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1 **The structural connectome in traumatic brain injury: A meta-analysis of graph metrics**

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## 1. Introduction

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Traumatic Brain Injury (TBI) is one of the leading causes of death and disability in young people, affecting 10 million people worldwide every year (Humphreys et al., 2013; Hyder et al., 2007). The severity of a brain injury is typically described as mild, moderate, or severe, based on time spent unconscious and/or coma rating score, the duration of post-traumatic amnesia, and neuroimaging results. Cognitive deficits (e.g., slow processing speed and poor concentration), motor control deficits (e.g., poor manual dexterity, balance deficits), and behavioural problems (e.g., impulsivity) are particularly common (Rabinowitz & Levin, 2014; Rossi & Sullivan, 1996). Approximately 15-30% of mild TBI cases (Shenton et al., 2012) and up to 65% of moderate-severe cases (Rabinowitz & Levin, 2014; Selassie et al., 2008) report long-term problems. These persistent deficits cause disability and interfere with a patient's ability to perform day-to-day tasks, for example getting dressed, planning ahead, and preparing food (Rabinowitz & Levin, 2014). Isolating neurological biomarkers holds promise as a means to identify which patients are at risk of long-term disability; which has implications for patient management and development of economically sustainable treatment options.

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There is mounting evidence supporting diffusion MRI as a sensitive diagnostic tool in the care of patients with TBI (for reviews, see Delouche et al., 2016; Hulkower et al., 2013; Hutchinson et al., 2018; Xiong et al., 2014). First, changes in white matter organisation following TBI have been demonstrated in several important fibre bundles of the brain (Bendlin et al., 2008), including the superior longitudinal fasciculus (e.g., Farbota et al., 2012; Spitz et al., 2013) and the corpus callosum (e.g., Levin et al., 2008; Mayer et al., 2010; Rutgers et al., 2008). For example, in a meta-analysis of 13 diffusion studies of TBI, significant increases in fractional

47 anisotropy (FA) and decreases in mean diffusivity (MD) were found in the posterior parts of the  
48 corpus callosum (Aoki et al., 2012).

49         Second, decreased white matter organization has been shown to predict poorer outcome  
50 in chronic TBI patients of all severity types (Kinnunen et al., 2011; Kraus et al., 2007), and in  
51 acute mild TBI patients with persistent symptoms (Niogi et al., 2008). Lower FA in the  
52 subregions of the corpus callosum has been associated with poorer bimanual coordination  
53 (Caeyenberghs et al., 2011a) and slower processing speed (e.g., Levin et al., 2008; Wilde et al.,  
54 2006) in moderate-severe TBI patients. Similarly, lower FA in the cerebellum has been  
55 associated with poorer manual dexterity (Caeyenberghs et al., 2011b). Despite multiple reports  
56 of altered diffusion metrics, the regional analyses reported in these studies cannot identify how  
57 whole brain networks are affected by white matter damage following TBI.

58         Because TBI may be considered a ‘disconnection syndrome’, where symptoms are  
59 accounted for by altered connectivity between regions of the brain, it is important to take global  
60 network disruption into account (Catani & Ffytche, 2005; Griffa et al., 2013). Where traditional  
61 diffusion approaches such as those outlined above examine isolated brain regions, graph  
62 theoretical analysis (GTA) can characterise the global structure of the brain network (or  
63 ‘connectome’; Bullmore & Bassett, 2011; Hagmann et al., 2008; Sporns, 2013). Structural GTA  
64 represents the brain as a set of ‘edges’ (white matter pathways) that pass between ‘nodes’ (brain  
65 regions), using the reconstruction of white matter tracts as weights. This graph is then used to  
66 calculate *graph metrics*, which estimate network properties such as global integration and  
67 functional segregation (see Supplementary Material 1 for definitions, interpretations, and  
68 calculations for the graph metrics included in this review).

69 Connectome analyses have rapidly found applications in the clinical neurosciences  
70 because the balance between integration and segregation necessary to support complex function  
71 may be affected by disease or injury. In their seminal review, Griffa et al. (2013) propose that  
72 graph metrics show promise as biomarkers in neurodevelopmental disorders such as ADHD  
73 (e.g., Cao et al., 2013), neurodegenerative diseases like Alzheimer’s disease (e.g., Lo et al.,  
74 2010), and psychiatric disorders such as schizophrenia (e.g., Fornito et al., 2012). In one of the  
75 first structural GTA studies of TBI, Caeyenberghs et al. (2012) have revealed that young TBI  
76 patients have decreased connectivity degree within the brain, which correlated significantly with  
77 poor balance. Similarly, Kim et al. (2014) found that longer path length in adults with moderate-  
78 severe TBI correlated with poorer higher-order cognitive processes like executive function and  
79 verbal learning. Since then, more research has suggested that graph metrics could be  
80 ‘biomarkers’ of TBI (e.g., Hellyer et al., 2015; Yuan et al., 2015; Yuan et al., 2017b).

