Personalized connectome-based modeling in patients with semi-acute phase TBI: relationship to acute neuroimaging and 6-month follow-up

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4 Following traumatic brain injury (TBI), cognitive impairments manifest through
5 interactions between microscopic and macroscopic changes. On the micro-scale a
6 neurometabolic cascade alters neurotransmission, while on the macro-scale diffuse
7 axonal injury impacts the integrity of long-range connections. Large-scale brain network
8 modeling allows us to make predictions across these spatial scales by integrating
9 neuroimaging data with biophysically based models to investigate how microscale
10 changes invisible to conventional neuroimaging influence large-scale brain dynamics. To
11 this end, we analyzed structural and functional neuroimaging data from a well
12 characterized sample of forty-four adult TBI patients recruited from a regional trauma
13 center, scanned at 1-2 weeks post-injury, and with follow-up behavioral outcome
14 assessed six months later. Thirty-six age-matched healthy adults served as comparison
15 participants. Using The Virtual Brain we fit simulations of whole-brain resting-state
16 functional MRI to the empirical static and dynamic functional connectivity of each
17 participant. Multivariate partial least squares (PLS) analysis showed that patients with
18 acute traumatic intracranial lesions had lower cortical regional inhibitory connection
19 strengths than comparison participants, while patients without acute lesions did not differ
20 from the comparison group. Further multivariate PLS analyses found correlations
21 between lower semi-acute regional inhibitory connection strengths and more symptoms
22 and lower cognitive performance at a 6-month follow-up. Critically, patients without
23 acute lesions drove this relationship, suggesting clinical relevance of regional inhibitory

24 connection strengths even when traumatic intracranial lesions were not present. Our
25 results suggest large-scale connectome-based models may be sensitive to
26 pathophysiological changes in semi-acute phase TBI patients and predictive of their
27 chronic outcomes.

28 **Significance Statement**

29 The variability of clinical outcomes following mild to moderate traumatic brain
30 injury (TBI) is underscored by complex pathophysiological mechanisms that take effect
31 across spatial scales. We used the neuroinformatics platform, The Virtual Brain, to model
32 individualized brain activity and make inferences across these spatial scales. Specifically,
33 this approach allowed us to link macroscopic brain dynamics with mesoscopic
34 biophysical parameters, distinguishing semi-acute mild to moderate TBI patients from
35 comparison participants and predicting the long-term recovery of these patients. Our
36 results demonstrate the sensitivity of our large-scale brain model to pathophysiological
37 changes following TBI and illustrates how computational modeling may be used to
38 advance understanding of chronic TBI outcome.

39 **Introduction**

40 Chronic clinical outcomes following traumatic brain injury (TBI) are heterogeneous
41 (Dabek & Caban, 2016; Si et al., 2018). Classifying patients based on the presence of
42 pathoanatomic features on computerized tomography (CT) and/or magnetic resonance
43 imaging (MRI) is a useful way to stratify variance of TBI patients (Iverson et al., 2012;
44 McMahon et al., 2014; Palacios et al., 2017; Yuh et al., 2014). However, even within
45 these patient subgroups significant variability in clinical outcomes and cognitive
46 performance can be observed (Iverson et al., 2012; Palacios et al., 2017). The sources of

47 this variability are diverse (Kenzie et al., 2018) and may include forms of pathology not
48 visible with conventional neuroimaging.

49 TBI has been described as a multi-scale system deficit, with cognitive impairments
50 manifesting through interactions between microscopic and macroscopic changes (Kenzie
51 et al., 2018). On the macro-scale, TBI is associated with decreased integrity of white
52 matter pathways and an imbalance and inefficiency of functional networks (Hayes,
53 Bigler, & Verfaellie, 2016). Studies using diffusion weighted MRI imaging (dwMRI)
54 have consistently detected decreases in fractional anisotropy (FA) (Douglas et al., 2015;
55 Filley & Kelly, 2018; Niogi & Mukherjee, 2010; Shenton et al., 2012) that correlate with
56 cognition (Palacios et al., 2020; Wallace, Mathias, & Ward, 2018) and if assessed in the
57 semi-acute phase, long-term clinical outcomes (Yuh et al., 2014). Functional connections
58 are also sensitive to TBI, with alterations observed in multiple intrinsic connectivity
59 networks (for reviews: Hayes et al., 2016; Sharp, Scott, & Leech, 2014). Early phase
60 functional connectivity (FC) between and within networks may be predictive of long-
61 term symptom severity (Madhavan et al., 2019; Palacios et al., 2017), while changes to
62 FC dynamics have been noted in the acute (Hou et al., 2019) and semi-acute phase
63 (Mayer et al., 2014; Vergara, Mayer, Kiehl, & Calhoun, 2018) following TBI.

64 On the micro-scale, TBI causes a neurometabolic cascade that alters
65 neurotransmission and can have long-lasting effects (Giza & Hovda, 2015). The initial
66 injury causes a sudden imbalance in glutamatergic, and GABAergic neurotransmitter
67 levels, as well as NMDA receptor malfunction (Giza & Hovda, 2015). Magnetic
68 resonance spectroscopy (MRS) is capable of detecting changes to neuromodulatory
69 concentrations *in vivo*. A recent meta-analysis found evidence for elevated glutamate

70 concentrations in adult patients after a single mild TBI (mTBI) in the acute and sub-acute
71 phases (Eisele, Hill-Strathy, Michels, & Rauen, 2020). Furthermore, some studies have
72 shown these elevated glutamate concentrations are predictive of long-term outcomes
73 (Shutter, Tong, & Holshouser, 2004).

74 Connectome-based brain network modeling provides a novel perspective to TBI by
75 allowing access to local and global parameters related to both micro-level
76 neuromodulatory changes and macro-level connectivity changes. We used the
77 neuroinformatics platform The Virtual Brain (TVB) to simulate whole-brain dynamics
78 composed of interacting neural population models (Ritter, Schirner, McIntosh, & Jirsa,
79 2013; Sanz Leon et al., 2013). Our model simulated brain areas as excitatory and
80 inhibitory neural populations connected via GABA and NMDA synapses (Deco,
81 McIntosh, et al., 2014; Schirner et al., 2018). Personalized simulations were constrained
82 by each subject's structural connectome and fitted to their static and dynamic functional
83 connectomes, which were computed from dwMRI and rsfMRI (Schirner, Rothmeier,
84 Jirsa, McIntosh, & Ritter, 2015). The parameter fitting procedure tuned the parameters
85 global coupling and regional inhibitory connection strengths to yield FC predictions for
86 each subject. Global coupling is a scaling factor related to the level of
87 integration/segregation in the system (Deco, Tononi, Boly, & Kringelbach, 2015), while
88 regional inhibitory connection strength indicates the level of inhibitory influence at each
89 brain region. These model parameters have been used to describe healthy neural
90 dynamics (Jirsa et al., 2010; Roy et al., 2014) and those of clinical populations (Aerts et
91 al., 2018; Falcon et al., 2016; Jirsa et al., 2017; Zimmermann et al., 2018).

105 Participants

7

114 previous significant TBI (LOC>5mins) were also excluded. Overlapping patient and
115 comparison participant samples have been described in detail in two previous
116 publications (Palacios et al., 2017; Yuh et al., 2014). Eight patients did not complete the
117 clinical and cognitive assessment at the six-month follow-up and were therefore removed
118 from analyses using this data ($n_{\text{patient}}=36$ for six month clinical/cognitive data).

119 Each patient's head CT upon ED presentation and semi-acute brain MRI (5-18
120 days post-injury) was characterized using the TBI common data elements (TBI-CDE)
121 criteria (Yue et al., 2013). Each CT and MRI was anonymized and reviewed by a board
122 certified neuroradiologist blinded to the data. The TBI patients were divided into two
123 subgroups: 1) CT/MRI positive ($n = 14$; $M_{\text{age}}=39$, $SD_{\text{age}}=13.7$), defined as patients with
124 any acute traumatic intracranial lesion (epidural hematoma [EDH], subdural hematoma
125 [SDH], subarachnoid hemorrhage [SAH], contusion, or evidence of traumatic axonal
126 injury [TAI]) and/or depressed skull fracture on either CT or MRI, and 2) CT/MRI
127 negative ($n = 30$; $M_{\text{age}}=31$, $SD_{\text{age}}=9.0$), defined as patients without any such abnormality
128 on either CT or MRI. There were no large lesions expected to adversely affect the
129 dwMRI or fMRI results. Patient characteristics are presented in Table 1. We note that all
130 the TBI patients meet the definition of mTBI by some standards (Yue et al, 2013) though
131 the patients with positive CT findings would be considered moderate by other criteria
132 (Krainin et al, 2011).

133 **Outcome Measures**

134 The outcome measures included the Extended Glasgow Outcome Scale (GOS-E)
 135 at 6 months post-injury performed through structured interviews with each participant by
 136 research assistants trained to uniformly assess the GOS-E. A trained neuropsychologist
 137 also administered the following behavioural and cognitive tests at 6 months after injury:
 138 Trail Making Tests (TMT) Part A and B, Wechsler Adult Intelligence Scale (WASI), 4th
 139 Ed (Wechsler, 1999), Satisfaction with Life Scale (SWLS) (Diener, Emmons, RJ, &
 140 Griffin, 1985), Brief Symptom Inventory (BSI) 18 (Derogatis, 1983), and California
 141 Verbal Learning Test-Second Edition (CVLT-II) (Delis et al, 2000). Higher scores on the
 142 GOS-E, SWLS, WAIS, and CVLT were coded such that higher scores indicate better
 143 outcome, while scores on the BSI and TMT are coded such that higher scores indicate
 144 poorer outcome.

145 **Principal Component Analysis**

146 Principal component analysis (PCA) was used to expose the latent structure
 147 within the collection of outcome measures and to reduce the dimensionality of the
 148 dataset. Data were transformed if significantly skewed ($p < 0.05$) using square root or
 149 log10 to improve the correlation structure. The point of inflection on a scree plot was
 150 used to identify the number of components to keep. After extracting this number of
 151 factors, a promax rotation was performed using the “principal” function in R (R Core
 152 Team, 2013). The correlation between factors was $r=0.33$, exceeding 0.32 and therefore
 153 indicating greater than 10% overlap in variance between factors, warranting an oblique
 154 rotation (Tabachnick & Fidell, 2007). As such, we used the two-factor solution with a

promax rotation for later analyses. Factors were designated as (1) TBI Symptoms, and (2) Age and Cognition based on the primary symptoms, cognitive functions, and characteristics assessed by the variables that strongly contributed to each (loading $>|0.3|$; Table 5). Factor scores for each participant represent the degree to which they express the factor. Higher factor scores on the TBI Symptoms factor indicates poorer outcome, while higher factor scores on the Age and Cognition factor implies older age and lower performance.

