Structure-Function Relationships in Brain-Injured Patients: A Scoping Review

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Abstract

The human brain is a dynamic network comprised of elements which are structurally connected and functionally interactive. A tight structure-function relationship is vital for this system to produce seamless cognition and behaviour. Brain injuries due to either neurological disease or single-event injuries alter the dynamics of normal structure-function interaction, resulting in poor neurobehavioural outcomes for patients. This scoping review is a synthesis of recent progress in understanding how brain injuries alter the structure-function relationship. We identified 16 studies that investigated the structure-function relationship in brain-injured cohorts, using fMRI and either T₁-weighted or diffusion-weighted MRI to calculate, respectively, grey matter density *or* structural connectivity. Overall, a reduced structure-function relationship was found in brain-injured patients relative to healthy controls. This weakened relationship coincided with impaired cognition. Structural and functional MRI information should also be reconciled into suitable graph theoretical frameworks such as the multilayer network approach, in order to yield more sensitive biomarkers to guide personalised neurorehabilitation.

Key words: functional connectivity, structural connectivity, multimodal MRI, brain injury

Introduction

The human brain is a dynamic network comprised of structurally connected elements that are functionally interactive. These elements have a close relationship, which is essential for the brain to seamlessly manifest cognition and subsequent behaviour. Brain injuries can alter this relationship, and preliminary multimodal MRI evidence is beginning to uncover the extent to which this relationship is affected. Brain injuries can occur due to acute trauma (e.g., traffic accident, sport injury, or falls), neurodegenerative disease (e.g., multiple sclerosis, Parkinson's disease, Huntington's disease), or various other medical conditions (e.g., stroke, tumours). These injuries often manifest in a range of cognitive and behavioural deficits, including memory impairment, reduced attention, slowed processing speed, impaired executive functioning, motor impairment and behavioural disinhibition, often with life-changing implications for daily functioning (Godefroy, 2003; McAllister et al., 2004; Ponsford et al., 2014; Poudel et. al., 2020; Poudel et. al., 2019; Poudel et. al., 2015; Poudel et. al., 2014). The direct impact of structural injury on the brain can be assessed non-invasively by using magnetic resonance imaging (MRI) modalities such as T₁-weighted and diffusion-weighted MRI (Kinnunen et al., 2010; Eirud et al., 2014; Selvadurai et al., 2016; Dennis et al., 2016; Wallace, Mathias and Ward, 2018; Wijeratne et. al., 2020). Functional MRI (fMRI) is used to measure secondary changes in brain activity patterns or synchronicity between brain regions (functional connectivity; FC) during performance of cognitive tasks (Xue et al., 2019; Kim et al., 2013; Gili et al., 2011) or at rest (Diez et al., 2017; Risen et al., 2015; Tuerk et al., 2019). Together, these MRI techniques provide complementary information about the neural consequences of brain injuries. Therefore, the strengths of these multi-modal MRI techniques can be leveraged to simultaneously characterise both the structural and functional alterations that drive brain injury symptomology.

Traditionally, there has been a focus on exploring how brain structure (S in the form of grey matter morphological features) relates to brain function (mostly in the form of task-based brain activation). More recently however, research has evolved to explore whole-brain functional *connectivity* measurements that allow the consideration of the brain as a complex network. To this end, resting-state functional connectivity (FC) represents a broad, robust and reproducible paradigm which can be directly contrasted with structural connectivity (SC; measured using diffusion weighted imaging) in an effort to determine if and how brain structure “*constrains, maintains and regulates*” brain function (Straathof et al., 2015:39).

In a review of the SC-FC relationship in mammalian brains (Straathof et al., 2015), 27 of the 28 studies included, reported a positive correlation between SC (diffusion MRI or neuronal tracer-based connectivity measures) and FC metrics. This same pattern has also been observed in healthy humans. For example, Honey and colleagues (2009) reported positive correlations between measures of SC (using diffusion spectrum imaging tractography) and resting state FC. Similarly, a review by Damoiseaux and Greicius (2009) found all eight studies showed positive correlations between measures of SC and FC. These and other studies provide support for the assumption that structural architecture is linked to how brain regions functionally interact. However, our current understanding of how this structure-function relationship in the brain is altered by acquired injury is limited (Suarez et al. 2020).

The earliest efforts to explore the SC-FC relationship can be traced back over a decade (Honey et al. 2009; Supekar et al., 2010) yet until recently, these efforts have been sparse. Due to advances in both diffusion MRI spatial sensitivity, functional MRI temporal sensitivity, and quantitative analytical techniques, the use of multimodal MRI is approaching a nexus where we can more reliably investigate the brain as a complex network. As such, there is a growing need to collate and critically assess this body of literature. The current evidence for changes in the SC-FC relationship due to brain injury arises from studies which have attempted to explore linear associations between structural and functional measures, with potential implications for cognition and behaviour (Wang et al., 2018; Sharp et al., 2011). For example, Garcia-Gorro and colleagues (2018) found that in Huntington's disease patients, reduced SC (as measured by apparent diffusion coefficient, axial and radial diffusivity) of the motor corpus callosum was significantly correlated with reduced FC during a motor task of the left and right sensorimotor cortices, which are connected by this tract. Both of these MRI measurements also correlated with reduced motor performance. Similarly, Reijmer et al. (2015) found SC-FC between the medial prefrontal and posterior cingulate cortex was reduced in individuals with white matter lesions, which correlated with lower executive functioning scores. Given the scattered evidence on the SC-FC relationship in patients with brain injuries, a systematic scoping review is vital in order to critically evaluate the findings in this area.

The primary aim of this paper is to critically review the literature investigating the quantitative SC-FC relationship in brain-injured patients. We included studies in which structural

connectivity was measured with either diffusion-weighted imaging (DWI) or anatomical (T₁-weighted) imaging and functional connectivity measured using resting-state fMRI. In this review, we: (1) summarize the existing evidence on the relationship S-FC or SC-FC according to brain-injury type; (2) examine whether changes in S-FC or SC-FC are related to clinical, behaviour or motor outcome measures; and (3) provide methodological recommendations for future research.

