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Title:
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Date:
2023-03-01

Citation:
Ryan, N. P., Catroppa, C., Beauchamp, M. H., Beare, R., Ditchfield, M., Coleman, L., Kean, M., Crossley, L., Hearps, S. & Anderson, V. A. (2023). Prospective Associations of Susceptibility-Weighted Imaging Biomarkers with Fatigue Symptom Severity in Childhood Traumatic Brain Injury. Journal of Neurotrauma, 40 (5-6), pp.449-456. https://doi.org/10.1089/neu.2021.0476.

Journal of Neurotrauma

DOI: 10.1089/neu.2021.0476

Prospective Associations of Susceptibility-Weighted Imaging Biomarkers with Fatigue Symptom Severity in Childhood Traumatic Brain Injury

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Running title: Biomarkers of long-term fatigue in childhood TBI

Key words: fatigue; childhood; brain injuries; magnetic resonance imaging

Words for abstract: 205

Words for manuscript: 2,991

Number of references: 31

Tables: 4

Figures: 0

Journal of Neurotrauma

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This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

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ABSTRACT

Fatigue may be among the most profound and debilitating consequences of pediatric traumatic brain injury (TBI); however, neurostructural risk factors associated with post-injury fatigue remain elusive. This prospective study aimed to evaluate the independent value of susceptibility-weighted imaging (SWI) biomarkers, over-and-above known risk factors, to predict fatigue symptom severity in children with TBI.

42 children were examined with structural magnetic-resonance imaging (sMRI), including a SWI sequence, within 8-weeks post-injury. The PedsQL Multi-Dimensional Fatigue Scale (MFS) was administered 24-months post-injury. Compared to population expectations, the TBI group displayed significantly higher levels of general fatigue **(Cohen's *d* = 0.44),** cognitive fatigue **(Cohen's *d* = 0.59),** sleep/rest fatigue **(Cohen's *d* = 0.37),** and total fatigue **(Cohen's *d* = 0.63).** In multi-variate models adjusted for TBI severity, child demographic factors and depression, sub-acute volume of SWI lesions was independently associated with all fatigue symptom domains. **The magnitude of the brain-behavior relationship varied by fatigue symptom domain, such that the strongest relationships were observed for the cognitive fatigue and total fatigue symptom scales.** Overall, we found that total volume of SWI lesions explained up to 24% additional variance in multi-dimensional fatigue, over-and-above known risk factors. SWI has potential to improve prediction of post-injury fatigue in children with TBI. Our preliminary findings suggest that volume of SWI lesions may represent a novel, independent biomarker of post-injury fatigue scores, which could help to identify high-risk children who are likely to benefit from targeted psychoeducation and/or preventive strategies to minimize risk of persisting fatigue.

INTRODUCTION

Fatigue, defined as a subjectively overwhelming sense of tiredness, lack of energy and feeling of exhaustion, is a common and disabling symptom of neurological disorders of childhood, and is associated with reduced participation and quality of life.[1, 2] While preliminary reports suggest that fatigue may be among the most debilitating consequences of pediatric traumatic brain injury (TBI) and may persist for several years post-injury in some children,[3, 4] factors contributing to individual variation in post-injury fatigue are less well understood.

Mechanisms of post-injury fatigue are multi-factorial and likely involve neuroanatomical, biochemical, endocrine, and psychological factors, contributing independently or in combination.[5] Indeed, studies of pediatric TBI have linked greater post-injury fatigue to child demographic risk factors, including older child age,[1, 4] single parent households,[6, 7] and female sex.[1, 8] Post-injury fatigue is also related to psychological factors such as depression, which may exacerbate and/or perpetuate fatigue symptom severity.[4, 9] Moreover, though there is some evidence linking more severe TBI with worse fatigue,[1, 8, 10] there exists a paucity of theory-driven research to identify novel predictors of post-injury fatigue.

