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Executive function mediates the prospective association between neurostructural differences within the central executive network and anti-social behavior after childhood traumatic brain injury

Running head: Neurostructural Correlates of Anti-Social Behavior in Childhood TBI

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Background: Despite increasing evidence of a link between early life brain injury and anti-social behavior, very few studies have assessed factors that explain this association in children with traumatic brain injury (TBI). One hypothesis suggests that childhood TBI elevates risk for anti-social behavior via disruption to anatomically distributed neural networks implicated in executive functioning (EF). In this longitudinal prospective study, we employed high-resolution structural neuroimaging to (i) evaluate the impact of childhood TBI on regional morphometry of the central executive network (CEN) and (ii) evaluate the prediction that lower EF mediates the prospective relationship between structural differences within the CEN and post-injury anti-social behaviors. **Methods:** This study involved 155 children, including 112 consecutively recruited, hospital confirmed cases of mild-severe TBI and 43 typically developing control (TDC) children. T1-weighted brain magnetic resonance imaging (MRI) sequences were acquired sub-acutely in a subset of 137 children [TBI: *n* =103; TDC: *n* = 34]. All participants were evaluated using direct assessment of EF 6-months post-injury, and parents provided ratings of anti-social behavior 12-months post-injury. **Results:** Severe TBI was associated with post-injury volumetric differences within the CEN and its putative hub regions. When compared with TD controls, the TBI group had significantly worse EF, which was associated with more frequent anti-social behaviors and abnormal CEN morphometry. Mediation analysis indicated that reduced EF mediated the prospective association between post-injury volumetric differences within the CEN and more frequent anti-social behavior. **Conclusions:** Our longitudinal prospective findings suggest that detection of neurostructural abnormalities within the CEN may aid in the early identification of children at elevated risk for post-injury executive dysfunction, which may in turn contribute to chronic anti-social behaviors after early life brain injury. Findings underscore the potential value of early surveillance and preventive measures for children presenting with neurostructural and/or neurocognitive risk factors. **Keywords:** Anti-social behavior; aggression; childhood traumatic brain injury; structural MRI; longitudinal design.

Introduction

A growing body of research highlights a disproportionately high prevalence of traumatic brain injury (TBI) among youth and adults with a history of violent offenses (Williams et al., 2018). In one longitudinal study, hospital-recorded TBI was associated with a 3-fold increased risk of conviction for violent offences relative to general population controls and a two-fold increased risk relative to non-exposed siblings (Fazel, Lichtenstein, Grann, & Långström, 2011). Although studies of this nature seldom indicate whether brain injury is sustained in childhood or adulthood, an increasing body of evidence suggests that childhood TBI may elevate risk for a range of anti-social behaviors, including violence, interpersonal aggression, rule-breaking and conduct problems (Bellesi, Barker, Brown, & Valmaggia, 2019; Li & Liu, 2013; McKinlay, Corrigan, Horwood, & Fergusson, 2014). Despite the significant societal, public health, and custodial implications of these data (Williams et al., 2018), the mechanisms that underpin the association between TBI and subsequent anti-social behavior are poorly understood, particularly in childhood brain injury populations.

The developmental taxonomy theory of anti-social behavior provides a useful framework for conceptualizing etiological risk factors that may underlie the association between early life brain injury and anti-social behavior (Moffitt, 1993; Moffitt, 2018). This model distinguishes between individuals with adolescent-limited anti-social behavior occurring only in adolescence and life-course persistent anti-social behavior, which emerges in childhood and persists across the lifespan. The model postulates that abnormal brain and neuropsychological development are fundamental in the etiology of life-course persistent but not adolescent-limited anti-social behavior (Carlisi et al., 2020; Moffitt, 1993). Specifically, individuals on the life-course-persistent trajectory are likely to exhibit neurostructural and neuropsychological vulnerabilities that are often characteristic of individuals with common childhood neuro-disabilities such as TBI (Ryan, Catroppa, et al., 2016), and may play a key role in the onset and maintenance of persistent behavior problems (Moffitt, 2018). This theory is supported by evidence showing that life-course persistent anti-social behavior typically begins in childhood and is linked with the presence of one or more neurocognitive

impairments, particularly in the domain of executive function (Moffitt, 2018; Moffitt & Caspi, 2001; Raine et al., 2005). However, to our knowledge, no study to date has assessed the relative contribution of neurostructural and neurocognitive risk factors to prediction of anti-social behavior after childhood TBI. Given the well documented link between childhood TBI and elevated rates of anti-social behavior such as rule breaking and aggression (Li & Liu, 2013; Raj et al., 2013; Schwartz et al., 2003), further research is needed to evaluate whether cognitive dysfunction, including impairments in EF, may mediate the association between the brain structure differences and post-injury anti-social behavior in these children.

The ability to engage in context appropriate behavior is dependent on executive functions; a multi-dimensional construct that includes skills involved in the planning and execution of goal directed behavior (Anderson, 2002; Miller & Wallis, 2009). EF shows rapid maturation from infancy to late childhood, and through adolescence and early adulthood (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001; Prencipe et al., 2011), corresponding to the extended structural and functional development of the central executive network (CEN), including the dorsolateral prefrontal cortex (dlPFC), posterior parietal cortex (PPC), thalamus and dorsal caudate (Menon, 2011; Seeley et al., 2007). Functional and structural abnormalities of the CEN and other higher-order cognitive control networks have been documented in children and adolescents with disruptive behavior disorders, including conduct disorder (Huebner et al., 2008; Lu, Zhou, Wang, Xiang, & Yuan, 2017; Zhang et al., 2018) and oppositional-defiant disorder (Alegria, Radua, & Rubia, 2016). In contrast, the role of the CEN in the behavioral sequalae of childhood acquired brain disorders including TBI is poorly understood. For instance, although executive skills subsumed by the CEN are vulnerable to disruption from childhood TBI (Levin & Hanten, 2005) and post injury executive dysfunction is correlated with maladaptive behavior after childhood TBI (Muscara, Catroppa, & Anderson, 2008; Tonks, Huw Williams, Yates, & Slater, 2011), the prognostic significance of post-injury structural differences within the CEN for anti-social behavior is poorly understood.

