

# Supplementary Material

## SUPPLEMENTARY APPENDIX

### Methods

#### Participants

Two pediatric patients with mild traumatic brain injury (pmTBI) and three healthy controls (HC) consented but then withdrew prior to completing questionnaires. One additional pmTBI was not administered retrospective questionnaires.

#### Procedures

Participants rated symptom severity retrospectively (i.e., for the month prior to injury) and at the subacute (SA) and early chronic (EC) assessments using a modified version of the Post-Concussion Symptom Inventory (PCSI). The PCSI<sup>1</sup> was modified in the following ways with author permission: 1) the version of the PCSI for 13- to 18-year-olds was also utilized for 12-year-old participants to equate the response scale, and 2) all references to an injury were removed from both questionnaires and instructions to avoid bias in

HC. The retrospective (i.e., 1 month prior to initial visit) and SA (day of initial visit) reporting instructions were also specified in the revised version. Additional secondary self-report symptom measures included Patient Reported Outcomes Measurement Information System (PROMIS) scales for sleep,<sup>2</sup> anxiety, and depression<sup>3</sup> and the Headache Impact Test (HIT-6),<sup>4</sup> which were also rated retrospectively. Finally, all participants completed a semi-structured questionnaire about history of previous head injuries and a self-reported Tanner stage of development questionnaire.<sup>5</sup>

### Results

#### Group comparisons without marijuana use

When removing those pmTBI positive for marijuana use, the Group×Time interaction ( $p=0.049$ ) for depression became significant, with follow-up tests indicating group differences at SA (pmTBI>HC) but not EC assessments.

SUPPLEMENTARY TABLE S1. MATHEMATICAL DETAILS OF PERSISTENT POST-CONCUSSIVE SYMPTOM (PPCS) BURDEN CLASSIFICATION METHODS

PPCS classification	Equation	Term definition
<i>Simple change methods</i>		
ICD-10 <sup>6</sup>	$\begin{cases} \sum_{i=1}^n [(Visit_i - R_i) > 0] \geq 3; X = 1 \\ \sum_{i=1}^n [(Visit_i - R_i) > 0] < 3; X = 0 \end{cases}$	$Visit_i = \text{subacute (SA) or early chronic (EC) visit}$ $i = \text{Post-Concussion Symptom Inventory (PCSI) item index}$
Smyth <sup>7</sup>	$\begin{cases} \sum_{i=1}^n [(Visit_i - R_i) \geq 2] \geq 1; X = 1 \\ \sum_{i=1}^n [(Visit_i - R_i) \geq 2] = 0; X = 0 \end{cases}$	$R = \text{retrospective measure}$ $X = \text{persistent post-concussion symptom (PPCS) designation}$
<i>Standardized change methods</i>		
RCI <sup>8</sup>	$\begin{cases} SE_{Meas} = SD_R \sqrt{(1 - r_{xx})} \\ SE_{diff} = \sqrt{2(SE_{Meas})^2} \\ RCI = \frac{x_{Visit} - x_R}{SE_{diff}} \end{cases}$	$SE_{Meas/diff/est} = \text{standard error of measure/difference score/estimate}$ $SD_R = \text{standard deviation of retrospective measure}$ $r_{xx} = \text{reliability of the measure}$ $X_{Visit}/X_R = \text{individual total SA/EC or retrospective visit PCSI score}$ $RCI = \text{reliable change index}$
RB <sup>16</sup>	<p>Within HC :</p> $\begin{cases} x_{Pred} = \beta_{VioR,HC} x_{R,HC} + C_{VioR,HC} \\ SE_{est} = \sqrt{\frac{\sum (x_{Visit} - x_{Pred})^2}{df_{resid}}} \end{cases}$ <p>Across Groups :</p> $\begin{cases} x_{Pred} = \beta_{VioR,HC} x_{R,j} + C_{VioR,HC} \\ RCI = \frac{x_{Visit,j} - x_{Pred,j}}{SE_{est}} \end{cases}$	$x_{Pred} = \text{predicted rating for SA/EC visit}$ $\beta_{VioR,HC} = \text{beta coefficient for retrospective measure}$ $C_{VioR,HC} = \text{constant for retrospective measure}$ $j = \text{group (healthy control [HC] or patient)}$ $df_{resid} = \text{residual degrees of freedom}$
$Z_{HC}(\text{Log}_{10})$	$\begin{cases} Z_{HC}(\text{Log}_{10}(x_{Visit} + 1)) \geq DisCo - Z_{1.64,j}; X = 1 \\ Z_{HC}(\text{Log}_{10}(x_{Visit} + 1)) < DisCo - Z_{1.64,j}; X = 0 \end{cases}$	$Z_{HC} = \text{Z-transformation based on HC statistical moments}$ $X_{Visit}/X_R = \text{individual total SA/EC or retrospective visit PCSI score}$ $DisCo-Z = \text{distribution-corrected z-score}^{10}$
$Z_{HC}(Visit - R)$	$\begin{cases} Z_{HC}(x_{Visit} - x_R) \geq DisCo - Z_{1.64,j}; X = 1 \\ Z_{HC}(x_{Visit} - x_R) < DisCo - Z_{1.64,j}; X = 0 \end{cases}$	$j = \text{group (HC or patient)}$ $X = \text{PPCS designation}$