According to the 'effort reward imbalance' (ERI) model,[11] post-injury fatigue likely stems from structural and functional abnormalities of cortico-striatal brain networks (CSNs) responsible for perception of energetic costs of an action (effort) and benefits of the resulting outcome (reward).[11] **More specifically, the ERI model suggests that motivation to complete a difficult task or action depends on a balance between the perception of energetic costs (i.e. effort calculation) and perceived benefits of the outcome (i.e. subjective goal value), such that we complete difficult tasks only when the rewards for doing so are sufficiently high.**[11-15] Indeed, studies of adult neurological conditions (e.g., stroke, TBI) have linked increased fatigue to structural and functional alterations of a distributed cortico-striatal network (CSN) involving subcortical nuclei of the basal ganglia (BG) and its projections from the anterior cingulate and prefrontal regions[16] involved in effort calculation and processing subjective goal value, respectively. Since the CSN involves distributed brain regions susceptible to primary and secondary damage from

pediatric TBI,[17] one might predict that higher lesion burden is more likely to disrupt connections of cortico-striatal circuitry, thereby increasing the likelihood of an 'effort-reward imbalance' reflected in the subjective experience of post-injury fatigue.[11]

Interestingly, studies of the association between post-injury fatigue and acute TBI severity have revealed mixed and often inconsistent findings.[3, 6, 9, 10] In a recent study of 35 adolescents, TBI severity (mild vs. moderate/severe) was not significantly associated with fatigue at six weeks post-injury.[9] In a subsequent follow-up involving a larger group of children and adolescents with TBI (*n*=109), moderate/severe TBI was associated with greater fatigue at 12 months postinjury, relative to mild TBI.[10] Contrasting with these findings, Bogdanov and colleagues found no significant association between TBI severity and fatigue outcomes in their sample of 44 children with moderate and severe TBI.[4]

In light of mixed findings regarding the role of TBI severity, advances in structural neuroimaging provide a unique opportunity to evaluate associations between post-injury fatigue and neurostructural biomarkers, including post-traumatic lesion burden. Of particular interest, susceptibility weighted imaging (SWI) is a high spatial resolution 3D gradient recalled-echo MR sequence that accentuates the magnetic properties of blood and blood product in the brain, rendering it more sensitive to post-traumatic brain lesions than techniques such as computed tomography and conventional magnetic resonance imaging sequences.[18-22] **Greater number and volume of SWI lesions have been linked to poorer performance on measures of global intellectual functioning and specific neuropsychological tests,**[18, 23-25] however, the independent value of SWI lesion burden to predict post-injury fatigue is largely unknown.

This prospective study aimed to evaluate the independent value of **sub-acute** susceptibility-weighted imaging (SWI) biomarkers **(i.e., lesion characteristics at 2-weeks post-injury),** over-and-above known risk factors, to predict multi-dimensional fatigue 2-years following childhood TBI. We predicted that after adjusting for TBI severity, child demographic factors (child age, sex, socio-economic status), and depression, elevated fatigue would be independently associated with increased SWI lesion burden, including larger volume and number of SWI lesions. We predicted that SWI lesion burden would explain significant additional variance in multi-dimensional fatigue, over-and-above TBI severity, child demographic factors, and depression.

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MATERIALS AND METHODS

Participants

The current sample was drawn from a larger longitudinal, prospective study.[26] It comprised 42 children and adolescents (40.38% of original sample) with mild-severe TBI, who had completed fatigue measures at 24-months post-injury. Children participating in the larger study were recruited at time of injury and represented consecutive admissions to The Royal Children's Hospital (RCH), Melbourne, Australia. All participants were ascertained between 2007 and 2010 and were aged between 5.3 and 15.4 years at time of recruitment. The present study reports on the relation between SWI lesion biomarkers and fatigue outcome measures administered at 24-months post-injury (range: 20.23- 41.60 months).

For the larger longitudinal study inclusion criteria were: (i) aged 5.0-16.0 years at recruitment: (ii) documented evidence of a closed head injury; (iii) medical records sufficiently detailed to determine injury severity; (iv) no documented history of pre-injury neurological or developmental disorder, or non-accidental injury or previous TBI; (v) no prior intervention for social impairment; (vi) English speaking.