81 With recent growth in the use of structural GTA in all types of TBI, there is a need to  
82 conduct a meta-analytical review to probe consistent patterns of change in graph metrics to see  
83 which hold promise as biomarkers. In the study presented here, we conduct a narrative review of  
84 diffusion MRI papers comparing healthy controls (HCs) using GTA, and the first meta-analysis  
85 to date of graph metrics in TBI. Heterogeneity in patient samples is addressed using subgroup  
86 analyses. This divides up an already small body of research, and as such the results are for  
87 hypothesis generation only. It was also our aim to draw inferences from this data about how  
88 graph metrics might be used as biomarkers in TBI, and to provide a framework for hypotheses in  
89 future GTA studies.

## 90 **2. Method**

### 91 *2.1 Search and Selection Strategy*

92 A systematic literature search was conducted using Medline, CINAHL, PsycINFO, and  
93 Web of Science for all relevant articles published from 1999 until the last search date (4<sup>th</sup> of  
94 April 2018; see Figure 1 for PRISMA diagram). The search terms were [((TI OR AB) “traumatic  
95 brain injur\*” OR TBI)) AND ((TI OR AB) connectom\* OR “structural connect\*” OR “graph  
96 theor\*” OR “graph metric\*” OR “graph analys\*” OR “network analys\*”)] (see Supplementary  
97 Material 2 for Mesh headings).

98 Abstracts and titles of 247 unique papers were returned from this search. The reference  
99 lists of review papers were searched for additional studies (but none were found). After  
100 screening titles and abstracts, we excluded studies of functional MRI, electro-encephalography  
101 (EEG) or magneto-encephalography (MEG), animal models of TBI, and other causes of acquired  
102 brain injury (such as brain tumours or stroke). Also excluded were studies that did not employ a  
103 network analysis (for example, tract-based comparisons of FA), any publications that were not  
104 peer-reviewed (e.g., conference abstracts), and review papers.

105 <<Figure 1. PRISMA flow diagram of the systematic literature search>>

106 The remaining 26 articles were examined in full to assess eligibility. Studies that did not  
107 compare the structural connectomes between TBI patients and HCs, or that did not calculate  
108 graph metrics or run network-based statistics (NBS) were excluded, leaving 15 studies for  
109 inclusion in the narrative review. Of these, ten studies were included in the meta-analysis,  
110 addressing *global* graph metrics that directly compared the structural connectomes of TBI  
111 patients and HCs. The five studies not included in the meta-analysis were Fagerholm et al.  
112 (2015) and Mitra et al. (2016), both of which applied machine learning techniques; Dall’Acqua  
113 et al. (2016) which employed Network Based Statistics (NBS) for the group comparisons; and

114 finally Solmaz et al. (2017) and Caeyenberghs et al. (2013), who only investigated group  
115 differences in *regional* graph metrics.

## 116 *2.2 Quality Assessment*

117 Two authors (PI, AC) assessed the methodological quality of each study independently,  
118 using a quality checklist for diffusion MRI studies adapted from Strakowski et al. (2000). This  
119 checklist has been used to measure methodological quality of papers in previous meta-analyses  
120 on schizophrenia (e.g., Baiano et al., 2007; Shepherd et al., 2012), major depressive disorder  
121 (e.g., Jiang et al., 2017), and bipolar disorder (Strakowski et al., 2000). As shown in  
122 Supplementary Material 3, the checklist included three categories: (i) subjects (items 1-4); (ii)  
123 image acquisition methodology and analysis (items 5-10); and (iii) results and conclusions (items  
124 11-13). For each item, scores of 1, 0.5, and 0 were assigned (1 = criteria fully met; 0.5 = criteria  
125 partially met; 0 = not met). Total scores vary from 0 to 13. Currently, there are no established  
126 cut-off scores for high- and low-quality studies using this tool, however, it was decided by the  
127 research team that any study with less than half the total score would be excluded from the  
128 analysis for poor methodological quality. Disagreements between reviewers were resolved by a  
129 third review from the senior author (KC).

