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Changes in brain-behavior relationships following a 3-month pilot cognitive intervention program for adults with traumatic brain injury

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Abstract

Facilitating functional recovery following brain injury is a key goal of neurorehabilitation. Direct, objective measures of changes in the brain are critical to understanding how and when meaningful changes occur, however, assessing neuroplasticity using brain based results remains a significant challenge. Little is known about the underlying changes in functional brain networks that correlate with cognitive outcomes in traumatic brain injury (TBI). The purpose of this pilot study was to assess the feasibility of an intensive three month cognitive intervention program in individuals with chronic TBI and to evaluate the effects of this intervention on brain-behavioral relationships. We used tools from graph

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theory to evaluate changes in global and local brain network features prior to and following cognitive intervention. Network metrics were calculated from resting state electroencephalographic (EEG) recordings from 10 adult participants with mild to severe brain injury and 11 age and gender matched healthy controls. Local graph metrics showed hyper-connectivity in the right inferior frontal gyrus and hypo-connectivity in the left inferior frontal gyrus in the TBI group at baseline in comparison with the control group. Following the intervention, there was a statistically significant increase in the composite cognitive score in the TBI participants and a statistically significant decrease in functional connectivity in the right inferior frontal gyrus. In addition, there was evidence of changes in the brain-behavior relationships following intervention. The results from this pilot study provide preliminary evidence for functional network reorganization that parallels cognitive improvements after cognitive rehabilitation in individuals with chronic TBI.

Keywords: Neurology, Evidence-based medicine, Rehabilitation

1. Introduction

Traumatic brain injury (TBI) is a serious and complex public health issue. In the USA alone, there are over 1.6 million TBI's reported every year (Langlois et al., 2006) with many more unreported. A complex and debilitating neurological disorder, TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force (Menon et al., 2010). Classified by severity, TBI ranges from mild to severe, based on the length of time of loss of consciousness, post-injury amnesia, Glasgow Coma Score (Teasdale and Jennett, 1974) and trauma related findings on neuroimaging (Malec et al., 2007). The hallmark of TBI is diffuse axonal changes combined with continually evolving secondary changes. This feature combined with the heterogeneity of external factors such as location of injury, severity of injury, previous history and individual response to brain injury, can result in unique and dramatic changes in brain structure and brain function at many levels ranging from microscopic tears in white matter to global changes in functional brain networks. Headaches, dizziness, sleep disturbances, and fatigue often occurs immediately post injury, and may be severe. Attention, memory, processing speed and executive functions (i.e. working memory, cognitive flexibility, etc.) are also compromised early (Rabinowitz and Levin, 2014) and recover inconsistently (Broglio and Puetz, 2008; McAllister et al., 2006). A significant proportion of individuals with TBI continue to suffer from persistent cognitive and behavioural complaints and disability (Kraus et al., 2005; McAllister et al., 2006), resulting in prolonged or lifelong disability and dependence on the health care system. It is estimated that 2% of the population live with permanent disability related to TBI, with an estimated economic impact of

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$60 Billion/year in the USA(Finkelstein et al., 2006). Developing effective rehabilitation strategies for this population is therefore of great importance.

At a behavioural level there is considerable evidence that targeted cognitive interventions can improve attention, executive function, and memory (Caeyenberghs et al., 2016; Jolles et al., 2013; Kundu et al., 2013). In addition, cognitive rehabilitation is reportedly effective in helping patients learn and apply compensatory mechanisms for remaining deficits (Cicerone et al., 2011). Improvements in specific tasks related to executive function and memory have also been shown to generalize to functional improvement in everyday activities (Kennedy et al., 2008). Given that cognition is dependent on the activity of widely distributed functional brain networks (Bressler and Menon, 2010), evaluating the characteristics of the underlying networks in response to behavioral change stimulated by cognitive intervention can provide important insights into the underlying neuroplastic process.

A powerful and elegant method of evaluating the characteristics of brain networks is through the use of graph theory. In this framework, the brain is viewed as a network with interactions and communication occurring over multiple levels between local and distant areas (Rubinov and Sporns, 2010). One approach to understanding the nature of these interactions is via functional connectivity. Functional connectivity refers to the statistical interdependencies between physiological time series recorded from the brain (Friston, 2011). Graph theory has emerged as a promising tool in recent years for characterizing brain connectivity at both global and regional levels (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). Graph theory allows for the quantitative analysis of network organization, characterizing the brain as a set of networks, with each network being composed of distinct brain regions or "nodes". The various nodes are functionally connected via edges. The relationship between nodes and edges provides information about the organization and efficiency of the network. Networks with an ordered structure have a high clustering coefficient (a measure that depicts the connectedness of immediate neighbors around individual vertices), long characteristic path length (an index reflecting the overall integration of the network), low global efficiency (defined as the average inverse shortest path) and low density or cost (the fraction of present connections to possible connections) (Wu et al., 2012). In contrast, randomly organized networks are characterized by a low clustering coefficient, short characteristic path lengths, and a high global efficiency and density.

