Amygdala response to emotional faces in adolescents with persistent post-concussion symptoms

Luisa Bohorquez-Montoya[a], Lezlie Y. España[a], Amy M. Nader[a], Robyn E. Furger[a], Andrew R. Mayer[b,c,d,e], Timothy B. Meier[a,f,g,*]

[a] Department of Neurosurgery, Medical College of Wisconsin, Milwaukee, WI, United States
[b] The Mind Research Network/Lovelace Biomedical and Environmental Research Institute, Albuquerque, NM, United States
[c] Department of Neurology, University of New Mexico School of Medicine, Albuquerque, NM, United States
[d] Department of Psychiatry, University of New Mexico School of Medicine, Albuquerque, NM, United States
[e] Department of Psychology, University of New Mexico, Albuquerque, NM, United States
[f] Department of Biomedical Engineering, Medical College of Wisconsin, Milwaukee, WI, United States
[g] Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, Milwaukee, WI, United States

ABSTRACT

Approximately 30% of adolescents with concussion develop persistent post-concussion symptoms (PPCS) that include emotional symptoms. Elevated amygdalae reactivity to emotional faces has been reported in a variety of psychopathologies characterized by emotional symptoms overlapping with those in PPCS. We tested the hypothesis that amygdalae reactivity to emotional faces in adolescents with PPCS + is elevated compared to concussed adolescents without PPCS and healthy controls. Concussed adolescents (ages 14–18) with (PPCS +; n = 23) and without PPCS (PPCS-; n = 13) participated in visits at least 4 weeks post-injury. Adolescents without prior concussion served as controls (HC; n = 15). All participants completed a detailed clinical battery and a common emotional face processing task that involved matching of emotional faces or shapes. Compared to HC and PPCS-, adolescents with PPCS + had elevated depression symptoms, anhedonia, general psychological symptoms, and anxiety symptoms. Contrary to our hypothesis, PPCS + had lower amygdalae activity to the emotional faces versus shapes condition relative to HC and a trend for lower activity relative to PPCS-. There was a non-significant inverse association between anhedonia amygdalae activity in adolescents with PPCS. Results suggest that adolescents with PPCS have altered amygdalae activity during the processing of emotional face stimuli.

Introduction

It is estimated that millions of pediatric concussions occur annually in the United States alone (DePadilla et al., 2018). Although many pediatric concussion patients recover relatively quickly, a recent large-scale study demonstrated that approximately 30% of these patients develop persistent post-concussion symptoms (PPCS; i.e., lasting 4 weeks or more; (Zemek, 2016)). PPCS are heterogenous and non-specific and include cognitive, neurosensory, and emotional symptoms that can negatively impact overall quality of life (Novak et al., 2016; Yeates et al., 2009). Emotional symptoms following brain injury may be especially troubling as they are associated with greater cognitive impairment and worse outcome (Ellis et al., 2015; Haagsma et al., 2015; Levin et al., 2001; Rapoport et al., 2003; van der Naalt et al., 2017).

Alterations in the processing of emotional or affective stimuli have

also been documented following brain injury. For example, a meta-analysis of 13 studies of adult patients with moderate to severe traumatic brain injury (TBI) found facial affect recognition deficits in TBI patients relative to controls (Babbage et al., 2011). Similar findings of impairments in facial emotion recognition have been reported in adolescents and children with TBI (Schmidt et al., 2010; Tonks et al., 2007, 2008; Turkstra et al., 2001). There is some evidence that concussion and mild TBI (mTBI) may also be associated with alterations in emotional processing and regulation. Complicated mTBI patients had impaired recognition of fearful faces relative to controls, though uncomplicated mTBI patients did not (Drapeau et al., 2017). In another study, collegiate athletes with at least two prior concussions were significantly worse at recognizing negative facial emotions relative to asymptomatic athletes without prior concussion (Léveillé et al., 2017).

Functional abnormalities during emotional processing tasks have

also been demonstrated following brain injury. Electrophysiological studies have shown various alterations in cortical processing of emotional expression in athletes with two or more prior concussions (Carrier-Toutant et al., 2018), in military personnel with mTBI (Zuj et al., 2017), and in children and adults with mTBI (D'Hondt et al., 2017; Drapeau et al., 2019). Task-based fMRI studies have also shown abnormalities associated with emotional processing. Greater bilateral amygdalae activity was observed in veterans with previous blast injury and current major depressive disorder (MDD) relative to veterans with prior blast injury and no MDD (Matthews et al., 2011). Reduced activity in the left superior parietal gyrus and bilateral orbitofrontal cortex was observed in response to fearful faces in mTBI patients two weeks following a motor vehicle collision (Wang et al., 2017). One relevant small study, however, reported no significant differences in activity in response to emotional go-no-go tasks in adolescents with elevated depressive symptoms following concussion relative to those without elevated symptoms (Ho et al., 2018). Finally, differences in amygdala reactivity to emotional faces (i.e., typically elevated activity) have also been reported in a variety of psychopathologies in adolescents characterized by emotional symptoms that are commonly observed in patients with PPCS (Demenescu et al., 2011, 2013; Ferri et al., 2014; Peluso et al., 2009; Prater et al., 2013; Yang et al., 2010).

The goal of this pilot study was to determine the effects of pediatric concussion with and without PPCS on amygdala activation in response to emotional faces using a common perceptual emotional matching fMRI task (Hariri et al., 2002). A priori analyses focused on the amygdala due to its central role in facial expression recognition (Adolphs et al., 1995) and emotional regulation (Banks et al., 2007; Demenescu et al., 2013). The amygdalae also have known sensitivity to brain injury and concussion due to the high shear strain that affects medial brain regions and the proximity to the sphenoid (Beauchamp et al., 2011; Bigler, 2007; Wilde et al., 2007). Based on this and the aforementioned literature on other psychopathologies that share similar symptoms with PPCS, we hypothesized that adolescents with PPCS would have elevated amygdalae activation in response to emotional faces compared to concussed adolescents without PPCS and healthy controls.

Methods

The Children's Hospital of Wisconsin Institutional Review Board approved all aspects of this study. Minors provided written assent; adults and parents of minors provided written consent. A total of 36 adolescents (ages 14–18) with concussion were recruited from a local concussion clinic ($n = 32$) or the community ($n = 4$) and are included in the current study. Concussions were diagnosed based on criteria outlined in the Zurich Consensus Statement of Concussion in Sport (McCrory et al., 2013). Concussed patients completed visits at least four weeks following injury to align with prior definitions of PPCS (Zemek, 2016). Patients reporting persistent symptoms at their visit were classified as having PPCS (PPCS+; $N = 23$), while patients no longer reporting persistent symptoms were classified as PPCS- ($N = 13$). Symptom presence was determined based on a combination of factors including whether the patient's healthcare provider had declared them fully recovered from their injury, the Sport Concussion Assessment Tool −3rd Edition symptom checklist scores, and/or a subjective report of the percentage that participants felt they were recovered relative to how they felt before their injury. Non-injured adolescents ($n = 15$; age 14–18) with no history of concussion were recruited from the community and served as healthy controls (HC). Exclusion criteria for all participants included history of moderate or severe TBI, history of psychiatric disease, autoimmune disease, neurodevelopmental disorder (e.g., ADHD), neurological conditions (e.g., epilepsy, migraines), endocrine disease, cardiovascular disease, use of neuroactive medications unrelated to PPCS (e.g., antidepressants, anxiolytics), or contraindications to MRI. For concussed adolescents,

injuries occurring during assault or motor vehicle accidents were also excluded; diagnosis of de novo psychiatric disorders following concussion was not exclusionary.

Clinical battery

Demographic and health information were collected, including self-report of Tanner stage development and an estimate of household socioeconomic status (SES). A battery consisting of cognitive measures, concussion symptom assessment, and psychological measures was administered. The Wechsler Test of Adult Reading (WTAR) was used to estimate premorbid intellectual functioning. Neuropsychological deficits were assessed using the Wechsler Adult Intelligence Scale -IV Processing Speed Index (WAIS-PSI) and Trail Making Test Forms A and B (Trails A, Trails B). Psychological measures included: Global Severity Index from the Brief Symptom Inventory - 18 (BSI-GSI) to measure general psychological distress; the Generalized Anxiety Disorder 7-item scale (GAD-7) to measure anxiety; the Patient Health Questionnaire – 9 (PHQ-9) to measure depression, and the Snaith-Hamilton Pleasure Scale (SHAPS) to assess anhedonia. The Sport Concussion Assessment Tool – 3rd Edition (SCAT3) symptom severity score was used to assess concussion symptom burden. Concussion patients also self-reported the percentage that they felt they were recovered relative to how they felt before their injury; this metric was used as a subjective measure of recovery (percent recovered).

