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Structural-functional connectivity bandwidth predicts processing speed in mild traumatic brain Injury: A multiplex network analysis

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ABSTRACT

An emerging body of work has revealed alterations in structural (SC) and functional (FC) brain connectivity following mild TBI (mTBI), with mixed findings. However, these studies seldom integrate complimentary neuroimaging modalities within a unified framework. Multilayer network analysis is an emerging technique to uncover how white matter organization enables functional communication. Using our novel graph metric (SC-FC Bandwidth), we quantified the information capacity of synchronous brain regions in 53 mild TBI patients (46 females; age mean = 40.2 years (y), σ = 16.7 (y), range: 18–79 (y). Diffusion MRI and resting state fMRI were administered at the acute and chronic post-injury intervals. Moreover, participants completed a cognitive task to measure processing speed (30 Seconds and Counting Task; 30-SACT). Processing speed was significantly increased at the chronic, relative to the acute post-injury intervals ($p = <0.001$). Nonlinear principal components of direct ($t = -1.84$, $p = 0.06$) and indirect SC-FC Bandwidth ($t = 3.86$, $p = <0.001$) predicted processing speed with a moderate effect size ($R^2 = 0.43$, $p < 0.001$), while controlling for age. A subnetwork of interhemispheric edges with increased SC-FC Bandwidth was identified at the chronic, relative to the acute mTBI post-injury interval (pFDR = 0.05). Increased interhemispheric SC-FC Bandwidth of this network corresponded with improved processing speed at the chronic post-injury interval (partial $r = 0.32$, $p = 0.02$). Our findings revealed that mild TBI results in complex reorganization of brain connectivity optimized for maximum information flow, supporting improved cognitive performance as a compensatory mechanism. Moving forward, this measurement may complement clinical assessment as an objective marker of mTBI recovery.

1. Introduction

The human brain is a complex and dynamic neural network comprising structural and functional elements. These elements can be mapped *in vivo* non-invasively using magnetic resonance imaging (MRI) techniques. Specifically, by leveraging diffusion MRI (dMRI), we can calculate structural connectivity (SC), using measurements such as the number of reconstructed streamlines of white matter fibre bundles. Also, we can leverage functional MRI (fMRI) to calculate functional connectivity (FC) using measurements such as Pearson's or partial correlation coefficients, between the average time series of gray matter regions. In addition, we can consider the brain as a graph, comprising nodes and edges using graph theoretical analysis (GTA; Bassett et al., 2011). Ample GTA studies have revealed a segregation–integration balance of the structural and functional connectomes in healthy populations, thought to empower the brain to support diverse higher-order cognitive functions. For example, stronger integration may support higher *general* cognitive ability and stronger segregation may support more *specific* higher-order cognition (e.g., processing speed; Wang et al., 2021). This balance may be impacted by the onset of neurologic disorders or insult such as traumatic brain injury (TBI) resulting in several cognitive and behavioral deficits (Raizman et al, 2020; Caeyenberghs et al., 2012; Matérne, Matérne, Strandberg & Lundqvist, 2018).

TBI has been termed a *"disorder of brain connectivity"* (Hayes et al.,

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2016) characterized by topological alterations of the brains structural network as measured with GTA metrics (e.g., normalized clustering coefficient and characteristic path length), irrespective of injury severity and chronicity (for a *meta*-analysis, see Imms et al., 2019). In mild TBI patients, several studies report alterations in structural connectome-based GTA measures including increased normalized clustering coefficient (van der Horn et al., 2016; Yuan et al., 2015; Yuan et al., 2017), as well as higher modularity, lower global integration, longer characteristic path-length and higher small-worldness compared to healthy controls (Yuan et al., 2015; Yuan et al., 2017). Collectively, these findings indicate that traumatic insult may distort the structural connectome, toward a regular (latticed) network which may contribute to cognitive *sequelae* (Kim et al., 2014; Königs et al., 2017; van der Horn et al., 2017). In addition, aberrant measures of the *functional* connectome have also been reported in mTBI patients (Morelli et al., 2021) across several large-scale functional networks, such as the default mode and attention networks (for reviews, see Sharp et al., 2014; Hayes et al., 2016).

Over a decade ago, a landmark article reported a moderate correlation coefficient between SC and FC in the healthy human brain (r = ~0.5; Honey et al., 2010), suggesting a tight relationship between these elements may be vital for this system to give rise to higher-order cognitive function in healthy individuals. More recently, mixed evidence has emerged in brain-injured populations indicating this relationship may be weakened compared to healthy controls with studies reporting SC-FC correlation coefficients ranging from r = -0.3 to r = -0.68 (Parsons et al., 2020). For example, several studies revealed significantly reduced SC-FC correlation in Parkinson's disease (Rosenberg-Katz et al., 2013), primary progressive aphasia (Mandelli et al., 2016), multiple sclerosis (Rocca et al., 2013) and TBI (Sharp et al., 2011) while others reported increased SC-FC correlation strength in TBI (Costanzo et al., 2014) and mild cognitive impairment (Wang et al., 2018).

Despite interesting findings, these studies bear a common limitation—they do not compare equidimensional SC and FC metrics of the same brain regions within a unified framework. This limitation may account for findings of mixed alterations in SC-FC correlation (i.e., both higher and lower, relative to controls) due to an oversimplification of the mechanism underpinning SC-FC. To overcome this limitation, several studies have employed GTA using both SC and FC data, to characterize *multimodal* brain connectivity in moderate-severe TBI patients. For example, Caeyenberghs et al., (2013) compared equidimensional GTA metrics (degree) of SC (derived from fiber tractography using diffusion MRI data) and task-related FC (event-related) in moderate-severe TBI patients. They reported no significant correlations between degree, connection strength, regional efficiency, or betweenness centrality compared with healthy controls. Others reported a positive correlation between SC and FC, with lower diffusivity of the splenium of the corpus callosum correlating with increased posterior cingulate cortex FC in chronic TBI patients (Sharp et al., 2011). More recently, Kuceyeski et al., (2019) leveraged GTA to report increased structural connectome segregation, and increased functional connectome integration in mTBI patients, coinciding with improved cognitive performance. The authors interpreted these findings as two connectome-based post-injury recovery mechanisms: (1) neuroplasticity in the form of increased functional connectome *integration* and (2) remote white matter degeneration inflicting structural connectome *segregation*. In addition, although one study reported no differences in global GTA metrics (Roine et al., 2022), another reported dissimilar structural network organization in mTBI patients relative to healthy controls (Osmanlıoğlu et al., 2022).

Though emerging studies provide unique insights into TBI, none have integrated SC and FC metrics into a so-called *'multiplex'* network paradigm, which models the relationship among SC and FC simultaneously across several levels of organization (for reviews, see Suarez et al., 2019; Vaiana & Muldoon, 2020). Specifically, this technique allows statistical analyses to be performed between the same nodes both within and between 2-dimensional layers (i.e., SC and FC adjacency connectivity matrices). We can then draw links between nodes across layers, termed "pseudo-edges", which can be used to represent relationships between nodes across layers (i.e., the relationship between SC and FC). These relationships can be modeled with a correspondence of one-to-one (i.e., multiplex), one-to-many, or many-to-many. Subsequently, multiplexes offer additional information over traditional GTA, allowing the exploration of how functional connectivity between brain regions is facilitated or mediated directly by single SC paths, or indirectly by multiple structural pathways (multi-paths). Several studies have employed multiplex network techniques, albeit in healthy cohorts. These studies uncovered different topological properties in fMRI and EEG frequency bands (De Domenico et al., 2016a; De Domenico et al., 2016b; Tewarie et al., 2016) while others uncovered lower assortativity of FC (-0.15), and higher assortativity of SC (0.1) which may indicate a robustness to acute injury or neurodegeneration (Lim et al., 2019). Recently, our lab developed a novel GTA metric to characterize the SC-FC Bandwidth (denoting high information transportation capacity) in 484 healthy subjects from the Human Connectome Project (HCP; https://www.humanconnectome.org) using weighted SC and FC matrices (Parsons et al., 2022). We found most pairs of FC nodes were connected by SC paths of length two and three (SC paths of length > 5 were virtually non-existent). We also found higher SC-FC Bandwidth of indirect connections predominated the somatomotor and default mode networks. This technique and subsequent GTA metric offers the capability to reconcile SC and FC of mTBI patients within a unified framework, toward understanding how aberrant connectivity gives rise to cognitive impairment.