The healthy brain has been shown to be a combination of ordered networks with a certain fraction of randomly rewired links which results in "small-world" networks, with tightly connected neighborhoods, short characteristic path lengths and a high local efficiency (Wu et al., 2012). These small-world networks balance

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between local specialization and global integration, which are optimal for information processing (Watts and Strogatz, 1998).

Graph theoretical approaches have recently been applied to understand the effect of brain injury from a network perspective. In adults with TBI there appears to be a shift towards sub-optimal network organization (Caeyenberghs et al., 2012; Nakamura et al., 2009; Pandit et al., 2013). We have previously shown that mild TBI in adolescents does not alter resting state global network efficiency but does cause change in the local networks within the prefrontal cortex (Virji-Babul et al., 2014). This provides evidence for local changes in the frontal regions of the brain that are likely to affect the efficient processing of cognitive functions following mTBI. Arnemann et al. (2014) applied graph theory to predict individual responses to cognitive training in individuals with brain injury (Arnemann et al., 2015). They found that modularity (a measure of the density of links within a community relative to ones between communities) was able to predict improvements in attention and executive function following cognitive training. This suggests that functional brain imaging and graph theory has the potential to provide valuable information for understanding the mechanisms that influence recovery from TBI.

The purpose of this study was to pilot measures using graph theory analysis to evaluate the feasibility of these measures in capturing change following intervention. The specific objectives of this study were: (1) To establish the baseline global and local functional connectivity in individuals with TBI and evaluate the association with neuropsychological functioning, (2) To evaluate the changes in global and local functional connectivity in individuals with TBI following a 3-month cognitive intervention program and (3) To determine if network reorganization as measured by functional connectivity is associated with changes in cognitive recovery following the 3-month cognitive intervention program.

2. Methods

2.1. Participants

Participants with TBI were recruited from brain injury associations across the Greater Vancouver (British Columbia, Canada) area. All TBI participants were chronic with injuries occurring a minimum of 1 year prior to the start of the intervention. All healthy controls were recruited from the lower mainland of Vancouver in close proximity to the university. All controls were screened to ensure that they had no history of head trauma, neuropsychiatric disorders, substance abuse or any other neurological conditions. The participants with TBI were first interviewed to determine eligibility and to evaluate the severity of TBI. Participants were excluded if they were involved in litigation, had a history of current or recent substance abuse or if they had other severe medical conditions

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affecting brain function. They were also excluded if they had a diagnosis of psychiatric illness based on self report or when assessed with the Mini-international neuropsychiatric interview (MINI) (Sheehan et al., 1998). TBI severity was classified mild or moderate/severe, as per ACRM criteria (Mild Traumatic Brain Injury Committee, Head Injury Interdisciplinary Special Interest Group, American Congress of Rehabilitation Medicine. 1993). using retrospective self report of the duration of loss of consciousness and length of post-traumatic amnesia.

The experiments described in this study were approved by the Human Ethics Review Board at the University of British Columbia. All participants provided written consent according to the guidelines set forth by the Clinical Research Ethics Board at the University of British Columbia and this study complies with all regulations.

Table 1. Demographic and clinical profile of participants with TBI and Controls. M = male; F = female; TBI = Traumatic Brain Injury; MVA = Motor Vehicle Accident.

