The Emergence of Age-Dependent Social Cognitive Deficits After Generalized Insult to the Developing Brain: A Longitudinal Prospective Analysis Using Susceptibility-Weighted Imaging

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Abstract: Childhood and adolescence are critical periods for maturation of neurobiological processes that underlie complex social and emotional behavior including Theory of Mind (ToM). While structural correlates of ToM are well described in adults, less is known about the anatomical regions subserving these skills in the developing brain or the impact of cerebral insult on the acquisition and establishment of high-level social cognitive skills. This study aimed to examine the differential influence of age-at-insult and brain pathology on ToM in a sample of children and adolescents with traumatic brain injury (TBI). Children and adolescents with TBI ($n = 112$) were categorized according to timing of brain insult: (i) middle childhood (5–9 years; $n = 41$); (ii) late childhood (10–11 years; $n = 39$); and (iii) adolescence (12–15 years; $n = 32$) and group-matched for age, gender, and socioeconomic status to a typically developing (TD) control group ($n = 43$). Participants underwent magnetic resonance imaging including a susceptibility-weighted imaging (SWI) sequence 2–8 weeks postinjury and were assessed on a battery of ToM tasks at 6- and 24-months after injury. Results showed that for adolescents with TBI, social cognitive dysfunction at 6- and 24-months postinjury was associated with diffuse neuropathology and a greater number of lesions detected using SWI. In the late childhood TBI group, we found a time-dependent emergence of social cognitive impairment, linked to diffuse neuropathology. The middle childhood TBI group demonstrated performance unrelated to SWI pathology and comparable to TD controls. Findings indicate that the full extent of social cognitive

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Received for publication 25 July 2014; Revised 20 November 2014; Accepted 16 December 2014.

DOI: 10.1002/hbm.22729

Published online 23 December 2014 in Wiley Online Library (wileyonlinelibrary.com).

deficits may not be realized until the associated skills reach maturity. Evidence for brain structure–function relationships suggests that the integrity of an anatomically distributed network of brain regions and their connections is necessary for the acquisition and establishment of high-level social cognitive skills. *Hum Brain Mapp* 36:1677–1691, 2015. © 2014 Wiley Periodicals, Inc.

Key words: child; brain injuries; magnetic resonance imaging; Theory of Mind; neurobiology

INTRODUCTION

Childhood and adolescence are critical periods for maturation of neurobiological processes that underlie complex social and emotional behaviors [Choudhury et al., 2006; Yurgelun-Todd et al., 2006], in particular Theory of Mind (ToM); a multidimensional construct that allows individuals to ascribe a variety of psychological states, such as intentions or emotions, to understand and subsequently predict behaviors [Blakemore, 2008; Herbet et al., 2013; Walz et al., 2010].

While cognitive ToM is concerned with basic, belief-based inferences traditionally assessed using paradigmatic false-belief tasks [Wellman et al., 2001], “complex cognitive-affective ToM” [Dennis et al., 2013a] can be partitioned into conative ToM, defined as the ability to understand how indirect speech acts involving irony and empathy are used to influence the mental or emotional state of the listener; and affective ToM, concerned with understanding that while facial expressions can convey emotions actually felt (emotion identification), they are also used for social purposes to convey emotions that we want people to think we feel [emotive communication; Dennis et al., 2013c; Hein and Singer, 2007; Shamay-Tsoory and Aharon-Peretz [2007]; see Fig. 1 for schematic representation].

Although false belief understanding matures rapidly during infancy and early childhood [Sodian et al., 2007; Surian et al., 2007; Wellman et al., 2001], the protracted development of complex cognitive-affective ToM through late childhood and adolescence [Choudhury et al., 2006; Dumontheil et al., 2010] corresponds to structural and functional development [Blakemore, 2008; Giedd et al., 1999; Shaw et al., 2008] of distributed brain regions critically involved in these functions, including medial prefrontal and lateral temporoparietal areas [Blakemore, 2011; Blakemore and Choudhury, 2006; Dumontheil et al., 2010; Nelson et al., 2005; Paus, 2005]. While structural maturation is likely associated with increasing functional specialization of anatomically distributed regions that underlie ToM [Blakemore, 2011; Scherf et al., 2013], little is known about the long-term impact of pediatric traumatic brain injury (TBI) on the acquisition and establishment of these high-level social cognitive skills.