High resolution structural neuroimaging studies have consistently shown that childhood TBI is associated with widespread disruption to large scale neuroanatomical networks within the first year of injury and beyond (Beauchamp et al., 2011; Bigler et al., 2010; Fearing et al., 2008; Levin et al., 2008; Wilde et al., 2005). Of these reports, several studies show that children with moderate to severe injury demonstrate widespread abnormalities in white matter organization, including disruption to regions implicated in executive function (Levin et al., 2008; Wozniak et al., 2007). Similarly, Dennis and

colleagues (2013) acquired structural MRI at least 1-year post-injury and found that children with severe TBI displayed regional volumetric differences within several large-scale functional brain networks, including the CEN. Despite the likely functional consequences of post-injury volumetric differences within brain networks that support EF, existing studies of brain-behavior relationships in childhood TBI have relied almost exclusively on cross-sectional volumetric MRI data acquired during the chronic stage of injury. As such, it remains unclear whether early sub-acute differences in regional brain morphometry may prospectively predict maladaptive behaviors in the childhood TBI population.

One hypothesis is that post-injury volumetric differences within the CEN increase risk for post-injury behavior problems via executive dysfunction. This theory receives support from previous work showing that neurostructural differences in children with TBI relate to poorer performance on measures of EF, including verbal working memory and cognitive flexibility (Kurowski et al., 2009; Wozniak et al., 2007) – tasks of which are also shown to correlate with post-injury behavioral problems in a small number of cross sectional studies (Muscara et al., 2008; Schwartz et al., 2003). In contrast, other cross-sectional studies have revealed no significant relationships between post-injury behavioural problems and performance-based measures of EF, including cognitive flexibility, abstract reasoning, and response inhibition (Robinson et al., 2014; Ryan et al., 2015). However, the strength of evidence from these studies is weakened by substantial methodological weaknesses, including reliance on very small samples and/or retrospective recruitment methods that cannot account for pre-morbid characteristics and contribute to substantial between-subject variation in time post-injury. Despite the limitations and inconsistencies of the extant literature, the weight of available evidence suggests that EF might mediate the association between regional morphometry of the CEN and anti-social behavior.

To address these substantial gaps in the extant literature, this longitudinal prospective study aimed to (i) evaluate the impact of childhood TBI on sub-acute regional morphometry of the CEN, executive functioning, and anti-social behavior, relative to a typically developing control group; and, (ii) prospectively evaluate the role of sub-acute CEN morphometry and EF in predicting anti-social behavior. In modelling factors that might help explain the association between childhood TBI and anti-social behavior, we aimed to determine whether lower EF at 6-months post-injury is a mediator of the prospective association between brain structure differences within the CEN and anti-social behavior at 12-months post-injury.

In this study, we distinguish between criminal convictions (i.e. a proxy for extremely severe anti-social behavior) versus anti-social behaviors assessed using well validated and respected measures of children's aggression and rule breaking behavior, the latter which formed the focus of the current study. We expected group differences in sub-acute regional brain morphometry within the CEN, such that children with severe TBI would show diminished network volume relative to typically developing controls. We also expected that children with TBI would show significantly poorer EF and more frequent anti-social behavior, and that lower EF would mediate the prospective relationship between brain volumetric differences within the CEN and chronic anti-social behavior.

Methods

Participants

Participants included children with TBI who were enrolled in the study at the time of injury and represented consecutive admissions to The Royal Children's Hospital (RCH), Melbourne, Australia between 2007 and 2010. All children were aged between 5.3 and 15.4 years at time of recruitment. Typically developing control (TDC) children were recruited from the community, through local schools chosen to provide a range of socio-economic backgrounds.

For the TBI group, inclusion criteria were: (i) documented evidence of closed head injury, including a period of altered consciousness or presence of at least two post-concussive symptoms; (ii) medical records sufficiently detailed to determine injury severity, including the Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974), and neurological and radiological findings; and, (iii) child and at least one parent fluent in English. Using emergency department (ED) records and information obtained from in-house, non-standardized parent interview form administered upon study enrolment, the following exclusion criteria were applied: (i) non-accidental head injuries; (ii) diagnosed congenital, neurological, developmental, or psychiatric condition; (iii) prior intervention for social impairment; and, (iv) previous TBI based on parent report.

One-hundred and twelve eligible children with TBI were enrolled in the study and were classified as: (i) mild TBI (n = 57): Glasgow Coma Score (GCS) 13-15, no evidence of mass lesion on CT or clinical MRI and no neurologic deficits; (ii) complicated mild TBI (n =

14): GCS 13-15, evidence of mass lesion on CT or clinical MRI; (iii) moderate TBI (n = 26): GCS 9-12, and/or mass lesion or other evidence of specific injury on CT/MRI, and/or neurological impairment; (iv) severe TBI (n =15): GCS 3-8, and/or mass lesion or other evidence of specific injury on CT/MRI, and/or neurological impairment. The TDC group included 43 children group-matched to the TBI sample on age, sex, and socio-economic status (SES). SES was determined using the Australian Socioeconomic Index 2006 (AUSE106), which translates data coded in accordance with the official occupational classifications of the Australian and New Zealand Standard Classification of Occupations (ANZSCO) into occupational status. This information was provided by the primary caregiver. The AUSE106 converts scores for ANZSCO major, sub-major, minor, and unit group codes into a continuous scale, ranging from 0 (laborers) to 100 (medical practitioners).