Imaging Procedure

MRIs were acquired on a 3T GE Signa EXCITE scanner equipped with an eight-channel phased array head radiofrequency coil. The following conventional 3T MRI sequences were performed: 1) axial three-dimensional (3D) inversion recovery fast spoiled gradient recalled echo T1-weighted images (TE = 1.5 ms; TR= 6.3 ms; inversion time [TI] = 400 ms; flip angle, 15 degrees) with 230mm FOV, 156 contiguous partitions (1.0 mm) at $256 \cdot 256$ matrix; 2) axial T2-weighted fluid-attenuated inversion recovery images (TE = 126 ms; TR= 10 sec; TI = 2200 ms) with 220mm FOV, 47–48 contiguous slices (3.0 mm) at $256 \cdot 256$ matrix; and 3) axial magnetization-prepared gradient echo T2*- weighted images (TE = 15 ms; TR= 500 ms; flip angle 20 degrees) with 220 · 170mm FOV and 47–48 contiguous slices (3.0 mm) at $256 \cdot 192$ matrix. A 7 min. rsfMRI single shot gradient-echo echo planar imaging (EPI) sequence was acquired (repetition time [TR] = 2000 ms, echo time [TE] = 28 ms; flip angle = 90 grad; field of view [FOV] = 220 mm; voxel size = $3.4 \cdot 3.4 \cdot 4.0$ mm). The subjects were asked to close their eyes, relax, not focus their attention on anything specific, and not fall asleep. Whole-brain DTI was performed with a multi-slice single-shot spin echo echoplanar pulse sequence (echo

time [TE] = 63 ms; repetition time [TR] = 14 sec) using 55 diffusion-encoding directions, isotropically distributed over the surface of a sphere with electrostatic repulsion, acquired at $b = 1000 \text{ sec/mm}^2$, seven acquisitions at $b = 0 \text{ sec/mm}^2$, 72 interleaved slices of 1.8-mm thickness each with no gap between slices, a $128 \cdot 128$ matrix, and a field of view (FOV) of $230 \cdot 230 \text{ mm}$. For DTI, parallel imaging was employed using the array spatial sensitivity encoding technique (ASSET) with an acceleration factor of 2. The MRI scanner and the scanning protocol used were the same for the patient and comparison groups.

186 **Parcellation Scheme**

The 96-region of interest (ROI) Regional Map parcellation (Kötter & Wanke, 2005) was used for construction of the structural and functional connectivity matrices. The RM-96 parcellation has 82 cortical and 14 subcortical ROIs (Bezgin, Solodkin, Bakker, Ritter, & McIntosh, 2017). It has been used previously in TVB models (Ritter et al., 2013; Shen, Bezgin, et al., 2019) and was developed to harmonize cytoarchitectonic, topographic and functional definitions of brain regions across primate species (Kotter & Wanke, 2005), which is an advantage for network modeling work that integrates structural and functional neuroimaging data.

195 **dwMRI Preprocessing and Tractography**

Preprocessing of dwMRI data, and subsequent tractography was completed using a Python implementation of a previously reported procedure (Shen, Goulas, et al., 2019). Eddy current induced distortions were corrected for using FSL's 'eddy_correct' command, and the diffusion gradient vectors rotated accordingly. The MNI152_T1_1mm

200 standard brain included with FSL was then registered to each subject's T1-weighted
201 image using a non-linear registration conducted with Advanced Normalization Tools
202 (ANTs). Warps produced in this step were used to map the 96-ROI Regional Map
203 parcellation (ANTs: Avants et al., 2011; RM-96 parcellation: Bezgin et al., 2017) onto
204 each subject's T1-weighted image using ANTs' 'WarpImageMultiTransform' executable
205 and a nearest neighbor interpolation. FSL's FLIRT function was used to register subject
206 T1-weighted images to dwMRI space. Seed and target ROI masks were defined as the
207 white matter (WM) voxels adjacent to each gray matter (GM) ROI within each region of
208 the RM-96 parcellation scheme. An exclusion mask for each seed mask was also created
209 using the GM voxels adjacent to the seed mask. For intrahemispheric tracking, exclusion
210 masks of the opposite hemisphere were also used. Diffusion tensor models were fitted at
211 each voxel by FSL's 'dtifit', and then a probabilistic diffusion model was fit using FSL's
212 'bedpostX'. Probabilistic tractography was performed between all ROIs of the RM-96
213 parcellation scheme using FSL's 'probtrackx2' function. Parameters used for tracking
214 were: 5000 seeds per voxel, 2000 steps, 0.5 mm step length, termination of paths that
215 loop back on themselves and rejection of paths that pass through an exclusion mask. The
216 curvature threshold was set to 0.2.

217 Two SC matrices were constructed from the tractography results representing
218 weights and lengths of connections, respectively. Weights were generated by taking the
219 number of streamlines detected between each ROI pair and dividing it by the total
220 number of streamlines that were successfully sent from the seed mask. In this way, they
221 were corrected for the number of voxels in each seed ROI. The length of each connection,
222 defined in millimeters, was obtained by taking the median length of all connecting

streamlines for each region pair. To obtain tract lengths using FSL's probtrackx2, tractography was run with and without the distance correction, and dividing the results gave an estimate of the lengths of each streamline. As tractography cannot provide information on directionality of connections, matrices were symmetrized such that the weights between areas A to B and B to A were averaged. To account for numerous false positives that are known to result from probabilistic tractography (Shen, Goulas, et al., 2019), any connections not present in at least 50% of the comparison subjects were set to zero (Roberts, Perry, Roberts, Mitchell, & Breakspear, 2017).

Resting State fMRI

Resting state fMRI preprocessing was done using FMRIB's FEAT toolbox. The following steps were performed: (1) motion correction with MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), (2) slice timing correction, (3) spatial smoothing (5mm), and (4) registration to anatomical volume. A nuisance regression removed signals from cerebral spinal fluid, white matter, and 6 motion parameters. Global signal regression was not performed. Lastly, a high-pass filter (100s) was applied.

A weighted average time series was calculated for every ROI, such that each voxel was weighted according to the probability it was within a given ROI (all voxels summed to one), with voxels more central in the ROI being favoured (Shen et al., 2012). This approach aimed to minimize partial volume bias. A FC matrix was calculated for each subject by finding the pairwise Pearson's correlation coefficient between each ROI pair's weighted average time series. To characterize the dynamics of the resting fluctuations, we calculated functional connectivity dynamics (FCD) matrices for each

245 subject. The 7-minute resting state scan was split into 92 windows of 30 seconds
 246 overlapping by 4 seconds. We calculated the FC matrix for each time window centred at
 247 time t , generating a timeseries of FC matrices, $FC(t)$. The FCD matrix is a t by t matrix
 248 with element $(t1, t2)$ calculated as the Pearson's correlation of the upper triangle's the FC
 249 matrices $FC(t1)$ and $FC(t2)$. This method of characterizing resting fluctuations with FCD
 250 has been used previously (Deco, Kringelbach, Jirsa, & Ritter, 2017).

251 No participants were removed due to head motion during the resting state fMRI
 252 scan (absolute head motion at a single time point was no greater than 3.5 mm and relative
 253 head motion did not exceed 2.5 mm for any participants. A one-way ANOVA showed the
 254 comparison participants ($M=0.27$, $SD=0.28$), CT/MRI positive patients ($M=0.25$,
 255 $SD=0.20$) and CT/MRI negative patients ($M=0.23$, $SD=0.17$) did not differ in mean
 256 absolute head motion, $F(2,77)=0.22$, $p=0.801$. Similarly the comparison participants
 257 ($M=0.06$, $SD=0.03$), CT/MRI positive ($M=0.07$, $SD=0.02$), and CT/MRI negative patients
 258 ($M=0.10$, $SD=0.09$) did not differ in mean relative head motion, $F(2,77)=2.00$, $p=0.14$.

259 The Virtual Brain

260 We simulated fMRI time series for each subject. Simulations were constrained by
 261 each subject's empirical SC and fitted to their FC and FCD matrices. The process for
 262 each subject may be summarized as follows: (1) SC matrices (weights and tract lengths)
 263 are input to fast_tvb (https://github.com/BrainModes/fast_tvb,
 264 https://hub.docker.com/r/thevirtualbrain/fast_tvb); (2) local and global parameters are
 265 chosen for the model; (3) fMRI is simulated based on local and global parameters and
 266 constrained by individual SC; (4) individual fMRI simulations are optimized by re-

267 running simulations with different local and/or global parameter values that yielded the
 268 best fit; (5) best-fitting local and global parameters are used for group comparisons, and
 269 to account for individual variability on our neuropsychological factors. The modeling
 270 process in TVB has been described more thoroughly previously (Ritter et al., 2013; Sanz
 271 Leon et al., 2013) and the mean field approximations used have been validated
 272 independently (Deco & Hugues, 2012). Readers may also refer to an excellent, more
 273 general review of dynamic models of large-scale brain activity (Breakspear, 2017).

274 **Dynamic Mean Field Model**

275 The dynamic mean field model represents each region of interest as a population
 276 of excitatory and inhibitory neurons coupled by excitatory NMDA synapses and
 277 inhibitory GABA synapses. The model is defined by a set of six stochastic nonlinear
 278 differential equations, modified slightly from those presented by Deco et al. (2014), such
 279 that the global, inter-region connections incorporated time delays (Deco, McIntosh, et al.,
 280 2014; Deco, Ponce-Alvarez, et al., 2014).

$$281 \quad I_i^{(E)}(t) = W_E I_0 + w_+ J_{NMDA} S_i^{(E)}(t) + G J_{NMDA} \sum_j C_{ij} S_j^{(E)} \left(t - \frac{D_{ij}}{s} \right) - J_i S_i^{(I)}(t) \quad (1)$$

$$282 \quad I_i^{(I)}(t) = W_I I_0 + J_{NMDA} S_i^{(E)}(t) - S_i^{(I)}(t) \quad (2)$$

$$283 \quad r_i^{(E)}(t) = \frac{a_E I_i^{(E)}(t) - b_E}{1 - \exp(-d_E (a_E I_i^{(E)}(t) - b_E))} \quad (3)$$

$$284 \quad r_i^{(I)}(t) = \frac{a_I I_i^{(I)}(t) - b_I}{1 - \exp(-d_I (a_I I_i^{(I)}(t) - b_I))} \quad (4)$$

$$\frac{dS_i^{(E)}(t)}{dt} = \frac{-S_i^{(E)}(t)}{\tau_E} + \left(1 - S_i^{(E)}(t)\right) \gamma r_i^{(E)}(t) + \sigma v_i(t) \quad (5)$$

$$\frac{dS_i^{(I)}(t)}{dt} = \frac{-S_i^{(I)}(t)}{\tau_I} + r_i^{(I)}(t) + \sigma v_i(t) \quad (6)$$

$I_i^{(E)}$ represents the input current to the excitatory population of region i , while $I_i^{(I)}$ denotes the input current to the inhibitory population at that region. Equations 3 and 4 convert input current to firing rates, $r_i^{(E/I)}$, for the excitatory, and inhibitory populations of region i respectively. Finally, the firing rate is used to calculate synaptic gating ($S_i^{(E/I)}$) of both the excitatory and inhibitory populations in equations 5 and 6.