In the present study, we aim to (1) measure cognitive performance on a processing speed task in mTBI patients at the acute, and chronic post-injury intervals, (2) map the anatomic (spatial) distribution of edges with high SC-FC Bandwidth values in mTBI patients, (3) identify subnetworks of altered SC-FC bandwidth at the chronic, relative to the acute post-injury interval, (4) examine the relationship between cognitive performance on a processing speed task, and SC-FC bandwidth at each post-injury interval and (5) examine whether change in SC-FC Bandwidth predict change in processing speed.

We hypothesize that (1) processing speed is increased at the chronic, relative to the acute post-injury interval, (2) SC-FC Bandwidth (time point 1) predicts performance in processing processing speed at the acute post-injury interval (time point 1), (3) increased SC-FC Bandwidth (change from time point 1 to timepoint 2) predicts better processing speed from the acute-chronic post-injury interval.

2. Materials and method

2.1. Participants

This study is part of a large-scale study monitoring the longitudinal effects of mild TBI, published elsewhere (Amgalan et al., 2022b; Robles et al., 2021). A total of 53 mild TBI (mTBI) participants were included (46 females; age mean = 40.2 years (y), σ = 16.7 y, range: 18–79 (y)). mTBI patients were recruited through community outreach (via advertisements and flyers) and/or with the assistance of healthcare professionals who had referred volunteers for neuroimaging and neurocognitive assessments. Inclusion criteria included (1) an acute GCS score of at least 13 upon initial evaluation ($mean \pm SD = 14 \pm 1$), (2) both diffusion-weighted and T_2*-weighted acquired within ~1 week (acute post-injury interval) and ~6 months post-injury (chronic post-injury interval), (3) a TBI related to a ground-level fall involving direct head trauma, (4) loss of consciousness (LOC) shorter than 30 min ($mean \pm SD \simeq 9 \pm 4$ min), and (5) post-traumatic amnesia shorter than 24 h ($mean \pm SD \simeq 3.6 \pm 2.1$ h). Exclusion criteria included (1) imaging findings other than those related to cerebral microbleeds, or cases of larger intracranial hemorrhage identified as susceptibility-weighted imaging (SWI) hypointensities, or and (2) a documented clinical history of pre-traumatic neurological disorder, psychiatric disorder, or

drug/alcohol abuse. This study was undertaken in accordance with US Code of Federal Regulations 45 (CFR 46) and with approval from the Institutional Review Board at the University of Southern California, and according to the ENIMA working group memorandum of understanding.

2.2. Cognitive evaluation

The Brief Test of Adult Cognition by Telephone (BTACT) was administered at the subacute (~7 days) and chronic post-injury interval (~6 months) of TBI (mean ± SD = 57 ± 2 days between the two timepoints) to assess the changes in cognitive performance following recovery in the mild TBI patients. The BTACT consists of five subscales, which measure cognition. These subscales include: (1) episodic verbal memory (immediate), (2) episodic verbal memory (delayed), (3) working memory (longest span correct), (4) reasoning (proportion correct) and (5) verbal fluency (number of items produced) and (6) processing speed. Herein, this paper focuses on the processing speed subscale only. This construct was operationalized using the 30 Seconds and Counting Task (30-SACT) which requires participants to verbally count items backward sequentially from 100 as quickly as possible in 30 s. Scores were computed as 100 minus the number reached, where the result represents how many numbers were counted (lower scores indicate better performance). Errors due to skipping or repeating numbers were tallied and subtracted from the total score (Lachman et al., 2014). Concurrent validity and test–retest reliability of the BTACT were examined by Lachman et al., (2014) showing good concurrent validity with corresponding Boston Cognitive Battery factors (Soederberg Miller & Lachman, 2000; Short-term Memory, Verbal ability, Reasoning, and Speed, respectively) ranging from $r = 0.42$ to 0.54 ($p < 0.001$). Test-retest reliability was also found to be high (between $r = 0.55$ and 0.94) apart from the verbal fluency subscale ($r = 0.28$), likely due to the category change (animals *vs*. foods; Strauss, Sherman, & Spreen, 1998).

2.3. MRI data acquisition

Neuroimaging data used in this study were part of a large-scale longitudinal study examining the longitudinal effects of mild TBI, published elsewhere (see papers: Amgalan et al., 2022b; Robles et al., 2021). MRI data were acquired at two timepoints, at ~ 1 week and ~ 6 months post-injury using a 3 T Siemens Skyra scanner with a 32-channel head coil. T_2*-weighted resting-state fMRI data in an eyes-open condition were collected for approximately 7 min (140 volumes) with repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle (FA) = 80, voxel size = 3.3125 mm × 3.3125 mm × 3 mm, field of view (FOV) = 208 × 180 mm^2 and 72 slices with anterior-posterior phase encoding direction (A≫P). In addition, T_1-weighted MRIs were acquired using a 3D magnetization-prepared rapid acquisition gradient echo sequence (MPRAGE); TR = 1950 ms; TE = 2.98 ms; inversion time (TI) = 900 ms; voxel size = 1.0 mm × 1.0 mm × 1.0 mm. Diffusion-weighted images (DWI) were acquired with 64 gradient directions (TR = 8,300 ms; TE = 72 ms; voxel size = 2.73 mm × 2.73 mm × 2.7 mm) FA = 90°, FOV = 128 × 84 with 59 slices, $b = 1300$, $b_0 = 1$).

2.4. Diffusion and functional MRI data Pre-processing

fMRI data was preprocessed using the FreeSurfer Functional Analysis Stream (FS-FAST, https://surfer.nmr.mgh.harvard.edu/fswiki/fsfast) with default parameters set to the defaults. Nuisance regression was included at the stage of FS-FAST analysis specification using the -nuisreg flag with ventricular/CSF (vcsf.dat) and WM (wm.dat) signals as regressor. No global signal regression was conducted. Motion correction, frame censoring, intensity normalization, co-registration of fMRI to T_1 image, FreeSurfer surface sampling, spatial smoothing and resampling to the Montreal Neurological institute (MNI) space was performed. DWI preprocessing was done using a standard pipeline in the FMRIB Software Library (FSL) as described elsewhere (Rostowski & Irimia, 2021).

2.5. Node definition

An overview of the data processing pipeline is shown in Fig. 1. We chose the Destrieux cortical atlas as a parcellation scheme (150 ROI excluding sub-cortical areas and medial wall) in line with previous network studies (Amico and Goñi, 2018; Koch et al., 2021; King et al., 2016). This atlas has been shown to reliably capture inter-subject variability of SC-FC, compared to other atlases (Zimmerman et al., 2018). The number of nodes in this atlas (150) balances SC path resolution, without oversampling FC edge weights, resulting in sparser, weaker FC graphs (Zalesky et al., 2010). A full description of each region and visual representation of each region can be found in Destrieux et al., (2010). As a conservative approach, we excluded subcortical regions from our connectome analysis, due to low signal-to-noise ratio, which may compromise accurate segmentation of subcortical regions and affect white matter microstructural connections with cortical regions.