Table 1 displays participant demographic information, including age, sex, and socioeconomic status according to the Australian and New Zealand System for Classification of Occupations (McMillan, Beavis, & Jones, 2009). The sample was predominantly Caucasian (95%). The remaining portion of the sample identified as Asian (3.6%), African (0.7%) and Latino (0.7%). As shown in Table 1, there were no statistically significant group differences on any of the demographic variables. Since group differences for SES were approaching statistical significance (p = .050; see Table 1), SES was included as a covariate in all analyses involving the primary outcome measures.

As shown in Table 2, the injury severity groups showed expected differences for lowest GCS, and for surgical involvement, such that the moderate and severe TBI groups were significantly more likely to require these interventions. Cause of injury was predominately falls or blows for the mild, complicated-mild, and moderate TBI groups. For the severe TBI group, falls or blows, and motor vehicle accidents (MVAs) were equally common.

Pre-injury measures

At the time of injury, parents provided retrospective ratings of their child's pre-injury adaptive functioning in the weeks preceding injury using the Adaptive Behavior Assessment System-II (Harrison & Oakland, 2003), a parent questionnaire that examines functional skills necessary for daily living. The Global Adaptive Composite (M = 100, SD = 15) is reported in Table 1. No significant group differences were identified when estimates of pre-injury functioning were compared with ratings provided by TDC parents who completed these same questionnaires about their child at initial recruitment. Similarly, the TBI groups did not

significantly differ from the TDC group on pre-injury externalizing symptoms or pre-injury internalizing symptoms on the Child Behavior Check List (Table 1).

Insert Tables 1 & 2 About Here

Executive function measures

Executive functions were assessed at 6-months post-injury using selected subtests from the Test of Everyday Attention for Children (TEA-Ch) and the Wechsler Intelligence Scale for Children- Fourth Edition (WISC-IV). The TEA-Ch 'Walk/Don't Walk' subtest was used to assess inhibitory control and requires a child to mark footprints on a path for a ''go'' tone and inhibit marking for a ''stop'' tone. The TEA-Ch Creature Counting subtest was administered to assess cognitive flexibility and requires a child to count creatures with one-to-one correspondence, but to use up and down arrows as to count forward or backward. The Digit Span subtest from the WISC-IV was used to assess auditory working memory. Finally, the Coding and Symbol Search subtests from the WISC-IV assess response speed, and require focused attention, organized response strategy and cognitive flexibility.

In keeping with previous studies of these same EF measures in childhood TBI samples (Robinson et al., 2014; Wolfe et al., 2015), principal components analysis using the five EF measures revealed one factor with loadings exceeding 0.5 for all variables. Therefore, a composite for EF was derived. Individual scores on the EF subtests were transformed to the same metric (i.e. standard scores), and the EF composite score was generated for each participant by averaging performance across the tasks. This yielded an overall indicator of EF for use in subsequent mediation analyses. Previously childhood TBI research has provided additional factor analyses that confirm the five measures appropriately load onto the derived EF composite (Robinson et al., 2014; Wolfe et al., 2015).

Anti-social behavior

Anti-social behavior was assessed using parent report of the Child Behavior Checklist (Achenbach & Rescorla, 2001). Items are rated on a 3-point Likert scale and based on behaviors exhibited in the preceding six months, with higher scores denoting more frequent behavior problems. We used the externalizing broadband scale to measure antisocial behavior, which consists of two subscales measuring rule breaking and aggressive behavior. The aggression scale consists of 20 items, such as destroying one's own and other's belongings, fighting with other children, and attacking others, arguing, bragging, and

boasting. The rule breaking scale is comprised of 13 items, including behaviors such as lying, cheating, setting fires, being truant, stealing at home and elsewhere, lacking guilt, and using drugs and alcohol.

Structural MRI

Image acquisition and processing. Children underwent a structural brain MRI sub-acutely at 6-weeks post-injury (*M* = 42.28, *SD* = 29.53 days). MR images were acquired on a 3 Tesla Siemens Trio scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-Channel matrix head coil. High-resolution T1-weighted structural MR images were acquired for each participant (TR = 1900 ms, FA = 9°, FOV = 256 x 224, 176 slices, slice thickness =1.0mm, in plane resolution 0.5 x 0.5 mm).

Coding of neuroanatomical lesions. The location of neuroanatomical lesions was identified based on visual inspection of conventional magnetic resonance (MR) and susceptibility weighted imaging (SWI) sequences by a paediatric neuroradiologist and neuropsychologist blind to patients' clinical details. Scans were coded according to a modification of the Coffey system (Coffey and Figiel, 1991; Catroppa et al., 2008) in order to determine the presence of lesions and haemorrhage, and their location and severity based on the extent of hyperintensities as seen on T1- or T2-weighted images. For this report, only basic information regarding the presence or absence of neuroanatomical lesions is presented (Table 2). "Extra-frontal" pathology was coded in instances where pathology did not affect the frontal cortices (i.e. temporal/parietal/occipital lobes, cerebellum, and subcortical structures).

Morphometric analysis. T1 images were subjected to quality control using a qualitative rating system that involves visually ranking the quality of T1-weighted images taking into account motion, ringing, and susceptibility (Backhausen et al., 2016). Of the 155 scans acquired, 18 participants (TBI: *n* = 9; TD Control: *n* = 9) were excluded because of poor imaging data resulting from motion artifact, dental artifact or early termination of the scan sequence mostly from claustrophobia or non-compliance resulting in incomplete data.

The resulting MRI data for 137 participants was subjected to morphometric analysis using the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu.au), which automatically segments and parcellates cortical gray matter and sub-cortical structures. This approach has been utilized in previous adult (Warner et al., 2010) and pediatric TBI research

(Merkley et al., 2008). Full details regarding the analysis steps are reported elsewhere (Dale, Fischl, & Sereno, 1999; Jovicich et al., 2006).

