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The role of sleep quality on white matter integrity and concussion symptom severity in adolescents

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ABSTRACT

Background: Sleep problems are common after concussion; yet, to date, no study has evaluated the relationship between sleep, white matter integrity, and post-concussion symptoms in adolescents. Using self-reported quality of sleep measures within the first 10 days of injury, we aimed to determine if quality of sleep exerts a main effect on white matter integrity in major tracts, as measured by diffusion Magnetic Resonance Imaging (dMRI), and further examine whether this effect can help explain the variance in post-concussion symptom severity in 12- to 17.9-year-old adolescents.

Methods: dMRI data were collected in 57 concussed adolescents (mean age[SD] = 15.4[1.5] years; 41.2 % female) with no history of major psychiatric diagnoses. Severity of post-concussion symptoms was assessed at study entry (mean days[SD] = 3.7[2.5] days since injury). Using the Pittsburgh Sleep Quality Index (PSQI), concussed adolescents were divided into two groups based on their quality of sleep in the days between injury and scan: good sleepers (PSQI global score $\leq$ 5; N = 33) and poor sleepers (PSQI global score > 5; N = 24). Neurite Orientation Dispersion and Dispersion Index (NODDI), specifically the Neurite Density Index (NDI), was used to quantify microstructural properties in major tracts, including 18 bilateral and one interhemispheric tract, and identify whether dMRI differences existed in good *vs* poor sleepers. Since the interval between concussion and neuroimaging acquisition varied among concussed adolescents, this interval was included in the analysis along with an interaction term with sleep groups. Regularized regression was used to identify if quality of sleep-related dMRI measures correlated with post-concussion symptom severity. Due to higher reported concussion symptom severity in females, interaction terms between dMRI and sex were included in the regularized regression model. Data collected in 33 sex- and age-matched non-concussed controls (mean age[SD] = 15.2[1.5]; 45.5 % female) served as healthy reference and sex and age were covariates in all analyses.

Results: Relative to good sleepers, poor sleepers demonstrated widespread lower NDI (18 of the 19 tracts; FDR corrected $P < 0.048$). This group effect was only significant with at least seven days between concussion and neuroimaging acquisition. Post-concussion symptoms severity was negatively correlated with NDI in four of these tracts: cingulum bundle, optic radiation, striato-fronto-orbital tract, and superior longitudinal fasciculus I. The multiple linear regression model combining sex and NDI of these four tracts was able to explain 33.2 % of the variability in symptom severity ($F[7,49] = 4.9$, $P < 0.001$, Adjusted $R^2 = 0.332$). Relative to non-concussed controls, poor sleepers demonstrated lower NDI in the cingulum bundle, optic radiation, and superior longitudinal fasciculus I (FDR corrected $P < 0.040$).

Conclusions: Poor quality of sleep following concussion is associated with widespread lower integrity of major white matter tracts, that in turn helped to explain post-concussion symptom severity in 12–17.9-year-old adolescents. The effect of sleep on white matter integrity following concussion was significant after one week, suggesting that acute sleep interventions may need this time to begin to take effect. Our findings may suggest an important relationship between good quality of sleep in the days following concussion and integrity of major

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white matter tracts. Moving forward, researchers should evaluate the effectiveness of sleep interventions on white matter integrity and clinical outcomes following concussion.

1. Introduction

Concussion is a transient disturbance in brain functioning induced by a traumatic event (McCrory et al., 2017). In the first week after injury (acute and sub-acute stages of concussion), post-concussion symptoms tend to be non-specific (e.g., irritability, fatigue, nervousness) and reflect severity of concussion (Kontos et al., 2012). These symptoms usually resolve within the first 4 weeks, but they can persist for longer (McCrory et al., 2017). Adolescents, relative to children and young adults, seem more vulnerable to post-concussion symptoms (Covassin et al., 2012; Iverson et al., 2017); likely reflecting the neuro-developmental changes happening in the brain during the transition from childhood to adulthood (Casey et al., 2008). In addition, female adolescents tend to report more post-concussion symptoms than male adolescents. Identifying modifiable factors associated with concussion-related abnormalities in adolescents may provide new tools to manage post-concussion symptoms. Sleep is a promising candidate due to its importance for adolescence health and brain development (Tononi and Cirelli, 2014; Jalbrzikowski et al., 2021;44(10):zsab120.; Dutil et al., 2018).

The relationship between sleep and brain is complex, particularly in adolescents (Tononi and Cirelli, 2014; Jalbrzikowski et al., 2021;44(10):zsab120.; Lebel and Beaulieu, 2011; Casey et al., 2008; Crowley et al., 2007; Tarokh et al., 2016; Crowley et al., 2018; Crowley et al., 2014). Adolescence is a period marked by important shifts in sleep(Crowley et al., 2007; Tarokh et al., 2016; Crowley et al., 2018; Crowley et al., 2014). There is a progressive delay in bedtime and thus sleep onset, which, in association with early rise times due to school, may lead to a chronic state of insufficient sleep(Tarokh et al., 2016; Crowley et al., 2018). During this period, the brain also undergoes several dynamic changes that begin to configure the mature brain(Lebel and Beaulieu, 2011; Casey et al., 2008). Previous studies have shown that these changes in sleep are linked to the maturational changes happening in the entire brain(Tononi and Cirelli, 2014; Jalbrzikowski et al., 2021;44(10):zsab120.). For some regions (e.g., medial orbitofrontal cortex, isthmus cingulate cortex), these relationships are stable throughout adolescence while for others (e.g., cuneus, superior parietal regions) they are only present at certain windows (e.g., early adolescence)(Jalbrzikowski et al., 2021;44(10):zsab120.). In addition, a recent systematic review has also shown that sleep disturbances during childhood and adolescence affect brain function (e.g., decreased memory consolidation and attention) and structure (e.g., decreased gray matter volume, cerebral blood flow, and myelin content)(Dutil et al., 2018). This evidence shows the importance of sleep during brain development. Yet, little is known about the relationship between sleep, brain, and concussion in adolescents. Following concussion, sleep disturbances are common and impact other clinical outcomes(Theadom et al., 2015; Bramley et al., 2017; Jaffee et al., 2015). A clinical study in adults has shown that poorer quality of sleep following concussion was associated with prolonged recovery, worse cognition and higher levels of depression and anxiety-one year after injury(Theadom et al., 2015), suggesting that sleep has restorative functions on the brain that may have long-lasting effects. However, this relationship has not been explored in adolescents.

