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

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1. Introduction

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.

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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176　　　　　　　　　　　　　　　　　**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: $g = 1.924$ $p = .014$, $I^2 = 92.440\%$).

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
463   **References**
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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