Emotional processing task

Two runs of an emotional face processing task adapted from Hariri and colleagues as part of the Human Connectome Project was used to elicit amygdala activity (Barch et al., 2013; Hariri et al., 2002). Stimuli were presented on a back-projected screen using E-Prime Software. Participants were presented with alternating blocks of trials of either emotional faces (i.e. angry or fearful) or shapes during which participants were asked to match one of two faces/shapes at the bottom of the screen to the face/shape at the top of the screen via a MR-safe button box response. Six trials of each stimulus (i.e., faces or shapes) were presented per block. Each trial consisted of a 2000 ms stimulus presentation and a 1000 ms inter-trial interval. Prior to each block, a 3000 ms cue period was presented, resulting in a total block duration of 21 s. Three face blocks and three shapes blocks were presented for each separate run, with an 8 s count down followed by a 12 s fixation period at the beginning of each run and an 8 s fixation at the end of each run.

Imaging parameters and processing

Imaging data were collected on a 3T GE MR750 scanner using a brain-dedicated 32-channel receiver coil. Due to an upgrade in scanner software version, two similar protocols were deployed over the course of the study. Task data were collected across two runs using gradient-echo echo-planar imaging (EPI) sequences with the following parameters: hyperband acceleration factor = 8, TR/TE 720/30 or 720/22 ms, flip angle = 50°, FOV = 210 or 208 mm, acquisition matrix = 104×104, slice thickness = 2 mm, plane of acquisition = sagittal or axial, phase encode direction = $P >> A$. Reverse phase-encoded scans were collected to allow susceptibility-induced distortion correction. A high-resolution T_1-weighted structural image was collected for anatomical reference ($1 \times 1 \times 1mm^3$ resolution). In addition, T_2-weighted, T_2-weighted fluid-attenuated inversion recovery, and susceptibility weighted images were collected to identify potential trauma-related pathology. Board-certified neuroradiologists, blinded to diagnosis, identified acute (i.e., trauma-related) or non-acute findings that prompted recommendation for clinical follow-up, as in our prior work (Klein et al., 2019). Parameters for anatomical scans are provided in the Supplementary Material.

MRI data were processed using Analysis of Functional NeuroImages

Table 1
Sample characteristics and clinical data.

Demographics	PPCS +	PPCS-	HC	Statistic
Total No.	23	13	15	
Sex (No. F)	14	7	8	$X^2(2) = 0.28$, $p = 0.87$
Race				FET, $p = 0.28$
No. White	17	12	14	
No. Other/NR	6	1	1	
Ethnicity				FET, $p = 0.36$
No. Not Hispanic	20	12	15	
No. Hispanic/NR/UN	3	1	0	
Age	16.20 ± 1.07	16.18 ± 0.77	16.35 ± 1.15	$F(2,48) = 0.12$, $p = 0.89$
SES	52.00 ± 6.97	48.85 ± 9.53	54.37 ± 5.27	$F(2,48) = 2.00$, $p = 0.15$
Puberty Status*				FET, $p = 0.87$
No. Pre-puberty	1	0	0	
No. Mid-puberty	4	2	3	
No. Late-puberty	13	9	8	
No. Post-puberty	2	2	4	
Injury Information				
Median Prior Concussions [IQR]	1[0–2]	1[0–2]	0[0–0]	$H = 14.76$, $p = 0.001$
Median Days Since Injury [IQR]	31[29–77]	35[30.5–68.5]	NA	$U = 173.5$, $p = 0.43$
Median Self-report% Recovered	80[60–90]	100[100–100]	NA	$U = 298$, $p < 0.001$
LOC (No. yes)	4	0	NA	FET, $p = 0.27$
PTA (No. yes)	5	4	NA	FET, $p = 0.69$
RGA (No. yes)	2	2	NA	FET, $p = 0.61$
Cognitive Battery				
WTAR	100.39 ± 13.93	103.31 ± 15.86	108.60 ± 7.29	Wald $X^2 = 3.89$, $p = 0.14$
Trails-A (sec)	21.31 ± 6.48	20.98 ± 5.95	19.89 ± 8.13	Wald $X^2 = 0.42$, $p = 0.81$
Trails-B (sec)	53.93 ± 16.80	44.35 ± 10.41	50.28 ± 14.61	Wald $X^2 = 3.70$, $p = 0.16$
WAIS-PSI	97.87 ± 13.31	104.00 ± 12.59	106.07 ± 17.14	Wald $X^2 = 3.56$, $p = 0.17$
Concussion Symptoms				
SCAT-3 Symp. Sev.	22.17 ± 19.94	2.08 ± 2.29	3.20 ± 5.10	Wald $X^2 = 48.43$, $p < 0.001$
Psychological Measures				
GAD-7	5.17 ± 4.62	2.62 ± 3.38	1.33 ± 1.63	Wald $X^2 = 11.40$, $p = 0.003$
SHAPS	25.78 ± 5.04	20.69 ± 4.79	22.73 ± 4.79	Wald $X^2 = 9.75$, $p = 0.008$
PHQ-9	8.39 ± 5.36	3.69 ± 4.07	2.20 ± 2.14	Wald $X^2 = 13.38$, $p = 0.001$
BSI-18 GSI	11.83 ± 11.77	2.69 ± 3.28	2.47 ± 3.56	Wald $X^2 = 24.11$, $p < 0.001$
Task/Scan Measures				
Scanner Software Version				$X^2(2) = 0.40$, $p = 0.82$
No. DV25	10	5	5	
No. DV26	13	8	10	
Euclidean Norm of Motion Parameters	0.06 ± 0.02	0.06 ± 0.01	0.06 ± 0.02	Wald $X^2 = 0.70$, $p = 0.70$
% Non-censored Volumes	99.14 ± 1.09	99.32 ± 0.95	98.69 ± 3.07	Wald $X^2 = 0.95$, $p = 0.62$
Task Accuracy	0.96 ± 0.03	0.98 ± 0.02	0.98 ± 0.01	Wald $X^2 = 10.37$, $p = 0.006$
Task Response Time	904.64 ± 189.67	781.33 ± 103.12	789.03 ± 132.19	Wald $X^2 = 7.88$, $p = 0.02$

Shown are means and standard deviations unless otherwise indicated. PPCS + = concussion patients with persistent post-concussion symptoms, PPCS- = concussion patients without persistent post-concussion symptoms, HC = healthy controls.

* Puberty status unavailable for 3 PPCS+ participants. No. = number, F = female, FET = Fisher's Exact Test, SES = socioeconomic status, IQR = interquartie range, LOC = loss of consciousness, PTA = post-traumatic amnesia, RGA = retrograde amnesia, WTAR = Wechsler Test of Adult Reading Standard Score, WAIS-PSI = Wechsler Adult Intelligence Scale -IV Processing Speed Index, SCAT-3 Symp. Sev. = Sport Concussion Assessment Tool – 3rd Edition Symptom Severity Score, GAD-7 = Generalized Anxiety Disorder 7-item scale, SHAPS = Snaith-Hamilton Pleasure Scale, PHQ-9 = Patient Health Questionnaire 9-item scale, BSI-18 GSI = Brief Symptom Inventory −18 Global Severity Index.