Input current to the excitatory population is defined by four sources: the overall effective external current ($W_E I_0$), recurrent excitatory currents [$w_+ J_{NMDA} S_i^{(E)}(t)$], recurrent inhibitory currents ($J_i S_i^{(I)}(t)$), and excitatory currents from other region's excitatory populations [$G J_{NMDA} \sum_j C_{ij} S_j^{(E)} \left(t - \frac{D_{ij}}{s}\right)$]. Long-range (inter-region) connections between regions i and j are constrained by the connectivity weight C_{ij} , where C_{ij} is the (i, j) -th entry in the SC weights matrix. Global coupling strength, G , scales the long-range connectivity weights C_{ij} . Time delays are incorporated through the division of the distance between regions i and j , (D_{ij}), by conduction velocity, s . The input current to the inhibitory population is defined by: external currents ($W_I I_0$), recurrent excitatory currents [$J_{NMDA} S_i^{(E)}(t)$], and recurrent inhibitory currents [$S_i^{(I)}(t)$]. Notably, noise is added in equations 5 and 6, where v_i is uncorrelated standard Gaussian noise, with amplitude scaled by σ .

304 To maintain an average firing rate between 2-5 Hz feedback inhibition control
 305 (FIC) was applied (Deco, Ponce-Alvarez, et al., 2014; Schirner et al., 2018). The FIC
 306 algorithm iteratively adjusts the inhibitory connection weights (J_i) at each region, so that
 307 each local excitatory population maintains an average firing rate of ~ 3 Hz. By
 308 maintaining local excitation-inhibition balance in this way, we produce simulations that
 309 fit better with empirical fMRI and show more realistic firing rates (Deco, Ponce-Alvarez,
 310 et al., 2014).

311 The differential equations were integrated with a step size of 0.1 ms. After starting
 312 a simulation, first the J_i values were fitted using an automatic routine, and then 8 minutes
 313 and 20 seconds of fMRI were simulated to match the duration of the empirical fMRI
 314 timeseries. Eighty seconds of simulated fMRI data were removed to account for initial
 315 transients. Simulated synaptic activity was fed through the Balloon-Windkessel
 316 hemodynamic model producing simulated fMRI data (Friston et al., 2000). All
 317 simulations were performed using an implementation of the dynamic mean field model in
 318 C (Schirner et al., 2018; code available: https://github.com/BrainModes/fast_tvb).

319 **Parameter Space Exploration**

320 Subject-specific parameter space explorations found the best-fitting value of
 321 global coupling to maximize their simulation's fit to their empirical FC and FCD. To
 322 avoid overfitting we used two features to define goodness-of-fit. Our first feature was
 323 maximal uncentered Pearson correlation of the upper triangle of each subject's empirical
 324 and simulated FC matrices. The second was the minimal Kolmogorov-Smirnov distance
 325 between the distributions formed by the upper triangle's of the simulated and empirical

326 FCD matrices. Uncentered Pearson correlation takes into account the difference in the
 327 mean values of the FC matrices (Deco, Ponce-Alvarez, et al., 2014) and fitting FCD
 328 matrix distributions with Kolmogorov-Smirnov distance has been used previously to
 329 effectively fit brain dynamics in network models (Deco, Kringelbach, Jirsa, & Ritter,
 330 2017). We explored 50 values of G for each subject and to account for the effect of intra-
 331 subject variability due to our stochastic model, we ran 20 iterations of the PSE for each
 332 subject with randomized initial conditions, resulting in 1000 simulations being run for
 333 every subject. Regional inhibitory connection strengths were fitted for each of these
 334 simulations via the FIC tuning algorithm described in the previous section. For each
 335 iteration of the PSE, we ranked the FC and FCD fits for each value of G and chose the
 336 optimal G value based on the best-combined rank. Then we chose the value of G that
 337 most frequently (mode) produced the best combined FC/FCD fit. We also used the
 338 regional inhibitory connection weights (J_i) for the best-fitting value of G , found by the
 339 FIC algorithm. We refer to global coupling and regional inhibitory connection weights
 340 (97 variables total) as the ‘TVB parameters’ collectively. Note that global coupling was
 341 used to maximize fit with empirical fMRI, while the fitting target for regional inhibitory
 342 connection strength was the average firing rate of the excitatory population at each
 343 region.

344 **Partial Least Squares**

345 Partial least squares (PLS) is a multivariate statistical method that relates two sets
 346 of variables by identifying linear combinations of variables in both sets that maximally
 347 covary together (McIntosh & Lobaugh, 2004; McIntosh & Mišić, 2013). We used PLS to
 348 find optimal relationships between a set of brain variables and either a study design

349 (mean-centering PLS) or a set of behavioural variables (behavioural PLS). In PLS,
 350 singular value decomposition (SVD) is used to find orthogonal latent variables that
 351 explain the maximal amount of covariance between brain variables and design or
 352 behaviour variables. For each latent variable brain saliences are calculated for each brain
 353 region that indicate the degree to which each region contributes to the relationship
 354 between brain and design/behaviour expressed by the latent variable. In mean-centering
 355 PLS, design saliences indicate the group, condition, or group $\times$ condition profiles that best
 356 describe the relationship between the set of brain and design variables. In behavioural
 357 PLS, behaviour saliences indicate the profile of behaviour variables that best characterize
 358 the relationship between brain and behaviour variables. Brain scores are calculated for
 359 each subject and latent variable by multiplying the matrix of brain variables by the brain
 360 saliences. Brain score indicates the degree to which each participant contributes to each
 361 latent variable. Lastly, singular values are the covariance between brain and
 362 behaviour/grouping variables. They can also be evaluated as percentage of the total
 363 covariance between measures that each latent variable accounts for.

364 In our study, we used mean centering PLS to determine the relationship between
 365 several brain measures and group status. The brain measures considered were a
 366 vectorized version of the upper triangle of the SC/FC matrices, FA values from all voxels
 367 within our white matter mask and TVB parameters (global coupling and regional
 368 inhibitory connection strength values). For each brain measure, an omnibus PLS was
 369 performed that found the optimal contrasts in brain measures between group membership.
 370 We also used behavioural PLS to determine the relationships between the TVB

371 parameters (global coupling and regional inhibitory connection strength) and factor
372 scores from a set of patient outcome variables.

373 Permutation testing was used to determine the significance of each latent variable.
374 Rows of the data matrix were randomly reordered and the singular value recalculated.
375 This was done 1000 times, creating a distribution of singular values. Then a p -value for
376 the original singular value was calculated by taking the proportion of singular values
377 from the sampling distribution that were larger than the original singular value. The p -
378 value can be thought of the probability of obtaining a singular value of this size under the
379 null hypothesis that there is no association between brain measure and design/behaviour.

380 Bootstrapping was used to estimate the reliability of each brain salience.
381 Participants were randomly resampled 1000 times with replacement, while respecting
382 group membership. The resampled matrices were used to recalculate the singular vector
383 decomposition, producing a sampling distribution for the weights in the singular vectors.
384 Standard error was calculated from this sampling distribution, reflecting the stability of
385 the weight regardless of which participants are included in the analysis. Then a bootstrap
386 ratio (BSR) was calculated for each brain salience (voxel, brain region, connection) by
387 dividing the brain salience by its bootstrap-estimate standard error. BSR is akin to z-score
388 ($|2.0|$ corresponds to approximately a 95% confidence interval) but is interpreted in terms
389 of reliability of the parameter rather than null hypothesis testing. Confidence intervals
390 were calculated around design/behavior salience using the percentiles derived from the
391 sampling distribution.

Results

Outcome Measures

Our PCA of background and outcome variables identified two factors: (1) TBI Symptoms, (2) Age and Cognition (Table 5), consistent with a previously reported PCA of neuropsychological outcome variables in mTBI patients (Levin et al., 2013). The CT/MRI subgroups did not significantly differ on the TBI Symptoms factor ($t(34) = 0.73$, $p=0.47$), or the Age and Cognition factor ($t(34) = 0.30$, $p=0.76$). We also tested for group differences on the individual variables contributing to both factors. We found the CT/MRI positive patients were significantly older than the CT/MRI negative patients ($t(42)=-2.5$, $p<0.01$) and comparison participants ($t(48)=4.3$, $p<0.01$). The CT/MRI negative patients were also significantly older than the comparison participants ($t(64)=2.2$, $p=0.03$). A chi-square test of independence indicated that the CT/MRI positive patients experienced a greater loss of consciousness than the CT/MRI negative patients ($X(1)^2=8.6$, $p=0.01$). There were no other significant differences between groups ($p>0.05$, see Table 1).

Empirical brain differences between patient subgroups and comparison participants

Structural connectivity

A group comparison PLS assessed potential differences in structural connectivity weights between the CT/MRI patient subgroups and comparison participants. The first latent variable ($p<0.0001$, 67% covariance, singular value=0.19) distinguished the CT/MRI positive patients from comparison participants (Figure 2A-C), indicating

413 CT/MRI positive patients had lower SC weights relative to the comparison participants in
414 many voxels, indicating a global effect. The second latent variable ($p=0.016$, 33%
415 covariance, singular value=0.13) distinguished CT/MRI negative patients from
416 comparison participants (Figure 2D-F) showing the CT/MRI negative patients also had
417 primarily lower SC than comparison participants especially in connections involving
418 occipital regions. These analyses were repeated with age regressed from the SC values
419 and the results did not change appreciably.

420 **Functional connectivity and functional connectivity dynamics**

421 A group comparison PLS comparing functional connectivity across the CT/MRI
422 patient subgroups and comparison participants did not find any significant differences
423 ($p=0.58$, 61.7% covariance, singular value=3.1). A one-way ANOVA did not
424 discriminate the patient groups or comparison subjects on the variance of their FCD
425 matrices, $F(2, 77)=0.1$, $p=0.91$. These analyses were repeated with age regressed from the
426 FC values and the results did not change appreciably.

427 **Fractional anisotropy**

428 A group comparison PLS compared fractional anisotropy across the whole-brain
429 white matter skeleton (Figure 3). The first latent variable ($p=0.01$, 65.1% covariance,
430 singular value=8.2) showed CT/MRI positive patients had lower FA than the comparison
431 group, especially in the left cingulum and anterior corona radiata. The second latent
432 variable indicated CT/MRI negative patients had primarily lower FA than comparison
433 participants, though it did not reach significance ($p=0.09$, 34.9% covariance, singular

434 value=6.0). These analyses were repeated with age regressed from the FA values and the
435 results did not change meaningfully.

436 **TVB Model Fitting**

437 All patients and comparison participants showed good fits between empirical and
438 simulated resting state fMRI, as assessed by high uncentered Pearson's correlation of FC
439 and low Kolmogorov-Smirnov distance between FCD matrices. The simulated FC and
440 FCD matrices of all participants were inspected visually to ensure they appeared as
441 reasonable FC/FCD matrices qualitatively. We also screened for outliers by converting
442 the FC and FCD fits to z-score, finding no participants with a z-scored FC fit lower than -
443 3 (minimum = -2.4) and no participants with a z-scored FCD fit higher than 3 (maximum
444 = 2.6). There were no significant differences between the three groups on the fitting
445 metrics (Table 5).