## 130 *2.3 Data Extraction for Quantitative Synthesis*

131 Global graph metrics estimating global integration (global efficiency, normalised path length,  
132 and characteristic path length); functional segregation (normalised clustering coefficient,  
133 transitivity, mean local efficiency, modularity); centrality, resilience (betweenness centrality,  
134 small-worldness, assortativity); and basic measures (degree, density, and strength) were  
135 extracted across studies (see Supplementary Material 1 for comprehensive definitions of these  
136 graph metrics). To calculate effect sizes, means and standard deviations were extracted from

137 published articles, supplementary materials, or via email correspondence with the authors  
138 (Caeyenberghs et al., 2014; Kim et al., 2014; van der Horn et al., 2016). In one study,  $p$ -values  
139 and  $t$ -scores were used to estimate the effect size (Hellyer et al., 2015). For longitudinal GTA  
140 studies (Yuan et al., 2017a; Yuan et al., 2017b), only the baseline ('pre-training') comparisons  
141 between TBI and HCs were included. Two papers reported TBI connectivity data in separate  
142 subgroups, one according to severity level (Königs et al., 2017), and the other by post-traumatic  
143 complaints (van der Horn et al., 2016). The latter provided pooled data for the purpose of the  
144 overall synthesis via email. For Königs et al. (2017) the averages across the TBI group were  
145 pooled for the global synthesis in Microsoft Excel (using calculations included in Supplementary  
146 Material 4). Graph metrics that were calculated at the local or nodal level were excluded (i.e.,  
147 local efficiency, eigenvector centrality, and betweenness centrality of singular nodes not  
148 averaged across the network) to constrain the scope of the analysis to network-level dysfunction.

#### 149 *2.4 Data Analysis for Quantitative Synthesis*

150 Hedge's  $g$ , the standardised mean difference score between groups, was calculated for *each*  
151 outcome variable (i.e., graph metric) using the Comprehensive Meta-Analysis software, and  
152 analysed using a random-effects model (CMA; Biostat, USA, v2.2.064). In basic terms, a  
153 separate meta-analysis for each graph metric was run, as each metric should be treated as a  
154 separate outcome measure. To calculate the overall effect sizes, mean effects of each metric were  
155 pooled across studies and weighted by sample size and the 95% confidence intervals (CI). A  
156 positive effect size indicated that the TBI group had a higher mean value of the graph metric  
157 compared with the HC group, while a negative value indicated higher mean values in the HC  
158 group. Effect sizes were regarded as small if  $g \geq 0.2$ , medium if  $g \geq 0.5$  and large if  $g \geq 0.8$  (Cohen,  
159 1988). Also, subgroup analyses on graph metrics were conducted for injury severity (mild,



160 moderate-severe), chronicity (time since injury) (acute: <6 months post injury; chronic: >6  
161 months post injury), and age at injury (paediatric : <18 years old; adult: 18-65 years old). The  
162 results of our meta-analysis should be considered as hypothesis generation only, as suggested by  
163 the Cochrane guidelines when the number of studies in the analysis is low (Sambunjak et al.,  
164 2017).

165 The  $I^2$  statistic was used to index heterogeneity in the data, i.e. the percentage of observed  
166 variability that is greater than what would be expected by chance or sampling error alone. High  
167 scores ( $I^2 >75\%$ ) suggest heterogeneity due to differences in sample demographics (Higgins et  
168 al., 2003). Low  $I^2$  scores ( $I^2 <50\%$ ) represent homogenous data, supporting a real effect between  
169 HC and TBI groups. Publication bias was assessed using Egger's test for asymmetry in a funnel  
170 plot (Egger et al., 1997).

171 Finally, *false discovery rate* (FDR) correction ( $p < 0.002$ ) was conducted for all analyses in  
172 accordance with recommendations by Wang and Ware (2013). Interdependencies between  
173 outcomes were accounted for using the Benjamini-Yekutieli procedure on the Bioinformatics  
174 toolbox in MATLAB\_R2018a (Benjamini & Yekutieli, 2001).

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### 3. Results

#### 177 3.1 Sample characteristics

178 The TBI patient pool included 429 participants, and the HC pool 306, with an age range of 8  
179 – 65 years old. Four studies included mTBI patients only, six studies included moderate-severe  
180 TBI patients only, and two studies included both severity types (see Table 1). Chronicity varied  
181 widely between studies, with TBI groups ranging from acute (e.g., within 96 hours post injury;  
182 Yuan et al., 2015) to chronic (e.g., 5.91 years post injury,  $\pm 3.1$  years; Yuan et al., 2017a). Six

183 studies recruited paediatric TBI patients, two studies included both children and young adults,  
184 and four studies recruited adult TBI patients.