(AFNI) software unless otherwise noted (Cox, 1996). Structural images were skull-stripped using a union mask of segmented gray and white matter from Statistical Parametric Mapping 12. The resulting skull-stripped brain was registered to the MNI-152 template using an affine registration followed by non-linear warp using FMRIB Software Library (FSL; (Jenkinson et al., 2012)). The first 27 volumes from each task run were removed to allow for stabilization of longitudinal magnetization and to account for auto-calibration data. The AFNI program 3dDespike was used to remove spike signal artifacts from each time series by interpolation of data from neighboring time points. FSL topup was used to correct for susceptibility-induced distortion (Andersson et al., 2003; Smith et al., 2004). All volumes from both task runs were registered to the first volume of the first run to account for head motion. FSL's FLIRT was used to calculate a 6°-of-freedom registration between the first EPI volume of the first task run and the structural scan using the boundary-based registration cost-function (Greve and Fischl, 2009; Jenkinson et al., 2002). This matrix was concatenated with the structural-to-standard template registration matrix to create a single transformation matrix that was applied with a non-linear warp to bring each task run to standard space with 2 mm isotropic resolution. EPI data were spatially smoothed using a Gaussian blur of 4 mm and each voxel was scaled to mean of 100.

For each participant, task data were modeled with a generalized least squares model to account for temporal autocorrelation using the AFNI program 3dREMLfit. Responses to faces and shapes were modeled by convolving 21 s block stimuli (via AFNI BLOCK model) to face blocks or shape blocks with a canonical hemodynamic response function. Motion parameters and their first derivatives were included as nuisance regressors, along with linear drift. Volumes with excessive head motion, calculated as Euclidean norm of the six motion parameters greater than 0.3, were censored from analyses with the preceding volume. The contrast of faces versus shapes was calculated for each participant.

The Automated Anatomical Labeling atlas (version 2) was re-sampled to 2 mm isotropic voxels and used to define left and right amygdala for *a priori* region-of-interest analyses (Rolls et al., 2015; Tzourio-Mazoyer et al., 2002). The mean beta weight corresponding to the faces versus shapes contrast was calculated for the left and right amygdalae of each participant. The left and right pre-central gyri were

defined as negative control regions-of-interest as no stimuli specific activity was expected in these regions.

Statistical analysis

Statistical analysis was conducted in SPSS v24. Group differences in demographic variables and injury characteristics were assessed using analyses of variance, chi-square tests, Fisher's Exact tests, Mann-Whitney U tests, or Kruskal-Wallis tests as appropriate. Generalized linear models were fit to assess group differences in self-reported symptom severity, cognitive measures, psychological measures, and task performance variables using either normal, Poisson, or negative binomial distributions (e.g., for count data) based on goodness of fit parameters. For amygdala activity, a repeated measures general linear model was performed with hemisphere (i.e., left and right hemisphere) as a within-subject variable and the between-subjects variables of group and scanner software version. Due to group differences in task performance (see Results), sensitivity analyses determined if group effects on amygdala activity changed with the inclusion of accuracy and response time as additional covariates. Associations between psychological measures and amygdala activity were limited to the PPCS+ group (see Results) and were assessed separately for each psychological measure using a repeated measures general linear model with hemisphere as a within-subject variable and controlling for scanner software version. A nominal significance level of alpha = 0.05 was used for all analyses.

Finally, a secondary voxel-wise general linear model assessed the effect of group on the faces versus shape contrast in gray matter, with scanner software version included as a covariate, using AFNI's 3dMVM program (Chen et al., 2014). For the voxel-wise analysis, Monte Carlo simulations (10,000 iterations in 2 mm isotropic space) determined the necessary correction for family-wise error rate of $p < 0.05$ based on the smoothness of the residuals, which were estimated using a non-Gaussian, spherically symmetric autocorrelation function in AFNI (smoothness parameters = 0.72, 2.77, and 5.87, effective FWHM = 6.59, voxel p value = 0.001, first-nearest neighbor clustering, minimum cluster volume = 177.6 µL).

Results

Demographics and clinical data

There were no significant group differences in sex, race, ethnicity, age, SES, puberty status, WTAR scores, head motion during the emotional processing task, or scanner software version ($ps > 0.10$; Table 1). Additional information for concussed patients (e.g., cause of injury) can be found in **Supplementary Table 1**. Similarly, the time since injury and the percentage of concussion patients with loss of consciousness, retrograde amnesia, or post-traumatic amnesia did not differ between PPCS+ and PPCS- ($ps > 0.10$). By design, PPCS+ patients reported significantly lower percent recovery relative to pre-injury baseline compared to PPCS- patients ($p < 0.001$), while PPCS+ and PPCS– had significantly more prior concussions than HC ($ps = 0.001$).

As expected, there was a significant effect of group on symptom severity scores ($p < 0.001$; Table 1, Table 2), with PPCS+ reporting more severe concussion symptoms than PPCS- and HC ($ps < 0.001$). There were also group differences in all psychological measures ($ps < 0.01$). PPCS+ patients reported significantly higher depression symptoms (PHQ-9) and more symptoms of general psychological distress (BSI-GSI) relative to both PPCS- and HC ($ps < 0.05$). PPCS+ patients also reported more anxiety symptoms (GAD-7) relative to HC ($p < 0.005$) and a non-significant trend for higher anxiety symptoms relative to PPCS- ($p < 0.10$). PPCS+ patients reported significantly greater anhedonia (SHAPS) relative to PPCS- ($p < 0.005$) and a non-significant trend of greater anhedonia relative to HC ($p < 0.10$). There were no significant group differences in cognitive performance (i.e., Trails A, Trails B, WAIS-PSI; $ps > 0.10$). Finally, board-certified

neuroradiologists did not identify any acute, trauma-related findings on anatomical MRI measures in any participant. For descriptive purposes, Spearman correlation coefficients of clinical measures and task performance are reported in **Supplementary Table 2**.

Task performance

There were significant group differences in both accuracy and reaction time on the emotional processing task in the scanner ($ps < 0.05$; Tables 1 and 2; Fig. 1), with PPCS+ performing less accurately and more slowly than PPCS- and HC ($ps < 0.05$). The group difference in task accuracy was still significant when excluding the outlier in the PPCS+ group ($p = 0.008$), with lower accuracy in the PPCS+ group relative to PPCS- and HC ($ps < 0.05$).

Emotional face activity

The repeated-measures general linear model for task-related amygdala activity (i.e., faces versus shapes) found a significant effect of group (F(2,47) = 5.68, $p = 0.006$, $\eta^2 = 0.20$), with PPCS+ having significantly lower amygdala activity in the faces versus shapes contrast relative to HC ($p = 0.002$) and a trend for lower amygdala activity relative to PPCS- ($p = 0.08$; Fig. 2). There was no significant hemisphere effect (F(1,47) = 0.34, $p = 0.56$, $\eta^2 = 0.007$) or group-by-hemisphere interaction (F(2,47) = 0.60, $p = 0.55$, $\eta^2 = 0.02$). Sensitivity analyses showed that the group effect remained significant (F(2,45) = 4.04, $p = 0.02$, $\eta^2 = 0.15$) when controlling for task performance (accuracy and response time), with significantly lower activity in PPCS+ relative to HC ($p = 0.007$), as in the primary analysis. Exploratory general linear models conducted for left and right hemisphere amygdala activity, separately, showed a significant group effect for right (F(2,47) = 6.90, $p = 0.002$, $\eta^2 = 0.23$) but not left amygdala activity (F(2,47) = 2.22, $p = 0.12$, $\eta^2 = 0.08$), with PPCS+ having significantly lower activity in the faces versus shapes contrast in the right amygdala relative to HC ($B = 0.20$, SE = 0.05, $p = 0.001$, 95%CI [0.09, 0.30]) and PPCS- ($B = 0.11$, SE = 0.06, $p = 0.049$, 95%CI[0.00, 0.22]). Parenthetically, we note that the effect of group was significant for the left amygdala with the exclusion of the two PPCS- participants with the lowest face versus shape beta weights ($p < 0.05$; see Fig. 2), although these points were not extreme outliers (< 3 standard deviations from the group mean).

The repeated-measures general linear model for task-related pre-central gyrus activity (i.e., faces versus shapes) found a significant effect of hemisphere (F(1,47) = 22.99, $p < 0.001$, $\eta^2 = 0.33$), with greater task-related activity in the right than left pre-central gyrus. There was no significant group effect (F(2,47) = 0.42, $p = 0.66$, $\eta^2 = 0.02$) or group-by-hemisphere interaction (F(2,47) = 0.33, $p = 0.72$, $\eta^2 = 0.01$).