Diffusion Magnetic Resonance Imaging (dMRI) has been proven to be a powerful tool in identifying abnormalities following concussion(Lima Santos et al., 2021; Fakhran et al., 2014; King et al., 2019;23:101842.; Murugavel et al., 2014; Manning et al., 2017). Previous studies have identified micro- and macro-structural concussion-related abnormalities in several white matter tracts, such as the cingulum bundle(Manning et al., 2017), corpus callosum(Wilde et al., 2008; Henry et al., 2011), corticospinal tract(Henry et al., 2011), inferior longitudinal fasciculus (Lima Santos et al., 2021; Murugavel et al., 2014), superior longitudinal fasciculus(Manning et al., 2017), and uncinate fasciculus(Lima Santos et al., 2021; Fakhran et al., 2014; King et al., 2019;23:101842.). In recent years, multi-compartmental models, such as Neurite Orientation Dispersion and Density Imaging (NODDI)(Zhang et al., 2012; Fukutomi et al., 2018; Beck et al., 2021/01/01/), have emerged as suitable methods for the study of developing brains(Lynch et al., 2020; Genc et al., 2017) and concussion(Palacios et al., 2020;6(32):eaaz6892.; Churchill et al., 2019). NODDI allows for the estimation of microstructural complexity of neurites (dendrites and axons) *in vivo*.(Zhang et al., 2012) Three indices are commonly extracted: Neurite Density Index (NDI), reflecting the intra-neurite density, Orientation Dispersion Index (ODI), reflecting the angular variation of neurites, and FISO (free-water isotropic volume fraction), representing free water volume fraction. (Zhang et al., 2012) NDI, in particular, has been correlated with an indirect index of myelination(Fukutomi et al., 2018; Qian et al., 2020) and has shown higher sensitivity for brain maturation than ODI(Lynch et al., 2020). While there are some reports of low NDI in concussed participants relative to controls and high ODI being associated with prolonged recovery following injury(Palacios et al., 2020;6(32):eaaz6892.; Churchill et al., 2019), no study has evaluated the role of sleep on NODDI measures following concussion. Characterizing this relationship using NODDI may provide more specific markers of concussed- and sleep-related abnormalities in the developing brain.

The goals of this study were twofold. *First,* we aimed to identify the effects of self-reported quality of sleep (Good *vs* Poor sleepers) measures during the days between concussion and scan (INTERVAL, mean[SD] = 6.9[2.5] days) on indirect measures of white matter integrity and/or collinearity. To this end, NDI metrics were extracted in 18 bilateral and one interhemispheric white matter tracts. *Second*, in concussed adolescents only, we examined the relationship between NODDI metrics and post-concussion symptoms. Due to the non-specificity of post-concussion symptoms, we included NDI of all tracts in a feature selection model to identify those that best explained the variability in total symptom severity (Covassin et al., 2009). Finally, age and sex-matched non-concussed controls were included as healthy reference for between-group analyses of tracts associated with post-concussion symptoms. We hypothesized that poor sleepers - relative to good sleepers (and non-concussed controls) - would show decreased NDI in most tracts and that abnormalities in these tracts would be associated with post-concussion symptom severity.

2. Material and methods

2.1. Participants

This study was approved by the Office of Research Protections at the University of Pittsburgh. After being informed on the nature of the study, all adolescents and parents/guardians signed an assent/consent form. Sixty-eight adolescents (age range = 12.1–17.9 years; mean[SD] = 15.4[1.5] years; 41.2 % female) with a recently diagnosed concussion (mean[SD] = 3.7[2.5] days) were recruited through the longitudinal study Investigating Concussion in Adolescents at Risk for Emotion dysregulation (iCARE). All adolescents were right-handed. Thirty-three age- and sex-matched non-concussed controls with no current/history of concussion nor Axis-I diagnoses (Controls; age = 12.5–17.9 years; mean [SD] = 15.2[1.5]; 45.5 % female) were recruited through a local recruitment website (https://pittplusme.org). Exclusion criteria are described in the Supplements.

Eight concussed adolescents were excluded from the analysis due to incomplete neuroimaging acquisition or poor image quality, while other

three adolescents were excluded due to history of major psychiatric disorders (N = 2, anxiety disorders) and use of psychotropic medication (N = 1, amitriptyline), leaving a total of 57 concussed adolescents (Concussed; age range = 12.1–17.5; mean[SD] = 15.3[1.6] years; 40.4 % female). Demographic characteristics of included and excluded participants are reported in Table 1 and Supplemental Table 1.

Table 1
Demographic and clinical characteristics at baseline.