185 <<Table 1. Demographics and Processing Methods for Graph Theoretical Studies of TBI>>

### 186 3.2 *Quality Assessment*

187 Table 2 summarises the quality of the 13 papers according to the diffusion MRI checklist  
188 categories, ranked according to overall score (maximum score 13). Most papers scored full  
189 points for describing parameters of the diffusion scanning sequences. Points were often deducted  
190 for poor description of graph metric calculations and failing to correct for multiple comparisons.  
191 The ‘subjects’ category of the checklist had the highest average score (3.6/4, 90.5%), followed  
192 by ‘methodology’ (5.4/6, 89.7%), and ‘results/conclusions’ (2.5/3, 83.3%). Overall, the total  
193 quality score was high, and varied from 9 to 12.5 points out of a possible 13 (average score:  
194 11.5/13, 88.5%). The study of Verhelst et al. (2018) had the highest methodological quality.  
195 There was no significant effect of publication bias (Egger’s regression intercept=1.81, CI: [-1.94,  
196 5.57],  $p=0.34$ ), and all studies met the benchmark for inclusion in the meta-analysis, showing  
197 that the published studies are a good representation of available evidence.

198 <<Table 2 Quality Assessment Results>>

### 199 3.3 *Meta-Analysis*

200 Table 3 summarises the differences in global graph metrics between TBI and HC cohorts  
201 across studies. For each graph metric, the direction of significant group differences between TBI  
202 and HCs was the same across studies, with the exception of small-worldness and normalised path  
203 length. The overall effect sizes for normalised clustering coefficient, global efficiency, density,  
204 and characteristic path length were found to be significant ( $p<0.05$ ), with moderate to large

205 Hedge's  $g$  effect sizes ( $g > 0.5$ ) (see Figure 2, and Supplementary Material 5 for statistics).  
206 However, only normalised clustering coefficient and characteristic path length remained  
207 significant following FDR correction ( $p < 0.002$ ). The subgroup analyses revealed longer  
208 normalised path length in acute/mild patients; higher small-worldness in chronic patients; higher  
209 small-worldness in paediatric TBI patients; and higher normalised clustering coefficient in  
210 paediatric TBI patients compared to HCs (FDR corrected,  $p < 0.001$ , see Table 4). In the next  
211 paragraphs, we will present the results of key overall effects and subgroup analyses for each  
212 graph metric that was significant after FDR correction.

213 <<Table 3. Graph Metrics in Patients with TBI compared to Healthy Controls>>

214 <<Figure 2. Inverted forest plot of the overall effect sizes for each graph metric>>

215 <<Table 4. Results of the Subgroup Analyses>>

### 216 *3.3.1 Global Integration*

217 Four of the ten studies investigated characteristic path length. (Caeyenberghs et al., 2014;  
218 Hellyer et al., 2015; Kim et al., 2014; Königs et al., 2017). Of the 142 patients in this analysis,  
219 114 were moderate to severe; 63 acute patients were on average 5.5 months post-injury, while 79  
220 chronic patients were on average 3.5 years post-injury; and 101 were adults (average age: ~26.9  
221 years) and 41 were paediatric (average age: ~10.5 years) at injury. Across this entire cohort,  
222 characteristic path length was longer in the TBI patients compared with HCs ( $g = 0.514$ ,  $p =$   
223  $0.002$ ,  $I^2 = 28.601\%$ ). The heterogeneity value of this graph metric was low, indicating that the  
224 dataset was homogenous.

225 Six studies investigated normalized path length (Caeyenberghs et al., 2012;  
226 Caeyenberghs et al., 2014; Verhelst et al., 2018; Yuan et al., 2017a; Yuan et al., 2015; Yuan et  
227 al., 2017b) with no overall group effect ( $g = 0.815$ ,  $p = 0.129$ ,  $I^2 = 92.1\%$ ). Of the 112 patients in  
228 this analysis, 67 were moderate to severe; 45 acute patients were between 96 hours and 4 months  
229 post-injury, while 67 chronic patients were on average 4 years post-injury; and 21 were adults  
230 (average age: ~21.3 years) and 91 were paediatric (average age: ~12.1 years) at injury.  
231 Subgroup analysis revealed that the acute/mild TBI group showed significantly increased  
232 normalised path length compared with HCs ( $g = 0.965$ ,  $p < 0.001$ ,  $I^2 = 0.0\%$ ), with a decreased  
233 heterogeneity value. The effect size for the chronic/moderate-severe group was not significant.

