Journal of the International Neuropsychological Society (2013), **19**, 911–924.

doi:10.1017/S1355617713000817

How Functional Connectivity between Emotion Regulation Structures Can Be Disrupted: Preliminary Evidence from Adolescents with Moderate to Severe Traumatic Brain Injury

Mary R. Newsome,[1] Randall S. Scheibel,[1] Andrew R. Mayer,[2,3] Zili D. Chu,[4,5] Elisabeth A. Wilde,[1,4,6] Gerri Hanten,[1] Joel L. Steinberg,[7] Xiaodi Lin,[1] Xiaoqi Li,[1] Tricia L. Merkley,[1,8] Jill V. Hunter,[4,5] Ana C. Vasquez,[1] Lori Cook,[9] Hanzhang Lu,[10] Kami Vinton,[9] AND Harvey S. Levin[1,6,11]

[1]Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, Texas
[2]The Mind Research Network, Albuquerque, New Mexico
[3]Neurology Department, University of New Mexico School of Medicine, Albuquerque, New Mexico
[4]Department of Radiology, Baylor College of Medicine, Houston, Texas
[5]Department of Pediatric Radiology, Texas Children's Hospital, Houston, Texas
[6]Department of Neurology, Baylor College of Medicine, Houston, Texas
[7]Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia
[8]Department of Psychology, Brigham Young University, Provo, Utah
[9]Center for Brain Health, University of Texas at Dallas, Dallas, Texas
[10]Advanced Imaging Research Center, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas
[11]Department of Neurosurgery, Baylor College of Medicine, Houston, Texas

(RECEIVED August 16, 2012; FINAL REVISION June 18, 2013; ACCEPTED June 19, 2013)

Abstract

Outcome of moderate to severe traumatic brain injury (TBI) includes impaired emotion regulation. Emotion regulation has been associated with amygdala and rostral anterior cingulate (rACC). However, functional connectivity between the two structures after injury has not been reported. A preliminary examination of functional connectivity of rACC and right amygdala was conducted in adolescents 2 to 3 years after moderate to severe TBI and in typically developing (TD) control adolescents, with the hypothesis that the TBI adolescents would demonstrate altered functional connectivity in the two regions. Functional connectivity was determined by correlating fluctuations in the blood oxygen level dependent (BOLD) signal of the rACC and right amygdala with that of other brain regions. In the TBI adolescents, the rACC was found to be significantly less functionally connected to medial prefrontal cortices and to right temporal regions near the amygdala (height threshold T = 2.5, cluster level $p < .05$, FDR corrected), while the right amygdala showed a trend in reduced functional connectivity with the rACC (height threshold T = 2.5, cluster level $p = .06$, FDR corrected). Data suggest disrupted functional connectivity in emotion regulation regions. Limitations include small sample sizes. Studies with larger sample sizes are necessary to characterize the persistent neural damage resulting from moderate to severe TBI during development. (*JINS*, 2013, *19*, 911–924)

Keywords: Resting state, fMRI, Adolescents, Empathy, TBI, Anterior cingulate

INTRODUCTION

Although overall rates of traumatic brain injury (TBI) in adolescents have decreased (Asemota, George, Bowman, Haider, & Schneider, 2013), incidence changes depend on age (Faul, Xu, Wald, & Coronado, 2010). For example, hospitalizations for falls and bicycle accidents in older adolescents have increased (Asemota et al., 2013). TBI often results in emotional processing deficits that are devastating to long-term prospects for recovery. Impairments in recognizing (Schmidt, Hanten, Li, Orsten, & Levin, 2010; Tonks et al., 2008) and regulating emotions (Ganesalingam, Sanson, Anderson, & Yeates, 2006) have been reported years after injury. A particular type of emotion regulation involves the ability to feel emotions similar to those of another (emotional empathy), which differs from taking the perspective of others to infer how they feel (cognitive empathy; Jolliffe & Farrington, 2006). Inability to recognize emotions of others

Correspondence and reprint requests to: Mary R. Newsome, Cognitive Neuroscience Laboratory Baylor College of Medicine, 1709 Dryden Road, Ste 12.59, Houston, TX 77030. E-mail: mnewsome@bcm.edu

and control emotional expression could limit emotional empathy. Although deficits in emotional empathy have been reported in adults with severe TBI (Wood & Williams, 2008), this type of emotional processing has not yet been measured when TBI occurs during development, when the brain is undergoing rapid changes (Lenroot et al., 2007).

Failure of emotion regulation in typically developing children has been attributed to an imbalanced neural network involving the amygdala, a structure in the temporal lobes associated with emotion processing, and the ventromedial prefrontal cortex (vmPFC), a frontal lobe region that includes the anterior cingulate cortex (ACC) and is associated with emotion regulation (Hare et al., 2008; Somerville, Jones, & Casey, 2010). Connection between the amygdala and ACC reportedly increases with healthy development. Decety, Michalska, and Kinzler (2012) found a negative relation between age and activation in the amygdaIa in healthy children and adults who completed a task that elicited empathy during functional magnetic resonance imaging (fMRI), which suggests the role of the amygdala in empathy reduces with age. The authors also found a positive relation between age and functional connectivity between the amygdala and the ACC, suggesting an increased response in the ACC across development (Decety et al., 2012).

Resting state fMRI provides a measure of the functional connectivity between structures. During fMRI scanning without task performance, low frequency spontaneous fluctuations in blood oxygen level dependent (BOLD) activity show patterns of significant correlations between regions (Biswal, Yetkin, Haughton, & Hyde, 1995), or functionally connected networks. The Default Mode Network (DMN) (Raichle et al., 2001) is one well-known example. BOLD signal in brain networks may be anticorrelated with that in other networks, as when the functional connectivity in the DMN decreases when functional connectivity between executive function regions increases during the performance of a cognitive task (Fox et al., 2005). Alterations to functional connectivity networks have been implicated in brain disorders (Etkin, Prater, Schatzberg, Menon, & Greicius, 2009; van Marle, Hermans, Qin, & Fernandez, 2010) and injuries (Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011). Because functional connectivity networks are linked to neuronal function (Shmuel & Leopold, 2008; Ansari, Oghabian, & Hossein-Zadeh, 2011), they may be affected by alterations in structural connectivity. Diffuse axonal injury and atrophy associated with TBI (Bigler et al., 2010) may impair both local and distant functional connections. However, due to diversity in characteristics of patients and methods used, information about how resting state networks adapt after TBI is still emerging. In adults with subacute mild TBI (mTBI), Mayer et al., (2011) found decreased connectivity within the DMN and hyperconnectivity between the DMN and frontoparietal network. In addition, a disruption between cingulum bundle white matter and functional connectivity of the rostral ACC (rACC) was found. The authors demonstrated that reduced connectivity within the DMN following mTBI may be related to structural abnormalities and suggested DMN disruption may be related to the increased distractibility often observed after mTBI. In adult patients, Sharp et al., (2011) reported increased functional connectivity within the DMN at least 6 months after TBI, which was related to white matter integrity. In a subsequent study of TBI patients studied 2–96 months after injury, regions of the DMN did not deactivate when subjects performed a cognitive task (Bonnelle et al., 2012). Nakamura, Hillary, and Biswal (2009) investigated recovery of functional connectivity in adults with moderate to severe TBI between 3 and 6 months after injury. They suggested that the recovery of networks entails the strengthening of current connections rather than generation of new ones.

Although these reports provide valuable information about reconfiguration of network connectivity in adults, it is unclear how disruption to functional networks after TBI presents during development, when the brain is undergoing systematic, continuing changes (Lenroot et al., 2007), and whether any disruption is long lasting. Additionally, information on how TBI affects the functional connectivity of regions outside of established functional networks is needed.

Measuring functional connectivity between the rACC and amygdala may elucidate effects of TBI on a neural system responsible for controlling emotions. Frontal and temporal lobes, locations of the rACC and amygdala, respectively, are the most common sites for focal lesions after TBI in children (Graham et al., 1989; Levin et al., 1997). In addition, children and adolescents with moderate to severe TBI show decreased cortical thickness in frontal regions that include the rACC (Wilde et al., 2012) and reduced amygdala volume (Wilde et al., 2007), suggesting that functional connectivity in this emotion regulation network may be impaired.

The right amygdala has been associated with heightened response when automatically perceiving and responding to emotions (Dyck et al., 2011; Glascher & Adolphs, 2003) and is involved in empathy (Decety, Michalska, & Akitsuki, 2008). The rACC has been linked to emotional conflict resolution (Egner, Etkin, Gale, & Hirsch, 2008; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010) and is activated in tasks involving impulsive choice (Hinvest, Elliott, McKie, & Anderson, 2011). Decreased emotion regulation has been linked to impulsivity (Schreiber, Grant, & Odlaug, 2012), and it is possible that impulsivity reported in patients after TBI (McAllister, 1992) may be linked to impaired functional connectivity reported in the rACC (Mayer et al., 2011).