Voxel-wise analyses found no significant main effect of group in the faces versus shapes contrast with appropriate multiple comparison correction (family-wise error $p > 0.05$). Brain activity associated with faces versus shapes across all participants is shown in Fig. 3. Greater activity to faces compared to shapes was observed in bilateral amygdalae, inferior frontal gyri pars orbitalis and pars triangularis, posterior orbitofrontal cortex, and frontal medial orbital cortex. Greater face-related activity was also observed in visual cortex, including bilateral lingual gyri, fusiform gyri, inferior and middle occipital gyri, and cuneus. Greater shape-related activity was observed in bilateral inferior parietal lobules, supramarginal gyri, middle frontal gyri, insula, Rolandic operculum, middle cingulate cortex and caudal anterior cingulate cortex.

Associations of amygdala activity and psychological measures

There were no significant associations between amygdala activity and psychological measures in PPCS+ ($ps > 0.05$; Table 3; Fig. 4), though there was a non-significant trend of greater anhedonia scores

Table 2
Pairwise comparisons for clinical measures and task performance.

[lower, upper]	Comparison[a]	Est.	SE	p-value	95% CI
Cognitive battery					
WTAR					
	HC	8.21	4.16	0.05	[0.05, 16.37]
	PPCS-	2.92	4.35	0.50	[−5.62, 11.45]
Trails-A (sec)					
	HC	−1.42	2.22	0.52	[−5.76, 2.92]
	PPCS-	−0.33	2.32	0.89	[−4.87, 4.21]
Trails-B (sec)					
	HC	−3.65	4.76	0.44	[−12.98, 5.68]
	PPCS-	−9.59	4.98	0.05	[−19.34, −0.18]
WAIS-PSI					
	HC	8.20	4.63	0.08	[−0.87, 17.27]
	PPCS-	6.13	4.84	0.20	[−3.35, 15.61]
Concussion Symptoms					
SCAT-3 Symp. Sev.					
	HC	−1.94	0.36	≤*0.001*	[−2.65, −1.22]
	PPCS-	−2.37	0.40	≤*0.001*	[−3.15, −1.59]
Psychological Measures					
GAD-7					
	HC	−1.36	0.41	*0.001*	[−2.16, −0.55]
	PPCS-	−0.68	0.40	0.09	[−1.46, 0.10]
SHAPS					
	HC	−0.13	0.07	0.06	[−0.26, 0.01]
	PPCS-	−0.22	0.07	*0.003*	[−0.36, −0.08]
PHQ-9					
	HC	−1.34	0.38	≤*0.001*	[−2.09, −0.59]
	PPCS-	−0.82	0.38	*0.03*	[−1.57, −0.07]
BSI-18 GSI					
	HC	−1.57	0.38	≤*0.001*	[−2.30, −0.83]
	PPCS-	−1.48	0.39	≤*0.001*	[−2.25, −0.71]
Task Performance					
Task Accuracy					
	HC	0.02	0.01	*0.01*	[0.01, 0.04]
	PPCS-	0.02	0.01	*0.006*	[0.01, 0.04]
Task Response Time					
	HC	−115.61	50.13	*0.02*	[−213.87, −17.36]
	PPCS-	−123.31	52.41	*0.02*	[−226.04, −20.58]

[a] Reference group is patients with persistent post-concussion symptoms. PPCS- = concussion patients without persistent post-concussion symptoms, HC = healthy controls, Est. = estimate, SE = standard error, CI = confidence interval, WTAR = Wechsler Test of Adult Reading Standard Score, WAIS-PSI = Wechsler Adult Intelligence Scale -IV Processing Speed Index, SCAT-3 Symp. Sev. = Sport Concussion Assessment Tool – 3rd Edition Symptom Severity Score, GAD-7 = Generalized Anxiety Disorder 7-item scale, SHAPS = Snaith-Hamilton Pleasure Scale, PHQ-9 = Patient Health Questionnaire 9-item scale, BSI-18 GSI = Brief Symptom Inventory −18 Global Severity Index.
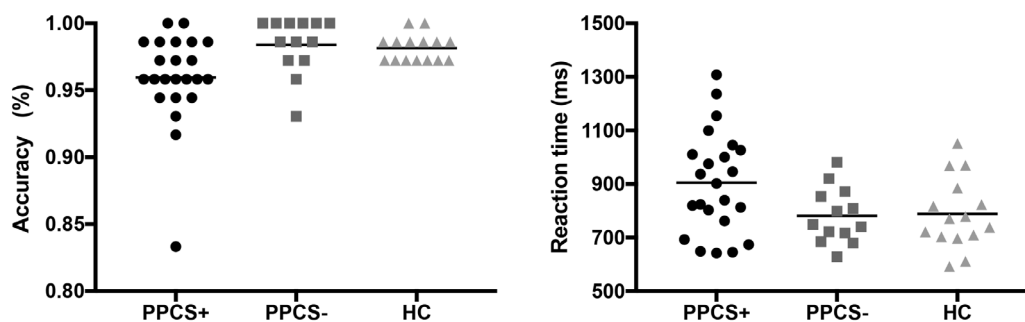

Fig. 1. Task performance on the emotional face task. Shown is the accuracy and response time for the task paradigm for adolescents with persistent post-concussion symptoms (PPCS+), adolescents without persistent post-concussion symptoms (PPCS-), and healthy control adolescents (HC) in the amygdalae and the pre-central gyri. Horizontal line represents group mean.

being associated with lower mean amygdala activity (F(1,20) = 3.11, $p = 0.09$, $\eta^2 = 0.14$).

Discussion

This pilot study investigated the neural correlates of emotional face processing in concussed adolescents with and without persistent symptoms as well as non-injured controls. As expected, adolescents with PPCS had elevated psychological symptoms including depression symptoms, anxiety symptoms, anhedonia, and general psychological distress relative to concussed adolescents without PPCS and/or uninjured healthy controls. Adolescents with PPCS also had significantly

decreased bilateral amygdala activity to emotional faces compared to healthy controls; an effect largely driven by right amygdala activity. Importantly, this difference held when controlling for group differences in task performance. These pilot results suggest that amygdala hypoactivity in response to emotional faces may be a biomarker for persistent symptoms following concussion in adolescents and highlight the possibility that PPCS is associated with functional abnormalities in emotional processing.