Method

We performed a systematic search of the literature (23rd March 2020) using PubMed and PsycInfo (see search terms in supplementary material). Studies were included if they met the following criteria: (a) original research published in a peer-reviewed journal; (b) studies with a sample of participants with any form of post-natal brain injury or disease; (c) used multimodal MRI, including resting-state functional MRI and structural MRI (diffusion or anatomical); and (e) investigated the relationship between brain functional and structural connectivity. Studies were excluded if (a) full-text article was not available; (b) the article was published in a language other than English; (c) was a conference proceeding, editorial, letter, comment or review article; (d) or if article was a case series. We extracted the following information from each study: sample size, regions of interest, technique employed to measure the structure-functional connectivity, or structure-functional connectivity relationship, and any correlation with clinical/behavioural variables. Detailed search strategy information can be found in Supplementary Material 1.

Results

General overview of studies

Our systematic search identified 16 studies that met the inclusion criteria, with six studies that compared morphological measures with FC (S-FC) and 10 studies that used diffusion MRI to measure white matter structure and compared it with FC (SC-FC). To compare MRI measurements, these studies used Pearson's correlation ($n = 7$), partial correlation ($n = 4$), multiple regression ($n = 2$), Spearman rank correlation ($n = 1$), mediation analysis ($n = 1$) and comparison of effect sizes (Kim et al., 2013). There was no typical pattern of relationship in single group S-FC studies, where S-FC was either 'coupled' (increased grey matter was *positively* related to increased FC), or *vice versa* ($n = 4$). Studies that directly examined SC-FC within groups found lower diffusivity and/or higher fractional anisotropy correlated with increased FC (Reijmer et al. 2015; Costanzo et al. 2014; Sharp et al. 2011). Between groups however, five studies revealed a significantly reduced SC-FC correlation strength in brain-injured patients relative to controls (Rosenberg-Katz et al., 2013; Mandelli et al., 2016; Rocca et al., 2013; Sharp et al., 2011; Kehoe et al., 2015). Increased SC-FC correlation strength between groups was also observed in two studies (TBI; Costanzo et al., 2014; mild cognitive impairment; Wang et al., 2018). The strength of these SC-FC correlation coefficients was most commonly reported as moderate ($r = \sim 0.4$), with correlation coefficients ranging from $r = -0.033$ to $r = -0.68$.

Importantly, both S-FC and SC-FC were investigated using highly heterogeneous spatial scales, ranging from single regions of interest ($n = 1$) and subnetworks ($n = 8$) to whole brain networks ($n = 2$), with the default mode network most commonly investigated ($n = 7$).

Despite this variation, most SC-FC studies in this review compared connectivity between functional ROI with suitable white matter tract metrics. For example, three studies examined the default mode network (Liang et al., 2016; Reijmer et al., 2015; Sharp et al., 2015) and computed structural connectivity of the cingulum bundle and superior or inferior longitudinal fasciculi, well-known tracts that connect posterior and anterior DMN regions (Alves et al., 2019).

Only two studies (Gordon et al., 2018; Wang et al., 2018) examined SC-FC at the whole-brain level using structural and functional connectomes generated from the same parcellation scheme (i.e. the AAL atlas) across both MRI modalities measurements, although none examined S-FC at this scale. As can be seen in Table 1 (rightmost column), only two studies

explored the relationship between S-FC with behavioural variables, where S-FC was positively related to Parkinson's motor rating scales (O'Callaghan et al., 2016) and with executive function in Alzheimer's disease (Qian Zhang & Sun, 2015). Of the three studies that included behavioural or cognitive variables with SC-FC, executive functioning and episodic memory (Reijmer et al., 2015) were positively correlated with SC-FC. On the other hand, visual memory performance (Wang et al., 2018) was negatively correlated with SC-FC.

Table 1. S-FC and SC-FC relationship in brain injury cohorts: methods and findings

<i>Authors</i>	<i>Sample</i>	<i>Structure metric/met hod</i>	<i>SC metric/method</i>	<i>Structural ROI</i>	<i>FC metric/method</i>	<i>Functional ROI</i>	<i>S-FC/SC-FC Quantification</i>	<i>S-FC/SC-FC relationship</i>	<i>S-FC/SC-FC - Cognition relationship</i>
Parkinson's disease									
<i>O'Callaghan et al., (2016)</i>	Parkinson's disease: $n = 42$, HC: $n = 29$	Grey matter density (VBM)	NA	Cerebellum	Fisher's Z-Scores, pairwise seed-based analysis of group ICA defined ROI	Cerebellum, DMN, FPN, DAN, SMN	Pearson's correlation	Parkinson's disease: Cerebellar atrophy – default mode, sensorimotor and dorsal attention network, frontoparietal network FC relative to controls: ($Z = -5.4$, $Z = -4.4$, $Z = -15.4$, $Z = 7.5$) Postural gait difficulty:	S-FC – UPDRS III score: $r = -0.371$, $p = 0.008$
<i>Rosenberg-Katz et al., (2013)</i>	Parkinson's disease: postural gait difficulty: $n = 30$, tremor dominant: $n = 29$	Grey matter density (VBM)	NA	Primary motor area, postcentral gyri, supplementary motor area, cerebellum, thalamus, caudate nucleus, putamen, globus pallidus	No FC metric reported, pairwise seed-based analysis of atlas defined ROI	Primary motor area, postcentral gyri, supplementary motor area, cerebellum, thalamus, caudate nucleus, putamen, globus pallidus	Pearson's correlation	Pre-SMA - putamen GMD-FC ($r = 0.4215$, $p < 0.025$)	No correlation reported
Multiple sclerosis									
<i>Rocca et al., (2015)</i>	Multiple sclerosis: $n = 69$, HC: $n = 40$	T2 lesion volume (local thresholding segmentation)	NA	Hippocampus + >10 regions	Fisher's Z-Scores, pairwise seed-based analysis of ROI	Hippocampus + >10	Pearson's correlation	Multiple sclerosis: Decreased lesion volume-FC relative to HC (Range: $r = -0.33$ to -0.46)	No correlation reported
<i>Louapre et al., (2014)</i>	Multiple sclerosis w/cognitive impairment: $n = 20$, wo/cognitive impairment: $n = 15$, HC: $n = 20$	NA	FA, RD, AD ² Targeted tractography	Anterior cingulum	Fisher's Z-Scores, pairwise seed-based analysis of group ICA defined ROI	DMN, FPN, AN, DAN, MN	Spearman's rank correlation	Multiple sclerosis (both subtypes) Medial prefrontal cortex-posterior cingulate cortex FC- anterior cingulum FA ($\rho = 0.43$, $p = .0012$) Medial prefrontal cortex-posterior cingulate cortex FC- posterior cingulate cortex volume ($\rho = 0.42$, $p = .0012$)	No correlation reported