This preliminary study investigated functional connectivity between right amygdala and rACC in adolescents an average of 2 and a half years after moderate to severe TBI. We hypothesized that, relative to typically developing (TD) adolescents, functional connectivity between the two regions would be disrupted in adolescents with TBI. In addition, exploratory analyses investigated the relation of regional brain volumes and performance on empathy and impulsivity measures to the functional connectivity data.

METHODS

Participants

Nine adolescents with moderate to severe TBI as defined by a post-resuscitation score of 3–12 on the Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974), or GCS score of 13–15 with associated brain pathology on computed tomography (i.e., "complicated mild") were selected from a cohort of 75 pediatric TBI patients from a previous grant cycle (2004–2007) on the basis of availability, age 12 to 19 years, minimum 1-year post-injury, and compliant with MRI safety requirements. Patients with complicated mild injuries have worse outcome than those with mild TBI without lesions (Williams, Levin, & Eisenberg, 1990) and show no differences from patients with moderate TBI in neurobehavioral or functional performance (Kashluba, Hanks, Casey, & Millis, 2008; Williams et al., 1990). One complicated mild patient in this study (TBI1) had a GCS score of 15, measured 1 day after injury with no earlier record available. Thus, it is possible that a GCS score taken at the time of injury could be lower than 15. Excessive motion was observed in two patients, leaving seven adolescents with TBI (mean age at scanning = 17.67 years, standard deviation (*SD*) = 1.75, range = 14.42–19.13 years; 5 males) in the fMRI analyses (Table 1). All TBI patients had focal frontal lobe lesions on structural MRI (Table 2). Patients were recruited from hospitals in Dallas and Houston, Texas, and were studied between 1.99 and 3.63 years (mean = 2.55; *SD* = 0.61 years) post-injury. Ten TD adolescents served as the comparison group, although due to excessive motion in one TD subject, data from nine were included in fMRI analyses (mean age = 16.80 years; *SD* = 1.83; range = 13.94–19.30 years; 6 males). Groups did not differ in age, gender, ethnicity, IQ, and mother's education, a proxy for socioeconomic status (all p's $> .10$; Tables 1 and 3). All participants were right-handed (Oldfield, 1971). No child was taking psychoactive medications or had previous neurologic or psychiatric disorders. The study was completed in accordance with the Helsinki Declaration and was approved by the institutional review boards at Baylor College of Medicine and The University of Texas Southwestern Medical School at Dallas.

Behavioral Measures

The Basic Empathy Scale (Jolliffe & Farrington, 2006) is a 20-item self-report test of emotional and cognitive empathy. The Children's Impulsivity Scale (Landis & Hanten, unpublished), adapted for children from the Barratt Impulsiveness Scale-11 (Patton, Stanford, & Barratt, 1995) with the authors' permission, is a 30-item self-report scale assessing children's tendency to engage in impulsive behavior along three dimensions (motor impulsivity, non-planning, and attention). Because we predicted that the TBI adolescents would evidence decreased empathy and increased impulsivity, significant results are reported at $p < .05$, one-tailed.

Volumetric Measures

Brain volumetry is a measure of structure, as opposed to function, of the brain and can suggest regional abnormalities. TBI may result in degradation to neuronal cell bodies (gray matter) and/or the axons that connect them (white matter), reflected by volume loss of subcortical structures, cortical thickness reductions, or alterations in cortical folding patterns (Fischl et al., 2002). T1-weighted MR images are used for automatic segmentation of brain regions into the various structures, using information such as voxel intensities, global

Table 1. Features of seven patients with traumatic brain injury (TBI) and summary data for the comparison group [typically developing (TD)] adolescents

	Age at test (years)	Age at injury (years)	Post-injury interval (years)	Ethnicity/ race	Mother's education (years)	Gender	Mechanism of injury	GCS score
TBI1	18.33	16.01	2.32	AA	14	F	Fall	15 (+comp)
TBI2	16.03	13.07	2.96	H	12	M	Fall	3
TBI3	18.42	14.79	3.63	H	9	M	MVA	3
TBI4	18.66	16.67	1.99	C	16	M	MVA	10
TBI5	19.13	17.03	2.10	C	12	F	MVA	7
TBI6	14.42	12.37	2.06	C	9	M	MVA	8
TBI7	18.70	15.90	2.81	C	14	M	MVA	3
Mean	17.67 (1.75)	15.12 (1.80)	2.55 (0.61)	1 AA/ 2 H/ 4 C	12.3 (2.6)	2F / 5M		
TD $n = 9$	16.80 (1.83)	n/a	n/a	1 AA/ 4 H/ 4 C	14.2 (1.8)	3F / 6M	n/a	n/a

Note. AA = African American; C = Caucasian; F = female; GCS = Glasgow Coma Scale; H = Hispanic; M = male; MVA = Motor Vehicle Accident; n/a = not applicable; n = sample size; TD = typically developing; +comp = plus complications.

https://doi.org/10.1017/S1355617713000817 Published online by Cambridge University Press

Table 2. Pathology and associated anatomical location and size for each TBI patient

	Anatomical region	Matter	Pathology	Volume (cm^3)
TBI 1	Superior frontal gyrus (R)	White	Gliosis	0.21
		GWj	Gliosis	0.05
		GWj	Shearing injury	0.05
		GWj	Shearing & gliosis	0.22
	Superior frontal gyrus (L)	White	Gliosis	0.04
		GWj	Gliosis	0.07
		GWj	Shearing & gliosis	0.22
	Middle frontal gyrus (R)	GWj	Shearing & gliosis	0.21
	Inferior frontal gyrus (R)	GWj	Shearing & gliosis	0.10
	Inferior frontal gyrus (L)	GWj	Shearing & gliosis	0.05
	Medial frontal gyrus (R)	GWj	Shearing & gliosis	0.02
	Orbitofrontal gyrus (R)	GWj	Shearing & gliosis	0.05
	Temporal pole (R)	Gray	Siderosis, enceph & gliosis	0.71
TBI 2	Middle frontal gyrus (L)	Gray	Gliosis	0.04
		G + W	Gliosis	0.07
		White	VP shunt	0.64
	Inferior frontal gyrus (R)	Gray	Enceph	0.22
		Gray	Gliosis & enceph	0.23
	Inferior frontal gyrus (L)	G + W	Gliosis	0.28
		Gray	Enceph	0.10
		G + W	Gliosis & enceph	1.95
	Orbitofrontal gyrus (R)	G + W	Siderosis, enceph & gliosis	0.18
		G + W	Enceph & siderosis	0.17
		G + W	Enceph	0.48
	Orbitofrontal gyrus (L)	G + W	Siderosis, enceph & gliosis	4.44
	Gyrus rectus (L)	Gray	Siderosis, enceph & gliosis	0.24
		G + W	Siderosis, enceph & gliosis	0.86
	Temporal pole (R)	G + W	Gliosis & enceph	0.23
	Temporal pole (L)	Gray	Enceph	0.94
		G + W	Enceph	0.08
	Thalamus (L)	Gray	Gliosis and hemosiderin	0.19
TBI 3	Superior frontal gyrus (R)	Gray	Gliosis	3.38
	Superior frontal gyrus (R)	Gray	Gliosis & enceph	16.45
	Superior frontal gyrus (R)	G + W	Gliosis & enceph	3.82
	Superior frontal gyrus (L)	Gray	Gliosis	0.29
	Superior frontal gyrus (L)	Gray	Gliosis & enceph	0.44
	Superior frontal gyrus (L)	Gray	Gliosis and hemosiderin	0.97
	Middle frontal gyrus (R)	GWj	Hemorrhage & enceph	1.15
	Middle frontal gyrus (R)	GWj	Gliosis & enceph	4.39
	Inferior frontal gyrus (R)	Gray	Hemorrhage & enceph	0.75
	Inferior frontal gyrus (R)	GWj	Hemorrhage & enceph	2.29
	Orbitofrontal gyrus (L)	Gray	Gliosis	2.48
	Orbitofrontal gyrus (L)	Gray	Gliosis and hemosiderin	1.31
	Mid corpus callosum (L)	White	Gliosis and hemosiderin	0.14
	Occipital lobe (L)	Gray	Gliosis	1.40
	Cerebellum hemisphere (L)	Gray	Gliosis	0.09
TBI 4	Superior frontal gyrus (R)	Gray	Hemosiderin deposit	0.43
	Superior frontal gyrus (L)	Gray	Hemosiderin deposit	0.29
	Middle frontal gyrus (R)	GWj	Hemosiderin deposit	0.14
	Medial frontal gyrus (L)	Gray	Hemosiderin deposit	0.27
	Operculum (L)	Gray	Hemosiderin deposit	0.07
	Middle temporal gyrus (R)	Gray	Hemosiderin deposit	0.21
	Middle temporal gyrus (L)	Gray	Hemosiderin deposit	0.38
	Temporal pole (R)	Gray	Hemosiderin deposit	0.39
	Temporal pole (L)	Gray	Hemosiderin deposit	0.18