For the present study, participants with TBI were classified as: **(i) mild TBI (*n*=18): Glasgow Coma Score (GCS) 13-15, no evidence of mass lesion on CT or clinical MRI; (ii) mild complicated TBI (*n*=4): GCS 13-15, evidence of mass lesion on CT or clinical MRI;** (iii) moderate TBI (*n*= 14): GCS 9-12, mass lesion or other evidence of specific injury on CT/MRI; and (iv) severe TBI (*n*=6): GCS 3-8, mass lesion or other evidence of specific injury on CT/MRI. Due to small cell sizes, groups were collapsed into 'mild TBI' (*n*=22) versus 'moderate/severe TBI' (*n*=20).

Materials

Primary outcome measure

The PedsQL Multidimensional Fatigue Scale [27] was completed by parents, and assesses the frequency of child fatigue symptoms over the past month on a 5-point Likert scale (0 = never; 1 = almost never; 2 = sometimes; 3 = often; 4 = almost always). The PedsQL provides a Total Fatigue scaled score based on three subscales: (i) General Fatigue

(six items, e.g., 'he/she feels tired'; 'feels too tired to do things that he/she likes to do'); (ii) Sleep/Rest Fatigue (six items, e.g., 'feels tired when he/she wakes up in the morning'; he/she rests a lot'); and (iii) Cognitive Fatigue (six items, e.g., 'It is hard for him/her to keep his/her attention on things'; 'It is hard for him/her to remember what people tell him/her'). Items are reverse scored and linearly transformed to a 0–100 scale, such that higher scores indicate fewer symptoms of fatigue.

Risk factor covariates

Socio-economic status was determined at the time of recruitment using the Australian Socioeconomic Index 2006 (ANZSCO). The scale ranges from 0 to 100 with high scores reflecting higher occupational status for the primary caregiver.

Child depression was assessed using the Affective Problems DSM-oriented scale from the *Child Behavior Checklist* for ages 6–18 (CBCL/6–18),[28] which indexes frequency of depressive symptoms. Higher T scores (*M*=50; *SD* =10) denote greater symptoms.

Child sex, age at assessment, and TBI severity were extracted from parent demographic questionnaires and child medical records using a standardized clinical report form.

Susceptibility-weighted imaging

Image acquisition

MR images were acquired on a 3 Tesla Siemens Trio scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-Channel matrix head coil. Conventional MR sequences were performed using a standardized imaging protocol.[19] A SWI sequence was also included. SWI imaging is a variant of the standard 3D FLASH sequence that exploits the signal loss from shortened T2* characteristics of calcium- and deoxyhemoglobin-containing lesions. The images are T2* weighted because of the range of acceptable TEs used in the acquisition (18–22ms). The increased sensitivity to shortened T2* lesions is caused by the image reconstruction techniques used. Both magnitude and phase images are reconstructed from the data set. The phase images display a higher sensitivity to local susceptibility variations and, as such, are used as an image mask to be combined with the

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magnitude data set. The combined data set is then reconstructed using a sliding window (eight individual slices compressed into one image) minimum intensity projection (MIP) data set.

SWI lesion coding and segmentation

SWI images were visually reviewed to determine scan quality. One scan was rejected due to poor quality that prevented lesion segmentation. The location of neuroanatomical lesions was identified based on visual inspection of SWI scans by a paediatric neuroradiologist and neuropsychologist blind to patients' clinical details. Lesions were identified and coded according to location using a modification of the Coffey classification system,[19] which assessed the signal abnormality as seen on SWI images. Specifically, signal changes identified on SWI were coded in the following cortical and subcortical regions: frontal/temporal/parietal/occipital lobes, cerebellum, hippocampus, amygdala, corpus callosum, thalamus, and basal ganglia.