Demographic and clinical characteristics	Non-concussed (N = 33)	Concussed (N = 57)	t(88) or χ2	P[1]
Age, mean [SD], y	15.2 [1.5]	15.3 [1.6]	−0.4	0.720
Sex				
Male, No. (%)	18 (54.5 %)	34 (59.6 %)	0.1	0.802
Female, No. (%)	15 (45.5 %)	23 (40.4 %)		
Race[2]				
Caucasian, No. (%)	25 (75.8 %)	51 (89.5 %)	–	0.331
Non-Caucasian, No. (%)	6 (24.2 %)	6 (10.5 %)		
History of ADHD[2], No. (%)	1 (3.0 %)	4 (7.0 %)	–	0.648
Pubertal Development Scale[3] – total score, mean [SD]	3.9 [1.2]	3.9 [1.0]	−0.1	0.864
PSQI – global score, mean [SD]	4.4 [2.5]	5.1[2.7]	−1.1	0.290
PSQI – SLEEP groups				
Good sleepers, No (%)	21 (63.6 %)	33 (57.9 %)	0.1	0.755
Poor sleepers, No (%)	12 (36.4 %)	24 (42.1 %)		
Demographic and clinical characteristics	Concussed Good sleepers (N = 33)	Concussed Poor sleepers (N = 24)	t(55) or χ2	P[1]
Age, mean [SD], y	15.4 [1.7]	15.3 [1.4]	0.1	0.907
Sex				
Male, No. (%)	20 (60.6 %)	14 (58.3 %)	<0.1	>0.999
Female, No. (%)	13 (39.4 %)	10 (41.7 %)		
Race[2]				
Caucasian, No. (%)	29 (87.9 %)	22 (91.7 %)	–	>0.999
Non-Caucasian, No. (%)	4 (12.1 %)	2 (8.3 %)		
INTERVAL, mean [SD], days	6.6 [2.4]	7.2 [2.3]	−1.0	**0.307**
Pubertal Development Score[3] – total score, mean [SD]	3.9 [1.0]	3.9 [1.0]	0.1	0.877
PSQI – global score, mean [SD]	3.2 [1.3]	7.7 [1.8]	−10.1	**<0.001**
PCSS – total score[4,5], mean [SD]	26.1 [17.8]	36.4 [21.4]	−1.9	*0.061*
Causes of current concussion[2]				
Sports, No. (%)	29 (87.9 %)	17 (70.8 %)	–	0.173
Fall/accident/other, No. (%)	4 (12.1 %)	7 (29.2 %)		
History of previous concussions, No. (%)	8 (24.2 %)	8 (33.3 %)	0.2	0.649
History of migraine, No (%)	8 (24.2 %)	9 (37.5 %)	0.6	0.431

Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; PSQI, Pittsburgh Sleep Quality Index; PCSS, Post-Concussion Symptom Scale.

[1] P values ≤ 0.05 are reported in bold characters; P values between 0.05 and 0.10 are reported in italics.

[2] Fisher exact test was used for these variables due to the small number of participants in each category.

[3] The Pubertal Development Scale (PDS)Petersen et al. (1988) was used to assess pubertal status. Overall score (1–5) was calculated for all adolescents.

[4] There was no correlation between PCSS – total score and PSQI – global score (r < 0.1, P = 0.973).

[5] A mediation model including SLEEP groups as independent variable, averaged NDI of all tracts as the mediator, and PCSS total score as the dependent variable was tested using R. Age and sex were included as covariates. Findings did not reach significance level.

2.2. Clinical assessments.

2.2.1. Concussion and post-concussion symptoms

Concussion was diagnosed by licensed healthcare professionals trained in concussion at the University of Pittsburgh Medical Center Concussion Clinic and identified using the current consensus on sport-related concussion(McCrory et al., 2017): a transitory disturbance in brain functioning caused by complex pathophysiological processes induced by a traumatic brain injury(McCrory et al., 2017). Adolescents who met the concussion criteria were invited to participate in the study. Concussed adolescents were then assessed using the Post-Concussion Symptom Scales (PCSS)(Covassin et al., 2009) at study entry (mean days[SD] = 3.7[2.5] days since injury). PCSS is a symptom inventory in which symptoms are rated using a 0–6 Likert scale. In this scale, 0 indicates no difficulty and 1–6 indicate mild-to-severe difficulties with the symptom. A score combining all symptoms was calculated (range: 0–132).

2.2.2. Quality of sleep

Quality of sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI)(Buysse et al., 1989) in all adolescents at scan. PSQI is a self-rated questionnaire with 19 questions that evaluate seven sleep components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of medication, and daytime dysfunction. To investigate the effect of quality of sleep following concussion on the brain, questions were adapted to assess sleep in the time between injury and scan (INTERVAL). A global score was calculated combining the seven sleep components (range: 0–21). Prior research has shown that a global score greater than five has high sensitivity and specificity in distinguishing good and poor sleepers.(Buysse et al., 1989) Therefore, based on the global score, two sleep groups (SLEEP) of concussed adolescents were created: 1) Good sleepers (global score ≤ 5) and 2) Poor sleepers (global score > 5).

2.3. Neuroimaging data

Acquisition, preprocessing, and quality control steps are described in the Supplements. After correction of eddy current, subject motion, and echo planar imaging distortions,(Andersson et al., 2003; Smith et al., 2004) the NODDI model(Zhang et al., 2012) was fitted using the NODDI toolbox, implemented in Matlab (https://www.nitrc.org/projects/noddi_toolbox/). NDI I maps were derived for each participant and registered to the Montreal Neurological Institute (MNI) space for group-level analyses. Preprocessed dMRI data were also analyzed using *TractSeg*, (Wasserthal et al., 2018; Wasserthal et al., 2018) a convolutional neural network approach that segments white matter tracts using fiber orientation distribution function (fODF) peaks, derived using *Mrtrix3*.(Tournier et al., 2019) Fiber Orientation Distribution (FOD) images were derived in native space and warped into MNI space. The following major white matter tracts were reconstructed: 18 bilateral tracts (anterior thalamic radiation, arcuate fasciculus, cingulum bundle, corticospinal tract, fronto-pontine tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, optic radiation, parieto-occipital pontine tract, striato-fronto-orbital tract, striato-premotor tract, superior longitudinal fasciculus I-III, thalamic-occipital tract, thalamic-parietal tract, thalamic-premotor tract, and uncinate fasciculus) and one inter-hemispheric tract (corpus callosum). ODI and FISO measures were similarly extracted. For bilateral tracts, NDI, ODI, and FISO were averaged across hemispheres to minimize multiple comparisons; however, the presence of a laterality effect on main findings was explored.