TBI commonly involves pathology to anterior brain regions implicated in ToM processes [Tasker et al., 2005; Wilde et al., 2005]. In addition, traumatic axonal injury (TAI) is common and may disrupt formation of white matter connections between regions that contribute to the ana-

tomically distributed “social brain” network, including the superior temporal sulcus, fusiform gyrus, temporal pole, medial prefrontal cortex, orbitofrontal cortex, amygdala, temporoparietal junction, and inferior parietal cortex [Adolphs, 2009; Beauchamp and Anderson, 2010; Johnson et al., 2005; Yeates et al., 2007]. It has been argued that the social brain network is vulnerable to early disruption from TBI, and that deficits in social skills following such injuries may represent a failure to develop and acquire these skills at an age appropriate rate [Johnson et al., 2005; Yeates et al., 2007].

Cross-sectional studies indicate that children with TBI demonstrate deficits in recognizing and interpreting emotions from nonverbal cues [Ryan et al., 2013, 2014; Schmidt et al., 2010; Tlustos et al., 2011; Tonks et al., 2007a,b], as well as impairments in high-level aspects of social cognition including cognitive, affective, and conative ToM [Dennis et al., 2012, 2013a,b,c; Snodgrass and Knott, 2006; Walz et al., 2009, 2010]. While these studies provide preliminary evidence for the vulnerability of the immature social brain network to disruption from TBI [Ryan et al., 2014], the challenge remains to characterize longitudinal outcome and recovery of high-level social cognition after pediatric TBI, and evaluate the utility of newer and more sensitive structural imaging techniques to quantify the extent of TBI-related neuropathology, and predict outcome and recovery of high-level social cognition.

There is evidence to suggest that the immature brain is more vulnerable to damage and associated cognitive impairment [Anderson and Moore, 1995; Donders and Warschausky, 2007; Hebb, 1942]. It has been argued that this vulnerability might be specific to more complex behaviors (e.g., social cognition) that rely on more distributed neural representations. The relationship between age at brain injury and outcome for these behaviors is not explained by a simple linear association, but rather by a critical period model, with outcome dependent on neurological and cognitive development at the time of insult [Anderson et al., 2010, 2011; Crowe et al., 2012; Dennis, 1989; Dennis et al., 2014; Kolb et al., 2004]. This possibility is in keeping with principles of developmental biology that characterize brain development as a stepwise process consisting of peaks and plateaus (critical periods), during which neural development is rapid and neural networks are refined and consolidated [Hudspeth and Pribram, 1990; Kolb et al., 2004]. Since adolescence coincides with substantial structural and functional development of medial prefrontal and lateral temporoparietal brain regions

Figure 1.

Dennis et al.'s tripartite model of Theory of Mind. From Dennis et al., *Dev Cogn Neurosci*, 2013c, Vol. 5, p. 26, © Elsevier B.V. reproduced by permission.

critically involved in social cognition and ToM in particular [Blakemore, 2008; Choudhury et al., 2006; Giedd et al., 1999; Shaw et al., 2008], a critical period model would predict that high-level social cognition would be particularly vulnerable to insult during late childhood and adolescence when neural maturation is rapid and underlying networks are undergoing refinement and consolidation [Anderson et al., 2010; Blakemore, 2008; Crowe et al., 2012; Mosch et al., 2005].