Scans rated positive for lesions on SWI were further investigated by manual segmentation using ITK-snap. Lesion counts were conducted using a connected component analysis of lesion masks, which accounts for the possibility that multiple posttraumatic lesions may be present in any single independent region of the brain. Repeatability of segmentation was checked by re-segmenting 5 scans after a delay of greater than 6 months and comparing volumes using intra-class correlation (ICC).

Procedure

Children underwent structural MRI research scans, including SWI sequences, between 2- and 8-weeks post injury (*M*=39.25, *SD*= 27.64 days). Standardized parent report measures of fatigue were collected at 24-months post-injury. The study was approved by The RCH Human Research Ethics Committee and the Victorian Government Department of Education Ethics Committee. All parents gave written, informed consent for children to participate in the study, and for retrospective extraction of clinical data from medical records.

Statistical analyses

All data were entered into SPSS statistical software (Version 21.0; SPSS, Inc., Chicago, IL) and screened for violations of normality. An alpha level of $p < 0.05$ was used to indicate significance, and effect sizes were calculated using Cohen's *d*. Independent-samples *t*-tests

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were employed to examine differences between participating and non-participating participants on demographic and clinical characteristics, and to evaluate mean differences between the study cohort and published PedsQL population sample norms.[29] Analysis of variance (ANOVA) or Chi-square test-for-independence was conducted to investigate injury severity group differences for demographic and injury-related variables. Bivariate correlations were conducted to examine associations between fatigue and SWI lesion burden.

To investigate the independent value of SWI lesion burden to predict fatigue 2 years post injury, we conducted four separate, hierarchical, multiple regressions for each of the three fatigue domains (sleep/rest, general, cognitive) and the PedsQL Fatigue Total Score. **In Block 1, child demographic factors (child age, sex, socioeconomic status), TBI severity (mild vs. moderate/severe TBI), and concurrent depression symptom severity were forced to enter as covariates.** In Block 2, measures of SWI lesion burden could enter. R^2 change provided the incremental variance accounted for by SWI lesion burden. Tests for multicollinearity were examined, using variance inflation factor analysis. **Power calculations were conducted for our multi-variable statistical models. Using a multi-linear regression model with 5 predictor variables and *n*=42, we were able to detect an effect of f^2=0.36 (medium to large effects).**

RESULTS

Participant demographic and clinical characteristics

As described previously, the current investigation of post-injury fatigue was a sub-study that involved recruiting patients from an existing research database including 112 patients who were enrolled in the original, longitudinal prospective study. Of the 112 children registered on the existing research database, 42 participants were enrolled in the current sub-study. Of the original cohort comprising 112 children, reasons for non-participation were: (i) lost to follow-up (*n*=28) and (ii) significant travel and/or time constraints (*n*= 42). Of note, there were no significant differences in any of the demographic, clinical, or primary imaging variables between participants in this sub-study and those in the larger prospective study (all *p*>.15).

Table 1 presents the demographic and injury characteristics of participants with moderate/severe TBI (*n*=20) and mild TBI (*n*=22). Groups did not significantly differ in terms of sex, SES, or age at assessment. Definitionally, the moderate/severe TBI group had significantly lower GCS, longer length of hospital stays, and were significantly more likely to require surgical intervention. With respect to cause of injury, motor vehicle accidents were more common in the moderate/severe TBI group. Falls were equally common in both groups. **The mean time-since-injury was 25.18 months (*SD* = 4.33 months). Although time-since-injury was variable, 83% of participants were 20-25 months post-injury. A small proportion of participants (17%) were 26-40 months post-injury. Due to group differences in time since injury (see Table 1), this variable was entered as a covariate in all subsequent regression analyses.**

[Insert Table 1 about here]

Group comparisons of PedsQL-MFS ratings

As the moderate/severe TBI and mild TBI groups did not significantly differ on any of the PedsQL-MFS scales (all *p*>.15), these groups were collapsed into a single TBI group (*n*=42) for comparison to the normative sample.