Use of Iverson brackets note conditional summation of measure ratings for Simple Change Methods.  
ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, 10th revision.

SUPPLEMENTARY TABLE S2. PCSI SUBSCALE RATINGS

<i>Symptom measures</i>	<i>R HC</i>	<i>R pmTBI</i>	<i>SA HC</i>	<i>SA pmTBI</i>	<i>EC HC</i>	<i>EC pmTBI</i>	<i>HC stability</i>
<b>PCSI</b>							
Physical	1(0–3)	3(0–12)	0(0–2)	7(2–18)	0(0–2)	2(0–11)	R>SA ≈ EC
Cognitive	1(0–3)	1(0–8)	0(0–3)	7(1–16)	0(0–2)	2(0–8)	R>SA ≈ EC
Emotional	1(0–4)	1(0–5)	0(0–3)	2(0–8)	0.5(0–3)	0(0–5)	R>SA ≈ EC
Fatigue	1(0–2)	2(0–5)	0(0–1)	3(1–8)	0(0–2)	1(0–5)	R ≈ EC < SA
<b>PCSI (Parent)</b>							
Physical	0(0–2)	1(0–3)	0(0–1)	5(1–15)	0(0–1)	2(0–5.5)	R>SA ≈ EC
Cognitive	0(0–1)	0(0–2)	0(0–1)	3(0–8)	0(0–1)	0(0–3)	-
Emotional	1(0–3)	1(0–4)	0(0–1.5)	2(0–6)	0(0–2)	1(0–4.5)	R>SA; EC <sup>n.s.</sup>
Fatigue	0(0–1)	0(0–2)	0(0–0)	3(0–8.5)	0(0–2)	0(0–3)	R>SA

All data are formatted as median (interquartile range).

EC, early chronic; HC, healthy control; n.s.,  $p > 0.05$ ; PCSI, Post-Concussion Symptom Inventory; pmTBI; pediatric mild traumatic brain injury; R, retrospective; SA, subacute.

SUPPLEMENTARY TABLE S3. TEST-RETEST RELIABILITY FOR SECONDARY MEASURES

<i>Measures</i>	<i>Test-Retest Reliability: Child</i>					
	<i>R to SA</i>		<i>R to EC</i>		<i>SA to EC</i>	
	<i>HC</i>	<i>pmTBI</i>	<i>HC</i>	<i>pmTBI</i>	<i>HC</i>	<i>pmTBI</i>
<b>PROMIS</b>						
Anxiety	0.85	0.72	0.53	0.56	0.56	0.57
Depression	0.88	0.72	0.63	0.65	0.65	0.67
Sleep	0.78	0.51	0.64	0.58	0.56	0.64
HIT-6	0.81	0.59	0.64	0.55	0.64	0.40

EC, early chronic; HC, healthy control; HIT-6, Headache Impact Test; ICC, intraclass correlation coefficient; pmTBI, pediatric mild traumatic brain injury; PROMIS, Patient Reported Outcomes Measurement Information Systems; R, retrospective; SA, subacute.