2.6. Edge definition

Edge weights of SC adjacency matrices were defined as the number of reconstructed streamlines between any two ROI of the atlas, in accordance with previous structural connectome studies (Basser et al., 2000; Mori et al., 1999; Conturo et al., 1999; Kuceyeski et al., 2016, Kuceyeski et al., 2019). This number of reconstructed streamlines was derived from the diffusion tensor model and deterministic tractography (See Fig. 3, Panel A). Moreover, we thresholded these SC matrices, by excluding cells with number of streamlines values lower than one, in accordance with recommendations for reliable tractography (Reid et al., 2020). The edge weight of the FC adjacency matrix (See Fig. 3, Panel C) consisted of partial correlations between any two pairs of gray matter regions of the parcellation scheme ($r > 0.2$). Important to note, we chose to focus on positive FC correlations only, as the current understanding of negative correlations/negative edge weights in the context of brain connectivity is limited (Zhan et al., 2017). At the individual level, weighted SC-FC (See Fig. 2, Fig. 3, Panel B) were constructed for each individual subject, resulting in 53 weighted FC, 53 weighted SC and 53 weighted SC-FC Bandwidth connectomes which were used for subsequent analyses. Moreover, a group-average weighted SC-FC matrix was computed for visualization purposes using the sum of all matrix values across individuals divided by the number of subjects. Post-processing of adjacency matrices was completed using Matlab 2018a (https://www.mathworks.com) and Python (version 3.0). Our full weighted multiplex connectivity python code can be found here: https://github.com/parsonsn/SC-FC-Multiplex-Bandwidth. Full mathematical details of our method are provided in supplementary material.

2.7. SC-FC Bandwidth

We quantify the bandwidth between two synchronous regions according to their minimum SC edge weight ("max–min method"; Parsons et al., 2022). These paths may support higher signal capacity and velocity (Hursch, 1939; Rushton, 1951; Paus et al., 2014; Avena-Koenigsberger et al., 2019) relative to other paths incident to a given FC edge. That is, the SC *throughput* of an SC-FC edge (direct = 1 SC edge; triangle = 2 SC edges; quad = 3 SC edges) is equal to its least restrictive bottleneck (See Fig. 2). Effectively, this measurement reflects the communication bandwidth of each FC edge. Higher bandwidth values incident to a given FC edge therefore reflect throughput of synchronous brain regions.

2.8. Nonlinear principal component analysis

As shown in Fig. 1, we applied nonlinear PCA on the SC-FC Bandwidth composite matrix to reduce high dimensionality data without loss of important information (Scholz et al., 2005; Scholz, 2012; Pearson, 1901; Hotelling, 1933). We utilized PCA to represent rich whole-brain

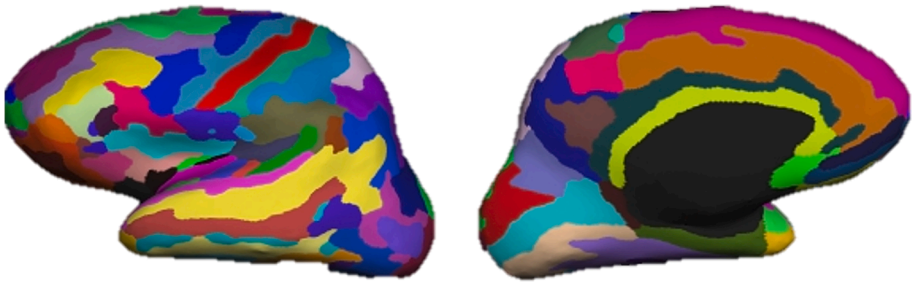


Fig. 1. The Destrieux cortical atlas, showing parcellations of the cortex in the lateral view (Left) and medial view (Right).

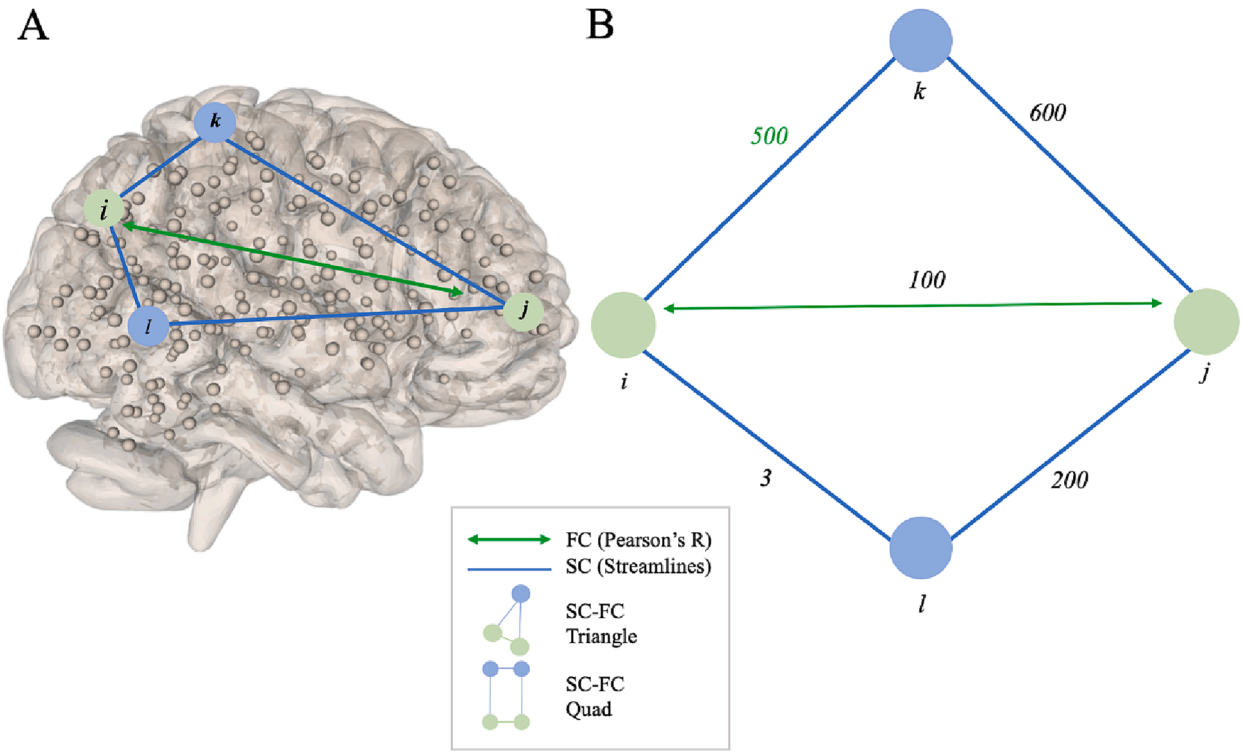


Fig. 2. SC-FC Bandwidth Schematic Diagram. Panel A shows functionally synchronous cortical nodes *i* and *j* connected by intermediary nodes *k* and *l*. Panel B shows the number of reconstructed streamlines connecting nodes *i* and *j* where the SC-FC Bandwidth of these regions is equal to 500 streamlines (the minimum, maximum (i.e., least restrictive path) enabling communication between nodes *i* and *j*.

SC-FC Bandwidth data as a singular input value for each subject within a multiple linear regression. That is, each input value for each subject is a beta weight (representing the explained variance) of each subject's SC-FC Bandwidth matrix principal component. However, a growing body of literature suggests that brain connectivity metrics exhibit nonlinear characteristics (particularly FC) which cannot be accurately modeled using a linear statistical assumption (Bassett et al., 2013; Battiston et al., 2018; De Domenico et al., 2016a; De Domenico et al., 2016b). Therefore, we used nonlinear PCA (NLPCA) to allow a more sensitive polynomial fit to each maximally orthogonal component.

NLPCA operates by training a feedforward neural network to perform identity mapping (Kramer, 1991). Here, network inputs are reproduced at the output layer. The neural network contains a bottleneck layer (i.e., fewer nodes than either input or output layers), to force the network to (i) develop a compact representation of input data, and (ii) create two additional hidden layers. Importantly, this approach inherently limits overfitting of data, where principal components are still modeled using a linear (i.e., not curved) fitting assumption where possible. Similar to linear PCA, a series of weights containing the explained variance of each maximally orthogonal principal component is created, where the user can choose to include one or more components for further analysis. Here, the output is a matrix of eigenvectors and a corresponding vector of eigenvalues, where the largest eigenvalue and the eigenvector belong to a component that explains the most variance in the data. We included one principal component vector for both direct and indirect SC-FC Bandwidth. Each component was selected based on the maximal explained variance identified in a scree plot (Supplementary data). Due to the relatively low sample size, each nonlinear principal component was derived using the entire dataset, without cross-validation (train-validation-test splits).