In this study, FreeSurfer was used to extract total intracranial volume (TIV) and whole brain volume (WBV). Using a probabilistic labelling algorithm that relies on gyral and sulcal information, the cortex was parcellated into anatomical regions of interest (ROIs) based on the Desikan-Killiany atlas and projected back into each subject's native space. From this automated procedure, ROIs were computed by extracting the volumes for each ROI bilaterally. ROIs defined in Freesurfer variables (Desikan et al., 2006) were assigned to the CEN defined by Dennis and colleagues (2013), including the dlPFC, PPC, caudate and thalamus. The ROIs within the CEN were summed to calculate overall volume of the CEN package of regions.

Procedure

The RCH Human Research Ethics Committee and the Victorian Department of Education Ethics Committee approved this study. All parents gave their written, informed consent for children to participate in the study, and for extraction of clinical data from medical records at the time of recruitment. For children older than 8 years, verbal assent was sought. Research MRI was conducted between 2- and 8-weeks post-injury. At 6-months post-injury, children participated in a face-to-face assessment, which included direct EF assessment. Parents completed standardized questionnaires of behavior, including anti-social behaviors, at 12-months post injury.

Statistical analysis

All analyses were performed using SPSS Version 25.00 (IBM Corporation). All variables were assessed for violations of normality. Normality plots indicated that all primary outcome measures were normally distributed, and preliminary analyses indicated no violation of statistical assumptions across analyses, unless otherwise stated. One-way analysis of covariance was used to examine group differences in brain morphometry, executive function, and antisocial behavior. Significant omnibus results were followed by *post hoc* pairwise comparisons to discern differences between groups.

Mediation analyses were conducted with bootstrap method using PROCESS V2.16 for SPSS (Hayes & Preacher, 2014). Bootstrap resampling is a powerful method for detecting

mediating effects with no assumptions required of the sampling distribution for these effects. Bootstrapping produces upper and lower bound confidence intervals for the point estimate of a mediating effect, which should exclude 0 in order to reject the null hypothesis (i.e. no mediating effect) (Hayes & Preacher, 2014; MacKinnon, Lockwood, & Williams, 2004). PROCESS was conducted using model 4 and bias-corrected 95% confidence intervals (CI) produced from 10,000 bootstrap resamples.

We computed models for the three measures of anti-social behavior described above (i.e. CBCL Aggression, Rule Breaking and Total Externalizing). In each model, CEN morphometry was entered as the independent variable, and the EF composite was entered as a mediator of the effect of CEN morphometry on each measure of antisocial behavior in the TBI sample. Because SES was significantly associated with the EF composite (r=.308; p<.05) and the CBCL measures of anti-social behavior (r range = -.210, -.279; all p<.05) but not CEN morphometry (r = .159; p>.10), we included SES as a covariate in all models. Additional covariates in each model included age at MRI, retrospective parent ratings of pre-injury CBCL externalizing symptoms, and estimated total intracranial volume (ICV).

Results

Group differences in network morphometry

Brain MRI for one-hundred and thirty-seven of the one-hundred and fifty-five scanned participants were of sufficient quality for Freesurfer to produce volumetric data (thirty-four TDC, fifty-three mild TBI, fourteen complicated mild TBI, twenty-four moderate TBI, twelve severe TBI). Sensitivity analysis comparing those with and without useable MRI and revealed no clinical or significant differences on any pre-injury, demographic, or injury-related variable (all p<.20). The five groups did not significantly differ in total intracranial volume [F (4, 137) = 1.752, p = .142] or whole brain volume [F (4,137) =.731, p=.573]. Time interval between day-of-injury and research MRI scan was not significantly related to any measure of regional or global brain volume (all p>.20), and therefore MRI time interval was not included as a covariate in subsequent analyses.

Table 3 displays the group means and SDs for CEN morphometry. There was a

significant main effect of injury severity group membership on the CEN. As shown in Table 3, post hoc pairwise comparisons revealed that the severe TBI group showed significantly diminished CEN volume relative to TD controls (p<.001), and children with mild, complicated-mild, and moderate TBI (all p<.001). Group differences for the individual hub regions are also displayed in Table 3.

The impact of TBI on task-based EF and anti-social behavior

One-hundred and forty-six participants enrolled in the study (forty-three TDC, fifty-two mild TBI, fourteen complicated mild TBI, twenty-five moderate TBI, twelve severe TBI) completed all five EF tasks and parent-report measures of anti-social behavior. A sensitivity analysis was also carried out between those with and without complete cognitive and behavioral data and revealed no clinical or significant differences on any pre-injury, demographic, or injury-related variable (all p>.15).

TBI versus TDC. As expected, the TBI group displayed significantly worse performance on the EF composite than TD controls (p= .013; η^2 =.042). Similarly, relative to TD controls, the TBI group exhibited significantly more frequent anti-social behaviors as measured by the CBCL aggression (p = .029; η^2 = .037), CBCL rule breaking (p =.052; η^2 = .029) and the CBCL Total Externalizing scales (p=.030; η^2= .037). Analysis of individual impairment ratings on the CBCL Externalizing Composite revealed a significantly greater proportion of clinically significant impairment in the TBI group compared to the TD control group (TBI: 17.4% versus TD control: 2.3%, p =.020).

Effect of TBI severity. As shown in Table 3, there was no significant effect of TBI severity on the EF composite (p=.105; η^2 = .052), CBCL Aggression (p=.162; η^2 = .05), CBCL Rule Breaking (p=.147; η^2 = .05), or the CBCL Externalizing composite (p=.182; η^2 = .05).

Insert Table 3 about Here

Prospective relationships between CEN morphometry, EF, and anti-social behaviors in the TBI sample

As expected, poorer EF at 6-months prospectively predicted more frequent parent rated aggression (p = .008) and total externalizing symptoms (p= .012) at 12-months post-injury.

The association between the EF composite and rule breaking behavior was not statistically significant (p= .103).