Given that INTERVAL varied across concussed adolescents, we evaluated the relationship between INTERVAL and averaged NDI, ODI, or FISO of all tracts using Pearson correlation. These correlations were not significant (NDI: r < 0.1, P = 0.973; ODI: r = -0.1, P = 0.407; FISO: r < 0.1, P = 0.949). In addition, given the impact of movements(Yendiki et al., 2014) on dMRI measures, the effects of rotation and translation

movements were evaluated and included in main analyses if significant ($P > 0.05$). Between-group analyses revealed no differences in rotation ($F[1,88] = 1.5$, $P = 0.211$) and translation ($F[1,88] = 1.1$, $P = 0.299$) between concussed and non-concussed adolescents.

2.4. Statistical approach

To test our hypotheses, we performed a two-level analytic approach in R (version 4.1.0)(Core Team R. R, 2017) combining Analyses of Covariance (ANCOVA), Group-Lasso Interaction-Net (GLINTERNET), (Lim and Hastie, 2015) and multiple linear regression models. GLINTERNET is a variable selection tool that fits interactions between variables in linear regression models.(Lim and Hastie, 2015) This method incorporates continuous and categorical variables, only selecting interactions when both main effects were also selected.(Lim and Hastie, 2015) In addition, to investigate the possible relationships between variables, PROCESS macro(Hayes, 2017) and Johnson-Neyman intervals were applied.(Johnson and Neyman, 1936; Long, 2019).

2.4.1. Level 1 analysis. Effect of quality of sleep on white matter tracts in concussed adolescents

Using ANCOVA, we investigated the effect of quality of sleep following concussion (SLEEP, 2 levels: Good sleepers; Poor sleepers) on the averaged NDI of all tracts. In this model, SLEEP was the Independent Variable (IV) and averaged NDI was the Dependent Variable (DV). Since the interval between concussion and neuroimaging acquisition varied among concussed adolescents, the variable INTERVAL was included as IV along with an interaction term with sleep groups (SLEEP * INTERVAL). Age and sex were included as covariates. Univariate analyses evaluated the effect of the same model on the averaged NDI of each tract. To account for multiple testing, False Discovery Rate (FDR corrected $P < 0.05$) was used.(Benjamini and Hochberg, 1995) Power analyses performed using R(Core Team R. R, 2017) revealed a power of 0.8 and small effect size for these models.

2.4.2. Level 2 analysis. Neural correlates of post-concussion symptoms

Using GLINTERNET, we performed feature selection to identify the strongest correlates of PCSS total score. The model included age, sex, and averaged NDI of each tract as potential correlates. GLINTERNET evaluated the main effects of all variables and the interaction effects between clinical variables (age and sex) and between clinical and neuroimaging variables. As previously done,(Jalbrzikowski et al., 2021) models were tested 100 times using 10-fold cross validation and one-standard deviation lambda (tuning parameter). Non-zero coefficients characterized variables associated with the outcome. Variables selected by the most common model were used as independent variables for multiple linear regressions to estimate the adjusted R2 and the contribution of each variable to PCSS total score (percentage).

2.4.3. Exploratory analyses

Between-group analyses. Analyses explored the NDI differences between each concussed (good or poor sleepers) and non-concussed (good and poor sleepers) groups. Age and sex were included as covariates.

Laterality effect of quality of sleep. To identify whether SLEEP had a lateralization (left or right hemispheres) effect on the NDI of tracts included in *Level 1 analysis*, we performed repeated measure ANOVA for each tract.

Association between SLEEP and ODI or FISO. Using ANCOVA, we investigated the effect of SLEEP and SLEEP * INTERVAL on averaged ODI or FISO of all tracts. Univariate analyses evaluated the effect of the same model on the averaged index of each tract. Age and sex were included as covariates.

Sensitivity analyses. To assess whether the inclusion of INTERVAL influenced the model identified in *Level 2 analysis*, we used ANOVA to compare the model identified in *Level 2 analysis* to a model that included the same correlates in addition to INTERVAL.

3. Results

3.1. Demographic characteristics

Demographic and clinical characteristics are reported in Table 1. Concussed and non-concussed adolescents showed no differences in age, sex, race, pubertal developmental scale, PSQI global score, and SLEEP groups distribution. Of note, four concussed and one non-concussed participants reported history of Attention-Deficit/Hyperactivity Disorder (ADHD), but there was no difference between groups. Out of the 57 concussed adolescents, 24 (42.1 %) reported a poor quality of sleep between concussion and dMRI acquisition (poor sleepers). Among concussed adolescents, there was no demographic or clinical difference between poor and good sleepers.

3.1.1. Level 1 analysis. Effect of quality of sleep on white matter tracts in concussed adolescents

ANCOVA analyses revealed a significant effect of SLEEP, SLEEP * INTERVAL, and age on the averaged NDI of all tracts (Table 2A). Johnson-Neyman analyses revealed that the difference between good and poor sleepers was significant when INTERVAL was equal or above approximately 7 days (INTERVAL > 6.7, $P < 0.05$, Supplemental Fig. 1). Univariate analyses revealed a significant effect of SLEEP * INTERVAL in 18 out of the 19 tracts (Table 2B; Fig. 1). The only tract not associated with SLEEP * INTERVAL was the parieto-occipital pontine tract ($P > 0.05$). In all tracts, relative to good sleepers, poor sleepers showed lower NDI.

Fig. 1 shows panels of the 18 reconstructed white matter tracts associated with quality of sleep following concussion. Tracts are shown in the following order: 1. Anterior thalamic radiation, 2. Arcuate fasciculus, 3. Cingulum bundle, 4. Corpus callosum, 5. Corticospinal tract, 6. Fronto-pontine tract, 7. Inferior fronto-occipital fasciculus, 8. Inferior longitudinal fasciculus, 9. Optic radiation, 10. Parieto-occipital

Table 2
A-B: Effect of quality of sleep following concussion on Neurite Density index (NDI).