2.9. Statistical analyses

To address our first hypothesis, we conducted one-sample t-tests between normalized processing speed scores at the acute, and chronic post-injury intervals for each subject. To address our second hypothesis, we conducted a series of multiple linear regression models to examine whether SC-FC Bandwidth predicts processing speed. Our independent variables included nonlinear principal components of FC, direct SC-FC, indirect SC-FC and age as a covariate (Amgalan et al., 2022b). To

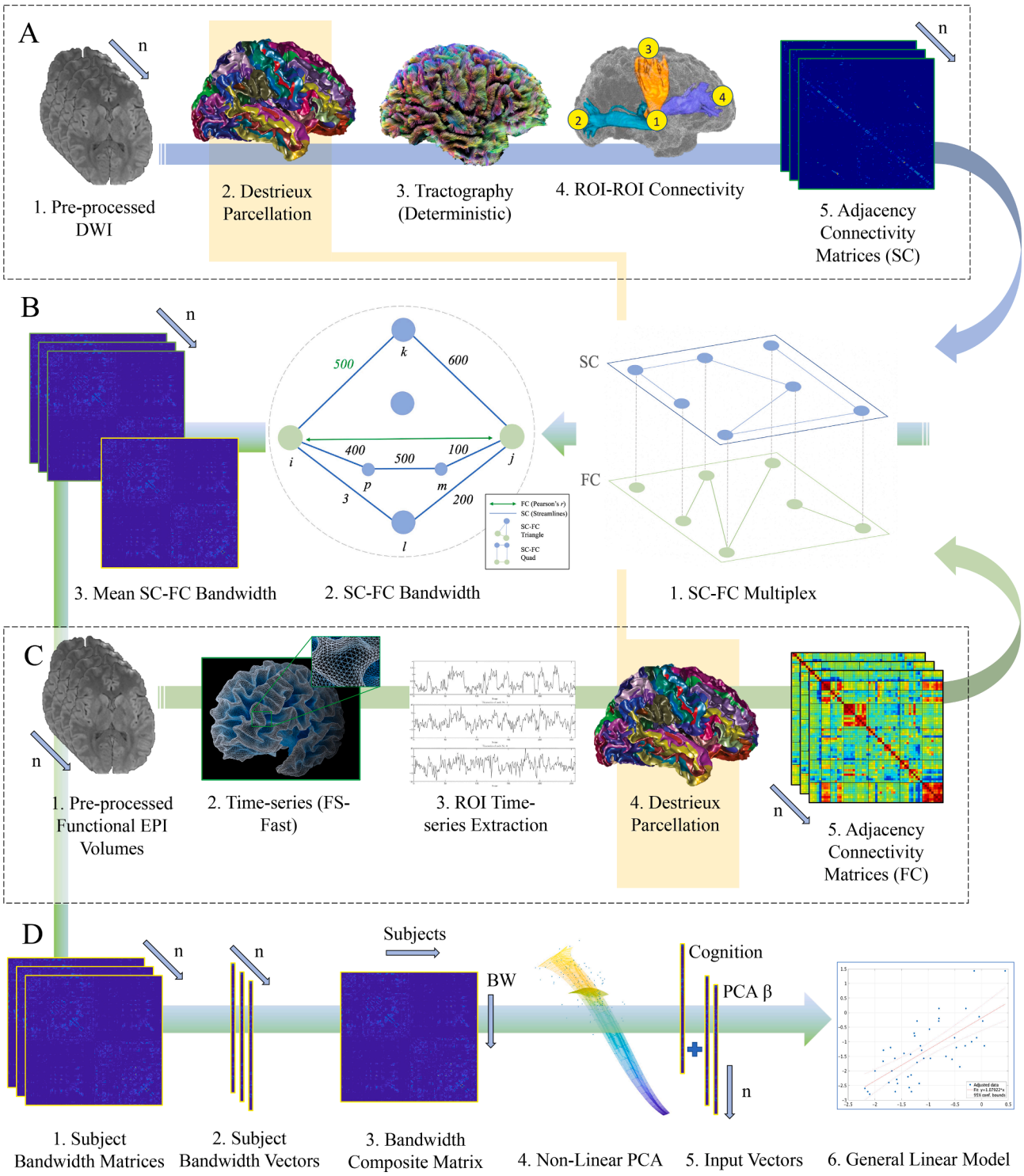


Fig. 3. Overview of SC-FC Bandwidth Pipeline. SC-FC Bandwidth is calculated using dMRI (Panel A) and fMRI (Panel C) connectivity data. These data are reconciled within a multiplex framework (Panel B). Panel D shows how SC-FC Bandwidth data are fed into a general linear model to predict processing speed. In chronological order, Panel A shows raw diffusion MRI data (1) are parcellated into the Destreiux Atlas (2) before deterministic tractography (3) is performed to calculate the number of reconstructed streamlines (SC) between every region of interest (4). SC adjacency matrices are then computed for each subject (5). Panel C shows preprocessed fMRI EPI data (1) are processed using FS-FAST (2) to compute a time series for each cortical vertex (3) before parcellation in the Destreiux atlas (4). Adjacency FC connectivity matrices are computed, comprising Pearson's correlation coefficients as each edge weight. Panel B shows SC and FC matrices are integrated into a multiplex framework (1) before SC-FC Bandwidth is calculated for each FC node (2) pair using the max–min method (Parsons et al., 2022). SC-FC Bandwidth adjacency matrices are then calculated for each subject (3). Panel D shows individual subject SC-FC Bandwidth matrices (1) are converted into vectors (2) and compiled into a composite matrix (3). Nonlinear PCA is then performed on this matrix (4) to calculate input weights in combination with cognition score vectors (5) for inclusion within a general linear model (6).

address our third hypothesis, we conducted a correlational analysis, using change in SC-FC Bandwidth and change in processing speed as the independent and dependent variables, respectively.

2.10. Network based statistics (NBS)

We performed statistical analysis to identify pairs of brain regions with altered SC-FC Bandwidth over time in mTBI patients. To test the null hypothesis of equality in the mean values of SC-FC Bandwidth between injury intervals, we used the Network Based Statistics Toolbox (NBS; Zalesky, Fornito & Bullmore, 2010). Herein, one-sample (repeated measures) t-statistics were calculated independently for each edge, using SC-FC Bandwidth matrices as inputs for each subject at the acute (Time 1) and chronic (Time 2) post-injury intervals in a Time 1 < Time 2 contrast. Any SC-FC connection with a t-statistic exceeding a set threshold of 2.5 (reflecting a *p*-value of 0.01) was included within a topological cluster (i.e., a network of edges/structural connections). Two networks were identified based on positive t-statistic values (i.e., increased over time) or negative t-statistic values (i.e., decreased over time). Finally, a False Discovery Rate (FDR)-corrected *p* value was then ascribed to each network using permutation testing. For each permutation, participants were randomly exchanged between Time 1 and Time 2 data. NBS was then applied to the randomized data, and the size of the largest connected component was recorded. A total of 5000 permutations were generated in this manner to yield an empirical null distribution for the size of the largest connected component.

3. Results

Using a general linear model, we found processing speed at the acute post-injury interval is predicted by nonlinear principal components of SC-FC Bandwidth, controlling for age with a moderate effect size (R^2 = 0.33, $p < 0.001$). Specifically, we found indirect SC-FC Bandwidth (t = -2.32, p = 0.02) contributed significant explained variance, however direct SC-FC Bandwidth did not contribute significant variance. At the chronic post-injury interval, we again found processing speed can be predicted by nonlinear principal components of SC-FC Bandwidth while controlling for age with a weaker effect size (R^2 = 0.26, $p < 0.001$). Significant predictor variables include indirect SC-FC Bandwidth (t = -2.37, p = 0.02) which contributed significant explained variance, however direct SC-FC Bandwidth also contributed significant variance (t = -1.94, p = 0.05).