(Continued)

https://doi.org/10.1017/S1355617713000817 Published online by Cambridge University Press

Table 2. Continued

	Anatomical region	Matter	Pathology	Volume (cm^3)
TBI 5	Hippocampal formation (R)	Gray	Gliosis	0.31
	Amygdala (R)	Gray	Gliosis	0.13
	Amygdala (L)	Gray	Gliosis	0.33
	Anterior corpus callosum (R)	Gray	Gliosis	0.07
	Posterior corpus callosum (R)	Gray	Gliosis	1.38
	Occipital lobe (R)	White	Gliosis	1.49
TBI 6	Superior frontal gyrus (L)	White	Gliosis	0.14
		GWj	Gliosis	0.02
		GWj	Shearing injury	0.03
		GWj	Gliosis and hemosiderin	0.15
	Middle frontal gyrus (L)	GWj	Gliosis	3.27
		White	Shearing injury	0.06
		GWj	Gliosis and hemosiderin	0.49
TBI 7	Superior frontal gyrus (R)	GWj	Gliosis	0.18
		White	Shearing injury	0.15
	Middle frontal gyrus (R)	Gray	Gliosis & enceph	0.10
	Middle frontal gyrus (L)	GWj	Gliosis	0.10
	Inferior frontal gyrus (L)	GWj	Shearing & hemorrhage	0.05
	Superior parietal cortex (R)	Gray	Shearing injury	0.14
		G + W	VP shunt	0.11
	Superior parietal cortex (L)	White	Gliosis	0.09
	Putamen (L)	White	Shearing & hemorrhage	0.05
	Thalamus (R)	Gray	Shearing & hemorrhage	0.09

Note. Enceph = encephalomalacia; GWj = gray-white matter junction; G + W = gray matter and white matter; L = left; R = right; VP = ventriculoperitoneal.

position in the brain, and position relative to other brain structures, which are then compared to a probabilistic brain atlas to facilitate classification of each voxel in the MR image (Fischl et al., 2002, 2004).

Functional Connectivity Measures

Functional connectivity is based on low-frequency fluctuations in the BOLD response that are postulated to follow intrinsic neuronal activity (Fox, Snyder, Vincent, & Raichle, 2007). During the measurement of functional connectivity, participants are asked to rest quietly in the scanner with their eyes open or closed. In the present study, gray and white matter volumes proximal to the rACC and right amygdala seeds were selected as regressors to understand how alterations in functional connectivity might be related to nearby tissue that may interact with blood flow (Schummers, Yu, & Sur, 2008).

Table 3. Mean Outcome Data for TBI and TD Groups and individual scores for TBI subjects*.

WASI			CIS			BES-Emotional			BES-Cognitive		
Subjects	Mean (StDev)	*p*, Cohen's *d*	Subjects	Mean (StDev)	*p*, Cohen's *d*	Subjects	Mean (StDev)	*p*, Cohen's *d*	Subjects	Mean (StDev)	*p*, Cohen's *d*
TBI1 = n/a			TBI1 = 38			TBI1 = 32			TBI1 = 30		
TBI2 = 79			TBI2 = 34			TBI2 = 21			TBI2 = 39		
TBI3 = 92			TBI3 = 35			TBI3 = 27			TBI3 = 26		
TBI4 = 118	99.0	$p = 0.261$	TBI4 = 44	36.7	$p = 0.278$	TBI4 = 29	27.4	$p = 0.081$	TBI4 = 31	30.3	$p = 0.207$
TBI5 = 103	(15.0)	$d = 0.803$	TBI5 = 30	(4.69)	$d = 0.338$	TBI5 = 32	(4.7)	$d = 1.004$	TBI5 = 28	(5.8)	$d = 0.442$
TBI6 = 89			TBI6 = 42			TBI6 = 21			TBI6 = 22		
TBI7 = 113			TBI7 = 37			TBI7 = 30			TBI7 = 36		
TD	109.3 (11.3)		TD	38.4 (5.2)		TD	32.5 (5.3)		TD	32.6 (4.8)	

Note. Standard deviations in parentheses. WASI data for one TBI participant and BES data for one TD participant were not available. Because predictions were that the TBI group would have increased impulsivity and impaired empathy, *p*-values are based on one-tailed Wilcoxon Rank Sums tests. For Cohen's *d*, 0.2 is small, 0.5 is moderate, and 0.8 is a large effect size.
BES = Basic Empathy Scale; CIS = Children's Impulsivity Scale; n/a = not available; TBI = traumatic brain injury; TD typically developing; WASI = Wechsler Abbreviated Scale of Intelligence.

https://doi.org/10.1017/S1355617713000817 Published online by Cambridge University Press

Procedure

Subjects completed the Basic Empathy Scale and the Children's Impulsivity Scale as part of a larger battery of tasks administered on the same day or within 1 week of the scanner session. During scanning, subjects completed an fMRI task designed to measure social cognition, published elsewhere (Newsome et al., 2010), followed by resting state and structural acquisitions. During resting state acquisitions, subjects were instructed to lie still and close their eyes without falling asleep. During scanning, they were monitored via a remote camera available at one site. At both sites, subjects were asked if they fell asleep, which none did.

Acquisition Parameters

Whole brain imaging data were acquired using a multi-channel SENSE headcoil on identical 3.0 Tesla Philips Achieva scanners in Houston and Dallas. BOLD T2*-weighted single-shot gradient-echo echoplanar images (EPI) were acquired in 32 axial slices 3.75 mm thick (1.0 mm gap), 240 mm × 240 mm field of view (FOV), 64 × 64 matrix, repetition time (TR) of 1700 ms, echo time (TE) of 30 ms, 73° flip angle, and SENSE factor of 2.0. After the functional scans, a set of high-resolution T1-weighted three-dimensional (3D) turbo field echo (TFE) anatomical images was acquired in 132 axial slices of 1.0 mm thickness (no gap) with 240 mm × 240 mm FOV, 256 × 256 matrix, TR = 9.9 ms, TE = 4.6 ms, 8.0° flip angle, SENSE factor of 1.2, producing 1-mm isotropic voxels. Additional anatomical series to assess neuropathology included T2-weighted gradient echo, T2-weighted fluid attenuated inversion recovery (FLAIR), and T2-weighted gradient- and spin-echo (GRASE) sequences. Lesion volume and nature of pathology were determined by a board certified neuroradiologist (J.V.H.). Similar ranges of values for Weisskoff stability measurements [minimum 1/SNR (signal-to-noise ratio) index, peak-to-peak and root mean square (RMS) stability] (Weisskoff, 1996) taken on the day of scan indicated stability of both scanners over time.

STATISTICAL ANALYSIS

Behavioral Measures

Wilcoxon Rank Sums tests were performed to test group differences. Effect sizes (Cohen's *d*) are included to document clinically meaningful effects lacking in statistical power.

Volumetric Image Processing and Analysis

Cortical reconstruction, cortical parcellation, and subcortical segmentation of the structural MRI scans were performed using the Freesurfer neuroimage analysis suite, as described previously (Bigler et al., 2010; Merkley et al., 2008) and detailed on the Freesurfer website. Cortical white and gray matter volumes of bilateral rACC and gray matter volumes for bilateral amygdala (as the amygdala is a gray matter structure) were computed. All volumes were corrected for head size by performing analyses of covariance with total intracranial volume (TICV) (Wilde et al., 2011). Wilcoxon Rank Sums tests were performed to test group differences.

Functional Connectivity Image Processing and Analysis

Functional BOLD connectivity data were spatially registered in 2D and 3D space to minimize effects of head motion, temporally interpolated to correct for slice-time acquisition differences, and de-spiked using the AFNI software package (Cox, 1996). A regression analysis was then conducted on individual subjects' time-series to remove potential sources of noise (physiological and machine-based) from the data based on established methodologies (Fox et al., 2005). Briefly, individual T1-weighted anatomical images were segmented into maps of white matter, gray matter, and cerebral spinal fluid (CSF); the resultant CSF and white matter masks were then used to obtain an average time-series for these tissues. Next, all six movement parameters, the region of interest (ROI) -based time-series for CSF and white matter, a constant term, and a linear term were entered into a linear regression against the extended resting state time-series. A global gray matter term was not entered into the regression to minimize likelihood of increased anticorrelations (Fox, Zhang, Snyder, & Raichle, 2009; Murphy, Birn, Handwerker, Jones, & Bandettini, 2009). The residual time-series data were then transformed into a standardized coordinate space (Talairach & Tournoux, 1988) in AFNI using a linear transformation.