### 234 3.3.2 Functional segregation

235 Seven studies calculated normalized clustering coefficient (Caeyenberghs et al., 2012;  
236 Caeyenberghs et al., 2014; van der Horn et al., 2016; Verhelst et al., 2018; Yuan et al., 2017a;  
237 Yuan et al., 2015; Yuan et al., 2017b). Of the 165 patients in this analysis, 67 were moderate to  
238 severe; 98 acute patients were between 96 hours and 4 months post-injury, while 67 chronic  
239 patients were on average 4 years post-injury; and 74 were adults (average age: ~27.4 years) and  
240 91 were paediatric (average age: ~12.1 years) at injury. Normalised clustering coefficient was  
241 higher in TBI patients in the overall meta-analysis ( $g = 1.445$ ,  $p = 0.002$ ,  $I^2 = 91.484$ ). In the  
242 chronicity and severity subgroup-analysis, the effect remained significant in the  
243 chronic/moderate-severe patients only (chronic/moderate-severe:  $g = 1.924$ ,  $p = 0.014$ ,  $I^2 = 92.440\%$ ).  
244 However, this effect retained a high heterogeneity value. Similarly in the age at injury subgroup  
245 analysis, normalised clustering coefficient was significantly higher in the paediatric TBI patients  
246 than HCs ( $g = 2.00$ ,  $p = 0.001$ ,  $I^2 = 89.82$ ). This effect was not observed for adult TBI patients.

247 However, grouping by age at injury only lowered the observed heterogeneity in normalised  
248 clustering coefficient by ~2%.

### 249 3.3.3 Small-Worldness

250 Six studies reported on small-worldness differences between TBI and HCs (Caeyenberghs et  
251 al., 2012; Caeyenberghs et al., 2014; Hellyer et al., 2015; Yuan et al., 2017a; Yuan et al., 2015;  
252 Yuan et al., 2017b), with no significant effect size overall; however, a trend was evident for  
253 larger values in TBI patients ( $g = 0.794$ ,  $p = 0.06$ ,  $I^2 = 89.736\%$ ). Of the 158 patients in this  
254 analysis, 105 were moderate to severe; 108 acute patients were between 96 hours and 5.5 months  
255 post-injury, while 50 chronic patients were on average 4.6 years post-injury; and 84 were adults  
256 (average age: ~26.6 years) and 74 were paediatric (average age: ~11.8 years) at injury.  
257 Subgroup analysis showed a significant effect size for chronic patients only, with increased  
258 small-worldness in chronic TBI patients compared with HCs ( $g = 0.950$ ,  $p = .001$ ,  $I^2 = 39.536\%$ ).  
259 Grouping by chronicity also greatly reduced heterogeneity in the chronic group. Subgroup  
260 analysis by severity revealed larger small worldness values for the mild group ( $g = 1.309$ ,  $p = .020$ ,  
261  $I^2 = 81.922\%$ ); however, heterogeneity remained high and did not survive FDR correction.  
262 Finally, small-worldness was significantly higher in the paediatric TBI patients (but not adult  
263 TBI patients) compared to HCs ( $g = 1.25$ ,  $p < 0.001$ ,  $I^2 = 56.949$ ). Grouping by age at injury  
264 reduced the heterogeneity observed in small-worldness, meaning that age at injury could be  
265 explaining some of the differences in small-worldness between TBI patients and HCs.

## 266 4. Discussion

267 Our study is the first meta-analysis to assess the consistency of recent graph theoretical  
268 studies of TBI. The overall quality of the papers was high, and all met the benchmark for

269 inclusion in the review. Findings suggest that *normalized clustering coefficient* and  
270 *characteristic path length* may be sensitive diagnostic biomarkers to distinguish TBI patients  
271 from HCs, with the former particularly high in chronic/moderate-severe and paediatric TBI  
272 patients after subgroup analyses. Furthermore, we suggest that values of normalised path length  
273 may be increased in acute/mild patients, and small worldness may be higher in chronic and  
274 paediatric TBI patients. In the following sections we will examine the use of graph metrics from  
275 a critical view. Specifically, we will discuss the following topics: (4.1) evidence that the TBI  
276 network is closer to a regular lattice structure than HCs, and (4.2) the use of graph metrics as  
277 diagnostic and prognostic biomarkers in longitudinal studies. In (4.3) we will also point out a  
278 number of methodological issues and provide recommendations for the future study of structural  
279 connectomics in TBI. Finally, in (4.4) we will address any limitations of this pooled analysis,  
280 including heterogeneity in patient samples and parcellation schemes.

#### 281 *4.1 Towards a regular network structure in TBI patients*

282         The hypotheses presented in the research papers reflect the exploratory nature of GTA in  
283 TBI studies. Clear rationales and *a priori* hypotheses regarding the specific choice of graph  
284 metrics (together with the expected direction of effect) was omitted in many of the studies  
285 analysed. For example, Yuan et al. (2017b) ambiguously predicted that metrics would be  
286 “*abnormal* at baseline but would *normalise* after training”. Only Yuan et al. (2015) and Königs  
287 et al. (2017) justified their choice of each graph metric. While exploratory research is necessary,  
288 a clear rationale concerning the selection of graph metrics will advance theoretical reasoning in  
289 the field. Furthermore, having *a priori* hypotheses about the expected direction of effect will  
290 minimise multiple comparisons, thereby reducing chance findings that inflate the false positive

291 rate. The findings from our meta-analysis, outlined in the following paragraphs, can serve as a  
292 guide in the development of hypotheses for the next generation of GTA studies in TBI.