Participant ID	Sex	Age	Years of education	Time since injury (years)	Etiology	Mechanism of injury	Severity
S001	M	51	14	22	TBI	MVA	Severe
S002	F	50	18	29	TBI	MVA	Severe
S003	M	36	16	24	TBI	Multiple Concussion	Mild
S004	M	41	12	8	TBI	MVA	Severe
S005	M	18	13	2	TBI	Multiple Concussion	Mild
S007	F	48	20	4	TBI	MVA	Mild
S008	M	26	13	6	TBI	Fall	Severe
S009	F	35	13	8	TBI	MVA	Severe
S011	F	38	18	7	TBI	MVA	Severe
S012	F	50	17	7	TBI	MVA	Mild
C001	F	53	20	NA	Healthy	NA	NA
C002	M	36	20	NA	Healthy	NA	NA
C003	M	30	18	NA	Healthy	NA	NA
C004	M	52	20	NA	Healthy	NA	NA
C005	M	21	16	NA	Healthy	NA	NA
C006	M	38	14	NA	Healthy	NA	NA
C008	F	50	14	NA	Healthy	NA	NA
C009	M	24	16	NA	Healthy	NA	NA
C010	F	27	12	NA	Healthy	NA	NA
C011	M	45	14	NA	Healthy	NA	NA
C012	M	21	16	NA	Healthy	NA	NA

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2.2. Demographic characteristics

Table 1 shows the demographic features and clinical features for all the participants in this study. The mean age of the TBI participants was 39.6 years (18, 54), with a mean of 15.3 years of formal education. The gender distribution was 50% male. Time since initial injury for the TBI group ranged from 2 to 29 years with an average of 11.7 years. The healthy controls had a mean age of 37.4 years (21, 53) with a mean of 16.6 years of formal education and a gender distribution of 73% male. There were no significant differences in age [$t(19) = 0.429$, $p = 0.673$, $d = 0.19$] or education [$t(19) = -1.055$, $p = 0.305$, $d = -0.46$] between groups. All participants were right handed. All participants with TBI were able to complete the 3-month program.

2.3. Neuropsychological testing

All subjects were administered several neuropsychological tests assessing processing speed, memory, and executive function, as deficits in these cognitive skills have been documented across a range of TBI (Podell et al., 2010). The specific tests used were as follows:

1. Rey Auditory Verbal Learning Test (RAVLT)(Lezak and Lezak, 2004): On this verbal learning and memory test, the primary variables employed were total recall during learning trials and delayed free recall.

2. Trailmaking Test Parts A and B (Reitan and Wolfson, 1993): The Trails A test measures visual attention and processing speed, and Trails B assesses more complex attentional shifting. The time to completion for each task was employed.

3. Verbal Fluency (Lezak and Lezak, 2004): On the phonemic verbal fluency task, subjects were asked to generate as many words beginning with the letters F, A, S. The main outcome was number of correct words produced.

For all tasks, demographics corrected z-scores were used as the primary measures. For the RAVLT and Verbal fluency tasks, alternate versions of the tests were used during follow-up testing (see below) to minimize practice effects. A global composite score was derived by averaging z-scores for the 5 primary measures described above.

2.4. EEG recording and analysis

EEG was recorded using a 64-channel HydroCel Geodesic SensorNet (EGI, Eugene, OR). The EEG cap was placed on each participant's head and 5 minutes of resting state data was recorded with their eyes closed. EEG was recorded and amplified using Net Amps 300 amplifier, at a sampling rate of 250 Hz. Scalp electrode impedances were generally under 50 kΩ. The signal was referenced to

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the vertex (Cz) and filtered from 4 to 40 Hz. A notch filtered at 60 Hz was applied. The EEG signals were analyzed offline using Brain Electrical Source Analysis (BESA) (MEGIS Software GmbH). An automated artifact scan was performed for extracting motion and excessive eye movement artifacts. BESA brain source montage was used to convert the EEG activity obtained from all the 64 scalp channels into predicted contributions of a set of 15 different brain source activity. The advantage of using a brain source montage is that the volume conduction effects are reduced in comparison with the surface electrodes and provides a better model of the underlying brain source activity.

2.5. Graph theoretical analysis

Based on the learned connectivity networks, graph theoretical analysis was used to extract the structural features from learned networks (Bullmore and Sporns, 2009). Traditional graph theoretical measures were used to characterize the network features in terms of density, global efficiency, clustering coefficient, and modularity. Density is defined as the fraction of present connections to all possible connections. Global efficiency describes the communication ability of the entire graph (Latora and Marchiori, 2001), and is defined as the average of the inverse shortest path. Clustering coefficient describes the degree to which nodes in a graph tend to cluster together. Modularity of the network is used to measure how well the network can be divided into the sub-modules (Newman and Girvan, 2004). A higher value of modularity demonstrates that the graph is better divided with tighter connections within modules. We used the Brain Connectivity Toolbox (Rubinov and Sporns, 2010) running Matlab (Natick, MA) to perform the graph theoretical analysis.