Moreover, for younger children in whom high-level social cognitive functions may be emerging or not yet fully developed at the time of insult, damage to immature social cognitive circuitry may adversely affect the acquisition and establishment of these skills [Anderson and Moore, 1995; Semple et al., 2012]. While lesion studies offer a link between deficits in social cognition and damage to particular areas of the frontal and temporal cortices [Yeates et al., 2007; Geraci et al., 2010; Muller et al., 2010], it has been argued that the structural integrity an anatomically distributed network of brain regions and their connections may be necessary for the development of social processes through childhood and adolescence [Kennedy and Adolphs, 2012; Semple et al., 2012]. In keeping with this model, it may be that diffuse damage to the developing brain irreversibly disrupts processes of myelination and gray matter synaptic pruning, leading to a time-dependent emergence of social deficits during later development (i.e., early to mid adolescence) when high-level social cognitive skills are expected to mature and come online [Dumontheil et al., 2010; Semple et al., 2012].

Susceptibility-weighted imaging (SWI) is a relatively new neuroimaging technique that is especially sensitive to microhemorrhagic lesions commonly associated with TAI [Haacke et al., 2008; Kinnunen et al., 2011; Mittal et al., 2008; Wu et al., 2010]. SWI is a modified high spatial resolution 3D gradient recalled-echo MR technique that accentuates the magnetic properties of blood products, thereby

rendering it useful for detecting small amounts of altered blood and blood product in the brain [Haacke et al., 2004; Reichenbach et al., 1997; Sehgal et al., 2005]. SWI is shown to be more sensitive to traumatic brain lesions than more traditional techniques such as computed tomography and magnetic resonance imaging [MRI; Babikian et al., 2005; Beauchamp et al., 2011a; Spitz et al., 2013; Tong et al., 2003], and is associated with global measures of outcome, such as intellectual functioning [Babikian et al., 2005; Beauchamp et al., 2013; Colbert et al., 2010; Tong et al., 2004]. Given these links and its increased sensitivity to post-traumatic lesions, SWI may represent a useful tool to quantify TBI-related neuropathology, and establish a putative link between impaired social cognition and structural brain alterations after pediatric TBI.

The purpose of the present prospective longitudinal study was to investigate (1) the differential influence of age-at-insult on high-level social cognition after TBI sustained in middle childhood (5–9 years), late childhood (10–11 years), and adolescence (12–15 years); and (2) evaluate whether social cognitive impairments at 6- and 24-months postinjury are related to the neuroanatomical location, extent, and number of hemorrhagic lesions detected using SWI sequences acquired at 2–8 weeks postinjury.

We predicted that since social deficits are less likely to be detectable among children in whom high-level social cognitive skills are emerging or not yet established at the time of brain injury, the middle childhood TBI group would demonstrate performance that was both comparable to typically developing (TD) controls at 6- and 24-months postinjury, and unrelated to SWI lesions. Conversely, we predicted that late childhood TBI would be associated with a time-dependent emergence of high-level social cognitive impairment at 24-months post-TBI, with these late-emerging impairments related to more diffuse neuropathology and a greater number of SWI lesions. In keeping with the critical period model [Anderson et al.,

2010, 2011; Crowe et al., 2012; Dennis, 1989; Dennis et al., 2014; Kolb et al., 2004], we predicted that adolescent TBI would be associated with social cognitive impairments at both 6- and 24-months post-TBI, with impairments linked to more diffuse neuropathology and a greater number of lesions detected using SWI.

METHOD

Sample

This prospective longitudinal study comprised 112 children and adolescents with TBI and 43 TD children and adolescents, group-matched for age, gender, and socioeconomic status (SES). This study reports data from the 6- and 24-month postinjury assessments. All participants were ascertained between 2007 and 2010, and were aged between 5.3 and 15.4 years at time of recruitment. Children and adolescents with TBI were recruited at time of injury, and represented consecutive admissions to the Royal Children's Hospital (RCH), Melbourne, Australia.

For the TBI group, inclusion criteria were: (i) age 5.0–16.0 at recruitment; (ii) documented evidence of a closed head injury; (iii) medical records sufficiently detailed to determine injury severity; (iv) no documented history of preinjury neurological or developmental disorder, nonaccidental injury or previous TBI; (v) no prior intervention for social impairment; (vi) English speaking. The TD group were required to meet inclusion criteria (i), (iv), (v), and (vi) above.