446 The parameter search space showed steady improvements in fit (increased FC
 447 correlation and decreased FCD Kolmogorov-Smirnov distance) as global coupling was
 448 increased until a best-fitting global coupling value was reached (Figure 4). After this
 449 point, the model becomes multistable and eventually the FIC tuning algorithm is no
 450 longer able to maintain biologically realistic firing rates of ~3 Hz. Across multiple
 451 iterations our model showed acceptable consistency in choosing the optimal value of
 452 global coupling across iterations (Table 6, Figure 4).

453 **TVB model group differences**

454 **Combined TBI patients versus comparison subjects**

455 A group comparison PLS compared the TVB parameters (global coupling and
 456 regional inhibitory connection strengths) of the comparison participants (n=36) and the
 457 combined CT/RMI positive and negative patient groups (n=44). A significant latent
 458 variable ($p=0.026$, singular value=0.30; Figure 5) distinguished the groups, showing the
 459 TBI patients had primarily higher inhibitory connection strengths, especially in bilateral
 460 subcortical regions. Regions that were reliably contributing (bootstrap ratio >2) to the
 461 relationship included the bilateral pallidum, a right thalamic ROI with major temporal
 462 connections and right thalamic ROI with major frontal connections, right superior
 463 temporal cortex, left inferior cortex, and left putamen. The results were not significantly
 464 affected when age was regressed from the variables and the analysis repeated.

465 **CT/MRI positive and negative patients versus comparison participants**

466 A group comparison PLS compared the TVB parameters (global coupling and
 467 regional inhibitory connection strengths) of the CT/MRI positive patients (n=14),
 468 CT/MRI negative patients (n=30), and comparison participants (n=36). The first
 469 significant latent variable ($p=0.03$, 70.9% covariance, singular value=0.43; Figure 6A-C)
 470 distinguished the CT/MRI positive patients from comparison participants, showing that
 471 they had primarily lower cortical and higher subcortical inhibitory connection strengths
 472 relative to the comparison subjects. Regions reliably lower in CT/MRI positive patients
 473 compared to comparison participants (bootstrap ratio < -2) included the left dorsomedial
 474 prefrontal cortex, left medial prefrontal cortex, left prefrontal polar cortex, left anterior
 475 insula, right centrolateral prefrontal cortex, right medial prefrontal cortex, and right
 476 orbitoinferior prefrontal cortex. On the other hand, the left/right pallidum were reliably
 477 higher in CT/MRI positive patients relative to comparison participants. The dot product
 478 of the brain salience vector from the first latent variable (Figure 6) and the brain salience
 479 vector from the group comparison PLS comparing the combined patients from
 480 comparison subjects (Figure 5) was high ($r=0.77$) indicating the CT/MRI positive patients
 481 were likely largely responsible for driving the group difference. These analyses were
 482 repeated with age regressed from the TVB parameters and the results did not change
 483 meaningfully.

484 **TVB-behaviour relationships**

485 A behavioural PLS analysis compared the correlations between the TVB
 486 parameters and the TBI Symptoms and Age and Cognition factors in all of the patients

487 (N=36). The analysis showed higher scores on the TBI Symptoms (indicating more
 488 symptoms) and Age and Cognition (indicating older age and poorer cognitive
 489 performance) factors were related to primarily lower regional inhibitory connection
 490 strength ($p=0.02$, 74% covariance, singular value=2.4; Figure 7). Regions reliably
 491 contributing to the latent variable (bootstrap ratios<-2) included the left/right gustatory
 492 cortex, the left caudate nucleus, secondary auditory cortex, primary visual cortex,
 493 hippocampus, orbitomedial prefrontal cortex, anterior insula, and temporal polar cortex,
 494 as well as the right frontal eye field, ventral temporal cortex, anterior visual area (ventral
 495 part), ventrolateral premotor cortex, gustatory cortex, and inferior temporal cortex.

496 Within group PLS models were calculated to determine the contributions of the
 497 CT/MRI positive and negative groups to the omnibus test shown in Figure 8. Both PLS
 498 analyses compared TBI Symptoms and Age and Cognition factor scores to the TVB
 499 parameters (global coupling and regional inhibitory connection strength) using either the
 500 CT/MRI positive or negative patients. The within CT/MRI negative behavioural PLS
 501 produced a single significant latent variable ($n=25$; $p=0.005$, 73.1% covariance, singular
 502 value=3.0; Figure 8A-C) indicating higher TBI Symptoms and Age and Cognition scores
 503 were related to lower inhibitory connection strength. Regions reliably contributing to the
 504 latent variable (bootstrap ratios < -2) included the right temporal polar cortex,
 505 orbitomedial prefrontal cortex, parahippocampal cortex, anterior visual area, ventral
 506 temporal cortex, and frontal eye field, as well as the left anterior insula, orbitomedial
 507 prefrontal cortex, hippocampus, frontal eye field, dorsolateral prefrontal cortex, and
 508 caudate nucleus. The left subgenual cingulate gyrus showed the inverse association with
 509 the factor scores compared to the other regions (bootstrap ratio >2). The same analysis

510 within the CT/MRI positive group did not produce a significant latent variable ($n=11$,
 511 $p=0.11$, 67.6% covariance, singular value=3.7; Figure 8D-F). We calculated the dot
 512 product of the brain salience vectors from the combined group PLS model (Figure 7) and
 513 the two within group analyses (Figure 8) to determine which subgroup was responsible
 514 for driving the effect observed when groups were combined. The dot product between the
 515 combined model and the CT/MRI negative model was very high ($r=0.90$). The same dot
 516 product was significantly lower ($r=-0.43$) between the combined model and the CT/MRI
 517 positive group ($z=4.68$, $p<0.0001$), suggesting the CT/MRI negative group was primarily
 518 responsible for the observed associations between TBI Symptoms and Age and Cognition
 519 factor scores and regional inhibitory connection strengths.

520 Discussion

521 Overview

522 Concussion outcomes are variable and difficult to predict. Few studies have
 523 looked longitudinally at patients with well-characterized acute and chronic phase
 524 assessments and fewer still have combined multimodal imaging with a computational
 525 approach. Here we combined the strengths of a well-characterized sample with
 526 multimodal imaging and computational approaches to reveal relationships between local
 527 neural dynamics and chronic patient outcomes. We found that the CT/MRI positive TBI
 528 patients showed lower cortical, but higher subcortical inhibitory connection strengths
 529 relative to the comparison participants. We did not distinguish CT/MRI negative patients
 530 from the comparison participants based on their TVB parameters, however, lower
 531 regional inhibitory connection strengths were related to higher scores on the TBI

Symptoms and Age and Cognition factors assessed six months post-injury in these patients. Together, our results show proof of concept that local brain dynamics modeled in TVB are sensitive to semi-acute TBI pathology and predictive of chronic outcomes.

Group Comparisons

The CT/MRI positive patients displayed higher subcortical, but lower cortical inhibitory connection strengths relative to the comparison participants. We speculate that lower inhibitory connection strength may reflect excitotoxicity or inhibitory dysregulation, which are known to play a role in secondary injury after TBI (Van Horn, Bhattarai, & Irimia, 2017; Yi & Hazell, 2006). Indeed, a study of tumour patients (Aerts et al., 2018) that used a similar model to our own demonstrated reduced inhibitory connection strength in tumour regions relative to comparison participants, which they posited to reflect the role of excitotoxicity in the pathogenesis of glaucoma (Casson, 2006). Aerts et al. (2018) also observed increased inhibitory connection strengths in the non-tumour regions of their patients compared to controls, paralleling the increased inhibitory connection strengths we observed in the subcortical regions of the CT/MRI positive patients compared to comparison participants. Higher subcortical inhibitory connection strengths may reflect a distal effect of small cortical lesions, or serve a protective function, as CT/MRI positive patients did not score more highly than CT/MRI negative patients on the TBI Symptoms factor. Future studies using neuroimaging with finer spatial resolution could quantitatively assess the sensitivity of our model's regional inhibitory connection strength parameter to the cellular processes underlying changes to excitation/inhibition caused by TBI.

554 The CT/MRI negative patients were not significantly differentiated from the
555 comparison participants by their TVB parameters. This was unexpected as a study of
556 mTBI patients experiencing active PCS symptoms (who were screened for focal lesions)
557 found decreased inhibitory connection strengths relative to comparison participants
558 (Good et al., in preparation). Notably, the present work investigates TBI patients scanned
559 1-2 weeks post-injury, while the other study considers patients in the chronic phase post-
560 injury, which may contribute to the discrepant findings. It is also possible that other
561 factors obfuscated a potential group difference between CT/MRI negative patients and
562 comparison participants. For example, history of substance abuse and other
563 neuropsychiatric disorders, such as depression, were not exclusion criteria in the present
564 study despite exerting effects via excitotoxicity (Miller, Maletic, & Raison, 2009; Walker
565 & Dantzer, 2014) similarly to mTBI. While this feature of our data increases our
566 finding's generalizability, it may also have limited our sensitivity to pathophysiology
567 caused by TBI.

568 Our empirical SC and FA findings suggested the CT/MRI positive and negative
569 patients were characterized by more disconnected structural connectomes than the
570 comparison participants. These results are in line with a previous study of the white
571 matter integrity of an overlapping patient sample (Yuh et al., 2014). In addition, previous
572 studies of humans (Imms et al., 2019; Kuceyeski, Jamison, Owen, Raj, & Mukherjee,
573 2019) and animals (Meningher, Bernstein-Eliav, Rubovitch, Pick, & Tavor, 2020) have
574 found the SC of TBI patients are more highly segregated than controls. Modeling studies
575 suggest structural disconnection in TBI patients produces reduced metastability, linked to
576 excitation-inhibition imbalance (Hellyer, Scott, Shanahan, Sharp, & Leech, 2015).

577 Similarly, the CT/MRI positive patients demonstrated structural disconnection as well as
578 altered local inhibitory dynamics compared to comparison participants.

579 When interpreting our findings, it should be considered that approximately one
580 third of our TBI sample (14 of 44 patients) showed signs of acute traumatic intracranial
581 lesions on CT or MRI scan upon presentation in the emergency department. This
582 classification of CT/MRI positive versus CT/MRI negative may be contrasted with
583 previous work considering ‘complicated’ mTBI solely on the basis of a positive acute
584 phase CT scan (Iverson et al., 2012; Voormolen et al., 2019). Many of our CT/MRI
585 positive patients were classified on the basis of very subtle MRI lesions at 3T, such as
586 one or two subtle isolated foci of hemorrhagic axonal injury. These patients would likely
587 be classified as uncomplicated if we had used CT alone. In fact, this nuance is supported
588 by early work that found dw-MRI evidence of white matter damage in patients classified
589 as uncomplicated by CT alone (Arfanakis et al., 2002; Bazarian et al., 2007; Chu et al.,
590 2010).