2.6. Construction of connectivity matrix

In this paper, we constructed the brain functional connectivity networks using the preselected EEG signals and an error-rate controlled network learning algorithm. Based on the learned connectivity networks, the graph measures were further calculated to extract the functional network features. EEG signals were interpolated at 27 locations (FP2, FPZ, FP1, F10, F8, F4, FZ, F3, F7, F9, A2, T8, C4, CZ, C3, T7, A1, P10, P8, P4, PZ, P3, P7, P9, O2, OA, O1) on the scalp using BESA's Virtual Standard 10–10 Average montage. EEG time series from these 27 locations were used to construct the brain connectivity networks with each channel representing one brain region in the network. The connectivity network graphs were then computed for each individual subject and for each emotional expression using false discovery rate controlled PC (PCFDR) algorithm, which is a statistical model that tests the conditional dependence/independence between any two regions based on all other brain regions (Li and Wang, 2009).

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We used partial correlation to evaluate the conditional independence, which estimates the directed interactions between any two brain regions after removing the effects of all other brain areas. The PC algorithm starts from a complete graph and tests for conditional independence in an efficient way. The PCFDR algorithm is designed to control the false discovery rate (FDR), which evaluates the proportion between the connections that are falsely detected to all those detected, below a specified predefined level. Compared to the traditional Type-1 and Type-2 error rates, FDR has more conservative error rate criteria for modeling brain connectivity due to its direct relation to the uncertainty of the networks of interest. The PCFDR algorithm and pseudo-code are described in details in (Li and Wang, 2009). F FDR threshold was set at the 5% level.

2.7. Baseline and Post-intervention testing

Prior to the start of the program all participants took part in a comprehensive baseline assessment, which included resting state EEG and neuropsychological testing. All testing was completed at the University of British Columbia. The neuropsychological testing and clinical scales took approximately 90–120 min to complete. All participants took part in the EEG testing. Only 6 TBI patients completed the initial neuropsychological testing at the first time point. 4 additional TBI patients received their baseline neuropsychological testing at the 3-month time point and thus we elected to exclude the additional 4 patients from analyses involving cognitive data.

Following the 3-month intervention program EEG was conducted on all 10 TBI patients. Symptoms of generalized anxiety, depression, and general psychological distress were assessed using the Generalized Anxiety Disorder – 7 (GAD-7; (Spitzer et al., 2006), Patient-Health Questionnaire (PHQ-9; (Kroenke et al., 2001), and Brief Symptom Inventory – 18 (BSI-18; (Derogatis and Melisaratos, 1983)).

2.8. Cognitive intervention

The Arrowsmith Program is a suite of cognitive exercises. The goal of these exercises is to improve cognitive functioning across a broad domain, for example, executive functions, reasoning and memory. Each individual's program was based on an assessment of that individual's learning profile to identify his or her specific areas of difficulty. Each individual had his or her specific schedule of tasks and exercises to be completed during the course of a day. The exercises for each individual student were uniquely based on their individually identified learning profiles. These include written, visual, auditory and computer exercises. Each cognitive program had a series of intensive and graduated tasks. Performance criteria of automaticity, consistency and accuracy are built in at all levels and an individual was required to meet these criteria before mastering to the next level of

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complexity. Goals were set daily, weekly and monthly and each month the individual's attained levels in each program was entered into a database and analyzed to see if progress met benchmark expectations. In order to maximize evaluation of transfer effects, the neuropsychological battery that was used to assess outcome was assembled independently of the cognitive exercise tasks that were used within the cognitive intervention program.

The cognitive intervention program took place four days a week for 4 − 5 hours a day for a 3-month period. Each day was composed of 6–8 blocks of different activities depending on individual's specific areas of weakness.

2.9. Analysis

Demographic data including age, gender and years of education were evaluated for between group differences with t-tests. T-tests were also performed to test differences in the EEG measures and the neuropsychological measures between groups at baseline. Two a priori EEG clusters of interest were selected for analysis based on our previous work examining changes in functional connectivity in adolescents with mTBI (Virji-Babul et al., 2014). EEG clusters of interest included F7 (L) inferior frontal gyrus (IFG) and F10 (R) inferior frontal gyrus. Paired t-tests were conducted to compare baseline and post-intervention scores in the TBI group. Pearson correlations were conducted to evaluate specific correlations between graph theory metrics and the individual and global composite neuropsychological scores.