The effects of concussion with and without persistent symptoms on emotional face processing are not well studied. Given the dearth of prior studies, we hypothesized that adolescents with PPCS would have elevated responses to emotional faces based on observations of
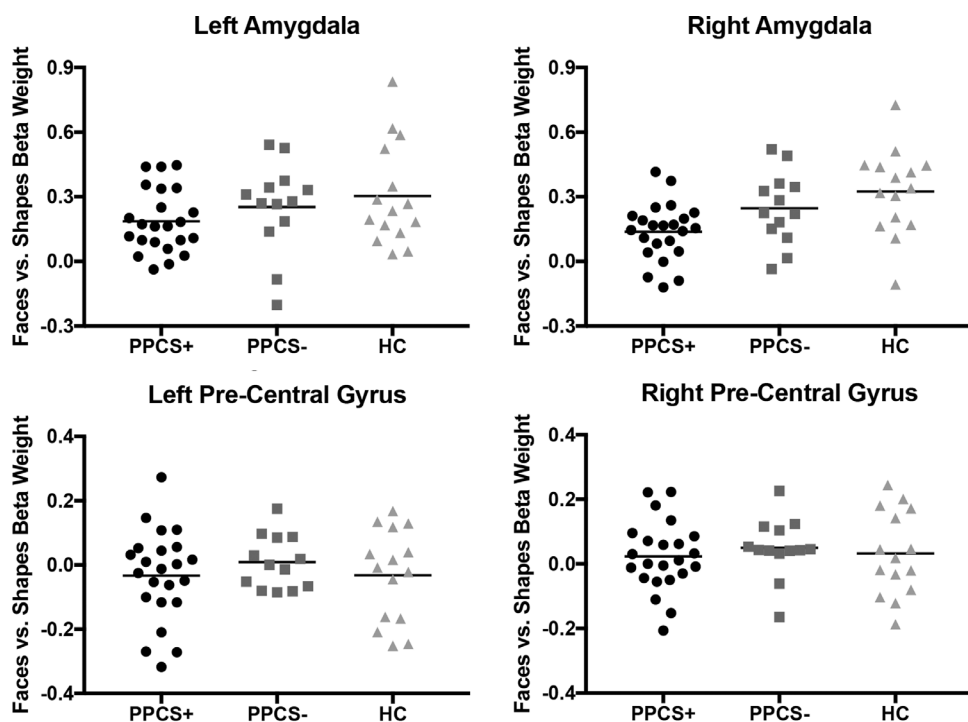
Fig. 2. Emotional face related activity in the amygdalae and pre-central gyri. Shown is the faces versus shapes activity during the emotional processing task for adolescents with persistent post-concussion symptoms (PPCS+), adolescents without persistent post-concussion symptoms (PPCS-), and healthy control adolescents (HC) in the amygdalae and the pre-central gyri. Horizontal line represents group mean.
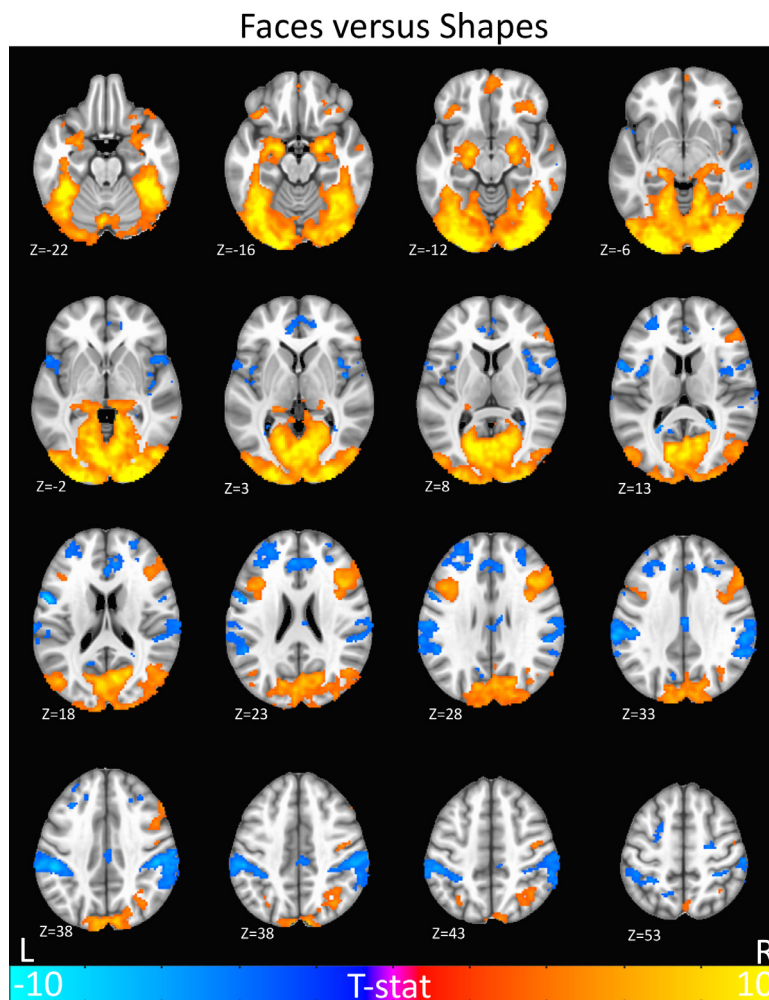

Fig. 3. Whole-brain faces versus shapes task-related activity across all participants. Shown is the average faces versus shapes task-related activity in all participants. Warm colors represent regions with faces > shapes task-related activity. Cool colors represent regions with shapes > faces task-related activity. R = right, L = left.

Table 3

Association between psychological measures and amygdalae activity in adolescents with persistent post-concussion symptoms.

	Hemisphere	Est.	SE	95%CI [lower, upper]	F	p-value	Partial η²
SHAPS	left	−0.008	0.006	[−0.020, 0.003]	3.11	0.093	0.14
	right	−0.008	0.006	[−0.020, 0.003]			
GAD-7	left	−0.006	0.006	[−0.019, 0.007]	0.45	0.51	0.02
	right	−0.001	0.006	[−0.015, 0.012]			
PHQ-9	left	−0.007	0.005	[−0.018, 0.004]	1.93	0.18	0.09
	right	−0.006	0.005	[−0.017, 0.006]			
BSI-18 GSI	left	−0.003	0.002	[−0.008, 0.002]	1.26	0.28	0.06
	right	−0.002	0.002	[−0.007, 0.003]			

Est. = estimate, SE = standard error, CI = confidence interval, SHAPS = Snaith-Hamilton Pleasure Scale, GAD-7 = Generalized Anxiety Disorder 7-item scale, PHQ-9 = Patient Health Questionnaire 9-item scale, BSI-18 GSI = Brief Symptom Inventory −18 Global Severity Index.

amygdala hyperactivity in psychopathologies with symptoms similar to those reported in PPCS (e.g., pediatric depression)(Demenescu et al., 2011; Ferri et al., 2014; Prater et al., 2013; Yang et al., 2010). Although concussed patients with PPCS had elevated depression symptoms, anxiety symptoms, and anhedonia, contrary to our hypothesis, they also had decreased amygdala activity in response to emotional faces. Moreover, although it was non-significant, greater anhedonia in concussed patients with PPCS was associated with lower amygdala activity. Thus, current results suggest that the neurofunctional underpinnings of mood dysregulation following concussion are distinct from major depressive disorder despite the overlap in symptoms and the known associations between brain injury and depression (Chen et al., 2008; Ellis et al., 2015; Kontos et al., 2012; Durish et al., 2018).

Our observation of decreased amygdala activity to emotional faces is, however, in line with behavioral studies of emotional recognition in more severe forms of brain injury. For example, adults with severe TBI have problems interpreting and matching facial expressions to social situations (Knox and Douglas, 2009), impairments in face recognition or difficulties in emotional visual discrimination (Croker and McDonald, 2005; Green et al., 2004), and problems recognizing negative facial expressions (Hopkins et al., 2002; Marquardt et al., 2001; Rosenberg et al., 2014). The amygdala is critically involved in emotional face processing (Fusar-Poli et al., 2009; Sabatinelli et al., 2011), including visual attention to emotional salient features (Adolphs, 2002; Radice-Neumann et al., 2007) and internal replication of emotional experiences (Bastiaansen et al., 2009; Iacoboni and Mazziotta, 2007). Thus, as articulated elsewhere (Neumann et al., 2014), decreased amygdala activity in response to emotional faces in adolescents with PPCS could represent decreased attention to emotionally salient facial features or difficulties in the reproduction of the emotions expressed in the facial stimuli. Additional research is needed to determine the effects of concussion and PPCS on specific aspects of emotional recognition (e.g., perception versus replication), particularly given the known sensitivity of the amygdala to brain injury (Beauchamp et al., 2011; Bigler, 2007; Wilde et al., 2007).

Abnormalities in emotional processing associated with concussion

and PPCS might have important clinical implications. Emotional processing, and the processing of emotional faces in particular, is critical for successful social interactions and interpersonal relationships and has been associated with emotional dysregulation (Addington et al., 2008; Cooper et al., 2014; Knox and Douglas, 2009; Pettersen, 1991; Radice-Neumann et al., 2007). Evidence suggests that brain injury, including concussion, can result in social and behavioral problems that negatively affect quality of life (Ellis et al., 2015; Haagsma et al., 2015; Petchprapai and Winkelman, 2007; Zamani et al., 2019). For example, a recent large-scale study found that children with PPCS had significantly lower quality of life scores including physical, emotional, social, and school functioning impairments at 12 weeks post-injury compared to children without PPCS (Novak et al., 2016). It has been hypothesized that deficits in emotional recognition represent one potential cause for social and behavioral problems observed in more severe TBI patients, as TBI patients with facial affect recognition deficits often have inappropriate social interactions and emotion dysregulation (Cooper et al., 2014; Kelly et al., 2008; Knox and Douglas, 2009; Neumann et al., 2014; Osborne-Crowley and McDonald, 2018; Sabaz et al., 2014). Thus, it is possible that social problems associated with PPCS could be a result of, or exacerbated by, deficits in emotional processing.