Mean and SDs for the PedsQL multi-dimensional fatigue scales are presented in Table 2. Independent sample *t*-test comparisons of the TBI sample and the published normative sample (*n*=259)[29] revealed significant group differences for all PedsQL fatigue domains. As shown in Table 2, the TBI group had significantly lower mean scores (i.e., higher fatigue ratings) than the normative sample on PedsQL general fatigue (*p*=.011), sleep/rest fatigue (*p*=.023), cognitive fatigue (*p*<.001) and total fatigue (*p*<.001). All effect sizes were in the medium range (see Table 2).

[Insert Table 2 About Here]

Number and volume of sub-acute SWI lesions

SWI Lesions were detected in 24 patients (57%). Both lesion volume (min 7.00 mm^3, max 6374.11 mm^3) and lesion number (min 1, max 67) showed substantial

variability. Compared to children with mild TBI, the moderate/severe group had a significantly higher number of total SWI lesions (p=.027). Group differences in total volume of SWI lesions was in the expected direction but did not reach statistical significance (p=.098). Lesion segmentation procedures were reliable, with an intra-rater ICC score of .987 (95% Confidence Interval: .911, .999).

Prospective Associations between Susceptibility Weighted Imaging Lesion Number, Volume and PedsQL Fatigue Scales

Table 3 displays preliminary bivariate analyses of the relation SWI lesion burden (number, volume, location) and the PedsQL fatigue scales. As expected, PedsQL fatigue total scores were negatively correlated with SWI lesion number (r = -.50, p = .002) and total volume of SWI lesions (r = -.55, p<.001), with large effect sizes. All the PedsQL fatigue subscale scores were also significantly associated with total lesion number (r range: -.34, -.54; p = <.001-.043) and total volume (r range: -.46,-.52; p =.001-.005) in the expected negative direction. Further exploratory analyses of the association between fatigue and lesion location revealed no significant associations (all p>.10, see Table 3).

Total volume and number of SWI lesions were highly correlated (r =.83; p<.001). Because total lesion volume appeared to be a consistently stronger associate of fatigue symptom severity across all PedsQL scales, lesion volume alone was used in subsequent regression analyses to minimize multicollinearity.

[Insert Table 3 About Here]

Multivariate adjusted models to predict fatigue symptom severity

To investigate the independent value of SWI lesion burden to predict fatigue symptom severity, we conducted four separate, hierarchical multiple regressions for each of the three fatigue domains (sleep/rest, general, cognitive) and the PedsQL fatigue total score. As shown in Table 4, TBI severity, child demographic factors, and depression were entered as covariates in Block 1. In Block 2, measures of SWI lesion burden could enter. All variables had a variance inflation factor (VIF) of less than 2.0, indicating a lack of multicollinearity between predictors.

On their own, the covariates entered in Block 1 of linear regression models accounted for 22.2% of the variance in fatigue total scores, 16.5% in general fatigue, 23.5% in sleep/rest fatigue, and 13.2% in cognitive fatigue (all *P*s > .05; see Table 4). In Block 1, there were no significant independent predictors of total, general, sleep/rest or cognitive fatigue.

After introducing SWI lesion burden in Block 2, larger volume of SWI lesions was independently associated with higher levels of general fatigue (*p*=.019), sleep/rest fatigue (*p*=.006), cognitive fatigue (*p*=.002) and total fatigue (*p*=.002). We also found that, over-and-above TBI severity, child demographic factors and depression, the volume of SWI lesions explained an additional 22.4% of variance in total fatigue (R^2 change *p* =.002), 14.7% additional variance in general fatigue (R^2 change *p* =.019), 17.7% additional variance in sleep/rest fatigue (R^2 change *p* =.006) and 24.4% additional variance in cognitive fatigue (R^2 change p =.002). As shown in Table 4, older child age was also an independent predictor of higher sleep/rest fatigue (*p*=.049) and total fatigue (*p*=.046).