3. Results

3.1. Differences between groups at baseline

Table 2 shows the mean scores (SD) on the global composite score based on the mean of all test scores. As expected, at baseline the TBI group performed worse on the overall composite score although the difference did not reach statistical significance as a likely result of diminished power. Consistent with this, the

Table 2. Global composite scores for the controls, TBI participants at baseline and TBI participants at 3 months post intervention.

Cognititon Composite (Z score)		N	Mean	Std. Deviation	Significance (2 tailed)
Control vs. TBI	Control	12	.1166	.62026	.102
	TBI	6	-.5823	1.10851	
Baseline vs. 3 month	Baseline	6	-.5823	1.1085	.000
	3 Month	6	.0103	1.3002	

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Cohen's d effect size for the difference was .78, which indicates a moderate to large difference.

At baseline there were no significant differences between groups for any of the four graph metrics associated with global connectivity: density ($t(17) = 1.03$, $p = 0.32$, $d = 0.47$), global efficiency ($t(17) = -0.278$, $p = 0.78$, $d = -0.13$), modularity ($t(17) = 1.05$, $p = 0.31$, $d = 0.48$), clustering coefficient, $t(17) = 1.612$, $p = 0.125$, $d = 0.74$.

In contrast with the global metrics we found significant differences in local metrics at the F10 and F7 electrode clusters corresponding to the right and left inferior frontal gyrus, respectively between groups (Fig. 1). Specifically, the F10 hub value was significantly higher compared to the healthy control group, $t(17) = 2.24$, $p = 0.039$, $d = 1.01$. A number of graph metrics for F7, showed significant decreases in the TBI group in comparison with the healthy control group. These included F7 degree, $t(17) = -2.28$, $p = 0.036$, $d = -1.05$, F7 betweenness, $t(17) = -2.41$, $p = 0.028$, $d = -1.1$ and F7 hub value, $t(17) = -2.28$, $p = 0.035$, $d = -1.05$. These results suggest that network connections are denser in the right inferior frontal regions and less dense in the left inferior frontal regions in the TBI group.

3.2. Cognitive training related changes

Table 2 also shows the scores following the three-month cognitive intervention in the participants that completed testing at baseline and post-intervention. A paired-

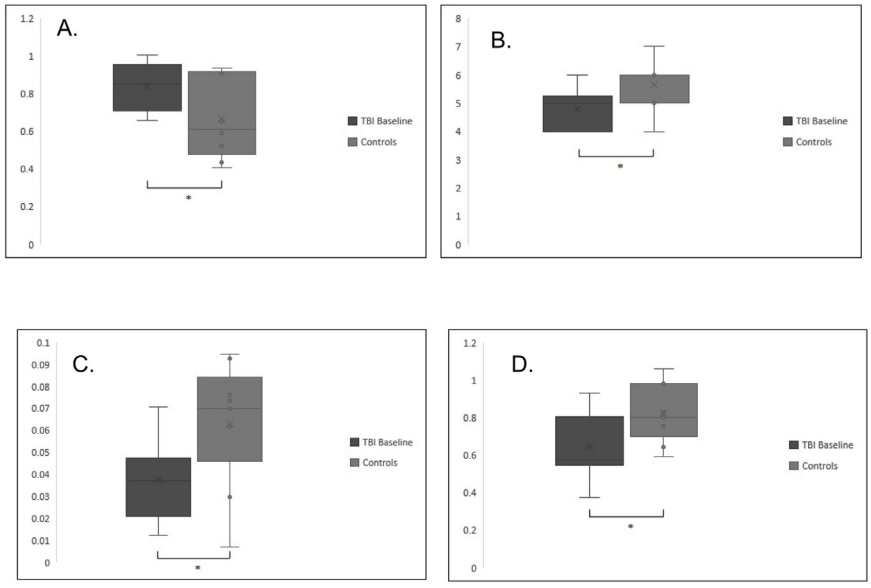

Fig. 1. Baseline functional connectivity measures showing differences between TBI – Baseline and controls in local connectivity measures. (A. F10 Hub Value; B. F7 Degree; C. F7 Betweenness; D. F7Hub Value).

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test showed that there was a statistically significant increase in the composite score between baseline and post-intervention in the TBI group. In addition, there were no significant changes in generalized anxiety, $t(5) = 0.08$, $p = 0.94$, depressive symptoms, $t(5) = 0.86$, $p = 0.43$, or general psychological distress, $t(5) = 0.58$, $p = 0.59$.

