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

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

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

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

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

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

2. Method

2.1 Search and Selection Strategy

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

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

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

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

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

2.2 Quality Assessment

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

2.3 Data Extraction for Quantitative Synthesis

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

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

2.4 Data Analysis for Quantitative Synthesis

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

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

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

Finally, *false discovery rate* (FDR) correction (p<0.002) was conducted for all analyses in accordance with recommendations by Wang and Ware (2013). Interdependencies between outcomes were accounted for using the Benjamini-Yekutieli procedure on the Bioinformatics toolbox in MATLAB_R2018a (Benjamini & Yekutieli, 2001).

3. Results

3.1 Sample characteristics

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

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

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

3.2 Quality Assessment

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

<<Table 2 Quality Assessment Results>>

3.3 Meta-Analysis

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

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

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

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

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

3.3.1 Global Integration

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

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

3.3.2 Functional segregation

Seven studies calculated normalized clustering coefficient (Caeyenberghs et al., 2012; Caeyenberghs et al., 2014; van der Horn et al., 2016; Verhelst et al., 2018; Yuan et al., 2017a; Yuan et al., 2015; Yuan et al., 2017b). Of the 165 patients in this analysis, 67 were moderate to severe; 98 acute patients were between 96 hours and 4 months post-injury, while 67 chronic patients were on average 4 years post-injury; and 74 were adults (average age: ~27.4 years) and 91 were paediatric (average age: ~12.1 years) at injury. Normalised clustering coefficient was higher in TBI patients in the overall meta-analysis (g =1.445, p =0.002, I^2 =91.484). In the chronicity and severity subgroup-analysis, the effect remained significant in the chronic/moderate-severe patients only (chronic/moderate-severe: g =1.924 p=.014, I^2 =92.440%). However, this effect retained a high heterogeneity value. Similarly in the age at injury subgroup analysis, normalised clustering coefficient was significantly higher in the paediatric TBI patients than HCs (g = 2.00, p = 0.001, I^2 = 89.82). This effect was not observed for adult TBI patients.

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

3.3.3 Small-Worldness

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

4. Discussion

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

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

4.1 Towards a regular network structure in TBI patients

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

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

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

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

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

4.2 Use of graph metrics as diagnostic and prognostic biomarkers

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

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

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

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

4.3 Methodological considerations and further recommendations

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

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

4.4 Limitations of the pooled analysis

4.4.1 Heterogeneity in parcellation schemes

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

4.4.2 Heterogeneity in the TBI samples

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

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

5.0 Conclusion

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

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Appendix A. Supplementary data

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

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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