### Stability of secondary symptom ratings

Generalized estimating equations models examined rating stability across retrospective, SA, and EC for secondary self-report assessments within HC only. For the headache measure, the Time effect was due to elevated retrospective ( $Wald-\chi^2=43.80$ ;  $p < 0.001$ ) and EC ( $Wald-\chi^2=4.50$ ;  $p=0.034$ ) ratings relative to SA, with no statistical difference between retrospective and EC ratings ( $p=0.09$ ). The Time effect for sleep was due to increased ratings at EC relative to both SA ( $Wald-\chi^2=9.48$ ;  $p=0.002$ ) and retrospective ( $Wald-\chi^2=5.50$ ;  $p=0.019$ ) periods, with no statistical difference between retrospective and SA ( $p=0.11$ ) ratings.

### Supplementary References

- Gioia, G.A., Collins, M., and Isquith, P.K. (2008). Improving identification and diagnosis of mild traumatic brain injury with evidence: psychometric support for the acute concussion evaluation. *J. Head Trauma Rehabil.* 23, 230–242.
- Buysse, D.J., Yu, L., Moul, D.E., Germain, A., Stover, A., Dodds, N.E., Johnston, K.L., Shablesky-Cade, M.A., and Pilkonis, P.A. (2010). Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep* 33, 781–792.
- Pilkonis, P.A., Choi, S.W., Reise, S.P., Stover, A.M., Riley, W.T., and Cella, D. (2011). Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS<sup>®</sup>): depression, anxiety, and anger. *Assessment* 18, 263–283.
- Kosinski, M., Bayliss, M.S., Bjorner, J.B., Ware Jr., J.E., Garber, W.H., Batenhorst, A., Cady, R., Dahlof, C.G.H., Dowson, A., and Tepper, S. (2003). A six-item short-form survey for measuring headache impact: the HIT-6. *Qual. Life Res.* 12, 963–974.
- Kriz, P.K., Stein, C., Kent, J., Ruggieri, D., Dolan, E., O'Brien, M., and Meehan 3rd, W.P. (2016). Physical maturity and concussion symptom duration among adolescent ice hockey players. *J. Pediatr.* 171, 234–239.
- Zemek, R., Barrowman, N., Freedman, S.B., Gravel, J., Gagnon, I., McGahern, C., Aglipay, M., Sangha, G., Boutis, K., Beer, D., Craig, W., Burns, E., Farion, K.J., Mikrogianakis, A., Barlow, K., Dubrovsky, A.S., Meeuwisse, W., Gioia, G., Meehan, W.P., III, Beauchamp, M.H., Kamil, Y., Grool, A.M., Hoshizaki, B., Anderson, P., Brooks, B.L., Yeates, K.O., Vassilyadi, M., Klassen, T., Keightley, M., Richer, L., DeMatteo, C., and Osmond, M.H. (2016). Clinical risk score for persistent postconcussion symptoms among children with acute concussion in the ED. *JAMA* 315, 1014–1025.
- Smyth, K., Sandhu, S.S., Crawford, S., Dewey, D., Parboosingh, J., and Barlow, K.M. (2014). The role of serotonin receptor alleles and environmental stressors in the development of post-concussive symptoms after pediatric mild traumatic brain injury. *Dev. Med. Child Neurol.* 56, 73–77.
- Jacobson, N.S., and Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J. Consult. Clin. Psychol.* 59, 12–19.
- Yeates, K.O., Kaizar, E., Rusin, J., Bangert, B., Dietrich, A., Nuss, K., Wright, M., and Taylor, H.G. (2012). Reliable change in post-concussive symptoms and its functional consequences among children with mild traumatic brain injury. *Arch. Pediatr. Adolesc. Med.* 166, 15–622.
- Mayer, A.R., Bedrick, E.J., Ling, J.M., Toulcuse, T., and Dodd, A. (2014). Methods for identifying subject-specific abnormalities in neuroimaging data. *Hum. Brain Mapp.* 35, 5457–5470.