[Insert Table 4 About Here]

DISCUSSION

Despite increasing recognition of the link between childhood TBI and elevated fatigue,[1, 3, 4, 10] early neurostructural risk factors associated with post-injury fatigue have remained elusive. To bridge this gap in knowledge, we aimed to evaluate the independent value of susceptibility-weighted imaging (SWI) lesion burden, over-and-above known risk factors, to predict fatigue symptom severity 24-months post-injury. As expected, we found that compared to the published normative sample, the TBI group showed significantly higher levels of fatigue across all symptom domains, including general, sleep/rest, cognitive and total fatigue. In multi-variate adjusted models, total volume of sub-acute SWI lesions was independently associated with all fatigue symptom domains and explained up to 24% additional variance in multi-dimensional fatigue, over-and-above TBI severity, child demographic factors, and depression.

In modelling prospective relationships between post-injury fatigue and susceptibility weighted imaging biomarkers, multi-variate models were adjusted for

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covariates previously linked to post-TBI fatigue in children,[3, 4, 6, 7] including child age, sex, socio-economic status, TBI severity, and concurrent depression. Interestingly, older child age was the only covariate independently associated with elevated fatigue. This finding is broadly consistent with previous evidence for developmental stage effects on fatigue in childhood TBI and other childhood chronic health conditions. [2, 30] Given that post-injury fatigue is likely associated with injury-related factors and their dynamic interaction with child-specific factors including developmental stage, we speculate that the increased extracurricular and structured learning demands of adolescence likely place older children at increased risk for post-TBI fatigue.[2, 30]

In keeping with predictions, total volume of SWI lesions was independently associated with higher levels of general, sleep/rest, cognitive and total fatigue, and explained an additional 14-24% of variance in multi-dimensional fatigue, over-and-above TBI severity and child demographic covariates**. This finding extends previous findings of robust associations between SWI lesion burden and post-injury neuropsychological outcomes in children with TBI,[18, 23, 25]** and suggests that inclusion of imaging markers, such as SWI lesion burden may provide a prognostic marker for post-injury fatigue symptom severity. Although the mechanism of this relationship remains to be established, the 'effort-reward imbalance' (ERI) model of post-injury fatigue[11] may offer a useful framework to interpret the current findings. The ERI model receives substantial support from adult TBI and stroke studies, which have linked post-injury fatigue to functional and structural disruptions to the cortico-striatal brain network responsible for maintaining balance between perceived energetic costs (effort) and benefits (rewards) of completing a given task.[16, 31, 32] Since SWI has increased sensitivity to micro-hemorrhagic lesions commonly associated with traumatic axonal injury (TAI), we speculate that greater TAI burden is more likely to disrupt connections of cortico-striatal circuitry, thereby increasing the likelihood of an 'effort-reward imbalance,' reflected in the subjective experience of post-injury fatigue.[11, 13]

Despite evidence of robust, independent associations of SWI lesion volume with post-injury fatigue symptom severity, exploratory analyses showed that lesion location was not significantly related to any measure of multi-dimensional fatigue. Although studies of adult TBI and stroke have linked elevated fatigue to functional and structural alterations

within the basal ganglia and frontal cortices, similar associations were not observed in our paediatric brain injury sample for whom cortico-striatal brain networks are likely undergoing rapid maturation and likely demonstrate lesser functional specialization than a fully matured, adult brain. In this context, our results are not surprising and are compatible with the hypothesis that the amount of damaged tissue, rather than its location, has greater value for prediction of fatigue in children with injury to the relatively immature, developing brain.[33]

Study implications

While our findings suggest that childhood TBI is associated with elevated fatigue at 2-years post-injury, TBI severity was not independently associated with any measure of post-injury fatigue. This result converges with prior findings of weak or inconsistent relationships between TBI severity and post-injury fatigue and cautions against sole reliance on clinical indicators of TBI severity to predict post-injury fatigue. Encouragingly, our findings suggest that SWI lesion burden represents a novel, independent marker of post-injury fatigue, which may help identify high-risk children for whom fatigue interventions could be beneficial. Although there is a scarcity of evidence-based interventions to address fatigue after childhood TBI, Australian clinical guidelines suggest that targeted family psychoeducation and fatigue prevention strategies are likely to be beneficial for those children presenting with risk-factors associated with fatigue (e.g., higher SWI lesion burden, older age).