We also conducted a *post-hoc* analysis to determine if principal components of FC alone predict processing speed, compared to the previous general linear models (i.e., direct and indirect SC-FC Bandwidth at each post-injury interval). We found that principal components of FC did not significantly predict processing speed at the acute post-injury interval (t = -0.16, p = >0.05), or the chronic post-injury interval (t = -1.9, p = >0.05), though adjusted whole models (which include age as a covariate) did significantly predict processing speed at both the acute (R^2 = 0.17, p = 0.001) and the chronic post-injury intervals (R^2 = 0.23, p = 0.002). Taken together, these findings suggest principal components of direct and indirect SC-FC Bandwidth are stronger predictors of processing speed than FC alone.

Using the NBS toolbox (Zalesky, Fornito & Bullmore, 2010) we conducted repeated measures, one-sample t-tests to reveal a fronto-parietal subnetwork of increased SC-FC Bandwidth (A) after False Discovery Rate (FDR) correction (A; p-FDR = 0.05). This subnetwork encompassing the LH fronto-marginal gyrus (of Wernicke) and sulcus with the left orbital gyri, the right orbital gyri with the opercular part of the RH inferior frontal gyrus, and the left medial orbital sulcus (olfactory sulcus) with RH supramarginal gyrus, RH angular gyrus and RH intraparietal sulcus and transverse parietal sulci (See Fig. 6). Each edge within this subnetwork exhibited increased SC-FC Bandwidth at the chronic post-injury interval relative to the acute post-injury interval. We also found significantly decreased SC-FC Bandwidth between the RH marginal branch of the cingulate sulcus and the RH middle occipital and lunatus sulcus at the chronic, relative to the acute post-injury interval (B; p-FDR = 0.05).

To examine identified subnetworks, we performed partial correlations between the change in SC-FC Bandwidth (values at time point 2 - time point 1) of each edge in the increased and decreased SC-FC Bandwidth subnetwork (shown in Fig. 5, above) and change in normalized processing speed (values at time point 2 - time point 1) scores for each subject while controlling for age. Here, positive change in processing speed scores corresponds with better performance, and positive change in SC-FC Bandwidth corresponds with improved SC-FC Bandwidth over time). We found a significant partial correlation whereby increased SC-FC Bandwidth of the medial orbital sulcus (olfactory sulcus) and RH angular gyrus was associated with decreased processing speed (partial r = 0.32, p = 0.02). In other words, increased SC-FC Bandwidth values over time, coincided with better performance on the processing speed task over time.

4. Discussion

Applying our novel graph metric (SC-FC Bandwidth; Parsons et al., 2022), we uncovered reorganization of SC-FC network connectivity following mTBI, corresponding with changes to processing speed. Our findings highlight the utility of reconciling multimodal connectivity data within a unified framework to characterize brain connectivity changes with recovery. Hereafter, we discuss our main findings with respect to our key aims, raise key methodological considerations, identify study limitations and provide suggestions moving forward.

4.1. Improvements in processing speed with recovery

As expected, we found that patients exhibited improved processing speed at the chronic (6-months) relative to the acute injury post-injury interval (3-weeks) operationalized with the 30 Seconds and Counting Task within the BTACT battery. Our findings are in line with previous studies examining cognitive recovery in mTBI. For example, previous work has reported spontaneous resolution of cognitive impairment ranging from weeks (Vanderploeg et al., 2005) to months (Schretlen & Shapiro, 2003; Flynn, 2010; Karr, Areshenkoff & Garcia-Barrera, 2014) to years (Heitger et al., 2006; Caroll et al., 2020). Here, our finding of

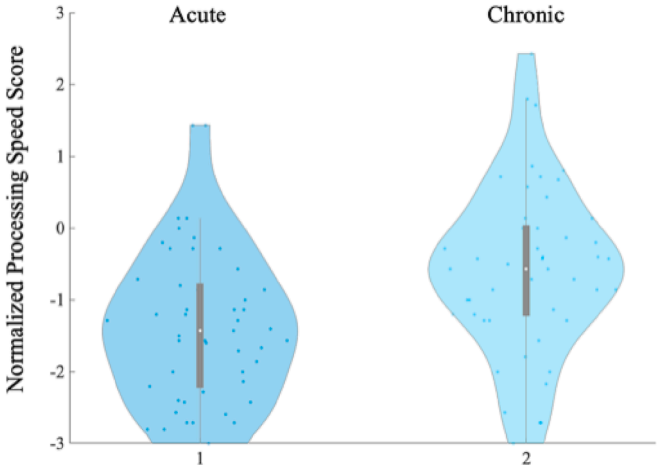
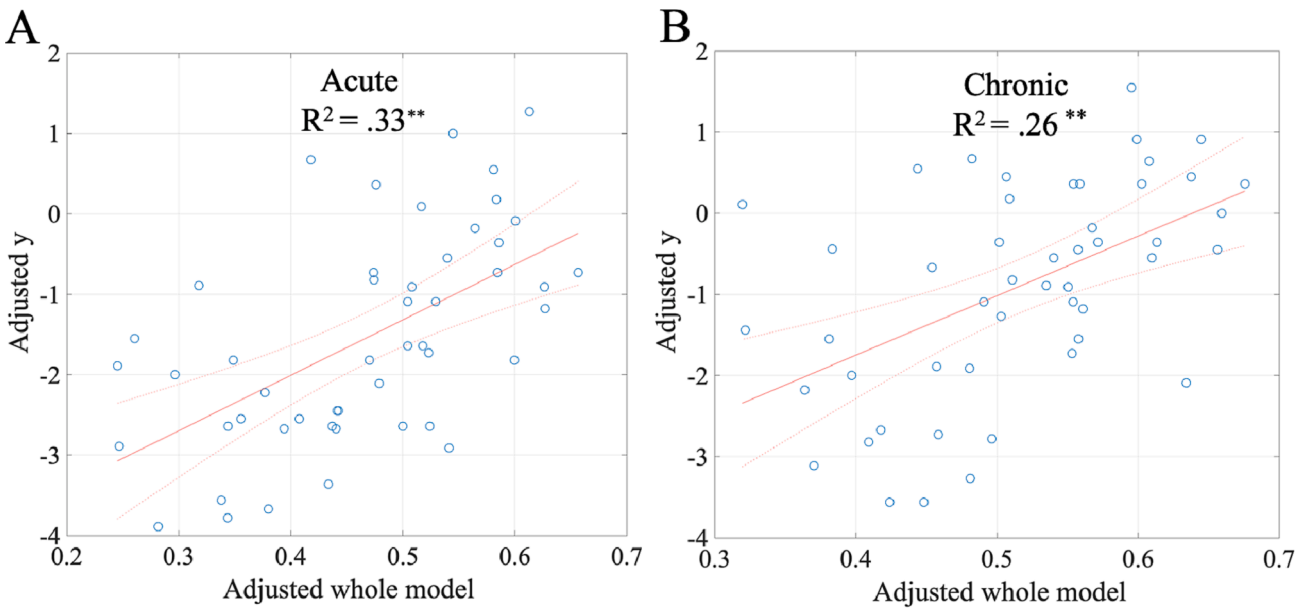


Fig. 4. Improved Processing Speed From Acute to Chronic Injury Post-injury Interval. Fig. 4shows the result of a repeated measures one-sample *t*-test performed to compare normalized processing speed scores in mTBI patients (using the 30 Seconds and Counting Task where lower scores indicate better performance) at the acute and chronic post-injury intervals. We found that normalized processing speed scores were significantly increased at the the chronic (M = -0.57, SD = 1.16) compared to the acute (M = -1.36, SD = 1.04) post-injury intervals t(48) = -8.60, p = <0.001). Black bars represent standard error.