591 **TVB-Behaviour Relationships**

592 Lower inhibitory connection strengths were associated with higher scores on the
593 TBI Symptoms and Age and Cognition factors in the CT/MRI negative group. The effect
594 included many regions including cortical and subcortical structures, and indicated that
595 lower inhibitory connection strengths were related to more severe TBI outcomes, older
596 age, less education, and lower cognitive performance. This effect is aligned with other
597 large-scale modeling work that showed structural disconnection associated with
598 decreased metastability, indicating excitation-inhibition imbalance, to be related to poorer

599 cognitive performance in TBI patients (Hellyer et al., 2015). Empirical studies using
 600 magnetic resonance spectroscopy have also found elevated concentrations of the
 601 neuromodulatory factor glutamate during the semi-acute phase were predictive of poorer
 602 chronic outcomes (Eisele et al., 2020; Shutter et al., 2004).

603 In the CT/MRI positive patients we did not observe a correlation between
 604 inhibitory connection strengths and the TBI Symptoms factor as expected. We suspect
 605 this was due to a lack of statistical power ($n=11$) in the within group behavioural PLS
 606 (Figure 8D-F). Forthcoming large-scale longitudinal and multi-site data acquisitions
 607 (such as full Track-TBI LONG [<https://tracktbi.ucsf.edu/>] sample) will be better
 608 equipped to establish robust correlations between parameters from brain network models
 609 and chronic TBI outcome.

610 **Limitations and Conclusions**

611 We note our study is limited by its modest sample size and lack of longitudinal
 612 imaging data to track recovery. Our exploratory findings will need to be confirmed in
 613 larger independent samples. Specifically, future studies should test whether lower
 614 inhibitory connection strength is indeed predictive of development of persistent post-
 615 concussion symptoms. Additionally, we acknowledge the lack of racial diversity (79%
 616 white) and the gender imbalance (65% male) of our patients. Our sample, obtained by an
 617 emergency room convenience sample, will limit the generalizability of our findings to
 618 more mild concussions that do not require hospitalization. Our choice of a relatively
 619 coarse (96 ROI) parcellation scheme may have also limited sensitivity. Future work
 620 should explore the effect of multiple parcellation schemes on modeling results. Similarly,

621 future work with larger sample sizes may allow for subtyping moderate to severe TBI
622 patients by lesion type and location, which would allow for greater power in detecting
623 changes to local network dynamics. Regarding our network model, we acknowledge a
624 mechanistic interpretation may not be possible as multiple processes at the micro-level
625 may contribute to similar observations at the macro-level. For example, local excitatory
626 connection strengths may produce similar dynamics as those observed through variations
627 to recurrent inhibitory connection strengths. We did not vary local excitatory connection
628 strengths in our parameter space exploration to ensure the model remained identifiable.

629 In conclusion, we used large-scale brain modeling to detect differences in local
630 inhibitory connection strengths between CT/MRI positive TBI patients in the semi-acute
631 phase and comparison participants. We did not distinguish semi-acute CT/MRI negative
632 patients from the comparison participants based on their inhibitory connection strengths,
633 however, lower inhibitory connection strengths were associated with more severe clinical
634 outcomes, older age and poorer cognitive performance at a 6-month follow-up in these
635 patients. The result suggests large-scale connectome based models may be sensitive to
636 pathophysiological changes in semi-acute phase TBI patients and predictive of their
637 chronic outcomes.

References

- 638
- 639 Aerts, H., Schirner, M., Jeurissen, B., Van Roost, D., Achten, E., Ritter, P., & Marinazzo,
640 D. (2018). Modeling Brain Dynamics in Brain Tumor Patients Using the Virtual
641 Brain. *Eneuro*, 5(3), ENEURO.0083-18.2018. [https://doi.org/10.1523/eneuro.0083-](https://doi.org/10.1523/eneuro.0083-18.2018)
642 18.2018
- 643 Arfanakis, K., Haughton, V. M., Carew, J. D., Rogers, B. P., Dempsey, R. J., &
644 Meyerand, M. E. (2002). Diffusion tensor MR imaging in diffuse axonal injury.
645 *AJNR. American Journal of Neuroradiology*, 23(5), 794–802.
- 646 Avants, B. B., Tustison, N. J., Song, G., Cook, P. A., Klein, A., & Gee, C. (2011). A
647 Reproducible Evaluation of ANTs Similarity Metric Performance in Brain Image
648 Registration. *NeuroImage*, 54(3), 2033–2044.
649 <https://doi.org/10.1016/j.neuroimage.2010.09.025>
- 650 Bazarian, J. J., Zhong, J., Blyth, B., Zhu, T., Kavcic, V., & Peterson, D. (2007). Diffusion
651 tensor imaging detects clinically important axonal damage after mild traumatic brain
652 injury: A pilot study. *Journal of Neurotrauma*, 24(9), 1447–1459.
653 <https://doi.org/10.1089/neu.2007.0241>
- 654 Bezgin, G., Solodkin, A., Bakker, R., Ritter, P., & McIntosh, A. R. (2017). Mapping
655 Complementary Features of Cross-Species Structural Connectivity to Construct
656 Realistic “ Virtual Brains .” *Human Brain Mapping*, 38, 2080–2093.
657 <https://doi.org/10.1002/hbm.23506>
- 658 Breakspear, M. (2017). Dynamic models of large-scale brain activity. *Nature*
659 *Neuroscience*, 20(3), 340–352. <https://doi.org/10.1038/nn.4497>
- 660 Casson, R. J. (2006). Possible role of excitotoxicity in the pathogenesis of glaucoma.
661 *Clinical and Experimental Ophthalmology*, 34(1), 54–63.
662 <https://doi.org/10.1111/j.1442-9071.2006.01146.x>
- 663 Chu, Z., Wilde, E. A., Hunter, J. V., McCauley, S. R., Bigler, E. D., Troyanskaya, M., ...

- 664 Levin, H. S. (2010). Voxel-based analysis of diffusion tensor imaging in mild
665 traumatic brain injury in adolescents. *American Journal of Neuroradiology*, 31(2),
666 340–346. <https://doi.org/10.3174/ajnr.A1806>
- 667 Dabek, F. J., & Caban, J. J. (2016). A K-Reversible Approach to Model Clinical
668 Trajectories. *AMIA ... Annual Symposium Proceedings. AMIA Symposium, 2016*,
669 460–469.
- 670 Deco, G., McIntosh, A. R., Shen, K., Hutchison, R. M., Menon, R. S., Everling, S., ...
671 Jirsa, V. K. (2014). Identification of Optimal Structural Connectivity Using
672 Functional Connectivity and Neural Modeling. *Journal of Neuroscience*, 34(23),
673 7910–7916. <https://doi.org/10.1523/JNEUROSCI.4423-13.2014>
- 674 Deco, G., Ponce-Alvarez, A., Hagmann, P., Romani, G. ., Mantini, D., & Corbetta, M.
675 (2014). How local excitation-inhibition ratio impacts the whole brain dynamics. *The*
676 *Journal of Neuroscience*, 34(23), 7886–7898.
677 <https://doi.org/10.1523/JNEUROSCI.5068-13.2014>
- 678 Deco, Gustavo, & Hugues, E. (2012). Neural network mechanisms underlying stimulus
679 driven variability reduction. *PLoS Computational Biology*, 8(3).
680 <https://doi.org/10.1371/journal.pcbi.1002395>
- 681 Deco, Gustavo, Kringelbach, M. L., Jirsa, V. K., & Ritter, P. (2017). The dynamics of
682 resting fluctuations in the brain: Metastability and its dynamical cortical core.
683 *Scientific Reports*, 7(1), 1–14. <https://doi.org/10.1038/s41598-017-03073-5>
- 684 Deco, Gustavo, Tononi, G., Boly, M., & Kringelbach, M. L. (2015). Rethinking
685 segregation and integration: contributions of whole-brain modelling. *Nature Reviews*
686 *Neuroscience*, 16(7), 430–439. <https://doi.org/10.1038/nrn3963>
- 687 Derogatis, L. R. (1983). The Brief Symptom Inventory: An Introductory Report.
688 *Psychological Medicine*, 13(3), 595–605.
689 <https://doi.org/10.1017/S0033291700048017>
- 690 Diener, E. R., Emmons, R., RJ, L., & Griffin, S. (1985). The Satisfaction With Life Scale.

- 691 *Journal of Personality Assessment*, 49(1), 71–75.
 692 <https://doi.org/10.4324/9781003035312-41>
- 693 Douglas, D. B., Iv, M., Douglas, P. K., Anderson, A., Vos, S. B., Bammer, R., ...
 694 Wintermark, M. (2015). Diffusion tensor imaging of TBI: Potentials and challenges.
 695 *Topics in Magnetic Resonance Imaging*, 24(5), 241–251.
 696 <https://doi.org/10.1097/RMR.0000000000000062>
- 697 Eisele, A., Hill-Strathy, M. J., Michels, L., & Rauen, K. (2020). Magnetic Resonance
 698 Spectroscopy following Mild Traumatic Brain Injury: A Systematic Review and
 699 Meta-Analysis on the Potential to Detect Posttraumatic Neurodegeneration.
 700 *Neurodegenerative Diseases*. <https://doi.org/10.1159/000508098>
- 701 Falcon, M. I., Riley, J. D., Jirsa, V., McIntosh, A. R., Elinor Chen, E., & Solodkin, A.
 702 (2016). Functional Mechanisms of Recovery after Chronic Stroke: Modeling with
 703 the Virtual Brain. *ENeuro*, 3(2), ENEURO.0158-15.2016.
 704 <https://doi.org/10.1523/ENeuro.0158-15.2016>
- 705 Filley, C. M., & Kelly, J. P. (2018). White Matter and Cognition in Traumatic Brain
 706 Injury. *Journal of Alzheimer's Disease : JAD*, 65(2), 345–362.
 707 <https://doi.org/10.3233/JAD-180287>
- 708 Friston, K. J., Mechelli, A., Turner, R., & Price, C. J. (2000). Nonlinear Responses in
 709 fMRI: The Balloon Model, Volterra Kernels, and Other Hemodynamics.
 710 *NeuroImage*, 12(4), 466–477. <https://doi.org/10.1006/nimg.2000.0630>
- 711 Giza, C. C., & Hovda, D. a. (2015). The New Neurometabolic cascade of Concussion.
 712 *Neurosurgery*, 75(0 4). <https://doi.org/10.1227/NEU.0000000000000505>.The
- 713 Hayes, J. P., Bigler, E. D., & Verfaellie, M. (2016). Traumatic brain injury as a disorder
 714 of brain connectivity. *Journal of the International Neuropsychological Society*,
 715 22(2), 120–137. <https://doi.org/10.1017/S1355617715000740>
- 716 Hellyer, P. J., Scott, G., Shanahan, M., Sharp, D. J., & Leech, R. (2015). Cognitive
 717 Flexibility through Metastable Neural Dynamics Is Disrupted by Damage to the