Limitations and Future Directions

Although our findings suggest that SWI lesion volume has independent prognostic value for predicting post-injury fatigue in our sample, the strength of study findings is weakened by sample size. Of note, our small sample size limited our statistical power to detect small effects and constrained our capacity to conduct more robust-analyses of potential sex-based differences in post-injury fatigue. Given our sample included a relatively small number of children with severe TBI, larger prospective studies of susceptibility-weighted imaging are needed to replicate our findings using a broader range of outcome instruments, including measures to assess cognitive and emotional

symptom burden. Future comparative studies should also evaluate the sensitivity of SWI for detection of post-traumatic lesions, relative to CT and clinical MRI.[21]

Though previous research supports concordance between parent and child ratings of fatigue on the PedsQL measure,[34, 35] our study was also limited by sole reliance on parent ratings of fatigue severity. In future research, it would be beneficial to examine the concordance between child and parent ratings of subjective fatigue in child TBI samples, and evaluate relationships between post-injury fatigue and functional outcomes, including participation, academic performance, and peer relational quality.[3] Moreover, our results should prompt further investigation into the neural correlates of post-injury fatigue in larger samples of children with TBI. In particular, diffusion MRI and tractography may assist to identify neurostructural biomarkers of post-injury fatigue through quantification of microstructural alterations in cortico-striatal projection fibers.[11]

CONCLUSIONS

This study assists to address the dearth of knowledge regarding neurostructural risk factors associated with post-injury fatigue in children with a history of TBI. Using a prospective design, we show that susceptibility weighted-imaging lesion burden is independently associated with post-injury fatigue and explains significant additional variance in these outcomes over-and-above injury severity, demographic factors, and depression. Overall, these preliminary findings suggest that volume of SWI lesions may represent a novel, independent biomarker of fatigue symptom severity, which may help identify high-risk children who are likely to benefit from targeted psychoeducation and/or preventive strategies to minimize risk of persisting fatigue after childhood TBI.

ACKNOWLEDGEMENTS

The authors wish to acknowledge all children and families who participated in the study.

AUTHOR CONFIRMATION STATEMENT

All authors have participated in the concept and design; analysis and interpretation of data; drafting or revising of the manuscript, and that they have approved the manuscript as submitted.

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AUTHOR DISCLOSURE STATEMENT

All authors report that no competing interests exist. All authors also declare that "no competing financial interests exist."

FUNDING STATEMENT

This work was supported by a grant from the Victoria Neurotrauma Initiative (CO6E1), Australia, the Australian National Health and Medical Research Council (fellowships for VA and CC) and the Victorian Government Operational Infrastructure Support Program. The funding bodies did not play a role in the design of the study, collection, analysis, and interpretation of the data, or writing of the manuscript.

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

DATA AVAILABILITY STATEMENT

Source data will not be made available since no patient approval was obtained for sharing anonymized data. However, detailed analytic methods and study materials, including output files of statistical analyses, will be made available to other researchers on request to the first author.

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Table 1. Injury and demographic characteristics of the TBI sample

	Moderate/Severe TBI	Mild TBI	*p*
N	20	22	-
Male, *n* (%)	13 (65)	19 (86)	0.104
SES, *M (SD)*	65.71 (21.94)	72.63 (19.19)	0.282
Age at injury, *M (SD)*	10.76 (2.60)	10.25 (2.43)	0.519
Age at Assessment, *M (SD)*	12.73 (2.61)	12.25 (2.53)	0.543
Time since injury (months), *M (SD)*	23.74 (2.41)	26.48 (5.25)	**0.039**
Lowest GCS, *M* (*SD*)	10.20 (2.97)	14.32 (1.04)	**<.001**
Hospital stay in days, *M (SD)*	6.99 (6.90)	.80 (1.49)	**<.001**
Surgical intervention, *n* (%)	8 (40.00)	0 (0.00)	**<.001**
Cause of Injury			**0.046**
MVA (Car), *n* (%)	3 (15)	0 (0)	-
MVA (Pedestrian/bike), *n* (%)	4 (20)	2 (9)	-
Fall (stationary), *n* (%)	6 (30)	7 (32)	-
Fall (moving), *n* (%)	7 (35)	7 (32)	-
Kicked/struck by object, *n* (%)	0 (0)	6 (27)	-