Ultimately, we are unable to determine the etiology of emotional processing deficits or psychological symptoms in adolescents with PPCS. We are also unable to infer causality between concussion, the observed amygdala hypoactivity, and psychological symptoms. As discussed, the observed abnormalities could be a result of the mechanical or secondary injury mechanisms affecting the middle temporal lobe (Bigler, 2007). Conversely, it is possible that the observed differences are reflective of unmeasured pre-existing factors or psychosocial factors (e.g., removal from typical social interactions or sport activities).

The current study has additional limitations that should be considered. First, the overall sample was relatively small. However, we carefully screened concussion patients to exclude several potentially confounding factors, such as premorbid psychiatric and neurodevelopmental disorders (Iverson et al., 2017). Nevertheless, pre-injury data
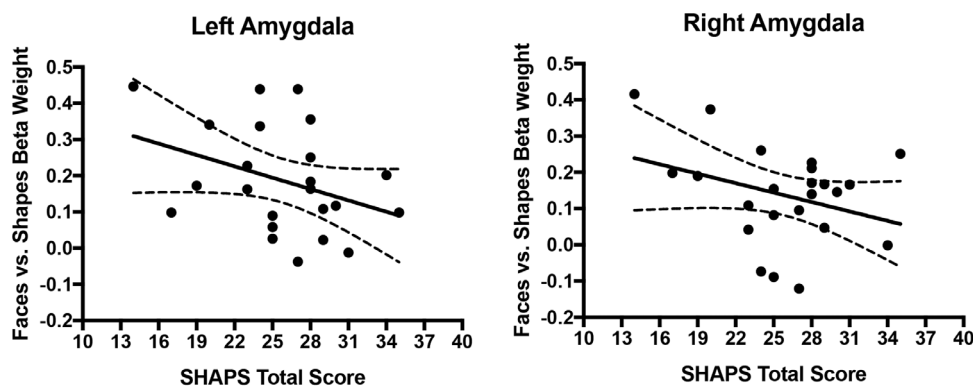

Fig. 4. Association between anhedonia and emotional face activity in the amygdalae in adolescents with persistent post-concussion symptoms, Individual amygdalae activity in the faces versus shapes contrast are plotted against scores on the Snaith-Hamilton Pleasure Scale (SHAPS). Regression lines with 95% confidence internal based on separate linear regressions for left and right hemisphere are shown.

is not available (e.g., scanning, pre-injury psychological symptoms) and we cannot definitively determine whether observed differences were result of the concussion or reflect preexisting differences in the participants. In addition, this study was cross-sectional in nature with a single visit. Finally, there are alternative voxel-wise approaches to analyze task-related fMRI data that could be used to investigate limbic system activity and connectivity during emotional face processing, such as independent component analysis and psychophysiological interactions. Future research in larger samples could extend the current findings to investigate functional connectivity of the limbic system during emotional processing. Moreover, additional research is needed to determine the time course of recovery for the observed abnormalities in emotional processing and their relationship with symptom recovery.

Conclusions

Results from this pilot study suggest that concussed patients with PPCS have altered amygdalae activity during processing of emotional face stimuli. Follow-up studies are needed to confirm this hypothesis, isolate specific aspects of emotional processing that are affected by PPCS, and to determine the role of these abnormalities in adverse social and emotional outcomes associated with PPCS.

CRediT authorship contribution statement

Luisa Bohorquez-Montoya: Conceptualization, Validation, Data curation, Formal analysis, Writing - original draft, Visualization. **Lezlie Y. España:** Conceptualization, Validation, Formal analysis, Data curation, Software, Writing - review & editing. **Amy M. Nader:** Investigation, Data curation, Resources, Project administration, Writing - review & editing. **Robyn E. Furger:** Investigation, Data curation, Resources, Project administration, Writing - review & editing. **Andrew R. Mayer:** Conceptualization, Writing - review & editing. **Timothy B. Meier:** Conceptualization, Methodology, Validation, Formal analysis, Writing - original draft, Supervision, Project administration, Funding acquisition.

Acknowledgements

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2020.102217.

References

Addington, J., Penn, D., Woods, S.W., Addington, D., Perkins, D.O., 2008. Facial affect recognition in individuals at clinical high risk for psychosis. Br. J. Psychiatry. https://doi.org/10.1192/bjp.bp.107.039784.

Adolphs, R., 2002. Recognizing emotion from facial expressions: psychological and neurological mechanisms. Behav. Cogn. Neurosci. Rev. 15 (9), 5879–5891. https://doi.org/10.1177/1534582302001001003.

Adolphs, R., Tranel, D., Damasio, H., Damasio, A.R., 1995. Fear and the human amygdala. J. Neurosci. 15 (9), 5879–5891.

Andersson, J.L.R., Skare, S., Ashburner, J., 2003. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. Neuroimage. https://doi.org/10.1016/S1053-8119(03)00336-7.

Babbage, D.R., Yim, J., Zupan, B., Neumann, D., Tomita, M.R., Willer, B., 2011. Meta-Analysis of facial affect recognition difficulties after traumatic brain injury. Neuropsychology. https://doi.org/10.1037/a0021908.

Banks, S.J., Eddy, K.T., Angstadt, M., Nathan, P.J., Luan Phan, K., 2007. Amygdala-frontal connectivity during emotion regulation. Soc. Cogn. Affect. Neurosci. https://doi.org/10.1093/scan/nsm029.

Barch, D.M., Burgess, G.C., Harms, M.P., Petersen, S.E., Schlaggar, B.L., Corbetta, M., Glasser, M.F., Curtiss, S., Dixit, S., Feldt, C., Nolan, D., Bryant, E., Hartley, T., Footer, O., Bjork, J.M., Poldrack, R., Smith, S., Johansen-Berg, H., Snyder, A.Z., Van Essen, D.C., 2013. Function in the human connectome: task-fMRI and individual differences in behavior. Neuroimage. https://doi.org/10.1016/j.neuroimage.2013.05.033.

Bastiaansen, J.A.C.J., Thioux, M., Keysers, C., 2009. Evidence for mirror systems in emotions. Philos. Trans. R. Soc. B: Biol. Sci. https://doi.org/10.1098/rstb.2009.0058.

Beauchamp, M.H., Ditchfield, M., Maller, J.J., Catroppa, C., Godfrey, C., Rosenfeld, J.V., Kean, M.J., Anderson, V.A., 2011. Hippocampus, amygdala and global brain changes 10 years after childhood traumatic brain injury. Int. J. Dev. Neurosci. https://doi.org/10.1016/j.ijdevneu.2010.12.003.

Bigler, E.D., 2007. Anterior and middle cranial fossa in traumatic brain injury: relevant neuroanatomy and neuropathology in the study of neuropsychological outcome. Neuropsychology. https://doi.org/10.1037/0894-4105.21.5.515.

Carrier-Toutant, F., Guay, S., Beaulieu, C., Léveillé, É., Turcotte-Giroux, A., Papineau, S.D., Brisson, B., D'Hondt, F., De Beaumont, L., 2018. Effects of repeated concussions and sex on early processing of emotional facial expressions as revealed by electrophysiology. J. Int. Neuropsychol. Soc. 24 (7), 673–683. https://doi.org/10.1017/S1355617718000231.

Chen, G., Adleman, N.E., Saad, Z.S., Leibenluft, E., Cox, R.W., 2014. Applications of multivariate modeling to neuroimaging group analysis: a comprehensive alternative to univariate general linear model. Neuroimage. https://doi.org/10.1016/j.neuroimage.2014.06.027.

Chen, J.K., Johnston, K.M., Petrides, M., Ptito, A., 2008. Neural substrates of symptoms of depression following concussion in male athletes with persisting postconcussion symptoms. Arch. Gen. Psychiatry. https://doi.org/10.1001/archgenpsychiatry.2007.8.

Cooper, C.L., Phillips, L.H., Johnston, M., Radlak, B., Hamilton, S., McLeod, M.J., 2014. Links between emotion perception and social participation restriction following stroke. Brain Inj. https://doi.org/10.3109/02699052.2013.848379.

Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. https://doi.org/10.1006/cbmr.1996.0014.