- 718 Structural Connectome. *The Journal of Neuroscience : The Official Journal of the*
 719 *Society for Neuroscience*, 35(24), 9050–9063.
 720 <https://doi.org/10.1523/JNEUROSCI.4648-14.2015>
- 721 Hou, W., Sours Rhodes, C., Jiang, L., Roys, S., Zhuo, J., Jaja, J., & Gullapalli, R. P.
 722 (2019). Dynamic Functional Network Analysis in Mild Traumatic Brain Injury.
 723 *Brain Connectivity*, 9(6), 475–487. <https://doi.org/10.1089/brain.2018.0629>
- 724 Imms, P., Clemente, A., Cook, M., D’Souza, W., Wilson, P. H., Jones, D. K., &
 725 Caeyenberghs, K. (2019). The structural connectome in traumatic brain injury: A
 726 meta-analysis of graph metrics. *Neuroscience and Biobehavioral Reviews*,
 727 99(November 2018), 128–137. <https://doi.org/10.1016/j.neubiorev.2019.01.002>
- 728 Iverson, G. L., Lange, R. T., Wäljas, M., Liimatainen, S., Dastidar, P., Hartikainen, K.
 729 M., ... Öhman, J. (2012). Outcome from Complicated versus Uncomplicated Mild
 730 Traumatic Brain Injury. *Rehabilitation Research and Practice*, 2012, 1–7.
 731 <https://doi.org/10.1155/2012/415740>
- 732 Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for
 733 the robust and accurate linear registration and motion correction of brain images.
 734 *NeuroImage*, 17(2), 825–841. [https://doi.org/10.1016/S1053-8119\(02\)91132-8](https://doi.org/10.1016/S1053-8119(02)91132-8)
- 735 Jirsa, V. K., Proix, T., Perdikis, D., Woodman, M. M., Wang, H., Bernard, C., ...
 736 Chauvel, P. (2017). The Virtual Epileptic Patient: Individualized whole-brain
 737 models of epilepsy spread. *NeuroImage*, 145, 377–388.
 738 <https://doi.org/10.1016/j.neuroimage.2016.04.049>
- 739 Jirsa, V. K., Sporns, O., Breakspear, M., Deco, G., & McIntosh, A. R. (2010). Towards
 740 the virtual brain : network modeling of the intact and the damaged brain. *Archives*
 741 *Italiennes de Biologie*, 148, 189–205.
- 742 Kenzie, E. S., Parks, E. L., Bigler, E. D., Wright, D. W., Lim, M. M., Chesnutt, J. C., ...
 743 Wakeland, W. (2018). The dynamics of concussion: Mapping pathophysiology,
 744 persistence, and recovery with causal-loop diagramming. *Frontiers in Neurology*,

- 745 9(APR), 1–16. <https://doi.org/10.3389/fneur.2018.00203>
- 746 Kotter, R., & Wanke, E. (2005). Mapping brains without coordinates. *Philosophical*
 747 *Transactions of the Royal Society of London. Series B, Biological Sciences*, 360,
 748 751–766. <https://doi.org/10.1098/rstb.2005.1625>
- 749 Kötter, R., & Wanke, E. (2005). Mapping brains without coordinates. *Philosophical*
 750 *Transactions of the Royal Society of London. Series B, Biological Sciences*,
 751 360(1456), 751–766. <https://doi.org/10.1098/rstb.2005.1625>
- 752 Krainin BM, Forsten RD, Kotwal RS, Lutz RH, Guskiewicz KM. (2011). Mild traumatic
 753 brain injury literature review and proposed changes to classification. *Journal of*
 754 *Special Operations Medicine: A Peer Reviewed Journal for SOF Medical*
 755 *Professionals*, 11(3), 38-47.
- 756 Kuceyeski, A. F., Jamison, K. W., Owen, J. P., Raj, A., & Mukherjee, P. (2019).
 757 Longitudinal increases in structural connectome segregation and functional
 758 connectome integration are associated with better recovery after mild TBI. *Human*
 759 *Brain Mapping*, 40(15), 4441–4456. <https://doi.org/10.1002/hbm.24713>
- 760 Levin, H. S., Li, X., McCauley, S. R., Hanten, G., Wilde, E. A., & Swank, P. (2013).
 761 Neuropsychological outcome of mTBI: A principal component analysis approach.
 762 *Journal of Neurotrauma*, 30(8), 625–632. <https://doi.org/10.1089/neu.2012.2627>
- 763 Madhavan, R., Joel, S. E., Mullick, R., Cogsil, T., Niogi, S. N., Tsiouris, A. J., ... Shetty,
 764 T. (2019). Longitudinal Resting State Functional Connectivity Predicts Clinical
 765 Outcome in Mild Traumatic Brain Injury. *Journal of Neurotrauma*, 36(5), 650–660.
 766 <https://doi.org/10.1089/neu.2018.5739>
- 767 Mayer, A. R., Ling, J. M., Allen, E. A., Klimaj, S. D., Yeo, R. A., & Hanlon, F. M.
 768 (2014). Static and Dynamic Intrinsic Connectivity following Mild Traumatic Brain
 769 Injury. *Journal of Neurotrauma*, 32(14), 1046–1055.
 770 <https://doi.org/10.1089/neu.2014.3542>
- 771 McIntosh, A R, & Lobaugh, N. J. (2004). Partial least squares analysis of neuroimaging

- 772 data: Applications and advances. *NeuroImage*, 23(SUPPL. 1), 250–263.
 773 <https://doi.org/10.1016/j.neuroimage.2004.07.020>
- 774 McIntosh, Anthony Randal, & Mišić, B. (2013). Multivariate statistical analyses for
 775 neuroimaging data. *Annual Review of Psychology*, 64, 499–525.
 776 <https://doi.org/10.1146/annurev-psych-113011-143804>
- 777 McMahon, P., Hricik, A., Yue, J. K., Puccio, A. M., Inoue, T., Lingsma, H. F., ... Vassar,
 778 M. J. (2014). Symptomatology and functional outcome in mild traumatic brain
 779 injury: Results from the prospective TRACK-TBI study. *Journal of Neurotrauma*,
 780 31(1), 26–33. <https://doi.org/10.1089/neu.2013.2984>
- 781 Meninger, I., Bernstein-Eliav, M., Rubovitch, V., Pick, C. G., & Tavor, I. (2020).
 782 Alterations in Network Connectivity after Traumatic Brain Injury in Mice. *Journal*
 783 *of Neurotrauma*, 2179, 2169–2179. <https://doi.org/10.1089/neu.2020.7063>
- 784 Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and Its Discontents: The
 785 Role of Cytokines in the Pathophysiology of Major Depression. *Biological*
 786 *Psychiatry*, 65(9), 732–741. <https://doi.org/10.1016/j.biopsych.2008.11.029>
- 787 Niogi, S. N., & Mukherjee, P. (2010). Diffusion tensor imaging of mild traumatic brain
 788 injury. *Journal of Head Trauma Rehabilitation*, 25(4), 241–255.
 789 <https://doi.org/10.1097/HTR.0b013e3181e52c2a>
- 790 Palacios, E. M., Owen, J. P., Yuh, E. L., Wang, M. B., Vassar, M. J., Ferguson, A. R., ...
 791 Mukherjee, P. (2020). The evolution of white matter microstructural changes after
 792 mild traumatic brain injury: A longitudinal DTI and NODDI study. *Science*
 793 *Advances*, 6(32), eaaz6892. <https://doi.org/10.1126/sciadv.aaz6892>
- 794 Palacios, Eva M., Yuh, E. L., Chang, Y. S., Yue, J. K., Schnyer, D. M., Okonkwo, D. O.,
 795 ... Mukherjee, P. (2017). Resting-state functional connectivity alterations associated
 796 with six-month outcomes in mild traumatic brain injury. *Journal of Neurotrauma*,
 797 34(8), 1546–1557. <https://doi.org/10.1089/neu.2016.4752>
- 798 Ritter, P., Schirner, M., McIntosh, A. R., & Jirsa, V. K. (2013). The virtual brain

- 799 integrates computational modeling and multimodal neuroimaging. *Brain*
800 *Connectivity*, 3(2), 121–145. <https://doi.org/10.1089/brain.2012.0120>
- 801 Roberts, J. A., Perry, A., Roberts, G., Mitchell, P. B., & Breakspear, M. (2017).
802 Consistency-based thresholding of the human connectome. *NeuroImage*, 145(March
803 2016), 118–129. <https://doi.org/10.1016/j.neuroimage.2016.09.053>
- 804 Roy, D., Sigala, R., Breakspear, M., McIntosh, A. R., Jirsa, V. K., Deco, G., & Ritter, P.
805 (2014). Using the Virtual Brain to Reveal the Role of Oscillations and Plasticity in
806 Shaping Brain’s Dynamical Landscape. *Brain Connectivity*, 4(10), 791–811.
807 <https://doi.org/10.1089/brain.2014.0252>
- 808 Sanz Leon, P., Knock, S. a, Woodman, M. M., Domide, L., Mersmann, J., McIntosh, A.
809 R., & Jirsa, V. (2013). The Virtual Brain: a simulator of primate brain network
810 dynamics. *Frontiers in Neuroinformatics*, 7, 1–23.
811 <https://doi.org/10.3389/fninf.2013.00010>
- 812 Schirner, M., McIntosh, A. R., Jirsa, V., & Deco, G. (2018). Inferring multi-scale neural
813 mechanisms with brain network modelling. *ELife*, 1–30.
- 814 Schirner, M., Rothmeier, S., Jirsa, V. K., McIntosh, A. R., & Ritter, P. (2015). An
815 automated pipeline for constructing personalised virtual brains from multimodal
816 neuroimaging data. *NeuroImage*, 117, 343–357.
817 <https://doi.org/10.1016/j.neuroimage.2015.03.055>
- 818 Sharp, D. J., Scott, G., & Leech, R. (2014). Network dysfunction after traumatic brain
819 injury. *Nature Reviews Neurology*, 10(3), 156–166.
820 <https://doi.org/10.1038/nrneurol.2014.15>
- 821 Shen, K., Bezgin, G., Hutchison, R. M., Gati, J. S., Menon, R. S., Everling, S., &
822 McIntosh, A. R. (2012). Information processing architecture of functionally defined
823 clusters in the macaque cortex. *The Journal of Neuroscience*, 32(48), 17465–17476.
824 <https://doi.org/10.1523/JNEUROSCI.2709-12.2012>
- 825 Shen, K., Bezgin, G., Schirner, M., Ritter, P., Everling, S., & McIntosh, A. R. (2019). A