								Medial prefrontal cortex-posterior cingulate cortex FC-inferior frontal gyrus volume ($\rho = 0.35, p = .04$)	
<i>Koubiyr et al., (2019)</i>	Clinically isolated syndrome: $n = 41$, HC: $n = 19$	NA	Streamline count Constrained spherical deconvolution Whole-brain tractography	Whole-brain (166x166 regions)	Fisher's Z-Scores, pairwise seed-based analysis	Whole-brain (166x166)	Pearson's linear correlation	<p>Clinically isolated syndrome:</p> <p>Baseline range: $r = 0.23$-0.45</p> <p>Follow-up range: $r = 0.24$-0.42</p> <p>Healthy controls:</p> <p>Baseline range: $r = 0.20$-0.49</p> <p>Follow-up range: $r = 0.20$-0.51</p> <p>Reduced SC-FC in salience, visual and somatomotor networks relative to HC ($p = 0.06, p = 0.06, p = 0.002$)</p>	No significant correlation with clinical/neuropsychological variables
<i>Alzheimer's disease</i>									
<i>Qian, Zhang & Sun, (2015)</i>	Alzheimer's disease: $n = 16$, cognitive impairment: $n = 12$	Grey matter density (VBM)	NA	Dorsal attention, visual network, frontal eye fields	Fisher's Z-Scores, pairwise seed-based analysis	Dorsal attention, visual network, frontal eye fields	Multivariate regression	<p>AD group:</p> <p>GMD-FC in bilateral FEF areas (right: $\beta=0.711, t=3.68, p=0.004$; left: $\beta=0.497, t=2.76, p=0.025$) and the left IPS area ($\beta=0.623, t=2.78, p=0.011$).</p> <p>GMD-FC in the posterior/middle cingulate cortex and precuneus ($\beta = -0.672, t = 3.92, p = 0.005$)</p> <p>GMD of the right ventral frontal cortex was correlated with FC deterioration in the right TPJ ($\beta = 0.718, t = 3.58, p=0.006$) and ventral frontal cortex ($\beta=0.518, t=2.57, p=0.036$)</p>	MMSE score - functional z-values in left FEF area ($r = 0.74, p = 0.002$), right FEF area ($r = 0.713, p = 0.004$), and left IPS area ($r = 0.629, p = 0.016$) in AD group

aMCI group:

GMD in the right dorsal frontal cortex was inversely correlated with FC in the left FEF area ($\beta = -0.846$, $t = 3.14$, $p = 0.021$).

(Range: $\beta = -0.846$ - $\beta = 0.718$)

<i>Kim et al., (2013)</i>	Alzheimer's disease: $n = 13$, HC: $n = 14$	Grey matter density (VBM)	NA	Hippocampus, para hippocampus, precuneus, postcentral gyrus, posterior cingulate cortex	Fisher's Z-Scores, pairwise seed-based analysis	Hippocampus, para hippocampus, precuneus, postcentral gyrus, posterior cingulate cortex	AD vs HC Effect size comparison: (atrophy) vs Cohen's d (FC)	Aberrant FC effect sizes ($d = -1.24$ - 1.49) were significantly greater than cortical atrophy ($d = -0.01$ - 1.09)	No correlation reported
<i>Wang et al., (2018)</i>	Moderate cognitive impairment w/no dementia: $n = 56$, mild cognitive impairment w/no dementia: $n = 61$, HC: $n = 97$)		DTI: streamline count Probabilistic tractography	Whole-brain	Fisher's Z-Scores, pairwise seed-based analysis	Whole brain	Pearson's correlation	No cognitive impairment whole-brain SC-FC: $r = 0.430$ Mild cognitive impairment whole-brain SC-FC: $r = 0.453$ Moderate cognitive impairment whole brain SC-FC: $r = 0.481$ HC vs CIND SC-FC; ($t = 2.21$, $p = 0.028$) HC: linear diffusion coefficient in the fornix and the FC of the thalamus-hippocampus ($r = 0.55$, $p = 0.008$), which was absent in the aMCI group ($r = -0.08$, $p = 0.81$).	Increased whole brain SC-FC correlated with poorer visual memory performance in no cognitive impairment ($t = -2.336$, $p = 0.022$) and mild cognitive impairment groups only ($t = -1.912$, $p = 0.061$)
<i>Kehoe et al., (2015)</i>	Mild cognitive impairment: $n = 19$, HC: $n = 22$.		FA, MD, Linear/planar diffusion coefficient Constrained spherical deconvolution Whole-brain tractography	Foxnix	Fisher's Z-Scores, pairwise seed-based analysis	Thalamus, hippocampus	Pearson's correlation		No correlation reported
White matter abnormalities									
<i>Liang et al., (2016)</i>	White matter lesions: $n = 42$, HC: $n = 30$		FA, MD DTI	Superior longitudinal fasciculus, cingulum bundle,	Fisher's Z-Scores, pairwise seed-based analysis	Default mode network, bilateral frontoparietal network	Multiple linear regression	White matter lesions SC-FC: range: $r = -0.56 - 0.54$, $p = 0.001$ - 0.03	No correlation reported