Croker, V., McDonald, S., 2005. Recognition of emotion from facial expression following traumatic brain injury. Brain Inj. https://doi.org/10.1080/02699050500110033.

D'Hondt, F., Lassonde, M., Thebault-Dagher, F., Bernier, A., Gravel, J., Vannasing, P., Beauchamp, M.H., 2017. Electrophysiological correlates of emotional face processing after mild traumatic brain injury in preschool children. Cogn. Affect. Behav. Neurosci. 17 (1), 124–142. https://doi.org/10.3758/s13415-016-0467-7.

Demenescu, L.R., Kortekaas, R., Cremers, H.R., Renken, R.J., van Tol, M.J., van der Wee, N.J.A., Veltman, D.J., den Boer, J.A., Roelofs, K., Aleman, A., 2013. Amygdala activation and its functional connectivity during perception of emotional faces in social phobia and panic disorder. J. Psychiatr. Res. https://doi.org/10.1016/j.jpsychires.2013.03.020.

Demenescu, L.R., Renken, R., Kortekaas, R., Van Tol, M.J., Marsman, J.B.C., Van Buchem, M.A., Van Der Wee, N.J.A., Veltman, D.J., Den Boer, J.A., Aleman, A., 2011. Neural correlates of perception of emotional facial expressions in out-patients with mild-to-moderate depression and anxiety. A multicenter fMRI study. Psychol. Med. https://doi.org/10.1017/S0033291711000596.

DePadilla, L., Miller, G.F., Jones, S.E., Peterson, A.B., Breiding, M.J., 2018. Self-reported concussions from playing a sport or being physically active among high school students — United States, 2017. Morbidity Mortality Weekly Rep. https://doi.org/10.15585/mmwr.mm6724a3.

Drapeau, J., Gosselin, N., Peretz, I., McKerral, M., 2017. Emotional recognition from dynamic facial, vocal and musical expressions following traumatic brain injury. Brain Inj. 31 (2), 221–229. https://doi.org/10.1080/02699052.2016.1208846.

Drapeau, J., Gosselin, N., Peretz, I., McKerral, M., 2019. Electrophysiological responses to emotional facial expressions following a mild traumatic brain injury. Brain Sci. 9 (6), 142. https://doi.org/10.3390/brainsci9060142.

Ellis, M.J., Ritchie, L.J., Koltek, M., Hosain, S., Cordingley, D., Chu, S., Selci, E., Leiter, J., Russell, K., 2015. Psychiatric outcomes after pediatric sports-related concussion. J. Neurosurg. Pediatr. https://doi.org/10.3171/2015.5.PEDS15220.

Ferri, J., Bress, J.N., Eaton, N.R., Proudfit, G.H., 2014. The impact of puberty and social anxiety on amygdala activation to faces in adolescence. Dev. Neurosci. https://doi.org/10.1159/000363736.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., Benedetti, F., Abbamonte, M., Gasparotti, R., Barale, F., Perez, J., McGuire, P., Politi, P., 2009. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci 34 (6), 418–432.

Green, R.E.A., Turner, G.R., Thompson, W.F., 2004. Deficits in facial emotion perception in adults with recent traumatic brain injury. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2003.07.005.

Greve, D.N., Fischl, B., 2009. Accurate and robust brain image alignment using boundary-based registration. Neuroimage. https://doi.org/10.1016/j.neuroimage.2009.06.060.

Haagsma, J.A., Scholten, A.C., Andriessen, T.M.J.C., Vos, P.E., Van Beeck, E.F., Polinder, S., 2015. Impact of depression and post-traumatic stress disorder on functional outcome and health-related quality of life of patients with mild traumatic brain injury. J. Neurotrauma. https://doi.org/10.1089/neu.2013.3283.

Hariri, A.R., Mattay, V.S., Tessitore, A., Fera, F., Smith, W.G., Weinberger, D.R., 2002. Dextroamphetamine modulates the response of the human amygdala. Neuropsychopharmacology. https://doi.org/10.1016/S0893-133X(02)00373-1.

Ho, R.A., Hall, G.B., Noseworthy, M.D., DeMatteo, C., 2018. An emotional go/no-go fMRI study in adolescents with depressive symptoms following concussion. Int. J. Psychophysiol. 132, 62–73. https://doi.org/10.1016/j.ijpsycho.2017.09.021. (October 2017).

Hopkins, M.J., Dywan, J., Segalowitz, S.J., 2002. Altered electrodermal response to facial expression after closed head injury. Brain Inj. https://doi.org/10.1080/02699050110103346.

Iacoboni, M., Mazziotta, J.C., 2007. Mirror neuron system: basic findings and clinical applications. Ann. Neurol. https://doi.org/10.1002/ana.21198.

Iverson, G.L., Gardner, A.J., Terry, D.P., Ponsford, J.L., Sills, A.K., Broshek, D.K., Solomon, G.S., 2017. Predictors of clinical recovery from concussion: a systematic review. Br. J. Sports Med. https://doi.org/10.1136/bjsports-2017-097729.

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 62 (6). https://doi.org/10.1016/S1053-8119(02)91132-8.

Jenkinson, M., Beckmann, C.F., Behrens, T.E., Woolrich, M.W., Smith, S.M., 2012. FSL 1. Neuroimage 62 (2), 782–790.

Kelly, G., Brown, S., Todd, J., Kremer, P., 2008. Challenging behaviour profiles of people with acquired brain injury living in community settings. Brain Inj. https://doi.org/10.1080/02699050802060647.

Klein, A.P., Tetzlaff, J.E., Bonis, J.M., Nelson, L.D., Mayer, A.R., Huber, D.L., Harezlak, J., Mathews, V.P., Ulmer, J.L., Sinson, G.P., Nencka, A.S., Koch, K.M., Wu, Y.C., Saykin, A.J., DiFiori, J.P., Giza, C.C., Goldman, J., Guskiewicz, K.M., Mihalik, J.P., Meier, T.B., 2019. Prevalence of potentially clinically significant magnetic resonance imaging findings in athletes with and without sport-related concussion. J. Neurotrauma. https://doi.org/10.1089/neu.2018.6055.

Knox, L., Douglas, J., 2009. Long-term ability to interpret facial expression after traumatic brain injury and its relation to social integration. Brain Cogn. https://doi.org/10.1016/j.bandc.2008.09.009.

Kontos, A.P., Covassin, T., Elbin, R.J., Parker, T., 2012. Depression and neurocognitive performance after concussion among male and female high school and collegiate athletes. Arch. Phys. Med. Rehabil. https://doi.org/10.1016/j.apmr.2012.03.032.

Durish, L., C., P., S., R., Yeates, K.O., 2018. Depression and depressive symptoms in pediatric traumatic brain injury: a scoping review. J. Head Trauma Rehabil. https://doi.org/10.1097/HTR.0000000000000343.

Léveillé, E., Guay, S., Blais, C., Scherzer, P., De Beaumont, L., 2017. Sex-related differences in emotion recognition in multi-concussed athletes. J. Int. Neuropsychol. Soc. 23 (1), 65–77. https://doi.org/10.1017/S1355617716001004.

Levin, H.S., Brown, S.A., Song, J.X., McCauley, S.R., Boake, C., Contant, C.F., Goodman, H., Kotrla, K.J., 2001. Depression and posttraumatic stress disorder at three months after mild to moderate traumatic brain injury. J. Clin. Exp. Neuropsychol. 23 (6), 754–769.

Marquardt, T.P., Rios-Brown, M., Richburg, T., Seibert, L.K., Cannito, M.P., 2001. Comprehension and expression of affective sentences in traumatic brain injury. Aphasiology. https://doi.org/10.1080/02687040143000429.

Matthews, S.C., Strigo, I.A., Simmons, A.N., O'Connell, R.M., Reinhardt, L.E., Moseley, S.A., 2011. A multimodal imaging study in U.S. veterans of operations iraqi and enduring freedom with and without major depression after blast-related concussion. Neuroimage 54 (SUPPL. 1), S69–S75. https://doi.org/10.1016/j.neuroimage.2010.04.269.