Table 2***A*** *– **Effect of quality of sleep on averaged NDI of all tracts***

Variables	F[1,51]	P^1
SLEEP	5.6	**0.021**
INTERVAL	0.1	0.716
Sex	0.0	0.924
Age	7.5	**0.008**
SLEEP * INTERVAL	6.8	**0.012**

Table 2***B*** *– **Univariate analyses – Effect of SLEEP * INTERVAL on NDI of each tract***

Tracts – averaged NDI	F[1,51]	P^1	FDR $P^{1,2}$
Anterior thalamic radiation	5.9	**0.019**	**0.048**
Arcuate fasciculus	4.7	**0.035**	**0.048**
Cingulum bundle	5.4	**0.024**	**0.048**
Corpus Callosum	6.2	**0.016**	**0.048**
Corticospinal tract	6.4	**0.014**	**0.048**
Fronto-pontine tract	4.8	**0.033**	**0.048**
Inferior fronto-occipital fasciculus	7.8	**0.007**	**0.048**
Inferior longitudinal fasciculus	5.7	**0.020**	**0.048**
Optic radiation	4.3	**0.043**	**0.048**
Parieto-occipital pontine tract	3.7	*0.060*	*0.060*
Striato-fronto-orbital tract	12.0	**0.001**	**0.020**
Striato-premotor tract	5.2	**0.027**	**0.048**
Superior longitudinal fasciculus I	4.8	**0.033**	**0.048**
Superior longitudinal fasciculus II	6.0	**0.018**	**0.048**
Superior longitudinal fasciculus III	4.2	**0.045**	**0.048**
Thalamic-occipital tract	4.2	**0.045**	**0.048**
Thalamic-parietal tract	4.4	**0.041**	**0.048**
Thalamic-premotor tract	4.2	**0.045**	**0.048**
Uncinate fasciculus	5.8	**0.020**	**0.048**

Abbreviations: NDI, Neurite Density Index.
[1] P values ≤ 0.05 are reported in bold characters; P values between 0.05 and 0.10 are reported in italics.
[2] FDR corrected P values.

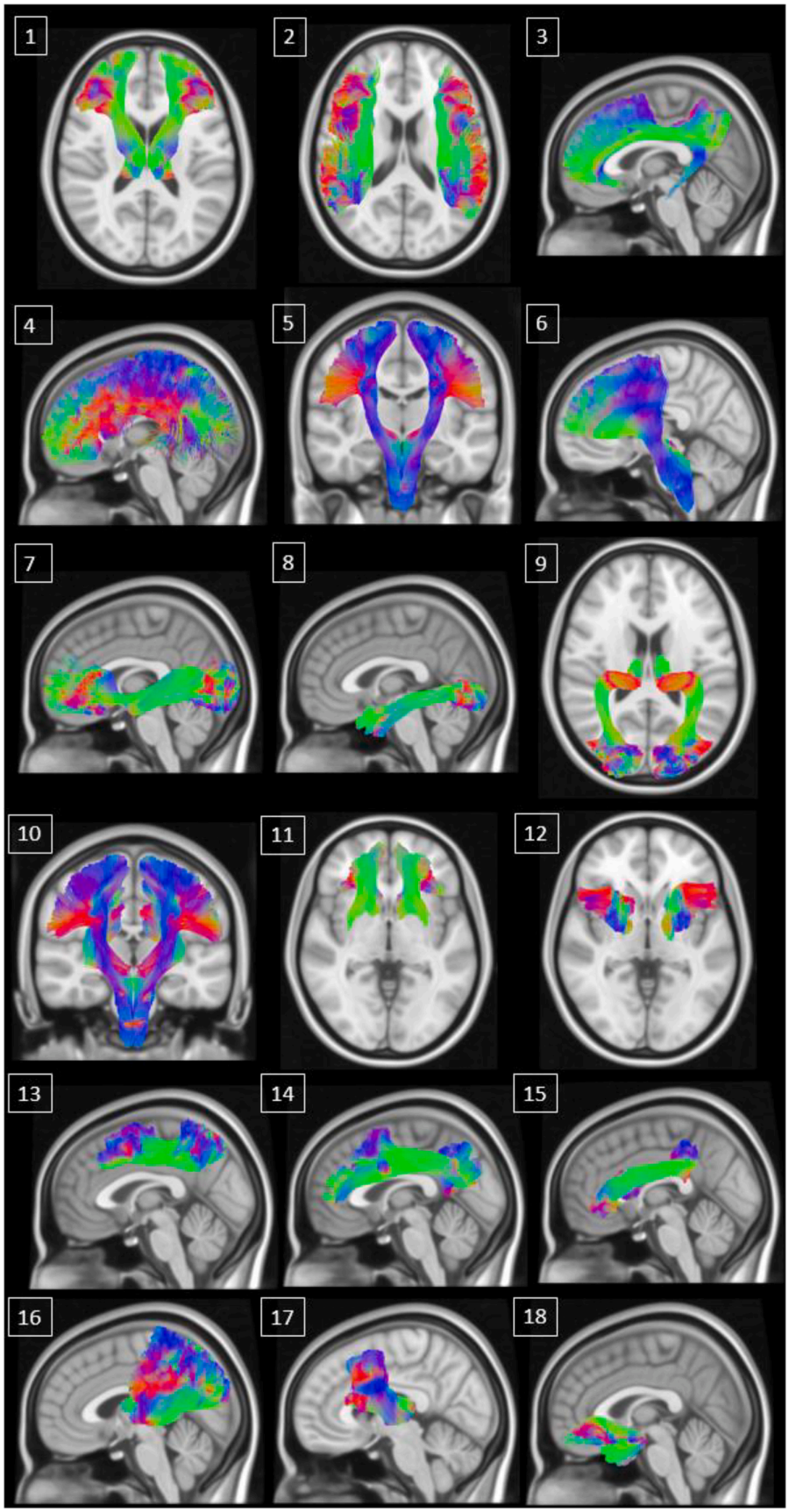

Fig. 1. White matter tracts associated with quality of sleep following concussion.

pontine tract, 11. Striato-fronto-orbital tract, 12. Striato-premotor tract, 13. Superior longitudinal fasciculus I, 14. Superior longitudinal fasciculus II,15. Superior longitudinal fasciculus III, 16. Thalamic-parietal tract, 17. Thalamic-premotor tract, 18. Uncinate fasciculus. The background in the panels is the standard MNI-152 1 mm brain.