The results from the mediation models are presented in Figure 1. In each model, CEN morphometry predicted EF performance, indicating that diminished CEN volume prospectively predicted poorer EF at 6-months post injury. We found that, after including the EF composite as a mediator in the models, CEN morphometry did not directly predict CBCL Aggression, CBCL Rule Breaking or CBCL Externalizing Total (see Figure 1).

Evaluating the indirect effect of CEN morphometry on anti-social behavior via EF in the TBI sample

The test of the indirect effect of the CEN on CBCL Externalizing Total, when the EF composite was included as a mediator in the model, was statistically significant (B = -.052; 95% CI: -.128, -.002), such that poorer EF at 6-months post-injury mediated the prospective association between abnormal sub-acute CEN morphometry and more frequent anti-social behavior at 12-months post-injury. The test of the indirect effect of CEN was significant for CBCL Aggression (B = -.038; 95% CI: -.097, -.001), but not CBCL Rule Breaking (B = -.010; 95% CI: -.027, .002).

Insert Fig. 1 About Here

Subgroup analyses of indirect effects

To assess whether the magnitude of indirect effects differed according to TBI severity**,** mediation models were calculated separately for the complicated mild-severe group (n = 50) and the uncomplicated mild TBI group (n =53). Subgroup analyses of the associations between CEN morphometry, EF, and anti-social behaviour are provided in Table S1.

Consistent with the effects observed in the main analyses reported above, mediation analyses in the complicated mild-severe TBI group only (n=50) revealed a significant indirect effect of CEN morphometry on CBCL Externalising Total (B = -.084; 95% CI: -.176, -.004) and CBCL Aggression (B = -.067; 95% CI: -.145, -.003), but not CBCL Rule Breaking (B = -.016; 95% CI: -.033, .002).

In contrast, when mediation models were calculated separately in the uncomplicated mild TBI group only (n=53), the indirect effect of CEN morphometry did not reach statistical significance for CBCL Externalising Total (B = -.049; 95% CI: -.164, .008), CBCL

Aggression (B = -.028; 95% CI: -.092, .003), or CBCL Rule Breaking (B = -.010; 95% CI: -.044, .005).

Discussion

Despite increasing evidence of a link between early life brain injury and anti-social behavior (Bellesi et al., 2019; Timonen et al., 2002), very few studies have modelled the factors that might help account for this relationship in the pediatric TBI population. In addressing the dearth of knowledge in this area, we used high-resolution structural neuroimaging and child direct assessments to evaluate the role of CEN morphometry and EF in prediction of anti-social behavior in a large prospectively recruited sample of children with hospital-documented TBI. We found that, relative to TDCs, children with severe TBI showed brain structural differences within the CEN and its putative hub regions 6-weeks post-injury. Moreover, EF task performance mediated the prospective relationship between sub-acute CEN morphometry and anti-social behavior at 12 months post-injury. These findings support our hypothesis that grey matter structural differences within the CEN prospectively predict anti-social behavior via reduced EF.

Findings showed that, relative to age- and sex-matched TDCs, rates of clinically significant anti-social behavior were higher in the TBI group. Similarly, we found that, when outcomes were examined dimensionally, the TBI group displayed significantly more frequent aggression, rule-breaking and overall externalizing symptoms relative to TDCs. While the link between childhood TBI and anti-social behavior has been previously documented (Bellesi et al., 2019; Li & Liu, 2013), findings from our relatively large sample of consecutive, hospital-confirmed cases suggest that heightened levels of anti-social behavior are evident as early as 12-months post-injury. Since many children with more severe injuries typically remain engaged with public health and rehabilitation services within the first 12 months of injury (Haarbauer-Krupa, Lundine, DePompei, & King, 2018), these findings may underscore the promise of targeted interventions tailored to those children presenting with risk factors within the first year of injury.

Interestingly, there was no evidence for a dose-response relationship between clinical indicators of TBI severity and anti-social behavior in our prospectively recruited sample. This is broadly consistent with previous research highlighting substantial heterogeneity in post-

injury social and behavioural outcomes, even among children with severe TBI (Hoskinson et al., 2019; Rosema, Crowe, & Anderson, 2012) and suggest that routine clinical indices of injury severity are insufficient to explain substantial individual variation in anti-social behaviour. Overall, this finding underscores the increased importance of theory-driven approaches for prediction of anti-social behaviour, including the need to assess the respective role of neuroanatomical and neurocognitive factors in mediating the association between childhood TBI and elevated rates of anti-social behviour (Li & Liu, 2013; Schwartz et al., 2003).

Consistent with expectations, analysis of regional CEN morphometry showed that children with severe TBI had diminished CEN volume, including significantly smaller grey matter volume within the dorsolateral prefrontal cortex, posterior parietal cortex, and caudate nucleus. In contrast to the pattern of global structural brain changes previously documented in children with chronic severe TBI (Beauchamp et al., 2011; Bigler et al., 2010; Wilde et al., 2005), no significant group differences were identified on measures of whole brain or total intracranial volume at 2-months post-injury. Rather, evidence for regional differences in CEN morphometry converge with previous evidence for the selective vulnerability of fronto-striatal brain circuits to the acceleration-deceleration forces of pediatric TBI (Bigler, 2013; Bigler et al., 2013; Ryan, Beauchamp, et al., 2016). Although these findings suggest that selective structural abnormalities within the CEN may be detectable as early as 2-months post-severe TBI, no study to date has examined the role of CEN morphometry in predicting anti-social behavior among this population of children.