293 Small-worldness is the ratio of normalised clustering coefficient to normalised path  
294 length, and represents the balance between segregation for local specialization and global  
295 integration (Watts & Strogatz, 1998). While all studies found that the TBI connectome is still a  
296 small-world network, there was evidence of a shift towards a regular lattice structure. Small-  
297 worldness values were significantly higher for TBI patients greater than 6 months post injury,  
298 and for children with TBI. These results suggest a shift in network structure, which is probably  
299 due to a secondary process of neurodegeneration and/or is specific to those patients injured  
300 during childhood. However, further research is needed to evaluate the neurobiological  
301 mechanisms underlying increases in small-worldness. Yuan et al. (2015) and Yuan et al. (2017a)  
302 suggested that higher small-worldness is primarily driven by an increase in local clustering. Still,  
303 changes in small-worldness alone do not provide insight into the nature of the group differences.  
304 Instead, researchers could focus on more specific metrics that can differentiate between  
305 alterations in segregation and integration (Fornito et al., 2013; Papo et al., 2016), including  
306 measures of clustering and path length as described next.

307 In line with the observed shift towards a regular network, our review revealed that  
308 *normalised clustering coefficient* was significantly higher in the TBI group compared to HCs.  
309 This result indicates that TBI patients have more ‘closed triangles’ in their network graph  
310 compared to the controls, denoting greater functional specialisation. We also observed that this  
311 effect remained significant in the paediatric group but not the adult group. Yuan et al. (2015)  
312 suggested that this finding in paediatric TBI patients reflected an adaptive response to the injury,  
313 whereby local connections are increased because they are less vulnerable to damage than long-

314 range connections. However, we argue that this is a costly adaptation, as it would increase the  
315 number of steps needed for information to travel between any two regions (Fornito et al., 2016;  
316 Sporns, 2011). In fact, our meta-analysis also showed that *characteristic path length* was  
317 significantly longer in the TBI population compared to the HCs, meaning there are a greater  
318 number of steps between any two nodes on average in the TBI network than in the HC network.  
319 Furthermore, the subgroup analysis demonstrated that *normalised path length* in the acute mild  
320 TBI group (but not the chronic moderate-severe group) was significantly higher than HCs.  
321 However due to the paucity of data available, it was impossible to determine whether this effect  
322 was driven by chronicity or severity. Despite the lack of data, our findings support the idea that  
323 the TBI network topology departs from the economical random-graph (Sporns, 2011).

#### 324 *4.2 Use of graph metrics as diagnostic and prognostic biomarkers*

325         The effects described in section 4.1 support the use of normalised clustering coefficient  
326 and characteristic path length as *diagnostic biomarkers* to identify group differences between  
327 TBI patients and HCs. Graph metrics can also be used to detect the presence or absence of  
328 diffuse axonal injuries (DAI) within TBI patients. Two papers included in the review (Fagerholm  
329 et al., 2015; Mitra et al., 2016) employed machine learning methods on graph metrics to classify  
330 patients. Fagerholm and colleagues were able to classify the presence of DAI in TBI patients  
331 with a high accuracy rate of 93.4%, and found that betweenness centrality had the highest  
332 ‘feature importance’ when differentiating between patients with microbleeds and HCs. Using a  
333 similar machine learning technique, Mitra et al. found that connectivity strength could  
334 differentiate mild TBI patients with DAI from HCs with an accuracy rate of 68.16%. These are  
335 very promising techniques that clearly demonstrate the use of graph metrics as diagnostic  
336 biomarkers.



337 Another important aspect of evaluating a diagnostic biomarker is the association of the  
338 metric with behavioural/clinical outcomes, which was done in all studies apart from one (Hellyer  
339 et al., 2015). For example, longer characteristic path length correlated with worse performance  
340 on verbal learning task as well as executive dysfunction in moderate-severe TBI patients (Kim et  
341 al., 2014). Longer characteristic path length also coincided with lower intelligence scores and  
342 shorter working memory span in moderate-severe TBI patients (Königs et al., 2017). Lower  
343 normalised clustering coefficient was found to be associated with slower processing speed in  
344 mild TBI patients (van der Horn et al., 2016). These significant correlations highlight the  
345 potential of normalised clustering coefficient and characteristic path length as biomarkers of  
346 behavioural deficits following TBI. However, reminding us of the preliminary nature of this  
347 work, a number of studies did not correct for multiple comparisons when running correlations  
348 between graph metrics and behavioural tests (Kim et al., 2014; Yaun et al., 2017a). While  
349 uncorrected thresholds can be useful for exploratory research, correction for multiple  
350 comparisons would strengthen the validity of these findings. Finally, comparison between  
351 studies is problematic because different outcome measures were used across studies. We  
352 recommend the use of a core set of behavioural tests in the future (e.g., Wefel et al., 2011).

