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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 (4th 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, ± 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

459 **Appendix A. Supplementary data**

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