Based on previous studies, the "seeds" for functional analyses were placed within midline rACC and right amygdala. Specifically, 12-mm spheres were generated based on voxels exhibiting maximal DMN activity in the rACC (0, 49, 9) in 42 healthy control subjects (Franco, Pritchard, Calhoun, & Mayer, 2009) and on voxels showing significant activation during the assessment of unfriendly behavior for the right amygdala (22.8, −10.9, −12.4; Scheibel et al., 2011; Schultz et al., 2003). Resultant Pearson's correlation coefficients were then converted to *Z*-scores using Fisher's method, blurred using an 8-mm root-mean square Gaussian kernel, and entered into group analyses.

Random effects group analyses (two-sample *t* tests and multiple regression (with constant) models) were performed using Statistical Parametric Mapping software (Friston et al., 1995); SPM8, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc., Sherborn, MA). The Talairach Daemon (Lancaster et al., 2000) was used to determine the anatomical locations and approximate Brodmann's areas (BA) of the Talairach coordinates. To isolate the effects of TBI, between group analyses are presented. For all results, significance was interpreted when voxel (height) threshold T = 2.5 and cluster threshold $p < .05$, false discovery rate (FDR) corrected for multiple comparisons across the whole brain. Due to small sample sizes, the p values reported are corrected for examining two tails but uncorrected for total number of regression analyses conducted. Data reduction was accomplished by including as regressors only behavioral and volume measures that showed decrements. In addition, only

https://doi.org/10.1017/S1355617713000817 Published online by Cambridge University Press

planned comparisons central to the main hypotheses are included, which resulted in six regression analyses.

RESULTS

Behavioral Measures

Shown in Table 3, marginal significance and a large effect size (where Cohen's $d = 0.2$ is small, 0.5 is moderate, and 0.8 is large) were found in the expected direction (TBI < TD) for the BES-Emotion scale, Wilcoxon $z = -1.40$, $p = .08$, $d = 1.00$. The BES-C and Child's Impulsivity Scale group comparisons were nonsignificant with small to moderate effect sizes; as a result, only the BES-E scores were subsequently regressed onto functional connectivity of the rACC and amygdala. No further analyses were performed with the BES-C and Child's Impulsivity Scale data.

Brain Volumes

Shown in Table 4, group difference for the right amygdala volume was marginally significant with a large effect size [TD > TBI; Wilcoxon $Z = -1.89$; $p = .059$ (two-tailed), Cohen's $d = 1.18$], as was group difference for the left rACC white matter volume [TBI > TD; Wilcoxon $Z = -1.82$; $p = .067$ (two-tailed), Cohen's $d = 1.00$] volumes. All other comparisons were non-significant and had zero to moderate effect sizes.

Functional Connectivity

Is the functional connectivity of the rACC and right amygdala altered an average of 2.5 years after TBI?

Table 4 presents coordinates, cluster sizes, and probability levels of significant clusters of activation observed in the between-group functional connectivity analyses for the two ROIs. Regions listed below are voxels within a cluster (local maxima) that are 1 mm apart.

Table 4. Volumes (cc^3) of amygdala and rostral anterior cingulate cortex (rACC) as a percentage of total intracranial volume*

	Left Amygdala		Right Amygdala	
TBI	0.12 (0.01)	$p = 1.000$	0.12 (0.01)	$p = 0.059$
TD	0.12 (0.01)	d = 0.010	0.14 (0.02)	$d = 1.179$
	Left rACC Gray Matter		Left rACC White Matter	
TBI	0.16 (0.05)	$p = 0.953$	0.13 (0.02)	$p = 0.067$
TD	0.15 (0.03)	$d = 0.274$	0.12 (0.01)	$d = 1.001$
	Right rACC Gray Matter		Right rACC White Matter	
TBI	0.13 (0.02)	$p = 0.376$	0.10 (0.02)	$p = 0.859$
TD	0.14 (0.03)	$d = 0.480$	0.10 (0.01)	$d = 0.067$

*Volumetric data for one TBI participant were not available. p values are based on two-tailed Wilcoxon Rank Sums tests. TBI = traumatic brain injury; TD = typically developing; ACC = anterior cingulate cortex. Standard deviations are provided in parentheses. For Cohen's d, 0.2 is small, 0.5 is moderate, and 0.8 is a large effect size.

rACC seed

SPM8 analysis revealed that the TD group had greater rACC connectivity than the TBI group in two clusters (FDR-corrected cluster $p = .02$ for each cluster). After further correction for two tails, the FDR-adjusted probability levels were $p = .04$ for each of the above clusters. There were no significant clusters where TBI had greater connectivity than TD for rACC (FDR-corrected cluster $p > .5301$) or for amygdala (FDR corrected cluster $p > .5721$). Compared to the TD group, the TBI group demonstrated lower bilateral frontal connectivity between the rACC and itself (BA32) and medial (BAs 6,8,9, right-only 10), middle (BA9; right-only BA8), and superior (BAs 8,9; left-only BA6; right-only BA10) frontal gyri. Lower connectivity was also found between ACC and right fusiform gyrus (BA20) and inferior (BAs 20,21), middle (BAs 21,22,38), and superior temporal (BAs 22,38) gyri. There were no regions where the TBI subjects showed significantly greater connectivity with the rACC than the TD subjects (Figure 1a, b; Figure 2a, b; Table 5).

Amygdala seed

SPM8 analysis also revealed that TD had greater amygdala connectivity in one cluster (FDR-corrected cluster $p = .03$; $p = .06$ after further correction for two tails). Compared to the TD group, the TBI group demonstrated lower frontal connectivity between right amygdala and right superior frontal gyrus (BAs 9,10), bilateral ACC (BAs 24,32) and medial frontal gyrus (BAs 9,10). There were no regions where the TBI subjects showed significantly greater connectivity than the TD subjects (Figures 1c, 2c; Table 5).

Are the negative correlations in the TBI group attenuated positive correlations or anticorrelations?

Negative correlations were found between temporal and medial frontal areas in some of the TBI subjects, denoted by the subjects whose *Z*-scores fell below zero in Figure 2a–c. A significant negative correlation (or anticorrelation) would indicate regions whose BOLD signal increases when other regions decrease (Fox et al., 2005). For example, in the present study significant anticorrelations could reflect increased functional connectivity in the rACC or amygdala associated with decreased functional connectivity in other portions of the rACC or amygdala. Using the within-group one-sample t test model in SPM8, analysis with data from the TBI group was performed to investigate the presence of any significant anticorrelations. Only posterior areas of the brain, primarily in bilateral occipital lobe and cerebellum, showed significant negative relation with the rACC, and bilateral parietal regions showed negative relation with the

https://doi.org/10.1017/S1355617713000817 Published online by Cambridge University Press

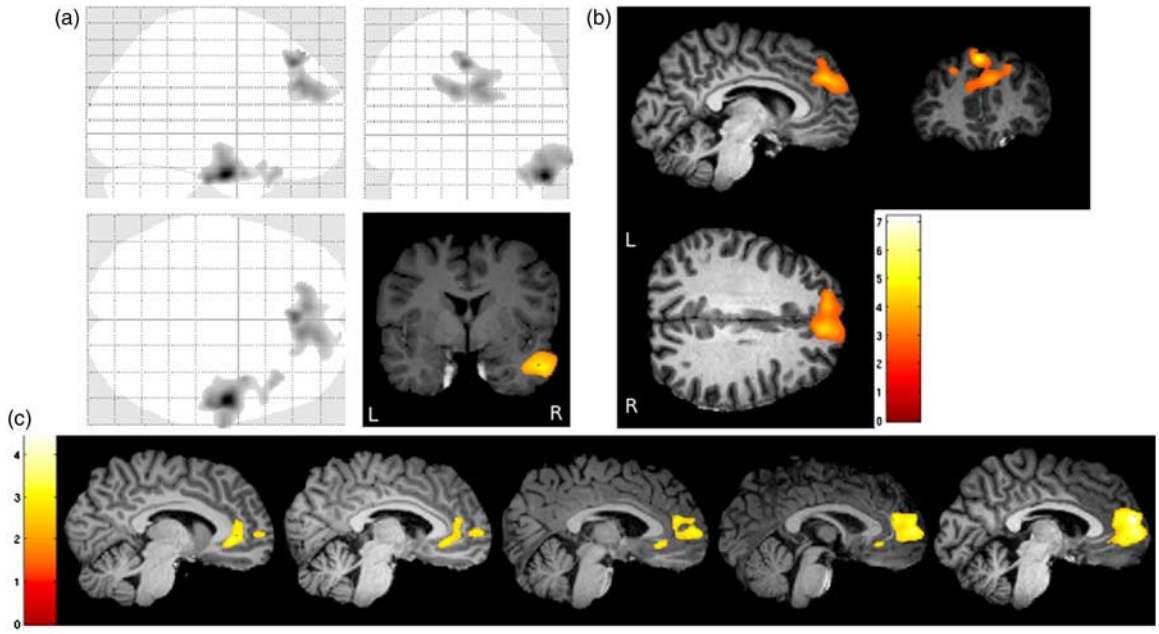

Fig. 1. Significant differences between groups. Relative to the typically developing (TD) group, the traumatic brain injury (TBI) group demonstrated lower functional connectivity between the rostral anterior cingulate cortex (rACC) seed and temporal pole (a) and dorsal medial prefrontal cortex (MPFC) (b), and between the right amygdala seed and rostral and ventral MPFC (c). Activation is overlaid onto an individual subject's brain transformed into Talairach space. Left side of brain is on left side of the figure.

right amygdala. These analyses suggest that the rACC and amygdala are not anticorrelated, and that the results from the between-groups analysis simply reflect attenuated positive correlations.