			Targeted tractography	inferior cingulum bundle, bilateral superior frontal occipital fasciculus and corpus callosum					
Reijmer et al., (2015)	White matter lesions: $n = 125$		FA, MD Constrained spherical deconvolution Deterministic whole-brain tractography	Inferior longitudinal fasciculus, cingulum	Fisher's Z-Scores, pairwise seed-based analysis	DMN	Absolute difference between Fisher's Z-Scores and MD (independent samples t-test and ANOVA)	Whole sample main effect of cingulum MD vs. PCC-MPFC FC: ($F_{1,107} = 4.28, p = 0.041$). Low WMH MD vs. PCC-MPFC FC: $\beta = -0.44, p < 0.001$	High white matter hyperintensities: reduced PCC-MPFC SC-FC strength correlated with worse executive functioning (β (95% CI) = -0.36 (-0.61 to -0.11), $p = 0.006$), and episodic memory ($\beta = -0.36 - 0.60$ to -0.12), $p = 0.004$.
Brain insult									
Mandelli et al., (2016)	Aphasia: $n = 34$, HC: $n = 30$	Grey matter density (VBM)	FA Q-ball targeted DTI tractography	Aslant, superior longitudinal fasciculus, arcuate fasciculus	Fisher's Z-Scores, pairwise seed-based analysis	Motor areas, prefrontal, temporal, DMN (control network)	Pearson's correlation & Partial correlation	Aphasia: Decreased language network nodewise GMD – FC relative to HC: $r = -0.03, p < .001$	No correlation reported
Chen & Schlaug (2013)	Stroke: $n = 11$, HC: $n = 12$		AD, RD, FA DTI Targeted tractography	Ipsilesional corticospinal tract, transcallosal tract between M1 and M1	Pairwise seed-based Pearson's correlations	Left and right M1, left parahippocampal gyrus	Partial correlation	Not significant ($r = 0.377, p = 0.179$)	No correlation reported
Costanzo et al., (2014)	mTBI/PTSD: $n = 11$, HC: $n = 11$		FA DTI Whole-brain tractography	Cingulum bundle	Fisher's Z-Scores, pairwise seed-based analysis	DMN, PCC, MFC	Pearson's correlation	TBI Left cingulum bundle SC, PCC-MPFC FC: increased in TBI relative to HC ($r = 0.31, p = 0.037$, HC: $r = 0.0014, p = 0.91$)	No correlation reported
Gordon et al., (2018)	HC: $n = 5$, mild TBI: $n = 17$, Moderate TBI: $n = 4$		FA DTI Targeted tractography	Whole-brain	Fisher's Z-Scores, pairwise seed-based analysis	Whole-brain	Pearson's correlation/partial correlation/ANCOVA	Not significant ($r = -0.22, p = 0.27$)	No correlation reported
Sharp et al., (2011)	TBI: $n = 21$, HC: $n = 23$		FA, MD DTI	Splenium, body and genu of corpus callosum, left and right	Group ICA, dual regression, voxelwise FC	Default mode, frontoparietal, executive network	Pearson's correlation	TBI: Decreased MPFC-PCC-Splenium FA ($\rho = -0.68, p = .001$) and body of corpus	No correlation reported

Targeted
tractography

corticospinal
tracts and
superior
longitudinal
fasciculi

callosum ($\rho = -0.52$, $p = 0.02$) relative to HC.

**AD = Alzheimer's disease, AD^2 = axial diffusivity, ANCOVA = analysis of covariance, AN = attention network, ATL = anterior temporal lobe, CIND = cognitive impairment with no dementia, DAN = dorsal attention network, DTI = diffusion tensor imaging, DMN = default mode network, FA = fractional anisotropy, FC = functional connectivity, FPN = fronto parietal network, HC = healthy controls, ICA = independent component analysis, LIFG = left inferior frontal gyrus, LIFGorb = left inferior frontal gyrus pars orbitalis, M1 = primary motor cortex, mATL = middle anterior temporal lobe, MD = mean diffusivity, MMSE = mini mental state examination, MN = motor network, MPFC = medial prefrontal cortex, MMSE = mini mental state examination, mTBI = mild traumatic brain injury, PCC = posterior cingulate cortex, PD = Parkinson's disease, PTSD = post-traumatic stress disorder, RD = radial diffusivity, SMA = sensory motor area, SMN = sensorimotor network, UPDRS = unified Parkinson's disease rating scale, VBM = voxel-based morphometry.*

Figure 1. Summary schematic figure of select findings showing SC-FC relationships between white matter fibre bundle tract SC measures and medial prefrontal cortex-posterior cingulate cortex FC across brain injury cohorts.

Figure 2. S/SC-FC correlation values in brain-injured and healthy cohorts.

Summary of studies

Parkinson's disease: Rosenberg-Katz et al., (2013) reported a significant positive correlation between grey matter volume in the pre-supplementary motor area (preSMA) and FC between the preSMA and the putamen in patients with postural instability gait difficulty subtype ($r = 0.4215$) but not in those with tremor dominant subtype. Similarly, O'Callaghan et al. (2016) showed that cerebellar atrophy (measured with grey matter density) was positively correlated with FC (Fisher's Z) and this relationship was directly related to disease rating scores ($r = -0.371$).

Multiple sclerosis: Rocca et al. (2015) reported a negative correlation between lesion volume (T1 grey matter density) and FC (Fisher's Z) between bilateral hippocampi and regions of the DMN, whereby increased lesion volume was associated with decreased hippocampal FC. Similarly, another study (Louapre et al., 2014; see fig. 1, 2) found a positive correlation between functional connectivity of the MPFC-PCC and fractional anisotropy of the anterior cingulum ($\rho = 0.43$, $p = 0.012$). In patients with clinically isolated syndrome (i.e a single neurological episode suggestive of multiple sclerosis), reduced SC-FC correlation strength ($r = 0.42$) was reported in the salience, visual and somato-motor networks compared to controls ($r = 0.51$) despite preserved cognitive performance (Koubiyr et al., 2019) which has also been reported in other neurodegenerative diseases such as Alzheimer's disease.