353 Finally, we wanted to explore whether graph metrics can be used as *prognostic*  
354 biomarkers to predict treatment response. Longitudinal studies are necessary to investigate which  
355 graph metrics change in response to training. Only two GTA studies (by the same group, Yuan et  
356 al., 2017a; Yuan et al., 2017b) so far have conducted longitudinal training studies. Yuan et al.  
357 (2017a) found that normalised clustering-coefficient and small-worldness values decreased  
358 following 10 weeks of attention and executive function training in TBI patients, but remained the  
359 same in the HCs. In an aerobic training study, Yuan et al. (2017b) found that improved Post-

360 Concussion Symptom Inventory scores following 4 – 16 weeks of training correlated with  
361 increased global efficiency and lower normalised path length. However, this study did not  
362 investigate the interaction effect between group and time directly. Overall, there is some  
363 evidence that network measures can be used as prognostic biomarkers, but further longitudinal  
364 analyses are needed to investigate the predictive value of graph metrics.

#### 365 *4.3 Methodological considerations and further recommendations*

366 As a tentative conclusion, our meta-analysis showed that normalized clustering  
367 coefficient and characteristic path length are potential diagnostic biomarkers that may be  
368 sensitive to group differences between TBI and controls. However, GTA is a mathematical  
369 framework that has only recently been applied in neuroscience (for a critical review, see Fornito  
370 et al., 2013), and the underlying biological mechanism of change (e.g., increase in axon density,  
371 diameter, myelination, sprouting of synapses) is so far unknown. Due to inherent limitations in  
372 tractography, we do not know yet whether graph metrics directly reflect white matter integrity  
373 (e.g., Jones et al., 2013). Therefore, it is important to refrain from diagnosing ‘abnormal’ graph  
374 metrics, when comparing TBI patients to HCs (e.g., Yuan et al., 2017b), until we know the  
375 biological mechanisms underpinning graph metrics. Validated neuro-psychometric testing could  
376 couple structural connectome measures such as graph metrics (and other diffusion-based  
377 measures) to multimodal data with known information processing properties. Until then,  
378 structural graph metrics represent the necessary but insufficient properties of the network to  
379 function (Sporns, 2012). However, we can get a better understanding if we first obtain reliable  
380 patterns of brain connectivity.

381           There are methodological challenges associated with investigating graph metrics in  
382 patients with TBI. These include applying appropriate MRI acquisition and preprocessing  
383 techniques, connectome construction, and specifying edge weights (see Table 1 for a summary of  
384 the methods used in the studies in this review). Future research should (a) utilise advanced  
385 diffusion sequences (e.g., multishell, not used by any studies in the review) with accelerated  
386 acquisition speed to accommodate for non-compliance due to poor concentration (e.g.,  
387 multiband/compressive sensing); (b) employ robust estimation approaches for diffusion MRI  
388 metrics (e.g., Slicewise OutLier Detection (SOLID; Sairanen et al., 2018)); and (c) apply a  
389 model that can resolve crossing fibre orientations (e.g., constrained spherical deconvolution, only  
390 used by two papers in the current review). Furthermore, although connection density has a  
391 noticeable impact on graph metrics (van Wijk et al., 2010), only six of the thirteen studies in the  
392 quality assessment accounted for differences in network density (as suggested by Bullmore &  
393 Basset, 2011) when comparing structural networks of TBI and HCs (Caeyenberghs et al., 2012;  
394 Hellyer et al., 2015; Königs et al., 2017; Solmaz et al., 2017; van der Horn et al., 2016; Yuan et  
395 al., 2015). Similarly, researchers should consider using multiple edge weighting and parcellation  
396 schemes to examine the robustness of data (Qi et al., 2015; Sotiropoulos & Zalesky, 2017), as  
397 was done by Caeyenberghs et al. (2012, 2013, 2014), Fagerholm et al. (2015), and Königs et al.  
398 (2017). Finally, future studies should employ advanced measures of white matter such as fibre  
399 density and cross section (Raffelt et al., 2017) as edge weights, because FA (used by three  
400 studies) and number of ‘streamlines’ (used by eight studies) lack the microstructural specificity  
401 to fully characterise the integrity of the structural network. In summary, by using more advanced  
402 MRI acquisition and pre-processing techniques we can get closer to an understanding of the  
403 biological underpinnings of the TBI structural connectome.