3.1.2. Level 2 analysis. Neural correlates of post-concussion symptoms

Variables selected with GLINTERNET are detailed in Table 3. The model combining all variables explained 33.2 % of the variance of PCSS total score at baseline ($F[7,49] = 4.9$, $P < 0.001$, Adjusted $R^2 = 0.332$). Overall, being female was associated with increased PCSS total score and represented the highest individual contribution to the model (36.3 %). However, the interaction between sex and NDI of two tracts (cingulum bundle and optic radiation) showed a higher contribution to the model (42.9 %). In these tracts, lower NDI was associated with increased PCSS total score in female adolescents only (Supplemental Table 2). In addition, two tracts (striato-fronto-orbital tract and superior longitudinal fasciculus I) showed effects not associated with sex in which lower NDI was associated with higher PCSS total score (Fig. 2). Age was not selected for the final model.

3.2. Exploratory analyses

3.2.1. Between-group comparison

Among the four tracts identified in *Level 2* analyses, concussed poor sleepers showed significantly lower NDI relative to non-concussed good, non-concussed poor sleepers, and concussed good sleepers in three of them: cingulum bundle, optic radiation, and superior longitudinal fasciculus I (Table 4, Fig. 2). There was no difference between concussed poor sleepers, concussed good sleepers, and non-concussed controls in the striato-fronto-orbital tract ($P > 0.05$). Concussed good sleepers showed no differences in comparison to non-concussed good and poor sleepers (Supplemental Table 4). In addition, non-concussed good and poor sleepers showed no differences (Supplemental Table 4).

Fig. 2 shows boxplots that depict the group differences upon NDI in the four white matter tracts associated with post-concussion symptoms: cingulum bundle, optic radiation, striato-fronto-orbital tract and superior longitudinal fasciculus I. Non-concussed controls are shown in blue color (good sleepers in light color; poor sleepers in dark color) and concussed participants are shown in green color (good sleepers in light color; poor sleepers in dark color). Asterisks show significant p-values for indicated between-group comparisons. Pound signs indicate p-values between 0.05 and 0.1. Outliers are represented by black dots.

3.2.2. Laterality effect of quality of sleep

There was no laterality effect on the association between SLEEP and NDI in any of tracts included in *Level 1 analysis* (Supplemental Table 5).

Association between SLEEP and ODI or FISO. There was no effect of SLEEP or SLEEP * INTERVAL on the averaged ODI or FISO of all tracts (Supplemental Tables 6 and 7). For ODI, univariate analyses revealed that SLEEP * INTERVAL had a significant effect on 3 out of 19 tracts (thalamo-premotor tract, striato-fronto-orbital tract, and uncinate fasciculus), but this effect did not survive multiple comparison (FDR $P > 0.05$; Supplemental Table 5). For FISO, there was no effect of SLEEP * INTERVAL in any of the tracts. (FDR $P > 0.05$; Supplemental Table 6).

Sensitivity analyses. ANOVA showed no difference between the model identified in *Level 2 analysis* and the same model after the addition of INTERVAL ($F[1,48] = 0.1$, $P = 0.803$).

Table 3
Coefficients and contribution of variables in the GLINTERNET model for concussed adolescents.

Variable		Coefficient	Contribution to the model (%)
Demographic	Sex[1]	0.258	36.3
Neuroimaging	Cingulum bundle NDI	−0.002	3.3
	Optic radiation NDI	−0.013	3.4
	Striato-fronto-orbital tract NDI	−0.135	8.7
	Superior longitudinal fasciculus I NDI	−0.029	5.4
Clinical and neuroimaging interactions	Sex[1] by cingulum bundle NDI	−0.005	15.8
	Sex[1] by optic radiation NDI	−0.235	27.1

Abbreviations: NDI, Neurite Density Index.
[1] Coefficient represents the effect of being female adolescent.

4. Discussion

The current study provides evidence that quality of sleep after the first week of concussion is associated with white matter tracts integrity of tracts implicated with post-concussion symptoms in adolescents. Concussed adolescents experiencing poor quality of sleep showed lower density of neurites (axons and dendrites; NDI) in the vast majority of the investigated tracts compared to concussed adolescents experiencing good sleep. Furthermore, the effect of quality of sleep on these tracts was significant after seven days of self-reported good or poor sleep. Among all tracts, four tracts associated with quality of sleep (cingulum bundle, optic radiation, striato-fronto-orbital tract, and superior longitudinal fasciculus I) were the strongest correlates of total severity of post-concussion symptoms, with lower NDI in these tracts being associated with increased severity of symptoms. In two of these tracts (cingulum bundle and optic radiation), the association between low NDI and increased severity of symptoms was present only in female adolescents. In three of these tracts (cingulum bundle, optic radiation, and superior longitudinal fasciculus I), concussed poor sleepers also showed lower NDI relative to non-concussed controls. The final model combining sex, NDI of these four tracts, and its interactions was able to significantly explain>30 % of the variability of the severity of post-concussion symptoms, with sex being the highest individual contributor for this model.