Alzheimer's disease: A positive relationship was found between grey matter density and FC in the frontal cortex (Qian et al., 2015). However, a negative relationship was found in a comparative MCI group. Kim et al. (2013) found that aberrant FC effect sizes ($d = -1.24$ to 1.49) were significantly greater than effect sizes of cortical atrophy ($d = -0.01$ to 1.09). In Alzheimer's disease, Wang et al. (2018) was the only study to identify and compare the strength of the SC-FC relationships across groups (using DTI streamline count as SC) and pairwise Pearson's correlations as FC). Three subgroups were defined by their cognitive function status, including 'no cognitive impairment', 'mild' cognitive impairment group and 'moderate cognitive impairment with no dementia'. The strength of the SC-FC relationship was higher in the moderate cognitive impairment no dementia subgroup ($r = 0.481$) compared to the no cognitive impairment subgroup ($r = 0.430$). The SC-FC relationship was negatively correlated with visual memory performance in the no cognitive impairment and

mild cognitive impairment subgroups, but not the moderate cognitive impairment subgroup, indicating that higher SC-FC strength coincided with increased disease severity. As such, these mixed findings suggest that both S-FC, and SC-FC relationships are not well characterised in Alzheimer's disease.

White matter abnormalities: A wide range of both positive and negative SC-FC relationships (FA, MD as SC and Fisher's Z as FC; $r = -0.56 - 0.54$) were reported in participants with mild white matter lesions visually rated on fluid attenuated inversion recovery (FLAIR) images. However, no results survived correction for multiple comparisons (Liang et al., 2016). Reijmer and colleagues (2015; see fig 1, fig 2) showed that MD of the cingulum bundle was negatively correlated with FC of the posterior cingulate cortex and medial prefrontal cortex (DMN) in individuals with low white matter intensity load (again, visually rated using FLAIR images). Despite this finding, no significant SC-FC relationship was found in patients with high white matter hyperintensities. Moreover, separate ANOVA's revealed that in this study, the SC-FC relationship was weaker in the low white matter hyperintensities group *relative* to the high white matter intensities group, which was reported as 'decoupling' of SC-FC. This 'decoupling' was related to worse performance on executive functioning and memory tests. Given the heterogeneity of methodologies and findings in this area, alterations in the SC-FC relationship in this cohort are inconclusive.

Brain insult: Our search yielded two multimodal MRI studies examining stroke or aphasia patients (Chen & Schlaug, 2013; Mandelli et al., 2016) and three examining traumatic brain injury (Sharp et al., 2011; Costanzo et al., 2014; Gordon et al., 2018). All of these directly investigated SC-FC except Mandelli et al (2016). In congruence with findings in other brain injured cohorts, Mandelli et al. reported a positive correlation whereby as grey matter density of the language network decreased (atrophy), FC was also reduced however this correlation strength was very weak ($r = -0.03$). The only SC-FC study identified in stroke patients (Chen and Schlaug) failed to detect a significant relationship between fractional anisotropy of the transcallosal motor fibres, and FC of the left/right primary motor cortex and left parahippocampal gyrus. In studies involving military veterans with TBI, one study found no significant association between whole brain fractional anisotropy values and within network FC measures (Gordon et al., 2018). However, in chronic TBI patients, a positive correlation was reported between SC and FC, with lower diffusivity of the splenium of the corpus callosum correlating with increased posterior cingulate cortex FC (Sharp et al., 2011). A

similar finding was reported by Costanzo et al. (2014), where a positive correlation was found between fractional anisotropy of the left cingulum bundle and FC between the medial frontal cortex and precuneus/posterior cingulate cortex in patients with combat-related mild TBI ($r = 0.31, p = 0.037$). However, no significant correlation was found in healthy controls ($r = -0.037, p = 0.919$).

Main finding

Overall, we found that measures of brain structure (S or SC) were positively correlated with FC. However, in some studies this relationship was impaired relative to controls across numerous brain injury groups or those with greater disease severity (see fig 1 and 2). Importantly, this weakened relationship coincided with reduced cognitive performance in patients with Parkinson's disease, Alzheimer's disease, and individuals with white matter lesions.

Discussion

In this scoping review, we focused on critically reviewing MRI studies examining the relationship between structural and functional connectivity in brain-injured patients. As expected, the SC-FC relationship was disrupted across numerous brain injury subtypes (see fig 1 and 2). Our findings raise several issues that hereafter we will discuss in greater detail: (i) methods used for measuring both S-FC and SC-FC relationships; (ii) how alterations in S/SC-FC relationships are interpreted; (iii) whether SC-FC can be used as a prognostic or predictive biomarker; and (iv), we raise methodological considerations and limitations.

Methods for measuring SC-FC relationship

All studies investigated either linear S-FC or SC-FC relationships. The majority of these studies operationalised the SC-FC relationship utilizing the Pearson's correlation coefficient (see Table 1, column 9), while one employed partial correlations (Mandelli et al., 2016) to remove or reduce potentially spurious indirect effects of other brain regions (Marralec et al., 2006; Ryali et al, 2012; Lim et al., 2019). However, given that partial correlations inherently require the number of observations (subjects) to be larger than the number of ROI included (Krämer et al., 2009; Lim et al., 2019; Smith, 2013), they may be more suitable for studies with larger samples. Multivariate analyses were only employed by Gordon et al., (2018), who incorporated TBI severity scores in a multiple linear regression, and Qian, Zhang and Sun, (2015) who also performed multiple linear regression analyses, incorporating age and education level.