	Estimate	SE	*t*-statistic	*p-value*
(Intercept)	-4.762	2.082	-2.290*	0.026
Direct BW	-0.801	0.435	-1.84	0.072
Indirect BW	-6.840	2.942	-2.324*	0.024
Age	-0.043	0.010	-3.960**	<.001

*p <.06
**p <.001
Number of observations: 49, Error degrees of freedom: 45
Root Mean Squared Error: 1.1
R-squared: 0.333, Adjusted R-Squared: 0.288
F-statistic vs. constant model: 7.49, p-value = 0.000361

	Estimate	SE	*t*-statistic	*p-value*
(Intercept)	-4.684	2.1768	-2.151*	0.03
Direct BW	-0.884	0.455	-1.942*	0.05
Indirect BW	-7.282	3.076	-2.370*	0.022
Age	-0.035	0.011	-3.130**	0.003

*p <.06
**p <.001
Number of observations: 49, Error degrees of freedom: 45
Root Mean Squared Error: 1.15
R-squared: 0.267, Adjusted R-Squared: 0.218
F-statistic vs. constant model: 5.45, p-value = 0.00278

Fig. 5. Linear Model to Predict Processing Speed at Acute and Chronic Post-Injury Intervals. Panel A shows a general linear model (processing speed) at the acute post-injury interval, using predictor (input) variables of direct SC-FC Bandwidth, indirect SC-FC Bandwidth and Age as a control variable. Panel B shows a general linear model (Processing speed) at the chronic post-injury interval, using predictor (input) variables of direct SC-FC Bandwidth, indirect SC-FC Bandwidth and Age as a control variable.

improved processing speed at the *chronic* post-injury interval contrast those of a recent longitudinal study reporting improved processing speed over a 2-year trajectory using a selection of computerized tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Caroll et al., 2020). However, this test measured rapid visual information processing which although linked with response latency, is primarily a measure of sustained visual attention. In the context of training studies, our finding of increased processing speed coincides with Cooper et al., (2017) which examined the Paced Auditory Serial Addition Test (PASAT) as a dependent variable, with several treatment arms (psychoeducation, computer-based cognitive rehabilitation; CR), therapist-directed manualized CR, and integrated therapist-directed CR combined with cognitive-behavioral psychotherapy) as independent variables in military mTBI patients at 3-week, 6-week, 12-week, and 18-week follow-ups. All 4 treatment groups showed a significant improvement over time in PASAT scores, including psychoeducation which was used as a control treatment. However, the lack of a true non-treatment control group precludes identification of spontaneous improvement in PASAT scores. In addition, our methodological design was limited to only two timepoints. That is, although we can model a linear trajectory using data at each time point for each subject, we cannot model a more sensitive (i.e., polynomial) trajectory to detect a recovery plateau in this sample (i.e., more than two time points for each subject). This notwithstanding, the cognitive trajectory of each patient is thought to be highly dependent on the injury mechanism and severity, where even homogenous samples (i.e., similar injury severity, GCS score, chronicity) still present with high inter-subject variability (Ware et al., 2017). Moving forward, this field must consider (a) collecting samples in the order of thousands, and (b) developing subject-specific trajectory predictions if we are to develop clinically valuable research outcomes. Finally, we focused on processing speed as a core function underpinning higher-order cognition. However, additional tests of processing speed may complement the BTACT, to measure features such as drift rate (Imms et al., 2020).

4.2. *Alterations in SC-FC Bandwidth of mTBI patients with recovery*

Our general linear model indicated the statistical influence of direct, and indirect SC-FC Bandwidth was similar at both the acute and chronic post-injury intervals, though indirect SC-FC Bandwidth exerted higher influence at both injury intervals. It can be conjectured that the relatively low frequency of direct SC-FC polygons in the brain (~10% of all SC-FC polygons in the healthy brain; Parsons et al., 2022) may explain less variance in the statistical model, as they mediate far fewer synchronous gray matter regions. That is, the likelihood of directly connected synchronous gray matter regions playing a critical role in processing speed performance, is inherently lower. The contribution of age was also stronger than both direct and indirect SC-FC Bandwidth at

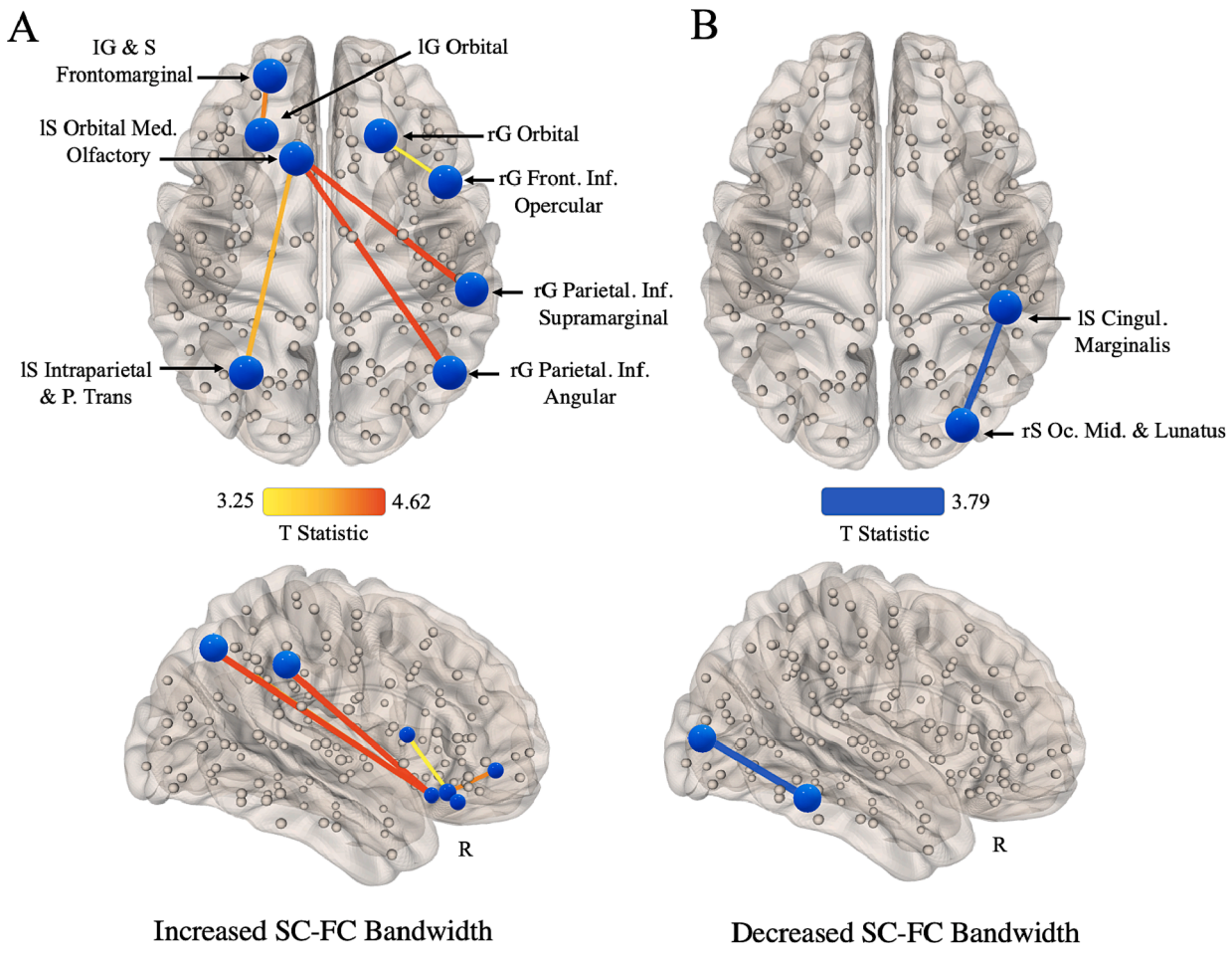


Fig. 6. SC-FC Bandwidth Subnetworks. Increased (A) and decreased (B) indirect SC-FC Bandwidth subnetworks. Each subnetwork edge is weighted by T-statistic (chronic > acute post-injury interval contrast, $p < 0.001$).

both post-injury interval, though this finding is unsurprising, given that white matter microstructure underpinning direct and indirect SC is known to change significantly across the lifespan and is associated with cognitive status (Yeatman, Wandell & Mezer, 2014; Cox et al., 2016; Coelho et al., 2022).