Sleep disruption following concussion is a common problem(Bramley et al., 2017; Jaffee et al., 2015). Prior research has shown that brain regions associated with sleep regulation are vulnerable to concussion (Singh et al., 2016). Furthermore, in addition to being a primary outcome of concussion, sleep disruption is also associated with secondary clinical outcomes such as persistence of post-concussion symptoms and depression and/or anxiety following concussion(Theadom et al., 2015; Singh et al., 2016). Interestingly, a recent clinical trial has shown that improving sleep after injury in children and adolescents with persistent post-concussion symptoms was associated with improvements in secondary outcomes, such as depressive symptoms(Barlow et al., 2021). In non-concussed participants, sleep has been associated with abnormalities on white matter(Raja et al., 2022; Bai et al., 2021; Telzer et al., 2015; Khalsa et al., 2017). One study showed that increased sleep variability in adolescents without mood or sleep disorders was associated with decreased fractional anisotropy (FA; a microstructural index of the fiber collinearity)(Jones and Leemans, 2011) one year later(Telzer et al., 2015). In line with our findings, this study showed significant effects of sleep on the anterior thalamic radiation, cingulum bundle, corpus callosum, and superior longitudinal fasciculus(Telzer et al., 2015). A study in young adults showed that poor quality of sleep was associated with lower FA in the cingulum bundle(Khalsa et al., 2017). To the best of our knowledge, this is the first study to show an association between quality of sleep, white matter integrity, and post-concussion symptoms. In particular, our findings indicate that the association between sleep and brain is evident in those with at least one week of good sleep. Supporting clinical evidence on the role of sleep on concussion recovery, our findings suggest a protective effect of 'sustained' good sleep on white matter integrity and PCSS. However, due to the cross-

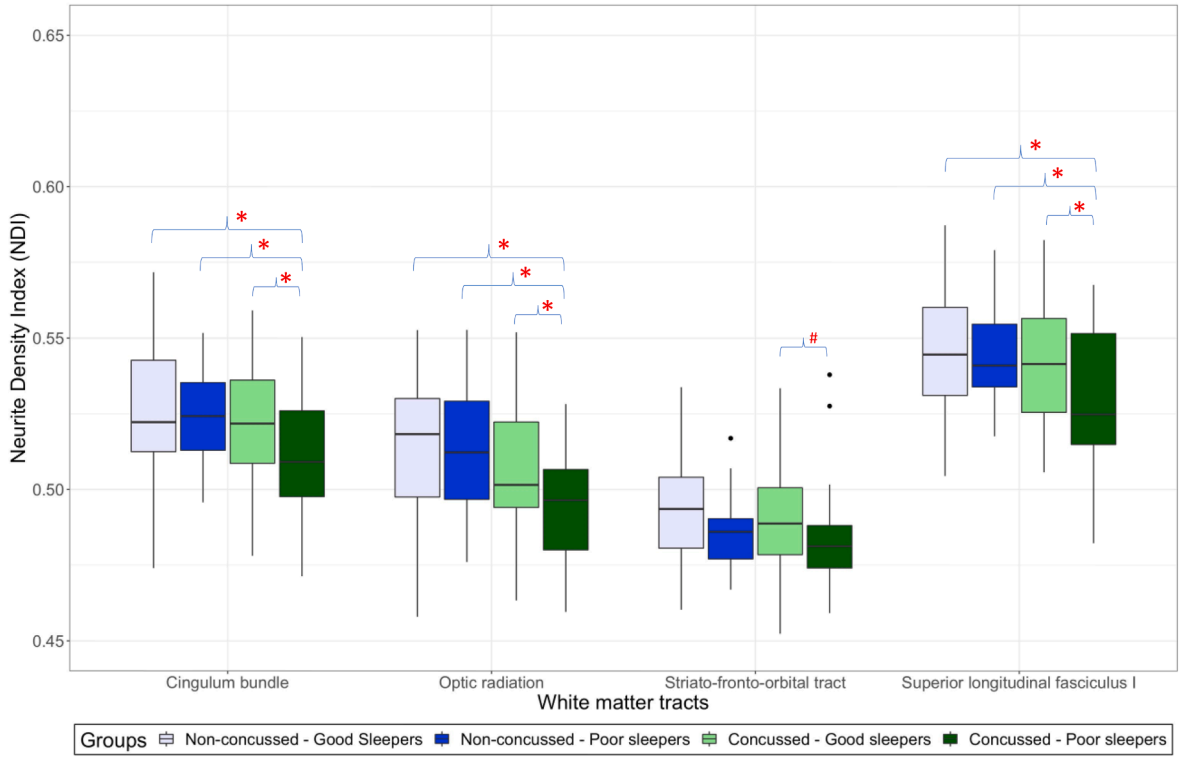

Fig. 2. Between-group differences in white matter tracts associated with post-concussion symptoms.

Table 4
Between-group analyses using Neurite Density Index (NDI) to compare concussed poor sleepers to non-concussed good and poor sleepers.

Concussed poor sleepers vs Non-concussed poor sleepers			
Tract – averaged NDI	F[1,32]	P^1	FDR $P^{1,2}$
Cingulum bundle	6.5	**0.016**	**0.040**
Optic radiation	6.0	**0.020**	**0.040**
Striato-fronto-orbital tract	0.9	0.343	0.343
Superior longitudinal fasciculus I	6.3	**0.017**	**0.040**
Concussed poor sleepers vs Non-concussed good sleepers			
Tract – averaged NDI	F[1,41]	P^1	FDR $P^{1,2}$
Cingulum bundle	6.9	**0.012**	**0.017**
Optic radiation	13.4	**0.001**	**0.005**
Striato-fronto-orbital tract	2.0	0.162	0.162
Superior longitudinal fasciculus I	8.7	**0.005**	**0.010**
Concussed poor sleepers vs Concussed good sleepers			
Tract – averaged NDI	F[1,53]	P^1	FDR $P^{1,2}$
Cingulum bundle	6.2	**0.016**	**0.032**
Optic radiation	5.0	**0.030**	**0.040**
Striato-fronto-orbital tract	3.4	*0.071*	*0.071*
Superior longitudinal fasciculus I	7.6	**0.008**	**0.032**