One study did not conduct direct *quantitative* analyses between structure and function measures (Kim et al., 2013). For example, Kim et al. (2013) only qualitatively compared differences in Cohen's *d* values, yet the authors concluded that aberrant FC may precede cortical atrophy. Of those that quantitatively investigated the structure-function relationship, one study reported a very weak yet significant finding (Mandelli et al; $r = -0.03$) and several failed to detect a significant S-FC or SC-FC relationship in brain injured groups at all (Rosenberg-Katz et al., 2013; Reijmer et al., 2015; Chen and Schlaug, 2013). These findings are in contrast with the view that structure and function (SC-FC) are closely linked albeit in healthy individuals (Damoiseaux and Greicius, 2009; Honey et al., 2010; Straathof et al., 2015; Suarez et al., 2020). As such, it is equally possible that the absence of significant relationships was due to (a)

degradation of this relationship due to injury, (b) small sample sizes and therefore insufficient statistical power or (c) weak *a priori* rationale for the choice of ROI, where affected areas may have been overlooked.

Only five studies tested the SC-FC relationship in brain regions or networks/subnetworks with a strong *a priori* hypothesis. For example, O'Callaghan et al., (2016) examined the SC-FC relationship in the cerebellum because of its well-known vulnerability in Parkinson's disease (Wu and Hallett, 2013; Benninger et al., 2009; Borghammer et al., 2010). However, the same study selected other resting state subnetworks (i.e., the dorsal attention and frontoparietal networks) in their secondary analyses *without* well-defined hypotheses. Another example is Qian Zhang & Sun, 2015, whereby the frontal eye fields were included as ROI with the dorsal and visual attention networks. Although both of these networks are commonly affected in Alzheimer's disease (Sorg et al. 2007; Li et al. 2012), it was not entirely clear why the frontal eye fields were included. The inclusion of regions without appropriate rationale/justification can increase the frequency of false positive findings, which is problematic for brain injury MRI studies or MRI studies in general (Poldrack et al., 2008; Botvinik-Nezer et al., 2020). Others such as Kehoe et al., (2015) did use *a priori* ROIs, given the known alterations in fractional anisotropy and radial diffusivity reported in amnesic mild cognitive impairment studies (Lee et al., 2012; Metzler-Baddeley et al., 2012; Oishi et al., 2012; Zhuang et al., 2013).

Interpretation of SC-FC relationship in brain-injured patients

Across studies, there was inconsistency in the terminology used to interpret the changes in structure-function relationship, which makes it difficult to reconcile and make sense of findings. The term 'decoupling' was used in six studies to interpret alterations in the structure-function relationship yet only three of these six studies (Qian, Zhang & Sun, 2015; Reijmer et al., 2015; Wang et al., 2018) used the term 'decoupling' to assess changes in the strength of SC-FC relationships *relative* to another group and/or timepoints (in the case of longitudinal designs). For example, Reijmer et al. (2015) interpreted SC-FC 'decoupling' as a statistically significant weaker relationship between mean diffusivity and FC between the posterior cingulate cortex and medial prefrontal cortex in a group with more white matter hyperintensities, *relative* to a group with less white matter hyperintensities. In line with Reijmer and colleagues, we suggest that the strength of the SC-FC relationships should be

directly tested between groups (for example using a t-test to examine the difference between Pearson's r values in more than one group or time-point).

Can the SC-FC relationship be used as a marker of disease progression?

The question remains as to whether the SC-FC relationship can be used as a prognostic biomarker in patients with disease severity levels that increase over time. Two studies (Reijmer et al. 2015; Wang et al., 2018) have indirectly examined this by comparing the strength of SC-FC relationships between subgroups of patients with different disease severity levels. For example, Reijmer et al. (2015) compared the MD-FC relationship in multiple white matter hyperintensity severity groups, reporting that patients with a greater number of hyperintensities had a weaker MD-FC relationship compared to those with fewer white matter hyperintensities. To date, only two longitudinal studies have investigated alterations in the SC-FC relationship from baseline to one-year later at follow-up in stroke patients with aphasia (Mandelli et al., 2016) and in clinically isolated syndrome (Koubiyr et al., 2019). In this study, aberrant SC-FC correlation strength preceded cognitive decline, which may indeed support the utility of the SC-FC relationship as a marker of future disease progression. There is still however, a need for longitudinal studies that measure changes in the strength in the SC-FC relationship over time in brain-injured patients.

Can the SC-FC relationship be used as a clinically relevant biomarker?

Only six studies contrasted or weighted the SC-FC relationship with clinical/behavioural scores. For example, Reijmer et al. (2015) revealed that reduced strength of SC-FC relationship coincided with worsened performance on executive function ($\beta = -0.11$ to 0.36) and episodic memory ($\beta = -0.60$ to -0.12). Unexpectedly, however, increased greater SC-FC strength was correlated with poorer visual memory performance scores in patients with white matter hyperintensities ($r = -0.249$; Wang et al., 2018). These authors speculated that reduced structural integrity observed in cognitively impaired patients may indicate a “more rigid structural network configuration, resulting in reduced functional interaction complexity between brain networks and hence stronger statistical SC-FC correlation”.

Although not all of these findings align, a preliminary pattern indicates that the SC-FC relationship can be used as a predictive biomarker of long-term cognitive outcomes; however, multivariate analyses incorporating cognitive and behavioural variables must be utilised in

future studies; for example, a repeated measures analysis of variance (ANOVA) including time by group interaction effects for cognitive/behavioural measures. Further, the correlations between these variables are still hampered by the spatiotemporal sensitivity of MRI acquisitions, which we discuss in detail below.

Methodological considerations and limitations

In this section, we will discuss important methodological limitations and advise future multimodal MRI studies in brain injured patients. We will outline important methodological challenges associated with the study of the SC-FC relationship in patients with brain injuries, including sample sizes, MRI scanning sequences, specific procedures to deal with lesions, as well as statistical analyses.