Do brain volumes relate to functional connectivity?

No significant between-group differences were observed in the relationships between rACC and right amygdala brain volumes and functional connectivity.

Do BES-E scores relate to functional connectivity?

Please see Table 6. The TD group showed a greater positive relation than the TBI group (FDR-corrected cluster $p = .016$; $p = .032$ after further correction for two tails) between BES-E and rACC connectivity in right middle frontal gyrus (BA6), precentral gyrus (BAs 3,5,6), postcentral gyrus (BAs 1,2,3,4,5,40), paracentral lobule (BA4), supramarginal gyrus (BA40), inferior parietal lobule (BA40), and superior parietal lobule (BA40) ($beta = 0.02$; $SE = 0.01$). TD and TBI adolescents did not differ on relation to right amygdala

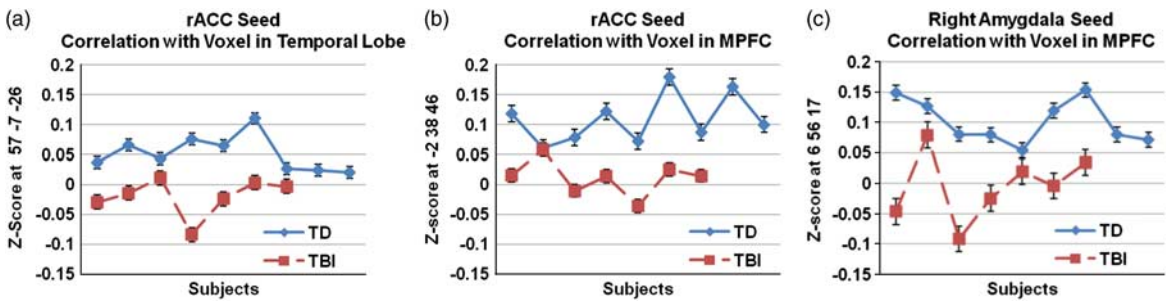

Fig. 2. Fisher *Z*-scores of the correlation coefficients and associated standard errors between seed regions [rostral anterior cingulate cortex (rACC) or right amygdala] and the most significant voxels associated with them in the between-groups [typically developing (TD) > traumatic brain injury (TBI)] comparisons. Plotted are the correlations a) between the rACC seed and a voxel in the right temporal lobe (52, −7, −26), b) between the rACC seed and a voxel in the left medial prefrontal cortex (MPFC) (−2, 38, 46), and c) between the right amygdala seed and a voxel in the right MPFC (6, 56, 17). The coordinate points for these voxels may also be seen in Table 5, which reports coordinates and summary statistics for the between-groups (TD > TBI) comparisons.

https://doi.org/10.1017/S1355617713000817 Published online by Cambridge University Press

Table 5. Statistical Parametric Mapping Summary Tables for Group Analyses

Cluster-level, *p* value (corrected)[a] (two-tailed), TD group > TBI group	Cluster size (k)[b]	Most significant coordinates[c] (x y z mm)	Location
rACC			
0.040	11,525	52, −7, −26	R fusiform gyr white matter
		39, 4, −25	R temporal lobe sub-gyral white matter
0.040	11,953	−2, 38, 46	L superior frontal Gyr
		9, 43, 32	R medial frontal gyr white matter
		−8, 46, 29	L medial frontal gyr (BA 9)
R amygdala			
0.060	10,668	6, 56, 17	R medial frontal gyr (BA 10)
		−21, 36, 0	L frontal sub-gyral white matter
		10, 51, 0	R medial frontal gyr (BA 10)

Note. Height (cluster-defining) threshold: T = 2.5, degrees of freedom = 8.0; smoothness: FWHM = 14.5 14.1 12.7 (voxels); search volume = 1737604 voxels = 619.6 resolution elements (resels). Coordinate points of local maxima (voxels within a cluster) are greater than 16 mm apart. For a more complete listing of activated regions, please see the text, which reports local maxima 1 mm apart.
BA = Brodmann area; gyr = gyrus; TBI = traumatic brain injury; TD = typically developing
[a]Probability at the cluster level of significance after random field theory FDR correction over the whole brain search volume.
[b]Number of voxels within a cluster.
[c]Negative values along the x-axis are defined to be in the subject's left hemisphere.

connectivity. There were no regions in which the TBI group had greater relation than the TD group between BES-E scores and either amygdala or rACC connectivity.

DISCUSSION

Is the Functional Connectivity of the rACC and Right Amygdala Altered an Average of 2.5 Years after TBI in Adolescents?

The results of this preliminary study suggest two ways that functional connectivity of emotion regulation structures may change after TBI. First, when measuring functional connectivity from the rACC seed, the TBI group showed lower functional connectivity compared to the TD group between the rACC and frontal regions, including a portion of ACC dorsal (superior) to the rACC. The TBI group also showed lower functional connectivity with the amygdala. Apparently, the reduction in rACC functional connectivity occurs along a pathway, in regions local to the rACC as well as those more distal. Future investigations may examine the integrity of the uncinate fasciculus, a white matter tract that connects the ventral (inferior) PFC to the temporal pole. Although the uncinate fasciculus does not directly connect the rACC to the amygdala, its proximity to both structures suggests it may play a major role. Indeed, Johnson et al. (2011) found that the integrity of the uncinate fasciculus following pediatric TBI was positively related to ability to regulate emotion. Of interest, the right uncinate fasciculus in the study by Johnson et al. (2011) was intact, while the present study suggests impairment of the uncinate on the right side. A lower age range and more acute injuries in the Johnson et al. (2011) study might contribute to this difference.

Second, the TBI group showed marginally reduced ($p = .06$) functional connectivity between the right amygdala and frontal regions, including bilateral ACC and vmPFC, implicated in emotion regulation (Decety et al., 2012; Hare et al., 2008; Sommerville et al., 2010). Moderate to severe TBI may prevent normal development of distributed functional connectivity (Fair et al., 2009). Future experiments that directly compare

Table 6. Statistical Parametric Mapping Summary Table for Regressions with BES-E

Cluster-level, *p* value (corrected)[a] (two-tailed), TD group > TBI group	Cluster size (k)[b]	Most significant coordinates[c] (x y z mm)	Location
rACC seed			
0.032	17,786	44, −23, 49	R postcentral gyr white matter
		40, −3, 33	R precentral gyr white matter

Note. Height (cluster-defining) threshold: T = 2.5, degrees of freedom = 12.0; Smoothness: FWHM = 16.8 16.3 15.0 (voxels); Search Volume = 1733721 voxels = 384.3 resolution elements (resels). Coordinate points of local maxima (voxels within a cluster are greater than 16 mm apart. For a more complete listing of activated regions, please see the text, which reports local maxima 1 mm apart.
BA = Brodmann area; gyr = gyrus; TBI = traumatic brain injury; TD = typically developing.
[a]Probability at the cluster level of significance after random field theory FDR correction over the whole brain search volume.
[b]Number of voxels within a cluster.
[c]Negative values along the x-axis are defined to be in the subject's left hemisphere.

https://doi.org/10.1017/S1355617713000817 Published online by Cambridge University Press

adolescents and adults with similar time since injury will be important for understanding age effects of functional connectivity and their relation to emotion regulation impairments.

Findings in the between-groups analysis reflected attenuated positive correlations in the TBI group rather than anticorrelations (Fox et al., 2005). A complete reversal in the type of relation between regions that are functionally connected in healthy subjects might have been surprising given the imprecise nature of blunt force trauma.