- macaque connectome for large-scale network simulations in TheVirtualBrain.
Scientific Data, 6(1), 1–12. <https://doi.org/10.1038/s41597-019-0129-z>
- Shen, K., Goulas, A., Grayson, D., Eusebio, J., Gati, J. S., & Ravi, S. (2019). Exploring the limits of network topology estimation using diffusion-based tractography and tracer studies in the macaque cortex. *Neuroimage (in Press)*, 1–37. <https://doi.org/https://doi.org/10.1016/j.neuroimage.2019.02.018>
- Shenton, M. E., Hamoda, H. M., Schneiderman, J. S., Bouix, S., Pasternak, O., Rathi, Y., ... Zafonte, R. (2012). A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging and Behavior*, 6(2), 137–192. <https://doi.org/10.1007/s11682-012-9156-5>
- Shutter, L., Tong, K. A., & Holshouser, B. A. (2004). Proton MRS in acute traumatic brain injury: Role for glutamate/glutamine and choline for outcome prediction. *Journal of Neurotrauma*, 21(12), 1693–1705. <https://doi.org/10.1089/neu.2004.21.1693>
- Si, B., Dumkrieger, G., Wu, T., Zafonte, R., Valadka, A. B., Okonkwo, D. O., ... Li, J. (2018). Sub-classifying patients with mild traumatic brain injury: A clustering approach based on baseline clinical characteristics and 90-day and 180-day outcomes. *PLoS ONE*, 13(7), 1–18. <https://doi.org/10.1371/journal.pone.0198741>
- Van Horn, J. D., Bhattarai, A., & Irimia, A. (2017). Multimodal Imaging of Neurometabolic Pathology due to Traumatic Brain Injury. *Trends in Neurosciences*. Elsevier Ltd. <https://doi.org/10.1016/j.tins.2016.10.007>
- Vergara, V. M., Mayer, A. R., Kiehl, K. A., & Calhoun, V. D. (2018). Dynamic functional network connectivity discriminates mild traumatic brain injury through machine learning. *NeuroImage: Clinical*, 19(March), 30–37. <https://doi.org/10.1016/j.nicl.2018.03.017>
- Voormolen, D. C., Haagsma, J. A., Polinder, S., Maas, A. I. R., Steyerberg, E. W., Vuleković, P., ... von Steinbuechel, N. (2019). Post-Concussion Symptoms in

- 853 Complicated vs. Uncomplicated Mild Traumatic Brain Injury Patients at Three and
 854 Six Months Post-Injury: Results from the CENTER-TBI Study. *Journal of Clinical*
 855 *Medicine*, 8(11), 1921. <https://doi.org/10.3390/jcm8111921>
- 856 Walker, A. K., & Dantzer, R. (2014). Is there a role for glutamate-mediated excitotoxicity
 857 in inflammation-induced depression? *Journal of Neuroal Transmission*, 121(8),
 858 952–932. <https://doi.org/10.1007/s00702-014-1187-1>
- 859 Wallace, E. J., Mathias, J. L., & Ward, L. (2018). The relationship between diffusion
 860 tensor imaging findings and cognitive outcomes following adult traumatic brain
 861 injury: A meta-analysis. *Neuroscience and Biobehavioral Reviews*, 92(March), 93–
 862 103. <https://doi.org/10.1016/j.neubiorev.2018.05.023>
- 863 Yi, J. H., & Hazell, A. S. (2006). Excitotoxic mechanisms and the role of astrocytic
 864 glutamate transporters in traumatic brain injury. *Neurochemistry International*,
 865 48(5), 394–403. <https://doi.org/10.1016/j.neuint.2005.12.001>
- 866 Yue, J. K., Vassar, M. J., Lingsma, H. F., Cooper, S. R., Okonkwo, D. O., Valadka, A.
 867 B., ... Sinha, T. K. (2013). Transforming research and clinical knowledge in
 868 traumatic brain injury pilot: Multicenter implementation of the common data
 869 elements for traumatic brain injury. *Journal of Neurotrauma*, 30(22), 1831–1844.
 870 <https://doi.org/10.1089/neu.2013.2970>
- 871 Yuh, E. L., Cooper, S. R., Mukherjee, P., Yue, J. K., Lingsma, H. F., Gordon, W. A., ...
 872 Sinha, T. K. (2014). Diffusion tensor imaging for outcome prediction in mild
 873 traumatic brain injury: a TRACK-TBI study. *Journal of Neurotrauma*, 31(17),
 874 1457–1477. <https://doi.org/10.1089/neu.2013.3171>
- 875 Zimmermann, J., Perry, A., Breakspear, M., Schirner, M., Sachdev, P., Wen, W., ...
 876 Solodkin, A. (2018). Differentiation of Alzheimer's disease based on local and
 877 global parameters in personalized Virtual Brain models. *NeuroImage: Clinical*,
 878 19(April), 240–251. <https://doi.org/10.1016/j.nicl.2018.04.017>
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880

Figures and Tables

881 **Table 1.** Patient Characteristics

Scale	Subscale	CT/MRI positive n=14	CT/MRI negative n=30	Comparison participants n=36	Analysis for group difference*
Age		39.9 (13.8)	31.2 (9.0)	26.6 (7.7)	F(2,79)=9.7, p=0.0001
Gender		9 Male; 5 Female 9 Caucasian, 2 More than one race; 1 African-American or African; 1 Asian; 1 Hawaiian or Pacific Islander	18 Male; 12 Female 23 Caucasian; 3 Asian; 2 Hawaiian or Pacific Islander; 1 African American or African; 1 More than one race	25 Male; 11 Female Unknown	X(2) ² =0.65, p=0.72
Race					
Education		14.6 (2.1)	14.6 (3.1)	Unknown	t(42)=-0.08, p=0.93
Glasgow Coma Scale		14.6 (0.63)	14.9 (0.43)	Na	t(42)=1.4, p=0.18
Loss of Consciousness		8 None; 6 <0.5 Hours	12 None; 18 <0.5 Hours	Na	X(1) ² =0.55, p=0.46
Post Traumatic Amnesia		5 None; 4 <0.5 Hours; 5 0.5-24 Hours	14 None; 15 <0.5 Hours; 1 0.5-24 Hours	Na	X(1) ² =8.6, p=0.01
		n=11	n=27	na	
Glasgow Outcome Scale Extended	6 month	6.8 (0.98)	7.0 (0.94)	na	t(36)=0.64, p=0.52
Brief Symptom Inventory	Anxiety	54.9 (7.7)	53.6 (10.6)	na	t(36)=-0.37, p=0.71
	Depression	54.2 (10.2)	52.6 (10.6)	na	t(36)=-0.42, p=0.67
	Somatic	55.8 (7.9)	53.0 (9.7)	na	t(36)=-0.86, p=0.39
	Global Severity Index	57.0 (7.3)	53.6 (10.8)	na	t(36)=-0.97, p=0.34
		n=11	n=26	na	
Satisfaction with life score		19.1 (7.6)	22.6 (5.9)	na	t(35)=1.5, p=0.14
		n=11	n=25	na	
Trail Making Test	Part A	30.7 (9.7)	28.3 (10.6)	na	t(35)=-0.65, p=0.52
	Part B	69.8 (25.0)	76.4 (65.2)	na	t(35)=0.32, p=0.75
Wechsler Adult	Processing Speed	109.2 (16.3)			

Intelligence Scale	106.5 (14.6)	na	t(35)=-0.49,p=0.62
California Verbal Learning Test	55.5 (9.8)	55.5 (9.2)	na
			t(35)=0.06,p=0.98

*The following statistics are reported: One-way ANOVA (age), Chi square test of independence (gender, loss of consciousness, post-traumatic amnesia), independent samples t test (Education, Glasgow Coma Scale, Glasgow Outcome Scale Extended (6 month), Brief Symptom Inventory, Satisfaction with Life Score, Trail Making Test Part A and B, Wechsler Adult Intelligence Scale, and California Verbal Learning Test.

886
887

Table 2. MRI Radiological Findings of the CT/MRI Positive TBI Group

1	4 contusions, 1 shear (MRI)
2	2 shear (MRI)
3	1 shear (MRI)
5	2 shear (MRI)
5	4 contusions (MRI)
	1 intracranial lesions, 1 skull fracture, 1 subdural hematoma, 1 contusion, 1 brain swelling (CT)
6	4 contusions, 3 shears (MRI)
7	2 shear (MRI)
8	1 skull fracture (CT)
9	1 contusion, 2 shear (MRI)
	1 intracranial lesions, 1 sub arachnoid haemorrhage, 1 contusion
10	1 subdural hematoma, 2 contusions (MRI)
	1 intracranial lesions, 1 subarachnoid haemorrhage, 1 contusion
11	1 subdural hematoma, 2 contusions, 2 shear (MRI)
	1 intracranial lesions, 1 skull fracture, 1 subdural hematoma, 1 subarachnoid hematoma
12	1 intracranial lesions, 1 subarachnoid hematoma (CT)
13	2 shear (MRI)

14 1 shear, 1 deep shear (MRI)

889 **Table 3.** Cortical and subcortical regions from the Regional Map parcellation from Kötter
890 & Wanke (2005)

Index		Region
Right	Left	
1	49	primary auditory cortex
2	50	secondary auditory cortex
3	51	amygdala
4	52	anterior cingulate cortex
5	53	posterior cingulate cortex
6	54	retrosplenial cingulate cortex
7	55	subgenual cingulate cortex
8	56	frontal eye field
9	57	gustatory cortex
10	58	hippocampus
11	59	anterior insula
12	60	posterior insula
13	61	primary motor cortex
14	62	inferior parietal cortex
15	63	intraparietal cortex
16	64	medial parietal cortex
17	65	superior parietal cortex
18	66	centrolateral prefrontal cortex
19	67	dorsolateral prefrontal cortex
20	68	dorsomedial prefrontal cortex
21	69	medial prefrontal cortex
22	70	orbitoinferior prefrontal cortex
23	71	orbitolateral prefrontal cortex
24	72	orbitomedial prefrontal cortex
25	73	prefrontal polar cortex
26	74	ventrolateral prefrontal cortex
27	75	parahippocampal cortex
28	76	dorsolateral premotor cortex
29	77	medial premotor cortex
30	78	ventrolateral premotor cortex
31	79	primary somatosensory cortex
32	80	secondary somatosensory cortex
33	81	central temporal cortex
34	82	inferior temporal cortex
35	83	temporal polar cortex
36	84	superior temporal cortex
37	85	ventral temporal cortex
38	86	visual area 1 (primary visual cortex)
39	87	visual area 2 (secondary visual cortex)
40	88	anterior visual area, dorsal part
41	89	anterior visual area, ventral part
42	90	thalamic roi with major frontal connections
43	91	thalamic roi with major temporal connections
44	92	thalamic roi with major occipitoparietal connections
45	93	caudate nucleus
46	94	putamen
47	95	pallidum
48	96	accumbens nucleus

891 **Table 4.** TVB model parameters

Parameter	Value (number of steps)	Description
Global Coupling (G)	1.4 – 2.8 (50)	scaling factor for inter-region (global) excitatory coupling
Noise (σ)	0.001	amplitude of noise kernel
Conduction	6	speed of inter-region (global) signal transmission
Velocity (m/s)		
w_+	1.4	Excitatory recurrent potential
J_{GABA} (nA)	1.0*	Local feedback inhibitory synaptic coupling
J_{NMDA} (nA)	0.15	Local excitatory coupling
Time steps (ms)	600000	Simulation duration
fMRI TR (ms)	2000	Simulation repetition time (TR)

892 * J_{GABA} values were initialized at 1.0 and adjusted iteratively by the FIC tuning algorithm
 893 during each simulation.