Participants with TBI were classified as: (i) mild TBI ($n = 58$): Glasgow Coma Score (GCS) 13–15, no evidence of mass lesion on CT or clinical MRI; (ii) mild complicated TBI ($n = 13$): GCS 13–15, evidence of mass lesion on CT or clinical MRI; (iii) moderate TBI ($n = 22$): GCS 9–12, and/or mass lesion or other evidence of specific injury on CT/MRI, and/or neurological impairment; (iv) severe TBI ($n = 13$): GCS 3–8, and/or mass lesion or other evidence of specific injury on CT/MRI, and/or neurological impairment.

TBI participants were further categorized into age-at-injury groups. The rationale for these groups was based on timing of cerebral growth spurts [Giza and Prins, 2006; Kolb et al., 2004; van Praag et al., 2000] and has previously been used in pediatric TBI research [Anderson et al., 2010; Crowe et al., 2012]. The sample was divided into three groups, which were well matched for injury severity: middle childhood ($n = 41$), 5–9 years at injury; late childhood ($n = 39$), 10–11 years at injury; and adolescence ($n = 32$), 12–15 years at injury. TD control children were similarly divided into three groups: middle childhood ($n = 18$), 5–9 years; late childhood ($n = 14$), 10–11 years; and adolescence ($n = 11$), 12–15 years.

The study was approved by the RCH Human Research Ethics Committee. All parents gave their written, informed consent for children to participate in the study, and for retrospective extraction of clinical data from medical records.

Behavioral Tasks

The emotional and emotive faces task [EEFT: Dennis et al., 1998, 2013a,c] measures affective ToM using 10 vignettes that assess children's understanding of real and deceptive emotion in short narratives about a hypothetical character. Consistent with the tripartite model of ToM (Fig. 1) and in keeping with the interpretative guidelines provided by the test developers [Dennis et al., 2013c], each vignette involves (1) affective ToM items requiring identification of emotions expressed for social purposes (look on face condition) compared to (2) otherwise identical control items that have comparable domain-general cognitive demands but do not require affective ToM processing [feel inside condition; Dennis et al., 2013c]. Control items are considered distinct from affective ToM since they measure the emotion on the face as a transparent read-out of the emotion experienced [Dennis et al., 2013c]. Sample items for both conditions are described in Appendix.

The EEFT is a recently developed tool, which has been used to differentiate children with autism and TBI, and associated social impairment from healthy controls [Dennis et al., 1998, 2000, 2013a]. Raw data were converted to percentage of correct responses for each score and the following variables were used in the analysis: feel inside total score (EEF: FEEL), look on face total score (EEF: LOOK), concealment information total score (EEF: CON), and EEF total score (EEF: TOT).

The ironic criticism and empathic praise task [Dennis et al., 2001, 2013b,c] measures conative ToM using vignettes that assess the child's ability to understand the use of indirect speech acts to influence the mental and emotional state of the listener. Consistent with the tripartite model of ToM (Fig. 1), and in keeping with the interpretative guidelines provided by the test developers [Dennis et al., 2013c], each vignette involves (1) conative ToM trials requiring the child to identify the beliefs and intentions underlying referentially opaque communications involving irony and empathy, compared to (2) otherwise identical control items that have comparable domain-general cognitive demands but do not require conative ToM processing [Dennis et al., 2013c]. Control trials are considered distinct from conative ToM since they probe beliefs and intentions in literally true statements, and thus do not require the child to infer how indirect speech acts (i.e., irony and empathy) are used to influence the mental and emotional state of the listener. Sample items for both conative ToM and control conditions are described in Appendix. Raw data were converted to percentage of correct responses for each score; and analyses were performed on variables as a function of the level (beliefs vs. intentions) and type (literal, irony, empathy) of inference required.