In terms of functional connectivity, no changes were seen in the global connectivity measures. For the local connectivity measures, we noted changes in specific graph theory metrics at the F10 and F7 electrode clusters. Fig. 2 shows that at F10, degree, [$t(9) = 3.35$, $p = 0.008$] (Fig. 2A), betweenness [$t(9) = 3.52$, $p = 0.007$] (Fig. 2B), and hub value [$t(9) = 3.53$, $p = 0.006$] (Fig. 2C) showed a statistically significant decrease following the intervention. At F7, measures increased, however none were statistically significant: degree, $t(9) = -0.896$, $p = 0.394$, betweenness, $t(9) = -1.05$, $p = 0.323$ and hub value, $t(9) = -1.01$, $p = 0.338$.

Fig. 3 shows the relationship between global density and the overall composite score. Note that there is a positive correlation in the controls with higher scores associated with higher global density (P=.63). In the TBI group there was a negative correlation between these variables at baseline (P = -.39). Following intervention, there was a trend towards a positive slope (P=.28). Fig. 4 shows the relationship between the RAVLT and global density (4A) and the RAVLT and F10 degree (4B). Both correlations show a change from a negative correlations at baseline (P = -.38; P = -.33) to a positive correlation at 3 months post intervention (P=.69; P=.77). No other correlations were found to be significant.

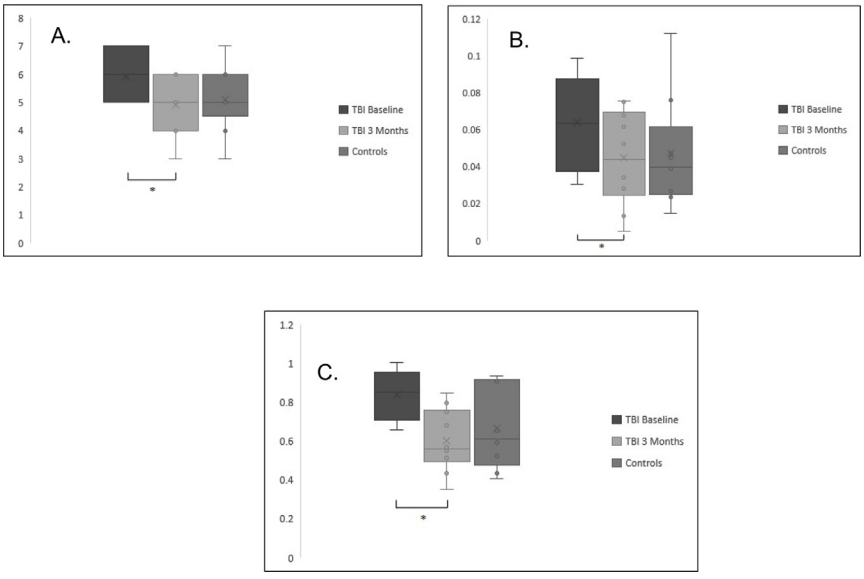

Fig. 2. Post-intervention connectivity measures for TBI – Baseline, TBI – 3 Months Post Intervention compared to Controls, showing significant changes after 3 months in F10 Degree (A.), F10 Betweenness (B.) and F10 F10Hub Value (C.).

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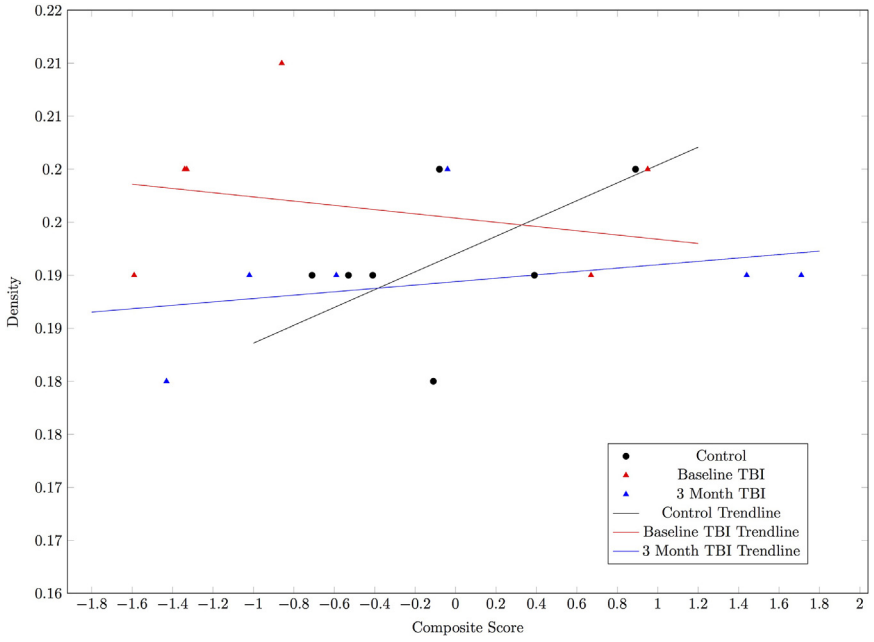

Fig. 3. Scatter plot showing relationship between Global Density and Global composite score in controls, TBI participants at baseline and TBI participants at 3 months post intervention.