Group difference for the impulsivity measure was not statistically significant and had only a small to moderate effect size, Cohen's $d = 0.338$. In a previous study of patients approximately 4 years post severe TBI, impulsivity was found only in patients with high intracranial pressure at time of injury (Slawik et al., 2009). Intracranial pressure and small sample sizes may contribute to the lack of significant impulsivity differences between groups.

The groups in this study also did not have significantly different IQ scores. Reduced IQ has been reported in children who sustained TBI at younger ages, for example, up to 9 years, but not at 10–12 years (Crowe, Catroppa, Babl, Rosenfeld, & Anderson, 2012). It may be that the later age of injury in the adolescents in this sample (mean years = 15.1; $SD = 1.8$) is late enough to mitigate some effects on IQ, possibly contributing to some extent to the low power.

Is Empathy Related to Functional Connectivity of the rACC and Amygdala?

Groups did not differ on the cognitive empathy behavioral measure (BES-C, Jolliffe & Farrington, 2006), and as a result any further analyses were not explored. Adults with TBI show emotional empathy deficits (de Sousa, McDonald, & Rushby, 2012). In the present study, group differences in emotional empathy were marginally significant though with a large effect size. In an exploratory analysis, BES-E scores were regressed onto the connectivity pattern associated with each ROI. Relation to the right amygdala was not significant. However, a greater positive relationship between BES-E scores and rACC connectivity was found in the TD group in right posterior frontal, including somatosensory and motor regions, and nearby parietal regions, including right postcentral gyrus and inferior parietal lobule, both regions associated with emotion and empathy. Right postcentral gyrus has been linked to the recognition of emotional faces (Adolphs et al., 2000), and both it and right inferior parietal lobe have been implicated in a neural system involved in empathy. Right postcentral gyrus is associated with taking the point of view of another person, and right inferior parietal lobe is associated with taking the perspective of another person in both neutral and emotional contexts (Ruby & Decety, 2004). Moreover, the primary somatosensory and motor cortices have been associated with a subcategory of emotional empathy, emotional contagion (Nummenmaa, Hirvonen, Parkkola, & Hietanen, 2008). Emotional contagion involves the mimicking of facial and other movements of another person, resulting in experiencing similar feelings (Hatfield, Cacioppo, & Rapson, 1993). Any reduced empathy experienced by patients after TBI may be associated with reduced connectivity between the rACC and these regions.

Are Volumes of the rACC and Right Amygdala Related to the Functional Connectivity of the rACC and Amygdala?

Groups did not differ in rACC volume, so further analyses were not performed. Groups differed marginally on the right amygdala, but with a large effect size, consistent with previous findings reported by our group (Wilde et al., 2007). Whereas the effect size of group differences was large for the right hemisphere, it was very small for the left (Cohen's $d = 0.01$). Amygdala volume asymmetries have been observed in major depression, a disorder with noted emotion dysregulation, where right amygdala was reduced compared to left (Mervaala et al., 2000; Xia et al., 2004). This is in contrast with a lateralization effect noted in healthy adults, where larger right amygdala volume compared to left has been reported for right-handed individuals (Szabo, Xiong, Lancaster, Rainey, & Fox, 2001). The current findings suggest that reduced emotional empathy and emotion regulation following TBI may be related to right amygdala volume reduction.

In an exploratory analysis to investigate relations between the volume of the right amygdala and functional connectivity, group differences were nonsignificant. Given that loss in gray matter may entail a reduction in neurons, replication with larger sample sizes would be necessary before completely ruling out the role of atrophy in functional connectivity alteration.

How Might the Lesions in the TBI Group Affect the Findings?

Corbetta (2012) described how locations of focal lesions can be very different from locations where associated functional aberrations are found, e.g., ventral frontal and temporoparietal lesions in stroke patients with spatial neglect (inability to attend to one side of space) have been associated with aberrant functional connectivity in dorsal frontal and parietal regions. To contribute to the uncertainty of how focal lesions and functional connectivity are related, the TBI sample in this study is representative of the TBI population in that it has heterogeneous lesions. Although frontal lesions occurred in six out of seven patients, the locations varied. Because the frontal lobes share connections with many parts of the brain (e.g., fronto-temporal, fronto-parietal, fronto-occipital, fronto-cerebellar networks), lesions may potentially have different effects on different networks, with the location of pathology within a network potentially having still further implications for aberration in functional connectivity. In an investigation of the effects of structural lesions on functional connectivity using a computational model, Alstott, Breakspear, Hagmann, Cammoun, and Sporns (2009) found that lesions to midline structures (including frontal), in the model resulted in extensive functional disruption between frontal, temporal, and

https://doi.org/10.1017/S1355617713000817 Published online by Cambridge University Press

parietal regions in both hemispheres. When lesions were made in lateral areas, the effects on functional connectivity tended to remain in the same hemisphere. Given that many of our TBI subjects had bilateral frontal lesions, we infer that extensive disruption in the functional connectivity occurred between frontal, temporal, and parietal regions. The disrupted functional connectivity between the rACC and right amygdala may be, in part, a product of the lesions to the frontal lobes and, in part, atrophy found in the right amygdala, which may have lateralized effects (Alstott et al., 2009) and affect functional connectivity on the right side.

Limitations

Limitations of this preliminary study include small sample sizes and should be viewed with caution. We also acknowledge that the findings may not be completely generalizable to adolescents who are unable to remain still in an MRI machine and may have diminished cognitive and/or motor control, which could be associated with differences in brain volume and connectivity. Regional brain volume is only one factor that may affect functional connectivity, and may itself reflect numerous physiological processes associated with glial cells and myelinated axons as well as developmental changes following TBI that have not yet been well characterized. It may be that a subset of those physiological processes do not have a large effect on functional connectivity and override any processes that are influential. Furthermore, future studies with Common Data Elements measures would facilitate a comparison of TBI adolescents to normative samples, which was not possible in our study because the behavioral measures we used were not standardized.

Studies with larger sample sizes will be important for investigating the relation of lesion characteristics on functional connectivity, and studies with a wide range of post-injury intervals will be important to investigate the role that time since injury may play in functional connectivity alterations. Furthermore, although correlative analyses of functional connections provide valuable information, analysis methods involving causal modeling would test the direction in which regions influence each other, adding another dimension to typifying how functional connections can be altered.

Conclusions

In this preliminary study, functional connectivity was altered on average 2 and a half years after moderate to severe TBI in adolescents. Reductions in functional connectivity were found between the right amygdala and medial prefrontal cortex, including the rACC, an area implicated in the ability to regulate emotions. Moderate to severe TBI may prevent normal development of distributed functional connectivity. Our results may suggest that adolescents are more vulnerable than adults to disruption of emotion regulation connectivity in the years following moderate to severe TBI. Thus, rehabilitation focused on regulating emotional response may be of particular relevance in adolescents.

ACKNOWLEDGMENTS

This work was supported by NINDS grant R01-NS21889 "Neurobehavioral outcome of head injury in children," Harvey S. Levin, PI. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. There are no potential conflicts of interest, including financial, between any of the authors and the work presented in this manuscript. We are grateful to the youth and their families for taking part in the research, to the South Central Mental Illness Research, Education, and Clinical Center (MIRECC) for providing facilities that allowed analyses of the fMRI data, to the Editor, Associate Editor, and to three anonymous reviewers who provided valuable feedback. Zachary Dorsey and Isaiah Tate aided in the preparation of the manuscript.

REFERENCES

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., & Damasio, A. R. (2010). A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *20*(7), 2683–2690.

Alstott, J., Breakspear, M., Hagmann, P., Cammoun, L., & Sporns, O. (2009). Modeling the impact of lesions in the human brain. [Research Support, Non-U.S. Gov't]. *PLoS Computational Biology*, *5*(6), e1000408. doi:10.1371/journal.pcbi.1000408

Ansari, A. H., Oghabian, M. A., & Hossein-Zadeh, G. A. (2011). Assessment of functional and structural connectivity between motor cortex and thalamus using fMRI and DWI. *Conference Proceedings IEEE Engineering in Medicine and Biology Society*, *2011*, 5056–5059. doi:10.1109/IEMBS.2011.6091252

Asemota, A.O., George, B.P., Bowman, S.M., Haider, A.H., & Schneider, E.B. (2013). Causes and trends in traumatic brain injury for United States adolescents. *Journal of Neurotrauma*, *30*(2), 67–75. doi:10.1089/neu.2012.2605

Bigler, E.D., Abildskov, T.J., Wilde, E.A., McCauley, S.R., Li, X., Merkley, T.L., … Levin, H.S. (2010). Diffuse damage in pediatric traumatic brain injury: A comparison of automated versus operator-controlled quantification methods. *Neuroimage*, *50*(3), 1017–1026. doi:S1053-8119(10)00008-X [pii] 10.1016/j.neuroimage.2010.01.003 [doi]

Biswal, B., Yetkin, F.Z., Haughton, V.M., & Hyde, J.S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, *34*(4), 537–541.