In line with our expectations, we also found that the TBI group performed significantly worse on the EF composite than TDCs, and that variation in EF performance was related to CEN morphometry, but *not* clinical indicators of TBI severity. Although executive dysfunction is a common and well documented consequence of childhood brain injuries (Horton, Soper, & Reynolds, 2010; Narad et al., 2017; Sesma, Slomine, Ding, & McCarthy, 2008), these findings further support the inadequacies of clinical severity indices to account for the substantial heterogeneity in EF outcomes. To the contrary, robust prospective links between regional brain morphometry and post-injury EF suggests that variability in these outcomes is at least partly explained by neuroanatomical differences within the CEN; a network with a well-established role in the development of EF (Dennis et al., 2013; Menon, 2011). Overall, this pattern of findings suggests that high-resolution structural MRI may have potential to complement clinical indicators of TBI severity in

improving prediction of EF difficulties, which may in turn contribute to anti-social behavior in children with TBI.

Our findings also revealed that poorer performance on the EF composite was prospectively associated with more frequent anti-social behaviors at 12-months post-injury. According to the dual taxonomy theory (Moffitt, 2018), neurocognitive impairments, particularly executive dysfunction, are a key etiological risk factor for life-course persistent anti-social behavior. Our results suggest that children with TBI are more likely to present with neurocognitive risk factors implicated in life-course persistent anti-social behavior (Carlisi et al., 2020; Raine et al., 2005), and that these same neurocognitive risk factors are prospectively linked with more frequent anti-social behaviors in our relatively large sample of children with hospital confirmed TBI.

The finding of prospective links between EF and anti-social behavior extend previous studies of childhood TBI cohorts, which have found weak or inconsistent links between executive dysfunction and behavior problems (Schwartz et al., 2003). For instance, recent cross-sectional analyses by Robinson and colleagues (2014) found that executive dysfunction was not a significant direct predictor of any measure of behavioral symptoms or social skills in children with chronic TBI. Similarly, Ryan and colleagues (2015) found that social communication, but not EF, was predictive of anti-social behavior at 15-years post-injury in a small sample of young adults with a history of childhood TBI. In addressing the limitations of these previous studies which have relied on cross-sectional data collected from small samples of individuals with TBI, our larger prospective study lends support to the suggestion that reduced EF is a key risk factor that at least partly explain the well documented association between childhood TBI and subsequent anti-social behavior.

Finally, mediation analyses provided evidence of a significant brain-behavior relationship, revealing that volumetric differences within the CEN indirectly contributed to more frequent anti-social behavior via their influence on post-acute EF. While these findings are broadly consistent with recent population-level evidence linking persistent anti-social behavior to widespread structural brain differences (Carlisi et al., 2020), there has been a paucity of research to model these relationships in children with a history of neurological trauma. Since post-injury neuroanatomical differences within the CEN represent a proxy for underlying brain disruption in neural circuitry known to support the development of EF (Bigler, 2013), our findings suggest that impaired EF represents both a primary symptom of underlying brain pathology, and one of several potential factors that links pediatric TBI to chronic anti-social behavior.

Implications

While we acknowledge that relationship between child TBI and anti-social behavior is likely complex and multi-factorial, our findings suggest that child brain injury confers heightened risk for anti-social behavior, and in some cases, post-injury executive dysfunction might partly contribute to this risk for anti-social behavior. From a clinical perspective, our findings may underscore the potential value of more intensive clinical follow-up, family psychoeducation, and when clinically indicated, child-focused interventions for those children presenting with early neurostructural and neurocognitive risk factors.

In particular, since poorer EF appears to have predictive value for later anti-social behavior at 12-month follow up, clinicians might consider routine screening of EF to identify higher risk children who may benefit from longer term follow-up and where appropriate, compensatory EF strategies. For instance, although neuropsychological evaluations of EF are often conducted as part of outpatient rehabilitation for children with TBI, these evaluations are not considered a routine component of service provision in the Australian context. Our findings suggest that post-acute neuropsychological evaluations of EF would facilitate early identification and subsequent intervention for EF difficulties, which may help reduce risk for anti-social behaviours that are apparent in our sample as early as 12-months post-TBI. Recent research has provided evidence for the efficacy of a web-based counsellor-assisted problem-solving (CAPS) therapy in addressing executive deficits following adolescent mild-severe TBI (Kurowski et al., 2013), however, it remains unclear whether these types of interventions may play a role in reducing the frequency of anti-social behavior in the child TBI population.

Study limitations and future directions

There are several methodological caveats that weaken our current study findings. Firstly, our study design and analyses do not permit casual inference. Therefore, it is not possible ascertain whether childhood TBI is the cause or a contributing factor to antisocial behavior. Namely, we cannot entirely rule out the possibility that anti-social behaviors in our TBI sample are at least partly explained by pre-injury psychiatric and/or developmental vulnerabilities, including symptoms of ADHD, disruptive behavior and executive dysfunction, which may place children at elevated risk for TBI. Nevertheless, there are several factors that do not support this possibility. Firstly, retrospective ratings of pre-injury functioning showed that the TBI groups did not significantly differ from typically developing controls on measures of pre-injury externalizing symptoms, adaptive behavior, or

internalizing symptoms. Secondly, additional subgroup analyses revealed that mediation effects were present only among those children with complicated mild-severe injuries and *not* children with uncomplicated mild TBI. Viewed collectively with the finding that all results remained statistically significant after covarying for pre-injury externalizing symptoms, our results suggest that anti-social behaviors in our TBI sample are more likely explained by brain injury-related processes than pre-injury developmental vulnerabilities.

Secondly, this study relies exclusively on retrospective and post-injury parent ratings of anti-social behavior, which has potential to introduce informant bias into the observed results. To more accurately characterize anti-social behavior that may emerge across multiple contexts, future studies would benefit from incorporating ratings collected from multiple sources, including direct observation the children, peers, teachers, and child self-report. Moreover, although we controlled for retrospective parent ratings of pre-injury anti-social behavior in all analyses involving the primary outcome measures, future research should also involve collection of retrospective parent ratings of pre-injury executive dysfunction. Similarly, for future studies, the inclusion of an orthopedic injury comparison group would help determine whether increased rates of anti-social behavior are unique to children with brain trauma (i.e. a *brain injury specific* effect), or whether the association is at least partly explained by pre-existing risk factors (e.g. premorbid psychiatric difficulties) that are often shared by children who experience orthopedic and neurological trauma. The contribution of other non-injury related risk factors to post-injury anti-social behavior also requires further investigation. For instance, previous research suggests that post-injury behavioral dysfunction is linked to poorer family functioning (Gerring et al., 2009; Wade et al., 2011), worse parent mental health (Ryan, van Bijnen, et al., 2016) permissive parenting styles (Chapman et al., 2010), and low maternal nurturance (Root et al., 2016).