Sample sizes

The reliability of the SC-FC relationships was likely affected by the small sample sizes of the surveyed studies (*mean sample size* = 35, *median* = 20, *mode* = 11, *min* = 4, *max* = 129). Therefore, future MRI studies in brain injured cohorts should include larger sample sizes (Mumford et al., 2012) and better justify the sample sizes used. Given the difficulty in recruiting large numbers of patients with brain injuries for MRI studies, data sharing may be useful to increase sample sizes, and therefore statistical power. Within the enhancing neuro imaging genetics through meta-analysis (ENIGMA) group (<http://enigma.ini.usc.edu/>; Thompson et al., 2019), aggregated MRI datasets can be collected independently across several institutes, which will enable more powerful analyses and provide greater insights on the S-FC or SC-FC relationships.

MRI acquisition

Studies included in this review were hampered by the spatial and temporal limitations of MRI sequences, clouding the SC-FC relationship and reducing the reliability of findings. With regards to resting state fMRI, studies had relatively long repetition times (TR ~2s) and short acquisition times (TA ~7min) resulting in reduced signal-to-noise ratio (Cohen et al., 2018) and network reliability (Birn et al., 2013) respectively. Recent studies have showed that a longer TR cannot delineate high frequency time course contributions from low frequency

signal(s) of interest, leaving these spurious intrusions unaccounted for, resulting in reduced correlation reliability (Parsons et al., 2019; Angrawal et al., 2020). Therefore, repetition times *below* 1 second are more appropriate in order to increase sensitivity to high and low frequency time course contribution. Further, acquisition times of at least 13 minutes should be used to reliably capture large scale networks (Birn et al., 2013). Although longer scanning sequences can be difficult to capture in TBI patients due to restlessness, they can be achieved by giving patients breaks every 30 mins, with additional breaks when necessary. This approach was taken by Gordon et al., (2018) who captured over 3 hours of MRI data per TBI subject. The acquisition of both fMRI and dMRI can also be bolstered by using multiband echo planar imaging (Feinberg & Yacoub, 2012; Feinberg et al., 2013) allowing the acquisition of multiple volumes in a shorter amount of time window. This therefore provides increased time points for increased correlation reliability, but at the expense of reduced contrast to noise ratio, and sensitivity to motion, highlighting the need to scan for longer (Reynaud et al., 2017; Seo et al., 2017).

With regards to diffusion MRI acquisitions in SC-FC studies, the majority ($n = 10$) used a single, low b -value (<1000) and a low number (<32) of gradient encoding directions ($n = 5$), which can limit spatial resolution depending on the tractography model used (Dell'Acqua & Tournier, 2018). Although higher order tractography models such as constrained spherical deconvolution can be performed on data with 30-45 directions and b -values of 1000s/mm^2 (Dell'Acqua and Tournier, 2018; Alexander and Baker, 2005; Tournier et al., 2013), it is *recommended* that studies use higher gradient encoding directions (>45) and multiple b -values, including a high b -value in the order of $2500\text{-}3000\text{ s/mm}^2$, for better estimation of partial volume effects and tissue delineation, and to achieve the highest angular resolution (Jeurissen et al., 2014; Chamberland et al., 2018; Chamberland et al., 2019; Tournier et al., 2013). However, single b -values of $\sim 1000\text{s/mm}^2$ can also be used in combination with the recently developed single-shell 3 tissue spherical constrained deconvolution model which may altogether obviate the need to acquire multiple shells, therefore reducing acquisition time (Dhollander, Raffelt and Connelly, 2016; Dhollander, Raffelt and Connelly, 2017; Khan et al., 2020).

Dealing with lesions

Focal lesions are problematic in all brain-injury cohorts, as they can introduce processing errors during normalisation, segmentation and registration steps. Therefore, visual inspection of the raw data of the structural/functional MRI scans is imperative. Despite this, only three studies explicitly reported how they dealt with lesions (Chen et al., 2013; Sharp et al., year Liang et al., 2016). Although Liang et al. rated the severity of lesions into three categories, no attempt was made to deal with the contribution of these lesions to structural or functional MRI measures. Others identified white matter and cortical lesions using T₁-weighted scans to obtain lesion mapping masks (Sharp et al., 2011). However, these masks were only used as a step to exclude patients with large focal lesions and therefore did not permit a quantitative analysis, limiting the representativity of samples studied. There was also no mention of how these lesions were defined (for instance using a specified mm² threshold, or manual identification). A more appropriate method employed by Chen et al., (2013) involved drawing lesions in each subject's structural space on the T₁- weighted images using the co-registered T₂-weighted diffusion images as a reference for lesion extension to calculate lesion volume and load in each patient. This lesion mask was then employed during the registration steps of the MRI analyses, whereby voxels in the lesioned areas were excluded during the normalization procedures. Lesion volume was then included as a covariate of interest in fMRI modelling. Importantly, although some have modelled the impact of lesions in healthy brain connectomes (Alstott et al., 2009; Cabral et al., 2012; Saenger et al., 2018; Va'sa et al., 2015), no study has been conducted so far to directly test the effect of lesions on the SC-FC relationship in brain-injured patients. As such, we suggest that focal lesions could be represented as nodes of interest within a graph theoretical analysis framework (GTA). Due to certain nodes no longer being represented in connectomes however, we recommend virtually repairing damaged tissue, then assigning 0 to edges that connect with damaged nodes.

Choice of SC-FC metrics

Most studies ($n = 11$) utilized transformed Fisher's Z values to characterise FC, which is a widely adopted approach for fMRI studies in general. However, a recent comparison of FC metrics (e.g., wavelet coherence and Euclidean distance) by Mohanty et al., (2020) reported