Bonnelle, V., Ham, T.E., Leech, R., Kinnunen, K.M., Mehta, M.A., Greenwood, R.J., & Sharp, D.J. (2012). Salience network integrity predicts default mode network function after traumatic brain injury. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(12), 4690–4695. doi:1113455109 [pii] 10.1073/pnas.1113455109 [doi]

Corbetta, M. (2012). Functional connectivity and neurological recovery. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Developmental Psychobiology*, *54*(3), 239–253. doi:10.1002/dev.20507

Cox, R.W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*, *29*, 162–173.

Crowe, L.M., Catroppa, C., Babl, F.E., Rosenfeld, J.V., & Anderson, V. (2012). Timing of traumatic brain injury in childhood and intellectual outcome. [Research Support, Non-U.S. Gov't].

Journal of Pediatric Psychology, *37*(7), 745–754. doi:10.1093/jpepsy/jss070

de Sousa, A., McDonald, S., & Rushby, J. (2012). Changes in emotional empathy, affective responsivity, and behavior following severe traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*, *34*, 606–623. doi:10.1080/13803395.2012.667067 [doi]

Decety, J., Michalska, K.J., & Akitsuki, Y. (2008). Who caused the pain? An fMRI investigation of empathy and intentionality in children. *Neuropsychologia*, *46*(11), 2607–2614. doi:S0028-3932(08)00216-9 [pii] 10.1016/j.neuropsychologia.2008.05.026 [doi]

Decety, J., Michalska, K.J., & Kinzler, K.D. (2012). The contribution of emotion and cognition to moral sensitivity: A neurodevelopmental study. *Cerebral Cortex*, *22*(1), 209–220. doi:bhr111 [pii] 10.1093/cercor/bhr111 [doi]

Dyck, M., Loughead, J., Kellermann, T., Boers, F., Gur, R.C., & Mathiak, K. (2011). Cognitive versus automatic mechanisms of mood induction differentially activate left and right amygdala. [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Neuroimage*, *54*(3), 2503–2513. doi:10.1016/j.neuroimage.2010.10.013

Egner, T., Etkin, A., Gale, S., & Hirsch, J. (2008). Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. [Comparative Study]. *Cerebral Cortex*, *18*(6), 1475–1484. doi:10.1093/cercor/bhm179

Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., & Hirsch, J. (2006). Resolving emotional conflict: A role for the rostral anterior cingulate cortex in modulating activity in the amygdala. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Neuron*, *51*(6), 871–882. doi:10.1016/j.neuron.2006.07.029

Etkin, A., Prater, K.E., Hoeft, F., Menon, V., & Schatzberg, A.F. (2010). Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *American Journal of Psychiatry*, *167*(5), 545–554. doi:10.1176/appi.ajp.2009.09070931

Etkin, A., Prater, K.E., Schatzberg, A.F., Menon, V., & Greicius, M.D. (2009). Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. *Archives of General Psychiatry*, *66*(12), 1361–1372. doi:66/12/1361 [pii] 10.1001/archgenpsychiatry.2009.104 [doi]

Fair, D.A., Cohen, A.L., Power, J.D., Dosenbach, N.U., Church, J.A., Miezin, F.M., … Petersen, S.E. (2009). Functional brain networks develop from a "local to distributed" organization. *PLoS Computational Biology*, *5*(5), e1000381. doi:10.1371/journal.pcbi.1000381 [doi]

Faul, M., Xu, L., Wald, M.M., & Coronado, V.G. (2010). Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002–2006. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Atlanta, GA.

Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., … Dale, A.M. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. [Comparative Study Research Support, U.S. Gov't, P.H.S.]. *Neuron*, *33*(3), 341–355.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D.H., … Dale, A.M. (2004). Automatically parcellating the human cerebral cortex. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Cerebral Cortex*, *14*(1), 11–22.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., & Raichle, M.E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. [Comparative Study Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S.]. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–9678. doi:10.1073/pnas.0504136102

Fox, M.D., Snyder, A.Z., Vincent, J.L., & Raichle, M.E. (2007). Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. *Neuron*, *56*(1), 171–184. doi:S0896-6273(07)00666-6 [pii] 10.1016/j.neuron.2007.08.023 [doi]

Fox, M.D., Zhang, D., Snyder, A.Z., & Raichle, M.E. (2009). The global signal and observed anticorrelated resting state brain networks. [Research Support, N.I.H., Extramural]. *Journal of Neurophysiology*, *101*(6), 3270–3283. doi:10.1152/jn.90777.2008

Franco, A.R., Pritchard, A., Calhoun, V.D., & Mayer, A.R. (2009). Interrater and intermethod reliability of default mode network selection. [Research Support, N.I.H., Extramural]. *Human Brain Mapping*, *30*(7), 2293–2303. doi:10.1002/hbm.20668

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.B., Frith, C.D., & Frackowiak, R.S.J. (1995). Statistical parametric maps in functional imaging – A general linear approach. *Human Brain Mapping*, *2*, 189–210.

Ganesalingam, K., Sanson, A., Anderson, V., & Yeates, K.O. (2006). Self-regulation and social and behavioral functioning following childhood traumatic brain injury. *Journal of the International Neuropsychological Society*, *12*(5), 609–621. doi:S1355617706060796 [pii] 10.1017/S1355617706060796 [doi]

Glascher, J., & Adolphs, R. (2003). Processing of the arousal of subliminal and supraliminal emotional stimuli by the human amygdala. [Clinical Trial Controlled Clinical Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Journal of Neuroscience*, *23*(32), 10274–10282.

Graham, D.I., Ford, I., Adams, J.H., Doyle, D., Teasdale, G.M., Lawrence, A.E., & McLellan, D.R. (1989). Ischaemic brain damage is still common in fatal non-missile head injury. [Research Support, Non-U.S. Gov't]. *Journal of Neurology, Neurosurgery, and Psychiatry*, *52*(3), 346–350.

Hare, T.A., Tottenham, N., Galvan, A., Voss, H.U., Glover, G.H., & Casey, B.J. (2008). Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biological Psychiatry*, *63*(10), 927–934. doi:S0006-3223(08)00359-4 [pii] 10.1016/j.biopsych.2008.03.015 [doi]

Hatfield, E., Cacioppo, J.L., & Rapson, R.L. (1993). Emotional contaion. *Current Directions in Psychological Science*, *2*, 96–99.

Hinvest, N.S., Elliott, R., McKie, S., & Anderson, I.M. (2011). Neural correlates of choice behavior related to impulsivity and venturesomeness. *Neuropsychologia*, *49*(9), 2311–2320. doi:S0028-3932(11)00085-6 [pii] 10.1016/j.neuropsychologia.2011.02.023 [doi]

Johnson, C.P., Juranek, J., Kramer, L.A., Prasad, M.R., Swank, P.R., & Ewing-Cobbs, L. (2011). Predicting behavioral deficits in pediatric traumatic brain injury through uncinate fasciculus integrity. [Research Support, N.I.H., Extramural]. *Journal of the International Neuropsychological Society*, *17*(4), 663–673. doi:10.1017/S1355617711000464

Jolliffe, D., & Farrington, D.P. (2006). Development and validation of the Basic Empathy Scale. *Journal of Adolescence*, *29*(4), 589–611. doi:S0140-1971(05)00109-0 [pii] 10.1016/j.adolescence.2005.08.010 [doi]

Kashluba, S., Hanks, R.A., Casey, J.E., & Millis, S.R. (2008). Neuropsychologic and functional outcome after complicated mild traumatic brain injury. [Comparative Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. *Archives of Physical Medicine and Rehabilitation*, *89*(5), 904–911. doi:10.1016/j.apmr.2007.12.029

Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Freitas, C.S., Rainey, L., … Fox, P.T. (2000). Automated Talairach atlas labels for functional brain mapping. [Research Support, U.S. Gov't, P.H.S.]. *Human Brain Mapping*, *10*(3), 120–131.

Lenroot, R.K., Gogtay, N., Greenstein, D.K., Wells, E.M., Wallace, G.L., Clasen, L.S., … Giedd, J.N. (2007). Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *Neuroimage*, *36*(4), 1065–1073. doi:S1053-8119(07)00234-0 [pii] 10.1016/j.neuroimage.2007.03.053 [doi]

Levin, H.S., Mendelsohn, D., Lilly, M.A., Yeakley, J., Song, J., Scheibel, R.S., … Bruce, D. (1997). Magnetic resonance imaging in relation to functional outcome of pediatric closed head injury: A test of the Ommaya-Gennarelli model. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Neurosurgery*, *40*(3), 432–440; discussion 440–441.