4. Discussion

The purpose of this study was to pilot measures using graph theory analysis to evaluate the feasibility of these measures to capture change following a 3 month program of cognitive intervention and to determine if these changes correlated with measures of cognition. The data from our pilot study provides preliminary evidence for improved performance in cognition and corresponding changes in local functional network connectivity in bilateral frontal regions following a 3 month cognitive intervention program in a small sample of adults with chronic TBI.

Graph theoretical analysis at baseline revealed that there were no significant differences in global measures of functional connectivity between groups suggesting that in this cohort, there was no change in resting state global network connectivity, although there was evidence of disruption in the relationship between global metrics and measures of cognition. We did find significant changes in local networks in this group. Specifically, we observed increases in graph metrics in F10 and decreases in F7. F10 corresponds to the (R) inferior frontal gyrus (IFG) and F7 to the (L) IFG (Koessler et al., 2009). The IFG is a key region involved in three processes of cognitive control: working memory, task switching and inhibitory control (Sundermann and Pfleiderer, 2012). The increase in hub value of IFG on the right and decrease on the left may seem paradoxical, but it suggests a disruption of network organization that is centered around the frontal regions. The hub value

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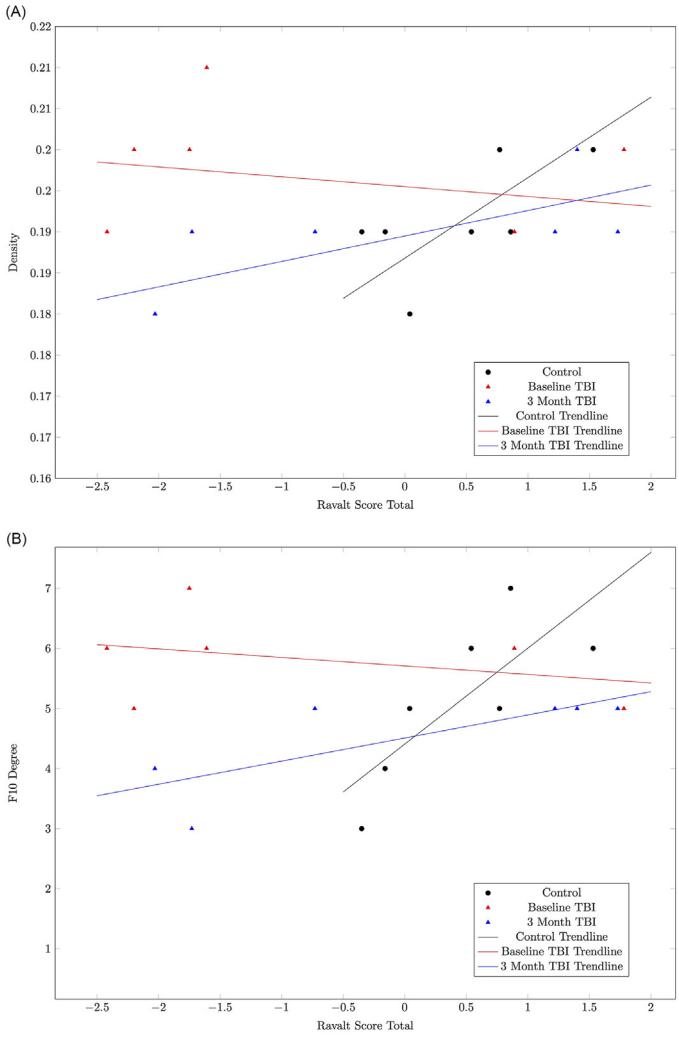

Fig. 4. (A). Scatter plot showing the relationship between RAVALT and Density in controls, TBI participants at baseline and TBI participants at 3 months post intervention. (B). Scatter plot showing the relationship between RAVALT and F10 Degree in controls, TBI participants at baseline and TBI participants at 3 months post intervention.