Moreover, given that single subtests tend to yield unreliable estimates of executive function, a strength of the study was our reliance on an executive function composite derived from several tasks that loaded on a single EF factor. To disentangle the unique contribution of each separate EF component (i.e. working memory, inhibition, cognitive flexibility), future studies should employ a larger battery of executive function tasks, including multiple subtests of each EF construct. Such an approach would allow for derivation of composite scores for each EF component. Similarly, further prospective research is needed to evaluate the contribution of EF to longitudinal trajectories of anti-social behaviour after childhood TBI. Such studies should incorporate measures of criminal convictions (i.e. a proxy for extremely severe anti-social behaviours), which were not captured in the current study.

Finally, it is noteworthy that although overall (mean) ratings of anti-social behaviour in the TBI severity groups did not fall within the borderline or clinically significant range, we found significantly higher rates of clinically significant anti-social behaviour in the TBI group compared to TD controls. Taken together, this pattern of findings cautions against sole reliance on clinical indicators of TBI severity in prognosticating post-injury behavioural outcomes. Rather, clinicians should consider the potential role of neuroanatomical and EF variables that may better explain substantial individual variation in post-injury anti-social behaviour.

Conclusions

To our knowledge, this study provides the first longitudinal prospective analysis of factors contributing to anti-social behavior in a well characterized cohort of children with hospital confirmed TBI. In one of the few studies to evaluate the subacute impact of pediatric TBI on regional morphometry of the CEN, we demonstrate that severe pediatric TBI is associated with grey matter structural differences within CEN and its putative hub regions as early as 2-months post-injury. In addressing the paucity of research examining factors that link pediatric TBI to anti-social behavior, poor EF task performance was found to mediate the prospective association between sub-acute volumetric differences within the CEN and anti-social behavior. Overall, findings suggest that sub-acute volumetric abnormalities of the CEN may represent valuable prognostic markers for early identification of children at elevated risk for post-acute EF difficulties, which may in turn contribute to anti-social behavior in this high risk population.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Prospective associations between CEN morphometry, EF and anti-social behaviour, r (p).

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Key points

- Despite increasing evidence of a link between early life brain injury and anti-social behavior, few studies have assessed factors that explain this association in children with a history of traumatic brain injury (TBI).
- Longitudinal studies are needed to identify early neurostructural and neurocognitive risk factors for subsequent anti-social behavior
- The present longitudinal prospective study tested structural brain and neurocognitive correlates of anti-social behavior in a relatively large sample of consecutive, hospital confirmed cases of childhood TBI
- Executive dysfunction (ED) mediated the prospective association between neurostructural differences within the central executive network (CEN) and anti-social behaviors in children with TBI
- Findings highlight the potential prognostic value of neurostructural and

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Table 1. Baseline and demographic characteristics of enrolled sample

	TD Control	Mild	Complicated-Mild	Moderate	Severe	F/χ^2	p
n	43	57	14	26	15	-	-
Male, n (%)	24 (55.81)	44 (77.19)	8 (57.14)	16 (61.54)	8 (53.33)	6.68	.154
SES, M (SD)	76.75 (14.19)	70.17 (19.64)	58.61 (27.09)	60.88 (24.76)	70.66 (25.09)	2.43	.050
Age at recruitment (yrs), M (SD)	10.25 (3.04)	10.67 (2.36)	9.47 (2.44)	10.33 (2.49)	9.72 (3.01)	0.80	.528
Age at research MRI (yrs), M (SD)	10.41 (2.76)	10.80 (2.33)	9.57 (2.43)	10.37 (2.58)	10.41 (3.10)	0.66	.621
Pre-injury baseline function, M (SD)							
ABAS-II Social	10.44 (2.74)	10.02 (3.37)	9.46 (3.20)	10.00 (2.08)	9.86 (3.42)	0.32	.862
ABAS-II Adaptive Composite	97.37 (15.38)	97.26 (17.15)	95.77 (16.15)	98.32 (13.08)	94.71 (15.75)	0.14	.965
CBCL Internalizing Total	**47.16 (8.31)**	**48.26 (11.25)**	**51.54 (12.33)**	**47.88 (9.58)**	**49.21 (9.58)**	**0.50**	**.733**
CBCL Externalizing Total	**46.63 (6.99)**	**48.13 (10.09)**	**51.39 (10.40)**	**48.04 (11.23)**	**50.50 (9.88)**	**0.86**	**.488**

Significant ($p<.05$) post-hoc analysis comparing ‡TBI-Mild vs. TBI-Moderate, †TBI-Mild versus TBI-Severe, # TBI-Complicated Mild versus TBI-Moderate, ǂ TBI-Complicated Mild versus TBI Severe, **TBI-Moderate versus TBI-Severe. ABAS-II, Adaptive Behavior Assessment System – Second Edition; SES, socioeconomic status.