Mayer, A.R., Mannell, M.V., Ling, J., Gasparovic, C., & Yeo, R.A. (2011). Functional connectivity in mild traumatic brain injury. *Human Brain Mapping*, *32*(11), 1825–1835. doi:10.1002/hbm.21151 [doi] 10.1002/hbm.21151 [doi]

McAllister, T.W. (1992). Neuropsychiatric sequelae of head injuries. *The Psychiatric Clinics of North America*, *15*(2), 395–413.

Merkley, T.L., Bigler, E.D., Wilde, E.A., McCauley, S.R., Hunter, J.V., & Levin, H.S. (2008). Diffuse changes in cortical thickness in pediatric moderate-to-severe traumatic brain injury. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Journal of Neurotrauma*, *25*(11), 1343–1345. doi:10.1089/neu.2008.0615

Mervaala, E., Fohr, J., Kononen, M., Valkonen-Korhonen, M., Vainio, P., Partanen, K., … Lehtonen, J. (2000). Quantitative MRI of the hippocampus and amygdala in severe depression. *Psychological Medicine*, *30*(1), 117–125.

Murphy, K., Birn, R.M., Handwerker, D.A., Jones, T.B., & Bandettini, P.A. (2009). The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? [Research Support, N.I.H., Intramural]. *Neuroimage*, *44*(3), 893–905. doi:10.1016/j.neuroimage.2008.09.036

Nakamura, T., Hillary, F.G., & Biswal, B.B. (2009). Resting network plasticity following brain injury. *PLoS One*, *4*(12), e8220. doi:10.1371/journal.pone.0008220 [doi]

Newsome, M.R., Scheibel, R.S., Hanten, G., Chu, Z., Steinberg, J.L., Hunter, J.V., … Levin, H.S. (2010). Brain activation while thinking about the self from another person's perspective after traumatic brain injury in adolescents. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Neuropsychology*, *24*(2), 139–147. doi:10.1037/a0017432

Nummenmaa, L., Hirvonen, J., Parkkola, R., & Hietanen, J.K. (2008). Is emotional contagion special? An fMRI study on neural systems for affective and cognitive empathy. *Neuroimage*, *43*(3), 571–580. doi:S1053-8119(08)00929-4 [pii] 10.1016/j.neuroimage.2008.08.014 [doi]

Oldfield, R.C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113.

Patton, J.H., Stanford, M.S., & Barratt, E.S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinincal Psychology*, *51*(6), 768–774.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., & Shulman, G.L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(2), 676–682. doi:10.1073/pnas.98.2.676 [doi] 98/2/676 [pii]

Ruby, P., & Decety, J. (2004). How would you feel versus how do you think she would feel? A neuroimaging study of perspective-taking with social emotions. [Comparative Study]. *Journal of Cognitive Neuroscience*, *16*(6), 988–999. doi:10.1162/0898929041502661

Scheibel, R.S., Newsome, M.R., Wilde, E.A., McClelland, M.M., Hanten, G., Krawczyk, D.C., … Levin, H.S. (2011). Brain activation during a social attribution task in adolescents with moderate to severe traumatic brain injury. [Research Support, N.I.H., Extramural]. *Social Neuroscience*, *6*(5–6), 582–598. doi:10.1080/17470919.2011.588844

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*, *48*(10), 2869–2877. doi:S0028-3932(10)00222-8 [pii] 10.1016/j.neuropsychologia.2010.05.029 [doi]

Schreiber, L.R., Grant, J.E., & Odlaug, B.L. (2012). Emotion regulation and impulsivity in young adults. *Journal of Psychiatric Research*, *46*(5), 651–658. doi:S0022-3956(12)00056-8 [pii] 10.1016/j.jpsychires.2012.02.005 [doi]

Schultz, R.T., Grelotti, D.J., Klin, A., Kleinman, J., Van der Gaag, C., Marois, R., & Skudlarski, P. (2003). The role of the fusiform face area in social cognition: Implications for the pathobiology of autism. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *358*(1430), 415–427. doi:10.1098/rstb.2002.1208

Schummers, J., Yu, H., & Sur, M. (2008). Tuned responses of astrocytes and their influence on hemodynamic signals in the visual cortex. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Science*, *320*(5883), 1638–1643. doi:10.1126/science.1156120

Sharp, D.J., Beckmann, C.F., Greenwood, R., Kinnunen, K.M., Bonnelle, V., De Boissezon, X., … Leech, R. (2011). Default mode network functional and structural connectivity after traumatic brain injury. *Brain*, *134*(Pt 8), 2233–2247. doi:awr175 [pii] 10.1093/brain/awr175 [doi]

Shmuel, A., & Leopold, D.A. (2008). Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: Implications for functional connectivity at rest. *Human Brain Mapping*, *29*(7), 751–761. doi:10.1002/hbm.20580 [doi]

Slawik, H., Salmond, C.H., Taylor-Tavares, J.V., Williams, G.B., Sahakian, B.J., & Tasker, R.C. (2009). Frontal cerebral vulnerability and executive deficits from raised intracranial pressure in child traumatic brain injury. [Research Support, Non-U.S. Gov't]. *Journal of Neurotrauma*, *26*(11), 1891–1903. doi:10.1089/neu.2009.0942

Somerville, L.H., Jones, R.M., & Casey, B.J. (2010). A time of change: Behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain and Cognition*, *72*(1), 124–133. doi:S0278-2626(09)00112-2 [pii] 10.1016/j.bandc.2009.07.003 [doi]

Szabo, C.A., Xiong, J., Lancaster, J.L., Rainey, L., & Fox, P. (2001). Amygdalar and hippocampal volumetry in control participants: Differences regarding handedness. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *AJNR American Journal of Neuroradiology*, *22*(7), 1342–1345.

Talairach, J., & Tournoux, P. (1988). *Co-Planar Stereotaxic Atlas of the Human Brain* (1st ed.). New York: Thieme Medical Publishers, Inc.

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet*, *2*(7872), 81–84.

Tonks, J., Williams, W.H., Frampton, I., Yates, P., Wall, S.E., & Slater, A. (2008). Reading emotions after childhood brain injury: Case series evidence of dissociation between cognitive abilities and emotional expression processing skills. *Brain Injury*, *22*(4), 325–332. doi:791714484 [pii] 10.1080/02699050801968303 [doi]

van Marle, H.J., Hermans, E.J., Qin, S., & Fernandez, G. (2010). Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. *Neuroimage*, *53*(1), 348–354. doi:S1053-8119(10)00822-0 [pii] 10.1016/j.neuroimage.2010.05.070 [doi]

Weisskoff, R.M. (1996). Simple measurement of scanner stability for functional NMR imaging of activation in the brain. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Magnetic Resonance in Medicine*, *36*(4), 643–645.

Wilde, E.A., Bigler, E.D., Hunter, J.V., Fearing, M.A., Scheibel, R.S., Newsome, M.R., … Levin, H.S. (2007). Hippocampus, amygdala, and basal ganglia morphometrics in children after moderate-to-severe traumatic brain injury. *Developmental Medicine and Child Neurology*, *49*(4), 294–299. doi:DMCN294 [pii] 10.1111/j.1469-8749.2007.00294.x [doi]

Wilde, E.A., Merkley, T.L., Bigler, E.D., Max, J.E., Schmidt, A.T., Ayoub, K.W., … Levin, H.S. (2012). Longitudinal changes in cortical thickness in children after traumatic brain injury and their relation to behavioral regulation and emotional control. *International Journal of Developmental Neuroscience*, *30*(3), 267–276. doi:10.1016/j.ijdevneu.2012.01.003 [doi] S0736-5748(12)00004-4 [pii] 10.1016/j.ijdevneu.2012.01.003 [doi]

Wilde, E.A., Newsome, M.R., Bigler, E.D., Pertab, J., Merkley, T.L., Hanten, G., … Levin, H.S. (2011). Brain imaging correlates of verbal working memory in children following traumatic brain injury. [Research Support, N.I.H., Extramural]. *International Journal of Psychophysiology*, *82*(1), 86–96. doi:10.1016/j.ijpsycho.2011.04.006

Williams, D.H., Levin, H.S., & Eisenberg, H.M. (1990). Mild head injury classification. [Research Support, U.S. Gov't, P.H.S. Review]. *Neurosurgery*, *27*(3), 422–428.

Wood, R.L., & Williams, C. (2008). Inability to empathize following traumatic brain injury. *Journal of the International Neuropsychological Society*, *14*(2), 289–296. doi:S1355617708080326 [pii] 10.1017/S1355617708080326 [doi]

Xia, J., Chen, J., Zhou, Y., Zhang, J., Yang, B., Xia, L., & Wang, C. (2004). Volumetric MRI analysis of the amygdala and hippocampus in subjects with major depression. *Journal of Huazhong University of Science and Technology, Medical Sciences*, *24*(5), 500–502, 506.