McCrory, P., Meeuwisse, W.H., Aubry, M., Cantu, R.C., Dvořák, J., Echemendia, R.J., Engebretsen, L., Johnston, K., Kutcher, J.S., Raftery, M., Sills, A., Benson, B.W., Davis, G.A., Ellenbogen, R., Guskiewicz, K.M., Herring, S.A., Iverson, G.L., Jordan, B.D., Kissick, J., Turner, M., 2013. Consensus statement on concussion in sport: the 4th international conference on concussion in sport, zurich, november 2012. J. Athl. Train. https://doi.org/10.4085/1062-6050-48.4.05.

Neumann, D., Keiski, M.A., McDonald, B.C., Wang, Y., 2014. Neuroimaging and facial affect processing: implications for traumatic brain injury. Brain Imaging Behav. 8 (3), 460–473. https://doi.org/10.1007/s11682-013-9285-5.

Novak, Z., Aglipay, M., Barrowman, N., Yeates, K.O., Beauchamp, M.H., Gravel, J., Freedman, S.B., Gagnon, I., Gioia, G., Boutis, K., Burns, E., Ledoux, A.A., Osmond, M.H., Zemek, R.L., 2016. Association of persistent postconcussion symptoms with pediatric quality of life. JAMA Pediatr. https://doi.org/10.1001/jamapediatrics.2016.2900.

Osborne-Crowley, K., McDonald, S., 2018. A review of social disinhibition after traumatic brain injury. J. Neuropsychol. https://doi.org/10.1111/jnp.12113.

Peluso, M.A.M., Glahn, D.C., Matsuo, K., Monkul, E.S., Najt, P., Zamarripa, F., Li, J., Lancaster, J.L., Fox, P.T., Gao, J.H., Soares, J.C., 2009. Amygdala hyperactivation in untreated depressed individuals. Psychiatry Res. Neuroimaging. https://doi.org/10.1016/j.pscychresns.2009.03.006.

Petchprapai, N., Winkelman, C., 2007. Mild traumatic brain injury: determinants and subsequent quality of life. a review of the literature. J. Neurosci. Nursing. https://doi.org/10.1097/01376517-200710000-00002.

Pettersen, L., 1991. Sensitivity to emotional cues and social behavior in children and adolescents after head injury. Percept. Mot. Skills 73 (3 Pt 2), 1139–1150.

Prater, K.E., Hosanagar, A., Klumpp, H., Angstadt, M., Phan, K.L., 2013. Aberrant amygdala-frontal cortex connectivity during perception of fearful faces and at rest in generalized social anxiety disorder. Depress. Anxiety. https://doi.org/10.1002/da.22014.

Radice-Neumann, D., Zupan, B., Babbage, D.R., Willer, B., 2007. Overview of impaired facial affect recognition in persons with traumatic brain injury. Brain Inj. https://doi.org/10.1080/02699050701504281.

Rapoport, M.J., McCullagh, S., Streiner, D., Feinstein, A., 2003. The clinical significance of major depression following mild traumatic brain injury. Psychosomatics. https://doi.org/10.1176/appi.psy.44.1.31.

Rolls, E.T., Joliot, M., Tzourio-Mazoyer, N., 2015. Implementation of a new parcellation of the orbitofrontal cortex in the automated anatomical labeling atlas. Neuroimage. https://doi.org/10.1016/j.neuroimage.2015.07.075.

Rosenberg, H., McDonald, S., Dethier, M., Kessels, R.P.C., Westbrook, R.F., 2014. Facial emotion recognition deficits following moderate-severe traumatic brain injury (TBI): re-examining the valence effect and the role of emotion intensity. J. Int. Neuropsychol. Soc. https://doi.org/10.1017/S1355617714000940.

Sabatinelli, D., Fortune, E.E., Li, Q., Siddiqui, A., Krafft, C., Oliver, W.T., Beck, S., Jeffries, J., 2011. Emotional perception: meta-analyses of face and natural scene processing. Neuroimage. https://doi.org/10.1016/j.neuroimage.2010.10.011.

Sabaz, M., Simpson, G.K., Walker, A.J., Rogers, J.M., Gillis, I., Strettles, B., 2014. Prevalence, comorbidities, and correlates of challenging behavior in community-dwelling adults with severe traumatic brain injury: a multicenter study. J. Head Trauma Rehabil. https://doi.org/10.1097/HTR.0b013e31828dc590.

Schmidt, A.T., Hanten, G.R., Li, X., Orsten, K.D., Levin, H.S., 2010. Emotion recognition following pediatric traumatic brain injury: longitudinal analysis of emotional prosody and facial emotion recognition. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2010.05.029.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. https://doi.org/10.1016/j.neuroimage.2004.07.051.

Tonks, J., Williams, H., Frampton, I., Yates, P., Wall, S., Slater, A., 2008. Reading emotions after childhood brain injury: case series evidence of dissociation between cognitive abilities and emotional expression processing skills. Brain Inj. https://doi.org/10.1080/02699050801968303.

Tonks, J., Williams, W.H., Frampton, I., Yates, P., Slater, A., 2007. Reading emotions after child brain injury: a comparison between children with brain injury and non-injured controls. Brain Inj. https://doi.org/10.1080/02699050701426899.

Turkstra, L.S., McDonald, S., DePompei, R., 2001. Social information processing in adolescents: data from normally developing adolescents and preliminary data from their peers with traumatic brain injury. J. Head Trauma Rehabil. https://doi.org/10.1097/00001199-200110000-00006.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. https://doi.org/10.1006/nimg.2001.0978.

van der Naalt, J., Timmerman, M.E., de Koning, M.E., van der Horn, H.J., Scheenen, M.E., Jacobs, B., Hageman, G., Yilmaz, T., Roks, G., Spikman, J.M., 2017. Early predictors of outcome after mild traumatic brain injury (UPFRONT): an observational cohort study. Lancet Neurol. https://doi.org/10.1016/S1474-4422(17)30117-5.

Wang, X., Xie, H., Cotton, A.S., Brickman, K.R., Lewis, T.J., Wall, J.T., Tamburrino, M.B., Bauer, W.R., Law, K., McLean, S.A., Liberzon, I., 2017. Early changes in cortical emotion processing circuits after mild traumatic brain injury from motor vehicle collision. J. Neurotrauma 34 (2), 273–280. https://doi.org/10.1089/neu.2015.4392.

Wilde, E.A., College, B., Bigler, E.D., Hunter, J.V., Children, T., Ma, M.A.F., Bs, J.L.J., Bachevalier, J., Fearing, M.A., Scheibel, R.S., Newsome, M.R., Johnson, J.L., Bachevalier, J., Li, X., Levin, H.S., 2007. Hippocampus, amygdala, and basal ganglia morphometrics in children after moderate-to-severe traumatic brain injury. Dev Med Child Neurol. 49 (4), 294–299.

Yang, T.T., Simmons, A.N., Matthews, S.C., Tapert, S.F., Frank, G.K., Max, J.E., Bischoff-Grethe, A., Lansing, A.E., Brown, G., Strigo, I.A., Wu, J., Paulus, M.P., 2010. Adolescents with major depression demonstrate increased amygdala activation. J. Am. Acad. Child Adolesc. Psychiatry. https://doi.org/10.1097/00004583-201001000-00008.

Yeates, K.O., Taylor, H.G., Rusin, J., Bangert, B., Dietrich, A., Nuss, K., Wright, M., Nagin, D.S., Jones, B.L., 2009. Longitudinal trajectories of postconcussive symptoms in children with mild traumatic brain injuries and their relationship to acute clinical status. Pediatrics. https://doi.org/10.1542/peds.2008-1056.

Zamani, A., Mychasiuk, R., Semple, B.D., 2019. Determinants of social behavior deficits and recovery after pediatric traumatic brain injury. Exp. Neurol. https://doi.org/10.1016/j.expneurol.2019.01.007.

Zemek, 2016. Clinical risk score for persistent postconcussion symptoms. JAMA.

Zuj, D.V., Felmingham, K.L., Palmer, M.A., Lawrence-Wood, E., Van Hooff, M., Lawrence, A.J., Bryant, R.A., McFarlane, A.C., 2017. Neural activity and emotional processing following military deployment: effects of mild traumatic brain injury and posttraumatic stress disorder. Brain Cogn. 118, 19–26. https://doi.org/10.1016/j.bandc.2017.07.001. (March).