Susceptibility-Weighted Imaging

Image acquisition

Children underwent structural MRI research scans between 2 and 8 weeks postinjury ($M = 39.25$, $SD = 27.64$

days). MR images were acquired on a 3 Tesla Siemens Trio scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-Channel matrix head coil. Conventional MR sequences were performed using a standardized imaging protocol [Beauchamp et al., 2011a,b]. SWI sequence was also included. SWI imaging is a variant of the standard 3D FLASH sequence that exploits the signal loss from shortened T2* characteristics of calcium- and deoxyhemoglobin-containing lesions. The images are T2* weighted because of the range of acceptable echo times (TEs) used in the acquisition (18–22 ms). The increased sensitivity to shortened T2* lesions is caused by the image reconstruction techniques used. Both magnitude and phase images are reconstructed from the dataset. The phase images display a higher sensitivity to local susceptibility variations and, as such, are used as an image mask to be combined with the magnitude data set. The combined data set is then reconstructed using a sliding window (eight individual slices compressed into one image) minimum intensity projection dataset. The total acquisition time for the MRI protocol was 31:53 min.

SWI Analyses

SWI images were visually reviewed to determine scan quality. One scan was rejected due to poor quality, and all of this participant's data were excluded from further analyses. The location of neuroanatomical lesions was identified based on visual inspection of SWI scans by a pediatric neuroradiologist and neuropsychologist blind to patients' clinical details. Lesions were identified and coded according to location (frontal, extrafrontal, and subcortical) using a modification of the Coffey classification system [Beauchamp et al., 2011a,b; Coffey and Figiel, 1991], which assessed the signal abnormality as seen on SWI images. Specifically signal changes identified on SWI scans were coded in gray and white matter in the following cortical and subcortical regions: frontal/temporal/parietal/occipital lobes, cerebellum, hippocampus, amygdala, corpus callosum, thalamus, and basal ganglia.

Scans rated positive for lesions on SWI were further investigated by manual segmentation using ITK-snap [Paul et al., 2006]. Lesion counts were conducted using a connected component analysis of lesion masks, which accounts for the possibility the multiple lesions may be present in any single independent region of the brain. Repeatability of segmentation was checked by resegmenting five scans after a delay of greater than 6 months and comparing volumes using intraclass correlation (ICC).

Lesion load provided an index of the extent of TBI-related neuropathology. Consistent with the approach employed by Kraus et al., [2007], lesion load was calculated as the total number of gray and white matter regions that showed signal abnormality as seen on SWI. This measure was used because it is thought to be sensitive to diffuse abnormalities given that it considers the actual

number of affected areas across the brain independent of individual variability in the specific location of these abnormalities [Kraus et al., 2007].

Statistical Analysis

All data were entered into SPSS statistical software (Version 21.0; SPSS, Chicago, IL) and screened for violations of normality. An alpha level of $P < 0.05$ was used to indicate significance, and effect sizes were calculated using Cohen's *d*. Effect sizes below 0.2 were considered small, those between 0.2 and 0.5 as medium, and those above 0.5, as large [Cohen, 1988]. Effect sizes greater than 0.67 were considered likely to be of clinical significance [Tabachnick and Fidell, 2001].

Analysis of variance (ANOVA) or χ^2 test-for-independence was conducted to investigate group differences for demographic and clinical variables. Independent-samples *t*-tests were conducted to investigate group differences for ToM outcomes in the age-at-injury groups. For each of the age-at-insult groups, Pearson partial correlations (1-tailed) were used to investigate directional relationships between ToM outcomes and the extent, number and location (frontal vs. extrafrontal) of SWI lesions, covarying for age at assessment, gender, and SES [Australian and New Zealand Standard Classification of Occupations (ANZSCO), McMillan et al., 2009].

RESULTS

Sample Characteristics

Table I presents characteristics for the age-at-insult and TD control subgroups. Groups did not differ on SES or gender. A significant age difference was identified between the adolescent TBI and TD control subgroups at 6-months postinjury, $t = -2.20$; $P = 0.04$, and thus age at assessment was included as a covariate in analyses of 6-month outcome in the adolescent groups. No other significant demographic differences were identified, $P > 0.05$.