Abbreviations: NDI, Neurite Density Index.
[1] P values $\leq$ 0.05 are reported in bold characters; P values between 0.05 and 0.10 are reported in italics.
[2] FDR corrected P values.

sectional nature of this study, we cannot exclude that severity of symptoms might have an impact on quality of sleep and/or white matter. Prospective longitudinal studies are needed to clarify these relationships. However, the pathophysiological mechanisms behind these associations are not completely elucidated. Animal models have suggested that sleep affects the expression of myelin-related genes(Bellesi et al., 2013) and sleep loss in adolescent mice is associated with thinner myelin. Our findings draw connections between these studies suggesting that 1) concussion and sleep are associated with white matter integrity, and potentially myelin, in many tracts, 2) good sleep may allow the brain to engage in restorative processes after injury while poor sleep may contribute to the persistence of concussed-related abnormalities, and 3) the effects of good sleep following injury become evident after the first week.

Among the four tracts identified as the strongest correlates of post-concussion symptoms, all four of them were associated with quality of sleep following concussion: cingulum bundle, optic radiation striato-fronto-orbital tract, and superior longitudinal fasciculus I. The cingulum bundle is a key component of the limbic system and connects structures involved in reward, default mode network, and emotional regulation(Bubb et al., 2018). The optic radiation is part of the visual pathway and connects the lateral geniculate body to the primary visual cortex in the occipital lobe(Hofer et al., 2010; Dayan et al., 2015). The striato-fronto-orbital tract is part of the corticostriatal circuitry and is involved with motor behaviors (Haber, 2016) Finally, the superior longitudinal fasciculus I connects the superior parietal lobe to frontal regions and is associated with language functions(Bernal and Altman, 2010; Wang et al., 2016). Altogether, our findings support that post-concussion symptoms are non-specific(Kontos et al., 2012) by showing that a combination of tracts involved with multiple functions have an important contribution to the clinical presentation of concussion. Interestingly, sex was a main component of the models associated with post-concussion symptoms and, in two of these tracts (cingulum bundle and optic radiation), the association between low NDI and increased severity of symptoms was present only in female adolescents. In line with these findings, previous studies have shown that female adolescents are more vulnerable than male adolescents to post-concussion symptoms(Chiang Colvin et al., 2009; Ledoux et al., 2019). This difference in clinical presentation may be a result of the different pace in pubertal development seen in male and female adolescents(Chiang Colvin et al., 2009; Ledoux et al., 2019). In addition, based on the evidence that female adolescents are more prone to sleep disturbances(Li et al., 2021; Johnson et al., 2006); these findings suggest that interventions focused on sleep, and possible tailored by sex, may be able to modify concussion outcomes.

We have investigated the effects of self-reported quality of sleep on

white matter following concussion using novel approaches, but there were limitations in this study. Although clinical and neuroimaging metrics were administered to capture abnormalities emerging within the first few days following concussion, we cannot exclude that the changes detected by this study were independent from one each other. The PSQI is a self-report measure of sleep and the information collected could be affected by self-report bias. The use of wrist actigraphy watches following concussion in future studies may provide more accurate information than self-reported assessments and allow for the identification of different trajectories of sleep and their effects on the brain and symptom recovery. In this study, the interval between concussion and neuroimaging acquisition varied among concussed adolescents. We have included an interaction term between INTERVAL and our sleep groups to examine its contribution to the model. However, future studies with sleep and MRI data collected at repeated, fixed intervals are needed to expand our findings. Although a group of non-concussed adolescents was included as healthy reference and cohort (concussed or non-concussed) was not associated with SLEEP groups, this study did not include pre-injury sleep or MRI data of concussed participants and cannot reject the possibility of pre-existing abnormalities in these concussed adolescents. Future studies should consider collecting this information in order to establish a baseline reference. Finally, future longitudinal studies with larger sample of adolescents are needed to evaluate the effect of pre-injury sleep, pubertal status and hormones on the relationship between concussion, sleep following injury, and brain.

5. Conclusions

To the best of our knowledge, this is the first study that aimed to identify the relationship between sleep and white matter abnormalities following concussion in adolescents. Our findings suggest an important relationship between good sleep following concussion and integrity of white matter tracts implicated with post-concussion symptoms. The association between quality of sleep and white matter integrity following concussion was evident after one week, indicating the importance of promoting good sleep in the days following concussion. These findings provide new targets for early intervention following concussion and may help change trajectory of symptoms in adolescents.

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CRediT authorship contribution statement

João Paulo Lima Santos: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualization, Writing – original draft, Writing – review & editing. **Anthony P. Kontos:** Conceptualization, Methodology, Funding acquisition, Supervision, Project administration, Resources, Writing – review & editing. **Cynthia L. Holland:** Project administration, Investigation, Writing – review & editing. **Richelle S. Stiffler:** Data curation, Project administration, Writing – review & editing. **Hannah B. Bitzer:** Investigation, Writing – review & editing. **Kaitlin Caviston:** Investigation, Writing – review & editing. **Madelyn Shaffer:** Investigation, Writing – review & editing. **Stephen J. Suss Jr.:** Investigation, Writing – review & editing. **Laramie Martinez:** Investigation, Writing – review & editing. **Anna Manelis:** Writing – review & editing. **Satish Iyengar:** Writing – review & editing. **David Brent:** Writing – review & editing. **Cecile D. Ladouceur:** Writing – review & editing. **Michael W Collins:** Writing – review & editing. **Mary L Phillips:** Writing – review & editing. **Amelia Versace:** Conceptualization, Methodology, Funding acquisition, Supervision, Project administration, Resources, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Drs. Kontos and Collins receive royalties from APA Books and research support through the University of Pittsburgh from the National Football League (NFL). Dr. Collins was co-developer and a former shareholder (relationship ended 12/16/19) of ImPACT Applications, Inc. Other authors report no biomedical financial interest or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103130.

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