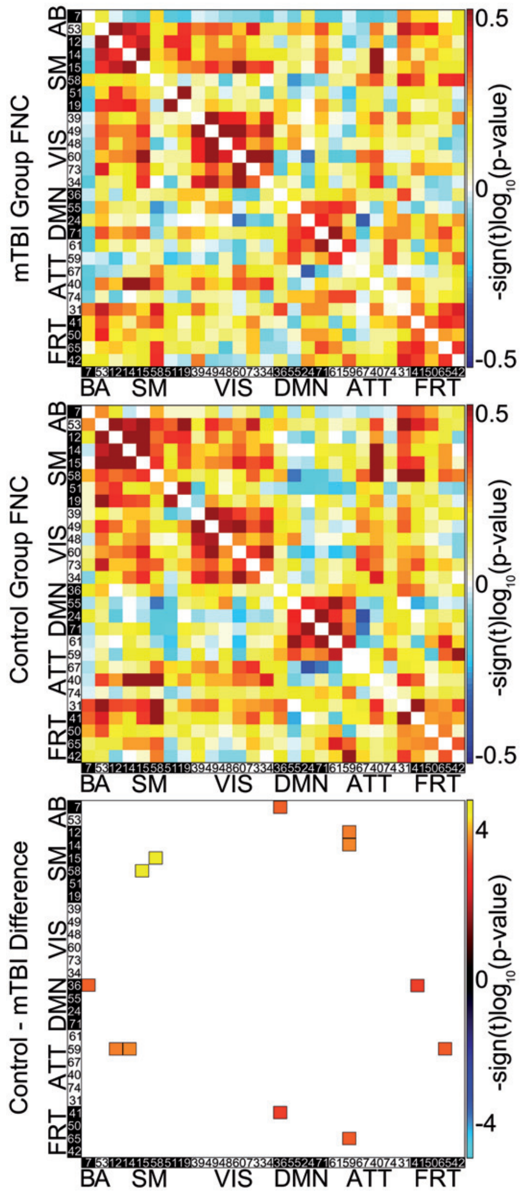

Figure 5. Functional Network Connectivity Results. The top matrix presents the connection strength of each of the 28 resting state networks with every other RSN network in the mTBI group. The matrix in the middle presents an analogous matrix for the control group. The matrix on the bottom shows the significant differences in FNC between the two groups ($p < 0.05$ FDR corrected). Six pairs of networks (36–7 (DMN–basal ganglia), 59–12 (attention–sensorimotor), 41–36 (frontal–DMN), 59–14 (attention–sensorimotor), 59–65 (attention–frontal), 58–15 (sensorimotor–sensorimotor) had significantly lower functional connectivities in mTBI subjects than in controls ($p < 0.05$ FDR corrected).

The small sample size in the described study limits the extent of the inferences one is able to make from the conducted analyses. Recruitment of purely blast-induced mTBI subjects has been a major bottleneck throughout the project. Although blast-induced mTBI contributes to a relatively large proportion of all injuries sustained in the military conflicts in the Middle East, the majority of combatants exposed to explosions also sustained other confounding injuries, such as blunt head trauma. Additionally, an optimal control group for use in the present study would consist of veterans who sustained no injuries during deployment, as Vasterling et al. [43] have previously demonstrated significant effects of military deployment on neuropsychological performance.

Another limitation of this study is the difficulty in precisely characterizing the conditions of blast wave exposure, direction, distance and magnitude. Only three of the mTBI subjects encountered blasts to the sides of their heads. Additionally, most subjects were oriented some number of degrees off true frontal or side blast directions. Given this variability in blast directions in the mTBI group, it was difficult to separate them into well-defined groups based on blast direction. Only three of the 13 subjects analysed in the present study had no LOC after the injury. Even with LOC, however, most veterans were able to relate remarkable detail about the circumstances of the events that led up to and followed the explosion. Most had recovered from pre-injury amnesia and had been informed of the events in detail by fellow soldiers who witnessed the explosion scenarios.

This is, to the authors' best knowledge, the first study to demonstrate disruptions due to purely blast wave encounters in resting brain function using fMRI. In contrast to the conventional fMRI analysis tools, independent component analysis was able to detect small differences in the three examined domains and present the results in a network-based, comprehensible way. This study has presented specific functional brain networks that have been affected along with the corresponding neuropsychological data that reflects such differences. Combined with the white matter disruptions that have been reported in the enormously complex mTBI field, the findings presented here are an important piece of the puzzle that demonstrates how structural damage manifests itself in cortical brain function after blast-related head injuries. The authors are currently analysing parallel modelling and simulation studies to investigate how blast-induced pressure and shear waves propagate through the human head and deposit localized energy. The distributions of these shear energy depositions relative to the observed changes in RSNs will be reported separately.

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Declaration of interest

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