For the first time, our findings revealed a subnetwork of increased SC-FC Bandwidth edges over the course of mTBI recovery, irrespective of how direct these connections were. Overall, we found maximum SC-FC Bandwidth was increased at the chronic, relative to the acute post-injury interval. Firstly, our findings can be compared to those derived from whole-brain *unimodal* MRI studies (SC; using probabilistic streamline tractography and FC; using Pearson's or partial correlation coefficient) within using longitudinal designs in mTBI patients. Here, our findings contrast those of a recent study (Roine et al., 2022) reporting no global differences in structural network properties (i.e., clustering coefficient, global efficiency, characteristic path length, small worldness, betweenness centrality) between mTBI patients and controls at 4-weeks and 8-months post-injury. Secondly, our findings can be compared to the few existing *multimodal* MRI studies that leverage SC and FC, without drawing direct statistical comparisons between each measure. For example, Kuceyeski et al., (2016) quantified the SC-FC using network diffusion model (NDM) propagation time which can be interpreted as how much of the SC connectome is utilized for the spread (i.e., diffusion) of functional activation, captured *via* the FC connectome. This propagation time is thought to be slower in TBI patients, where functional communication may be rerouted through alternate, less efficient pathways. Indeed, severe TBI patients demonstrated longer NDM propagation time than HC, though this effect was not significant ($t = 1.36$, $p = 0.31$). Kuceyeski et al., (2018) used a similar approach in mild TBI patients, reporting increased network diffusion propagation time from 3 to 6 months after TBI was related to better cognitive recovery (improved cognition scores over time). These findings speak to the impact of inefficient alternate SC pathways upon cognition and converge with the present findings regarding the relationship between efficient network communication (i.e., SC-FC Bandwidth) and cognition (i.e., processing speed). In the context of these findings, another reasonable conclusion may be that the application of our novel method uncovers changes in connectivity of mTBI patients, not ordinarily detectable with unimodal MRI connectivity alone. That is, given most brain regions are connected by two or more SC edges, yet these edges are not considered within direct SC analyses.

4.3. SC-FC Bandwidth and processing speed at the Acute-Chronic Post-Injury intervals

As hypothesized, we found increased SC-FC Bandwidth predicts improved processing speed albeit between the LH medial orbital sulcus (olfactory sulcus) and RH angular gyrus. This finding is interesting, given the RH angular gyrus is strongly implicated in language and number processing (Seghier, 2012) which were tested directly using the 30 Seconds and Counting Task. On the other hand, the role of the RH medial orbital sulcus is counterintuitive, with no discernible influence on cognitive processes underlying the 30 Seconds and Counting Task. A simple explanation for this finding, may be that the role of RH medial orbital sulcus in facilitating processing speed, cannot be appreciated without a more complex brain-behavior model. That is, cognitive

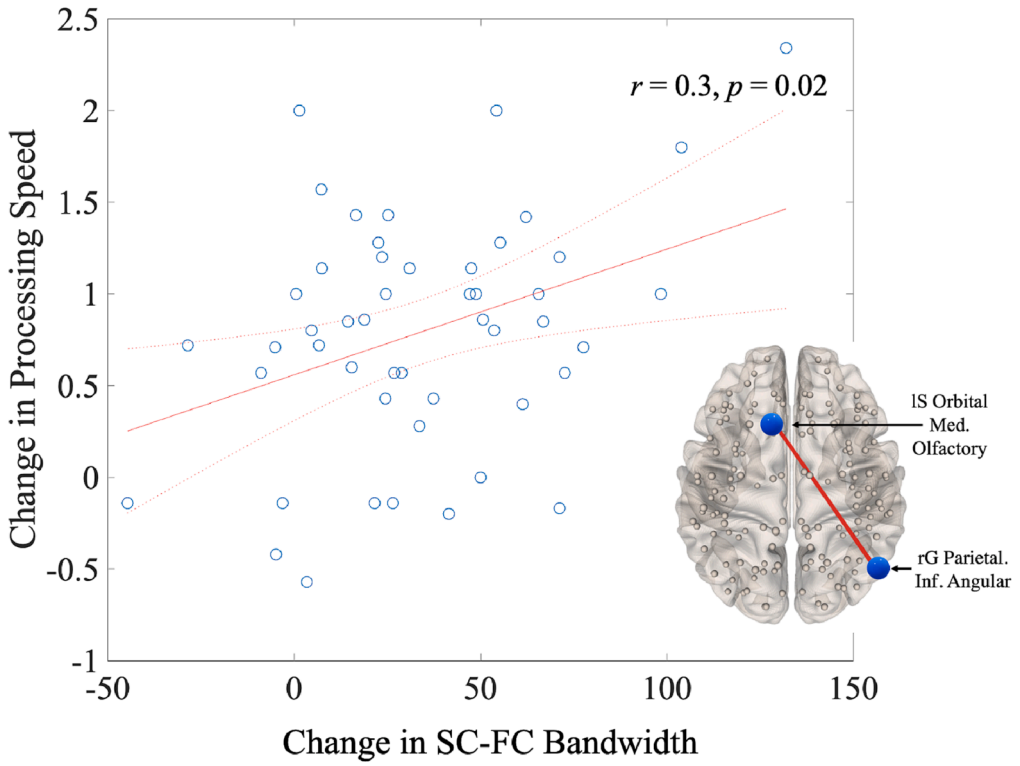


Fig. 7. Change in SC-FC Bandwidth with Change in Processing Speed. Fig. 7 shows a scatterplot comparing the change in indirect SC-FC Bandwidth values (x axis) to the change in processing speed values (y axis) of each subject and the partial correlation coefficient between these variables. Positive values indicate better recovery of processing speed and increased SC-FC Bandwidth.

measurements are indirect (i.e., latent) estimates of an underlying behavioral construct, which are abstractions from direct brain function or neurobiological information (i.e., connectivity measures; Tiego & Fornito, 2022). Therefore, it is unlikely that the structure or function of any brain region relates strongly to a complex measure of cognition (i.e., processing speed). Another possible explanation for this counterintuitive finding relates to the nature of SC-FC polygons. That is, by limiting SC-FC polygons to SC lengths of no more than three, we remove false positive paths by virtue of the assumption that longer SC-FC polygons are spurious. However, we may also exclude false negatives, where information may be sent further than the medial orbital sulcus. For example, information relating to numerical processing may be propagated to a proximal region such as Broca's area for speed production to facilitate the 30 Seconds and Counting Task requirement. Furthermore, given this edge represents an indirect, interhemispheric connection, we posit that this finding coincides with previous studies, showing significant associations between lower values of white matter organization in the corpus callosum and slower processing speed in TBI patients (Levin et al., 2008; Wilde et al., 2006) which has interesting implications in the context of our findings. That is, we found increased interhemispheric SC-FC Bandwidth predicts decreased processing speed at the chronic, relative to the acute mTBI post-injury interval. As mentioned already, given SC-FC polygons were restricted to SC paths of length 3 (i.e., three connected white matter pathways), increased SC-FC Bandwidth between source and target nodes necessarily includes SC of the corpus callosum within the SC-FC Bandwidth equation calculation. Here, our findings support the link between white matter and processing speed, with respect to unimodal SC studies. Specifically, when considering our finding in the context of the corpus callosum (i.e., Levin et al., 2008; Wilde et al., 2006) a reasonable interpretation may be that interhemispheric communication is restricted by weaker SC sub-paths (lower number of reconstructed streamlines) linked as an extension with the corpus callosum. Indeed, Bai et al., (2020) reported damage to frontal interhemispheric projections may inhibit frontal-subcortical neuronal circuits–ultimately predicting Processing speed as measured by the Trail Making Task (Arnett & Labovitz, 1995) in mTBI patients. Our *post-hoc* finding that FC alone did not significantly predict processing speed (unless coupled with age as a covariate) is unsurprising, since age has a negative linear relationship with processing speed (Amgalan et al., 2022a). Given this whole model was a weaker predictor of processing speed than our direct and indirect SC-FC Bandwidth model, it is reasonable to posit that SC-FC Bandwidth may have more utility in predicting processing speed than FC alone. Indeed, studies are beginning to relate multilayer network metrics with cognition. For example, Breedt et al., (2023) recently reported that higher multilayer centrality of the frontoparietal network, but not single-layer centrality, was related to improved executive function, albeit in healthy individuals. More broadly, our findings mark the importance of considering multilayer network connectivity metrics moving forward.