Table 2. Participant injury characteristics

	Mild TBI	Complicated-Mild TBI	Moderate TBI	Severe TBI	F/χ^2	p
Injury characteristics						
Age at injury (yrs), M (SD)	10.67 (2.36)	9.47 (2.44)	10.33 (2.49)	9.72 (3.01)	1.20	.312
Lowest GCS, M (SD)	14.54 (1.04)	13.93 (1.14)	11.50 (1.98) [‡, #]	5.60 (2.20) [†,ŧ,**]	148.99	p<.001
Length of hospital stay (days), M (SD)	0.48 (0.73)	2.30 (1.82)	4.75 (4.59) [‡, #]	17.7 (13.9) [†,ŧ,**]	38.83	p<.001
Surgical intervention, n (%)	0 (0)	0 (0)	8 (31)	7 (47)	32.07	p<.001
Cause of injury, n (%)					33.60	.001
Motor vehicle accident (MVA) (car)	1 (2)	1 (7)	5 (19)	4 (27)	-	-
MVA (pedestrian/bike)	3 (5)	1 (7)	5 (19)	5 (33)	-	-
Fall (stationary)	13 (23)	4 (29)	8 (31)	2 (13)	-	-
Fall (moving)	22 (39)	7 (50)	7 (27)	3 (20)	-	-
Kicked/struck by object	18 (32)	1 (7)	1 (4)	1 (7)	-	-
MRI Pathology, n (%)						

Frontal	13 (23)	4 (29)	14 (54)	10 (67)	27.46	p<.001
Extra-frontal	6 (11)	4 (29)	9 (35)	6 (40)	20.56	p<.001
Sub-cortical	2 (4)	1 (7)	4 (15)	4 (27)	16.27	.003

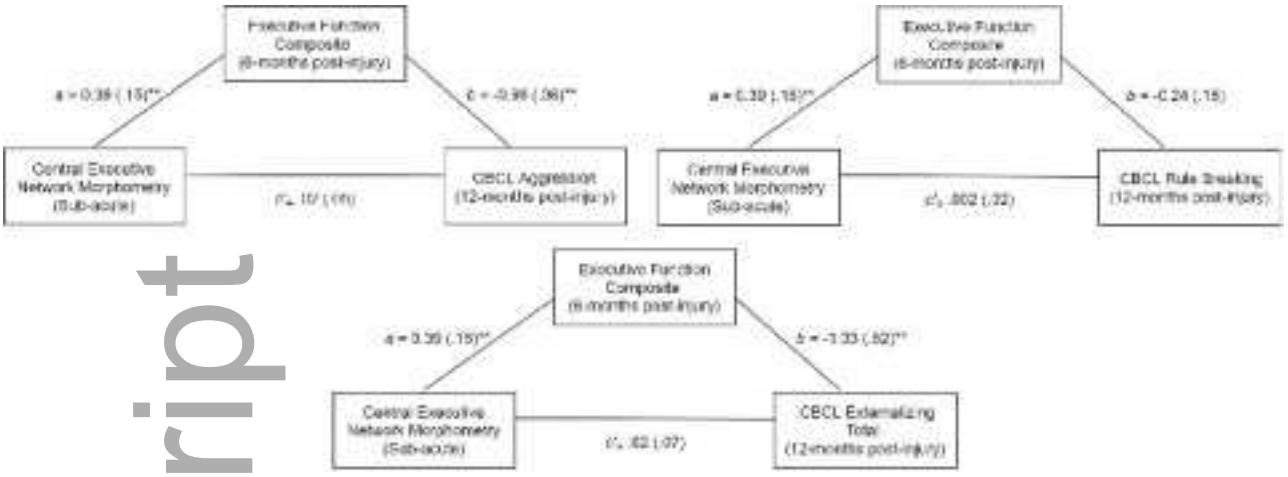
Significant (p<.05) post-hoc analysis comparing [‡]TBI-Mild vs. TBI-Moderate, [†]TBI-Mild versus TBI-Severe, [#] TBI-Complicated Mild versus TBI-Moderate, [ŀ]TBI-Complicated Mild versus TBI-Severe, [**]TBI-Moderate versus TBI-Severe. GCS, Glasgow Coma Score.

Table 3. Group differences in network-based morphometry, executive function, and anti-social behaviour

	TDC	Mild TBI	Complicated-Mild TBI	Moderate TBI	Severe TBI	F	P	η^2
Network Morphometry								
Central Executive Network	171,479	177,105	172,502	174,454	158,440[†,‡,*,ǂ]	4.38	.002	.12
dlPFC	83,690	88,404	85,137	86,545	77,555[†,‡,*,ǂ]	3.88	.005	.11
PPC	63,713	64,252	63,871	64,321	58,771[†,‡,*,ǂ]	2.46	.049	.07
CN	8087	8252	7982	7777	7462[‡]	1.47	.214	.04
TH	15,991	16,196	15,512	15,811	14,652[†,‡,*,ǂ]	3.54	.009	.10
Executive Function (6 m.)	10.24 (1.91)	9.52 (1.76)	8.86 (2.38)	9.39 (2.27)	9.03 (1.93)	1.95	.105	.05
CBCL Aggression (12 m.)	51.49 (4.28)	53.17 (6.73)	56.82 (9.03)	54.96 (8.50)	55.70 (5.83)	1.67	.162	.05
CBCL Rule Breaking (12 m.)	51.35 (2.84)	52.33 (4.67)	52.91 (4.01)	55.04 (7.91)	54.50 (6.22)	1.73	.147	.05
CBCL Externalising (12 m.)	45.26 (6.84)	46.14 (9.85)	52.00 (10.58)	48.83 (13.40)	52.30 (10.26)	1.59	.182	.05

Significant ($p<.05$) post-hoc analyses comparing [†]TD vs. TBI-Severe, [‡]TBI-Mild vs. TBI-Severe, [*]TBI-Complicated Mild vs. TBI-Severe, [ǂ]TBI-Moderate vs. TBI-Severe, [#]TDC vs. TBI-Moderate,[**]TBI-Mild vs. TBI-Complicated Mild, [≠]TDC vs. TBI-Mild. CBCL, Child Behaviour

Checklist; dlPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex; CN, caudate nucleus; TH, thalamus; TDC, typically developing control; 6 m., 6-months post-injury; 12 m., 12-months post-injury.



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