significant changes in large scale network FC as a function of FC *measures*. As such, these networks may in part be dependent on the metric used to quantify FC and should therefore be complemented with additional correlation measures, for instance regularised partial correlations as used recently by Lim et al., (2019). With respect to dMRI, the majority of studies used FA ($n = 8$) and streamline count ($n = 2$) as structural connectivity measures despite these inherently lacking tissue specificity (for critical reviews on this topic, see Jeurissen et al., (2013); Jones, (2010); Jones et al., (2013). As such, quantitative tractography (Smith et al., 2012; Smith et al., 2013; Smith et al., 2015) was under-utilised (table 1 column 4) making comparisons between findings difficult. Furthermore, the most widely used diffusion *model* used across studies to define SC was the tensor model (see Table 1, column 4) despite its limited ability to model complex ‘crossing fibers’ (Dell’Acqua & Tournier, 2018). Higher order models such as constrained spherical deconvolution (CSD; Tournier et al., 2004; Tournier, Calamante & Connelly, 2007) can resolve crossing fibres, yet were only implemented by Reijmer et al. (2015) and Koubiyr et al. (2019). Therefore, studies should utilise constrained spherical deconvolution or additionally employ a novel framework such as fixel-based analyses (FBA) developed by Raffelt and colleagues (2015). FBA typically utilizes the fiber orientation distributions estimated using CSD which allows examination of microstructural differences in fiber density (FD) and macrostructural (morphological) changes in fiber-bundle cross-section (FC) for each fibre population within a voxel, or fixel (Raffelt et al., 2017; Raffelt et al., 2015).

In order to reconcile both SC and FC information, a suitable graph theoretical framework should also be considered (Bullmore and Bassett, 2011; Hagmann et al., 2008; Sporns, 2013). Graph theory allows whole brain multimodal MRI connectivity information to be translated into connectivity adjacency matrices, where graph metrics within each modality can be calculated to *describe* the connectivity information within each matrix. For example, we can quantify the community structure using the modularity index (Q; Newman, 2006), or the amount of ‘segregation’ within a network (clustering coefficient; Battiston et al., 2014). Despite this, only two studies in this review used graph theoretical metrics (Mandelli et al., 2016; Koubiyr et al., 2019). Mandelli et al. (2016) used these measures only for FC despite also acquiring SC, however others such as Koubiyr et al. (2019) did calculate segregation properties (clustering coefficient), centrality properties (degree, betweenness centrality), and integration properties (global efficiency) individually for both SC and FC measures. However, there has long been concern about the meaningfulness of graph metrics (Battiston

et al., 2014; Mandke et al., 2018), and as such we suggest the use of *a priori* graph metrics that may provide more meaningful insight into SC or FC (Battiston et al., 2014; Mandke et al., 2018) such as characteristic path length and normalised clustering coefficient, which in a recent meta-analysis were found to be altered in TBI patients (Imms et al., 2019).

A new promising approach that is an extension of graph theoretical analysis is a multilayer network (MLN) analysis. Within the multilayer network framework, a network can be generated from each MRI modality in the form of a 2-dimensional block matrix, where each node from the SC matrix can be linked with a pseudo edge to a corresponding node on the FC matrix. These edges then form a supra-adjacency connectivity matrix, which among other properties, can represent functional and structural co-dependency (i.e., correlation) between each structural and functional ‘layer’ (De Domenico et al., 2013; Battiston et al., 2014; De Domenico, 2017; Mandke et al., 2018). As such, this framework has the added ability to incorporate spatiotemporal and multimodal MRI information (Vaiana & Muldoon, 2017; De Domenico 2016; Muldoon & Bassett, 2016) and has been employed in healthy adults to incorporate multimodal MRI information, for instance magnetoencephalography (MEG) frequency bands (Buldu and Porter, 2017), MEG and fMRI (Mandke et al., 2018) and time-resolved fMRI network switching (Pederson et al., 2018). However, this approach has not yet been implemented to examine SC-FC relationship in brain injured patients (Suarez et al, 2020).

Conclusion

Despite limited samples, highly heterogenous methodologies, and differences in disease severity and pathology, both S-FC and SC-FC relationships are positively correlated in brain injured groups, yet impaired relative to healthy controls. This impairment relates to worse cognitive and behavioural outcomes. As such, this measure is an important prognostic marker of injury and disease. Advancements in *how* SC and FC information is captured and incorporated will allow the use of this relationship as a sensitive marker of disease progression, response to injury and treatment.

Funding

Karen Caeyenberghs is supported by a National Health and Medical Research Council Career Development Fellowship. Nicholas Parsons is supported by a Deakin University Postgraduate Research Scholarship (DUPRS).

Financial disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

Declarations of interest

None.

Author contributions

Nicholas Parsons: data curation, writing, visualization, original draft preparation. Matthew E. Hughes, Govinda Poudel, Juan F Domínguez D, Karen Caeyenberghs: writing, reviewing and editing.

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Supplementary information

Search strategy

The present review was conducted according to PRISMA guidelines. A systematic search was performed using two electronic databases, including Pub Med and Psycinfo, with the final search on 21 March 2020. There were no limits specified for year of publication. Specific search terms are provided in supplementary material. After removal of duplicates, titles and abstracts were used to screen studies for relevancy. Reference lists of included studies were also screened for additional eligible studies.

There were no limits specified for year of publication using the terms “(“brain injur*” OR “ABI” OR “acquired brain injury” OR “TBI” OR “traumatic brain injury” OR “stroke” OR “aphasia” OR “cerebral infarction” OR “multiple sclerosis” OR “parkinson’s disease” OR “alzheimer’s disease” OR “Alzheimer’s disease” OR “dementia” OR “multiple sclerosis” OR “huntington’s disease” OR “motor neuron disease” OR “axonal injur*” OR “diffuse axonal injury” OR “focal lesion” OR “brain tumour” OR “stroke” OR “persistent post-concussion syndrome”) AND (“structural magnetic resonance imaging” OR “structural MRI” OR “diffusion MRI” OR “diffusion tensor imag*” OR “DTI” OR “diffusion tensor tractography” OR “voxel-based morphometry” OR “voxel-based morphometry” OR “VBM”) AND (“functional magnetic resonance imaging” OR “functional MRI” OR “fmri” OR “resting-state” OR “resting state” OR “functional connectivity”) AND (“coupling” OR “relationship between” OR “correlation between”)).

Titles and abstracts were used to screen studies for relevancy after duplicates were removed. Reference lists of included studies were also screened for additional eligible studies.

Competing interest statement: The authors have no competing interests to declare

Supplementary Figure 1. PRISMA (2009) Flow Diagram