894 **Table 5.** Factor loadings for 6-month outcome variables

Scale	Subscale	TBI Symptoms	Age and Cognition
Glasgow Outcome Scale Extended	6 month	-0.73	-0.033
Brief Symptom Inventory	Somatic	0.71	0.16
	Depression	0.86	-0.075
	Anxiety	0.87	-0.032
	Global severity index	0.99	-0.043
Satisfaction with life scale		-0.83	0.29
Education		-0.33	-0.51
Age		-0.036	0.42
Trail Making Test	Part A	0.19	0.62
	Part B	-0.085	0.89
Wechsler Adult Intelligence Scale	Processing Speed	0.25	-0.92
California Verbal Learning Test		-0.10	-0.31
Percent Covariance		37%	22%

895 *loadings $>|0.3|$ are bolded to assist interpretation

896 **Note: BSI and TMT scales are reverse coded such that higher scores indicate more
 897 symptoms or poorer performance

898 **Table 6.** Model fitting results

Fitting Metric	Descriptive statistic	CT/MRI positive n=14	CT/MRI negative n=30	Comparison n=36	Significance
Functional Connectivity, uncentered correlation	mean	0.66	0.66	0.68	F(2,77)=0.32, p=0.73
	standard deviation	0.11	0.09	0.12	
	minimum	0.50	0.33	0.35	
	maximum	0.79	0.84	0.88	
Functional connectivity dynamics, Kolmogorov-	mean	0.13	0.12	0.12	F(2,77)=0.03, p=0.97
	standard deviation	0.07	0.14	0.13	
	minimum	0.04	0.03	0.03	

Smirnov distance	maximum	0.31	0.70	0.74	
Percentage of iterations optimal solution was chosen for	mean	37.0%	34.5%	34.3%	$F(2,77)=0.15, p=0.86$
	standard deviation	13.7%	16.2%	14.9%	
	minimum	15.0%	15.0%	15.0%	
	maximum	75.0%	90.0%	90.0%	

899

900

901 **Figure 1. The Virtual Brain workflow.** Structural and functional connectomes were
 902 created from each subject's dwMRI and fMRI data respectively. Each subject's unique
 903 structural connectome constrained their personal brain simulation, wherein local
 904 dynamics were represented by the dynamic mean field (DMF) model (equations 1-6)
 905 (Deco, McIntosh, et al., 2014; Deco, Ponce-Alvarez, et al., 2014). The simulated local
 906 synaptic gating potentials were then fed through the Balloon-Windkessel hemodynamic
 907 model, producing simulated fMRI timeseries. Each subject's simulated fMRI timeseries
 908 was fitted to their functional connectome through parameter space exploration. The
 909 resulting subject-specific parameters were used in later analyses.
 910 *Abbreviations: Dynamic Mean Field model (DMF), excitatory neural population (E),*
 911 *inhibitory neural population (I), global coupling (G), recurrent potential (w_+), inhibitory*
 912 *connection strength (J_i), excitatory connection strength (J_{NMDA}), noise (σ).*

913

914 **Figure 2.** A group comparison PLS distinguished the SC of CT/MRI positive and
 915 negative patients from comparison participants. **A-C** Shows the first latent variable
 916 ($p<0.0001$, 67% covariance, singular value=0.19) that differentiated CT/MRI positive
 917 patients from the comparison participants, while **D-F** Shows the second latent variable
 918 ($p=0.016$, 33% covariance, singular value=0.13) that distinguished CT/MRI negative
 919 patients from the comparison participants. **A/D** Violin plots show the distribution of brain
 920 scores for each group. Brain scores indicate the degree to which participants express the
 921 pattern of SC shown in 'B'/'E'. Error bars are bootstrap-estimated 95% confidence
 922 intervals. **B/E** Show bootstrap ratios, which are a linear combination of SC weighted by
 923 how strongly they contribute to the latent variable. Bootstrap ratios may be interpreted
 924 similar to z-score ($>|2.0|$ akin to $p<0.05$), so regions with bars exceeding the dashed line
 925 may be considered reliably contributing to the latent variable. **C/F** Regional inhibitory
 926 connection strength bootstrap ratios that are reliably contributing to the latent variable
 927 ($>|2|$) from 'B'/'E' projected onto a brain.

928

929 **Figure 3.** A group comparison PLS distinguished the CT/MRI positive and negative
 930 patients from comparison participants via their fractional anisotropy. **A-B** Shows the first
 931 latent variable ($p=0.01$, 65% covariance, singular value=8.2) that distinguished CT/MRI
 932 positive patients from the comparison participants **A** Violin plot shows the distribution of

933 brain scores for each group. Brain scores indicate the degree to which participants
 934 express the pattern fractional anisotropy shown in 'B'. Error bars are bootstrap-estimated
 935 95% confidence intervals. **B** Shows bootstrap ratios, which are a linear combination of
 936 voxel-wise fractional anisotropy weighted by how strongly they contribute to the latent
 937 variable. Bootstrap ratios are superimposed onto a white matter skeleton. Bootstrap ratios
 938 may be interpreted similar to z-score ($>|2.0|$ akin to $p<0.05$), so only voxels with
 939 bootstrap ratios exceeding $|2|$ are illustrated.

940
 941 **Figure 4. Summary of modeling fitting procedure.** **A** The parameter space exploration
 942 map for a representative subject given a single iteration. The gray area denotes values of
 943 global coupling for which the model fails to converge because it becomes hyperexcited.
 944 The black dashed line represents the optimal value of global coupling. Note that
 945 combined fit (green) is defined by the sum of the FC and FCD fits ranked across all other
 946 values of global coupling at which the model converged. **B** Shows the full parameter
 947 space results for the same representative subject. Each grid shows model fits across all
 948 values of G on the x-axis, and iterations with randomized initial conditions on the y-axis.
 949 On the left, fits are defined by the uncentered correlation of the upper triangle of the
 950 empirical and simulated FC matrices. On the right, Kolmogorov-Smirnov (KS) distance
 951 between the upper triangles of the empirical and simulated FCD matrices defines fits. The
 952 red dots represent the optimal fit for each iteration.

953

954 **Figure 5.** Group comparison PLS of TVB parameters (global coupling [G] and regional
955 inhibitory connection strengths) across patients (combined CT/MRI positive and negative
956 subgroups) and comparison participants ($p=0.026$, singular value=0.30). Patients showed
957 mostly higher inhibitory connection strength relative to comparison participants,
958 particularly in the subcortical regions. **A** The violin plot shows the distribution of brain
959 scores for each group. Brain scores indicate the degree to which participants express the
960 pattern of global coupling and regional local inhibitory connection strength shown in 'B'.
961 Error bars are bootstrap-estimated 95% confidence intervals. **B** Shows bootstrap ratios,
962 which are a linear combination of global coupling and regional local inhibitory
963 connection strength weighted by how strongly they contribute to the latent variable.
964 Bootstrap ratios may be interpreted similar to z-score ($>|2.0|$ akin to $p<0.05$), so regions
965 with bars exceeding the dashed line may be considered reliably contributing to the latent
966 variable. Error bars are one standard error. Bars representing subcortical regions are
967 shaded. **C** Regional inhibitory connection strength bootstrap ratios from 'B' projected
968 onto a glass brain.
969 Note: J_i = inhibitory connection strength

970

971 **Figure 6.** Group comparison PLS of TVB parameters (global coupling [G] and regional
 972 inhibitory connection strengths) across CT/MRI positive patients, CT/MRI negative
 973 patients, and comparison participants. **A-C** Shows the first latent variable ($p=0.03$, 70.9%
 974 covariance, singular value=0.43) that differentiated CT/MRI positive patients from
 975 comparison participants **A** Violin plot shows the distribution of brain scores for each
 976 group. Brain scores indicate the degree to which participants express the pattern of global
 977 coupling and regional local inhibitory connection strength shown in in 'B'. Error bars are
 978 bootstrap-estimated 95% confidence intervals. **B** Shows bootstrap ratios, which are a
 979 linear combination of global coupling and regional local inhibitory connection strength
 980 weighted by how strongly they contribute to the latent variable. Bootstrap ratios may be
 981 interpreted similar to z-score ($>|2.0|$ akin to $p<0.05$), so regions with bars exceeding the
 982 dashed line may be considered reliably contributing to the latent variable. Error bars are
 983 one standard error. Bars representing subcortical regions are shaded. **C** Regional
 984 inhibitory connection strength bootstrap ratios from 'B' projected onto a brain.
 985 Note: J_i = inhibitory connection strength

986
 987 **Figure 7.** A behavioural PLS analysis assessed the associations between the TBI
 988 Symptoms and Age and Cognition factors and TVB parameters (global coupling and
 989 regional inhibitory connection strengths) in the patients (combined CT/MRI positive and
 990 negative subgroups). The first significant variable is illustrated ($p=0.02$, 74% covariance,
 991 singular value=2.4) **A** The bars represent the correlation between each factor and the
 992 pattern of TVB parameters shown in the corresponding bar graph 'B'. The error bars
 993 represent 95% confidence intervals, so the error bars of variables significantly
 994 contributing to the latent variable do not cross zero. **B** Bootstrap ratios, which are a linear
 995 combination of global coupling and regional local inhibitory connection strength
 996 weighted by how strongly they contribute to the latent variable. Bootstrap ratios may be
 997 interpreted similar to z-score ($>|2.0|$ akin to $p<0.05$), so regions with bars exceeding the
 998 dashed line may be considered reliably contributing to the latent variable. Error bars are
 999 one standard error. Bars representing subcortical regions are shaded. **C** Regional
 1000 inhibitory connection strength bootstrap ratios from 'B' that are reliably contributing to
 1001 the latent variable ($>|2|$) projected onto a brain.
 1002 Note: J_i = inhibitory connection strength

1003

1004 **Figure 8.** Within group behavioural PLS analyses show the relationships between the
1005 TBI Symptoms and Age and Cognition factor scores and the TVB parameters (global
1006 coupling [G] and regional inhibitory connection strengths) for the CT/MRI negative (A-
1007 C) and CT/MRI positive patients (D-F). **A-C** Shows the first latent variable ($p=0.005$,
1008 73.1% covariance, singular value=3.0) for the within CT/MRI negative patients, while **D-F**
1009 illustrates the first latent variable ($p=0.11$, 67.6% covariance, singular value=3.7) for
1010 the CT/MRI positive patients. **A/D** The bars represent the correlation between each factor
1011 with the pattern of TVB parameters shown in the corresponding bar graph 'B'. The error
1012 bars represent 95% confidence intervals, so the error bars of variables significantly
1013 contributing to the latent variable do not cross zero. **B/E** Shows bootstrap ratios, which
1014 are a linear combination of global coupling and regional local inhibitory connection
1015 strength weighted by how strongly they contribute to the latent variable. Bootstrap ratios
1016 may be interpreted similar to z-score ($>|2.0|$ akin to $p<0.05$), so regions with bars
1017 exceeding the dashed line may be considered reliably contributing to the latent variable.
1018 Error bars are one standard error. Bars representing subcortical regions are shaded. **C/F**

1019 Regional inhibitory connection strength bootstrap ratios that are reliably contributing to
1020 the latent variable ($>|2|$) from 'B'/'E' projected onto a brain.
1021 Note: J_i = inhibitory connection strength