#### 404 4.4 Limitations of the pooled analysis

##### 405 4.4.1 Heterogeneity in parcellation schemes

406 One limitation of combining different graph analyses is that it inevitably requires pooling  
407 data obtained with different parcellation schemes. Differences in the way the cortex is  
408 parcellated can significantly impact the results of GTA (Zalesky et al., 2010). As shown in Table  
409 1, five different parcellation schemes (e.g., the Desikan atlas from Freesurfer and the Automated  
410 Anatomical Labeling atlas) were used across the papers included in the meta-analysis, each with  
411 a different number of regions of interest or ‘nodes’ (range: 82-164). Parcellation schemes with  
412 higher resolution (i.e., more nodes) will demonstrate gradual increases in normalised path length  
413 and reductions in normalised clustering coefficient (Bassett et al., 2011), while measures of  
414 network organisation (e.g., small-worldness) will remain largely the same (Qi, Meesters,  
415 Nicolay, ter Haar Romeny, & Ossenblok, 2015). However, because whole brain node templates  
416 in this current study were of similar spatial scales, impact on pooled graph metrics should be  
417 negligible (Zalesky et al., 2010), and it is therefore likely that this effect is small and does not  
418 detract from the overall findings.

##### 419 4.4.2 Heterogeneity in the TBI samples

420 Patients with TBI are diverse, and several clinical and demographic factors (such as  
421 severity, chronicity, and age at injury) will impact the comparability of patient cohorts across  
422 studies. In the present meta-analysis, we attempted to address the issue of heterogeneity in our  
423 pooled TBI population by conducting subgroup analyses. However, the heterogeneity values  
424 remained above 75% for the majority of the subgroup analyses, indicating that results may still  
425 have been driven by differences in sample demographics (Higgins et al., 2003). This is not

426 surprising given the diversity present in the structure of an injured brain, which may include  
427 focal lesions, diffuse axonal injury, or both. There were also limited studies that could be  
428 included in this review, making some subgroup analyses hard to interpret. For example, there  
429 were no studies of moderate-severe TBI patients in the acute phase, or mild TBI patients in the  
430 chronic phase that could be included in the normalised path length subgroup analyses (see Table  
431 4). Therefore it is impossible to determine whether normalised path length was increased in the  
432 acute/mild group due to the time since injury, or the severity of the injury. Overall, this meta-  
433 analysis allows us to see universal trends that are present in the structural connectome of TBI  
434 patients; however more research is needed that spans across all TBI subgroups, so that future  
435 pooled analyses can better distinguish between all TBI populations.

## 436 **5.0 Conclusion**

437 Despite the complexity of applying GTA to the heterogeneous TBI population, our meta-  
438 analysis of structural connectivity studies revealed that normalised clustering coefficient and  
439 characteristic path length can be regarded as diagnostic biomarkers of TBI. These findings  
440 provide an evidentiary framework for future research. The emerging evidence suggests that  
441 average path length and clustering is increased in TBI patients, with the overall network more  
442 closely resembling a regular lattice. Using graph metrics we are able to differentiate between  
443 TBI population and healthy controls on the one hand, and the presence/absence of DAI on the  
444 other hand. Also, there is preliminary evidence that graph metrics predict future response to  
445 training. Despite the promising results, the biological mechanisms underlying alterations in  
446 graph metrics is unclear. Future research should employ advanced diffusion MRI tools and  
447 obtain biologically-validated measures of structural connectivity in longitudinal studies.

448

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456

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458

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460 Supplementary material related to this article can be found, in the online version, at doi:

461

462

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683

#### 684 **Figure Captions**

685 *Figure 1.* PRISMA flow diagram of the systematic literature search.

686 *Figure 2.* Inverted forest plot of the overall effect sizes and 95% confidence intervals for each  
687 graph metric, including heterogeneity values ( $I^2$ ). The size of the markers on the  $I^2$  graph  
688 represent the number of studies in each pooled analysis (range:  $n=1$  to  $n=7$ ), with larger circles  
689 indicating a larger  $n$ .

690

691 **Table 1.** Demographics and Processing Methods for Graph Theoretical Studies of Traumatic  
692 Brain Injury

693 **Table 2.** Quality Assessment Results for Graph Theoretical Studies of Traumatic Brain Injury

694 **Table 3.** Graph Metrics in Patients with Traumatic Brain Injury compared to Healthy Controls.

695 **Table 4.** Results of the Subgroup Analyses