GCS: Glasgow Coma Scale; MVA: Motor Vehicle Accident; SES: Socioeconomic status.

Bold denotes statistical significance

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Table 2. Fatigue Mean Score Comparisons of TBI sample and normative sample

	TBI Sample (*n*=42)		Normative Data (*n*=259)[25]				
	Mean	*SD*	Mean	*SD*	*p*	*t*	*d*
Total Fatigue	80.3	14.0	88.2	11.1	**<.001**	4.12	0.63
General Fatigue	83.6	11.4	88.8	12.3	**.011**	2.57	0.44
Sleep/Rest Fatigue	82.4	14.9	87.6	13.5	**.023**	2.28	0.37
Cognitive Fatigue	77.2	20.8	88.2	16.0	**<.001**	3.95	0.59

d: Cohen's *d* effect size estimate; *SD*: standard deviation

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Table 3. Pearson Partial Correlations between Fatigue and SWI lesion burden, r (p)

SWI Variable	Total Fatigue	General	Sleep/Rest	Cognitive
Total SWI Lesion Volume	**-.55 (<.001)**	**-.46 (.005)**	**-.52 (.001)**	**-.50 (.002)**
Total SWI Lesion Number	**-.50 (.002)**	**-.34 (.043)**	**-.54 (<.001)**	**-.49 (.002)**
SWI Frontal Pathology	-.03 (.863)	-.07 (.853)	-.13 (.415)	-.02 (.885)
SWI Extra-Frontal Pathology	-.05 (.773)	.08 (.641)	-.02 (.920)	-.13 (.417)
SWI Basal Ganglia Pathology*	**	**	**	**
SWI Corpus Callosum Pathology	.23 (.151)	.21 (.184)	.24 (.136)	.13 (.415)

Bold denotes a statistically significant association (p<.05).

**SWI lesions of basal ganglia were not identified in this sample

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Table 4. Multi-variable regression models predicting post-injury fatigue

		Total Fatigue		General		Sleep/Rest		Cognitive	
		β	*p*	β	*P*	β	*p*	β	*p*
Step 1									
Injury severity		-.126	.463	.043	.806	-.287	.096	-.164	.364
Sex		-.096	.570	.047	.790	-.098	.559	-.130	.469
Age		-.217	.208	-.207	.246	-.231	.178	-.070	.697
SES		.306	.070	.092	.590	.110	.502	.261	.141
Depression		-.103	.548	-.267	.139	-.143	.404	.009	.959
	Step R^2	.222	.162	.165	.338	.235	.135	.132	.486
Step 2									
Injury severity		.026	.866	.166	.334	-.153	.336	-.007	.968
Sex		-.226	.139	-.059	.726	-.214	.173	-.266	.103
Age		-.308	**.046**	-.280	.098	-.312	**.049**	-.165	.300
SES		.225	.123	.026	.868	.038	.797	.176	.251
Depression		.070	.652	-.127	.467	.012	.941	.190	.254
SWI Volume		-.547	**.002**	-.443	**.019**	-.487	**.006**	-.571	**.002**
	Step R^2	.446	**.006**	.312	.073	.412	**.012**	.376	**.024**
	R^2 change	.224	**.002**	.147	**.019**	.177	**.006**	.244	**.002**

SES: socio-economic status; SWI: susceptibility-weighted imaging

Bold denotes statistical significance

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