of one node is related to the structure of its neighbors, where a high value means that there are other key nodes that are connected with that hub. The increased value of the hub on the right indicates hyper-connectivity and the decrease on the left suggests hypo-connectivity. Overall, the consequences of disruption in the physical network due to TBI are reflected in disruptions in functional connectivity. These types of disruptions in functional connectivity have previously been reported in the literature. Hillary et al. (Hillary et al., 2014) found increased functional connectivity specifically in the brain regions that are most highly connected or "rich hubs". We have also previously found increased functional connectivity in adolescents with mTBI in frontal regions (Borich et al., 2014). Palacios and colleagues recently reported increased functional connectivity within the frontal

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lobe in patients with chronic TBI. In contrast, Pandit et al., reported decreased functional connectivity in patients with chronic TBI (Pandit et al., 2013).

Although initial hypotheses in the literature related to increased connectivity have focused on compensatory strategies as a mechanism to account for loss of structural connectivity, more recently, Hilary et al. (Hillary et al., 2015) have shown that hyper-connectivity is a common finding across a range of neurological conditions including TBI, multiple sclerosis, mild cognitive impairment and Alzheimer's disease. They hypothesize that increased connectivity may allow the brain to continue to meet task demands in the face of network disruption. Importantly, they suggest that this increased connectivity comes at the cost of slowed processing speed and cognitive fatigue. Our data shows that increased connectivity in the frontal regions is in fact correlated with lower cognitive scores suggesting that greater resources are being used that may lead to lower information processing efficiency.

Although hyper-connectivity is a common finding across a range of neurological disorders, from a network perspective it is unlikely that this is the only response to structural changes in the brain. Across all brain networks it is more likely that there is a combination of hyper and hypo connectivity that reflects the changes in different brain networks (Hillary et al., 2015). Indeed, our data supports this by showing that hyper-connectivity is not uniform across brain regions following TBI. Furthermore, the pattern of connectivity that we observed in each hemisphere provides data for the hypothesis that detailed analysis of network organization across the whole brain is necessary to understand and map the patterns of brain connectivity that underlie the cognitive deficits in individuals with TBI.

4.1. Training related changes in cognition

Within several important constraints of the present study (i.e. small sample size and a lack of a TBI control group who did not receive cognitive intervention which is necessary to rule out practice effects for cognitive improvements), the analysis of cognitive performance from baseline to post-treatment in patients suggested trends in improvements in overall cognition. Importantly, these improvements were observed in a sample of chronic patients. There are few published studies that have examined the effectiveness of cognitive intervention in patients who are in the chronic stages of recovery(Cook et al., 2014).

In a recent re-analysis of meta-analytic studies assessing the effects of cognitive rehabilitation on acquired brain injury, it was concluded that patients with traumatic brain injuries were more likely to receive benefit from cognitive retraining targeting attention based tasks (Cicerone et al., 2011). Because the cognitive measures included in the neuropsychological battery within this study

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were highly attention-based, this likely maximized the likelihood of observing cognitive gains as a result of the cognitive intervention.

4.2. Training related changes in functional connectivity

Interestingly, our data show that cognitive intervention lead to changes in the organization of brain networks such that connectivity within hub areas are reorganized, and this occurred with a parallel improvement in cognition. In particular, we found a small shift in the correlation between overall Global density and the global composite score in the TBI group which was negatively correlated at baseline and moved to a slight positive trend following the intervention period. We also observed shifts in correlations between auditory verbal learning and global connectivity as well as measures related to brain regions in the right inferior frontal gyrus. These changes suggest a subtle reorganization between brain and behavior relationships that were disrupted at baseline.

Our results provide preliminary evidence that participating in an intensive cognitive intervention program was associated with neuroplastic changes in adults with chronic TBI that occurred in parallel with improvements in cognition. Overall, we observed a shift from a baseline pattern of network organization that may be characterized by neural inefficiency and decreased cognition to a reorganization that reflected improved efficiency with possible improvements in fluid cognition. Importantly this data suggests that brain network organization is capable of reorganization even in chronic patients with intense intervention. Further work with a larger sample is clearly needed to understand the nuances of how brain organization impacts on cognitive ability and performance.

Declarations

Author contribution statement

Shaun Porter: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Ivan Torres: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

William Panenka: Conceived and designed the experiments.

Zahra Rajwani: Performed the experiments; Analyzed and interpreted the data.

Delrae Fawcett, Amna Hyder: Analyzed and interpreted the data.

Naznin Virji-Babul: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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