4.4. *Study limitations and suggestions moving forward*

The first important study limitation pertains to our sample, which comprised mostly female patients which may have implications when generalizing our findings to male patients. Although no direct evidence has been reported that changes in whole-brain white matter microstructure following mTBI varies as a function of gender, there is evidence of altered functional connectivity of large-scale resting-state networks between males (increased FC) and females (both increased and decreased FC; Amgalan et al., 2022) likely driven by a greater neuroprotective immune response in females, as well as differences in sex-hormone levels and endocrine function (Stein, 2008). In addition to gender differences, our sample was homogeneous with respect to injury mechanism (ground-level falls only) which limits generalizability to other causes of TBI (i.e., blast-, traffic- or violence-related). Beyond alterations in SC and FC at the chronic post-injury interval, brain aging profiles (i.e., widening of the cortical sulci, ventricular enlargement, and thinning of the cortex) also differ between males and females. For

example, a recent paper used machine learning to estimate "brain-age" (Cole et al., 2015; Cole et al., 2018) relative to chronological age. This paper reported stronger feature weights of males pertaining to temporal and dorsolateral frontal lobes, whereas female feature weights pertained to bilateral posterior and medial occipital regions, medial aspects of the parietal lobes, supramarginal gyri and callosal sulcus, among other regions (Yin et al., 2023). Taken together, preliminary evidence supports the notion that mTBI recovery may be influenced by subtle, gender-driven neurobiology, warranting further research. In our study, gender was controlled for as a covariate, though a small male sub-sample precluded a statistically appropriate group-level contrast of SC-FC Bandwidth.

Another important limitation of this study pertains to a lack of healthy control group, precluding a group by time interaction analysis to control for alterations in processing speed and SC-FC Bandwidth in otherwise healthy individuals. Secondly, though our measure of processing speed offers good concurrent validity and test–retest reliability with corresponding Boston Cognitive Battery factors (Lachman et al., 2014; Miller & Lachman, 2000) there is an important limitation regarding the difficulty of this test in mTBI patients. That is, processing speed task difficulty (i.e., cognitive load) is not manipulated as part of the BTACT assessment. This has important implications for predicting processing speed using SC-FC Bandwidth, because this graph metric is an apparent measure of total information transportation *capacity* (i.e., the full capacity is reached when signal traffic accumulates at nodal junctions or bottlenecks; Mišić et al., 2014; Tombu et al., 2011). As a result, the explained variance of SC-FC Bandwidth within our general linear model may be underrepresented. That is, patients may not have reached a difficulty threshold associated with maximum SC-FC Bandwidth. Mild TBI patients may also be particularly susceptible to this threshold effect as evidence suggests moderate-severe TBI patients exhibit lower accuracy on cognitive assessments when given less time to respond, relative to healthy controls (Capruso & Levin, 1992; Gronwall et al., 1974). Therefore, future studies may wish to examine the association between SC-FC Bandwidth and processing speed in a cognitive test that offers variation in difficulty such as the trail-making test (Salthouse et al., 2000; Arnett & Labovitz, 1995) or the n-back task (Kirchner, 1958).

As hypothesized, we found processing speed can be predicted when using nonlinear components (i.e., subnetworks of edges) relating to direct and indirect SC-FC Bandwidth, while controlling for age. These findings uncover the *relative* variance in Processing speed explained when considering several global (i.e., direct and indirect) input data. This notwithstanding, there are several important considerations regarding the use of PCA in our analysis. First, although nonlinear PCA is arguably a superior method to capture complex relationships in brain connectivity data compared to linear PCA (Scholz et al., 2005; Scholz, 2012), the subnetwork of edges that each component represents cannot be mapped back into 3-dimensional brain space without reverting to linear PCA. Therefore, nonlinear principal components are inherently difficult to interpret. For this reason, we use these components only to (a) reduce highly dimensional data for inclusion in a regression model, and (b) quantify the *relative* importance of SC-FC Bandwidth values, justifying our subsequent analyses.

It is important to note that brain-behavior relationships cannot be explained entirely using behavioral and macroscopic brain connectivity data alone, within any single SC-FC model. For example, communication models (Graham & Rockmore, 2011; Goñi et al., 2014; Crofts and Higham, 2009) consider one or more signaling mechanisms ranging from fully centralized (i.e., routing model) to fully decentralized (i.e., diffusion of signals throughout the connectome). On the other hand, biophysical models (Honey et al., 2007; Breakspear, 2017; Sanz-Leon et al., 2015) are able to simulate spontaneous or stimulation-induced neural activity, constrained to physical infrastructure (i.e., SC connectomes). Indeed, alternate SC-FC models leverage different assumptions, and require different input data (i.e., transcription profiles, cytoarchitecture, receptor densities, laminar differentiation, temporal dynamics and gene expression) yet these models still do not account for sociocultural, phylogenetic, genetic and ontogenetic variables that influence brain-behavior relationships at an individual level (Suárez et al., 2020; Fornito & Tiego, 2022). Moving forward, a *more* unified framework must be considered if we are to harness the power of each SC-FC model, toward explaining behavior and cognition. For example, "neuromaps" (Markello et al., 2022) allows users to access, transform and analyze structural and functional brain annotations. Herein, curated reference maps and biological brain ontology maps are provided (molecular, microstructural, electrophysiological, developmental and functional) to facilitate standardization and comparison of brain maps.

From a clinical standpoint, the utility and feasibility of our measure remains to be explored.

This notwithstanding, SC-FC Bandwidth could be calculated at the individual subject level, and benchmarked against an appropriate comparative sample (i.e., similar injury location, severity, chronicity) to more sensitively track the trajectory of each patient throughout their recovery. Indeed, several studies have recently applied advanced analysis of structural MRI at the single-subject level to characterize structural connectomes (Imms et al., 2022) and white-matter organization using fixel-based analysis (Clemente et al., 2023) in moderate-severe TBI patients. These studies provide ample evidence that injuries in each subject cannot be properly characterized without more advanced analysis of MRI data. However, these analyses are notoriously time- and resource-intensive, which calls for teamwork between clinicians and neuroscientists, to translate cutting-edge technology into clinical settings moving forward. In the context of patient management, this novel metric may provide the foundation for a more direct (i.e., neurobiological) measurement underpinning processing speed, such that lower values identified in individuals who do not yet show lower processing speed scores on neuropsychological testing, may indicate a future predisposition to challenges with daily functioning.

5. Conclusion

Applying our novel GTA metric SC-FC Bandwidth, we show for the first time that mTBI triggers complex reorganization of brain connectivity from the acute-chronic post-injury intervals, optimized for maximum information flow—ultimately driving improved processing speed. Our findings highlight the importance of considering indirect SC-FC to characterize neuroplasticity following trauma. Specifically, SC-FC Bandwidth in mTBI may be used to flag patients with impaired recovery trajectory to provide early therapeutic intervention.

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CRediT authorship contribution statement

Nicholas Parsons: Conceptualization, Methodology, Formal analysis, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Andrei Irimia:** Conceptualization, Methodology, Writing – review & editing. **Anar Amgalan:** Conceptualization, Methodology. **Julien Ugon:** Conceptualization, Methodology, Writing – review & editing. **Kerri Morgan:** Conceptualization, Methodology, Writing – review & editing. **Sergiy Shelyag:**

Conceptualization, Methodology, Validation. **Alex Hocking:** Software, Validation, Formal analysis. **Govinda Poudel:** Supervision, Writing – original draft, Writing – review & editing. **Karen Caeyenberghs:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103428.

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