Adolescents were more likely to have required surgical intervention, $\chi^2 = 61.90$, $P < 0.001$, and cause of injury also varied with age, with younger children more likely to suffer falls, $\chi^2 = 22.29$, $P < 0.001$. There were no significant differences for injury variables: neurological signs, length of hospital stay, or loss of consciousness (hours). Of particular note, no significant differences were identified for lowest GCS, $F(2, 111) = 0.52$, $P = 0.60$. In addition, there was no significant relationship between age at injury group membership and injury severity rating (mild/moderate vs. severe TBI), $\chi^2 = 2.44$, $P = 0.30$ (Table I).

Pediatric TBI and Neuropathology

Lesions were detected in 37 patients (35%) across all severity groups. SWI lesions were detected in 11 patients originally clinically classified as "mild TBI" based on

TABLE I. Characteristics of age-at-injury groups and age-matched control participants

	Middle childhood (5–9 years)		Late childhood (10–11 years)		Adolescence (12–15 years)	
	Control	TBI	Control	TBI	Control	TBI
<i>Demographics</i>						
Total <i>n</i>	18	41	14	39	11	32
Male, <i>n</i> (%)	10 (47.6)	24 (58.5)	10 (83.3)	29 (74.4)	4 (40.0)	23 (71.9)
SES <i>M</i> (SD) ^a	69.51 (20.98)	60.57 (26.77)	75.15 (16.96)	65.53 (23.41)	74.18 (15.27)	66.83 (23.48)
Age at injury, <i>M</i> (SD) ^b	—	7.50 (1.17)	—	10.91 (.57)	—	13.19 (.83)
Age at 6-month assessment, <i>M</i> (SD) ^{b, c}	7.38 (1.04)	8.05 (1.18)	11.85 (1.33)	11.47 (.59)	12.93 (2.90)	13.72 (.87)
Age at 24-month assessment, <i>M</i> (SD) ^b	8.94 (1.08)	9.48 (1.22)	13.30 (1.36)	13.02 (.63)	14.04 (3.03)	15.24 (.89)
<i>Injury characteristics</i>						
Lowest GCS, <i>M</i> (SD)	—	12.39 (3.51)	—	13.00 (2.96)	—	12.25 (3.65)
Neurological signs, <i>M</i> (SD)	—	1.27 (.63)	—	1.36 (.67)	—	1.41 (.56)
Length hospital stay (days), <i>M</i> (SD)	—	3.65 (5.86)	—	3.76 (7.64)	—	4.76 (10.28)
Surgical intervention, <i>n</i> (%) ^b	—	4 (9.76)	—	5 (12.82)	—	6 (18.80)
LOC (Hours), <i>M</i> (SD)	—	3.20 (2.93)	—	3.69 (3.49)	—	3.53 (3.04)
<i>Cause of injury</i> ^b						
MVA (Car), <i>n</i> (%)	—	2 (5)	—	4 (10)	—	5 (16)
MVA (Pedestrian/bike), <i>n</i> (%)	—	5 (12)	—	6 (15)	—	3 (9)
Fall (stationary), <i>n</i> (%)	—	16 (39)	—	6 (15)	—	5 (16)
Fall (moving), <i>n</i> (%)	—	12 (29)	—	13 (33)	—	14 (44)
Kicked/struck by object, <i>n</i> (%)	—	6 (15)	—	10 (26)	—	5 (16)

^aSES is based on the ANZSCO. The scale ranges from 0 to 100 with high scores reflecting higher occupation status for the primary caregiver.

^bSignificant difference between age-at-injury subgroups.

^cSignificant difference between TBI v. Control

available clinical information. Basing severity classification on the presence of lesions on SWI suggests that they suffered “mild complicated” injuries. No SWI lesions were detected in the TD group. Lesion number (min 1, max 77) showed substantial variability. Segmentation procedures were reliable, with an intrarater ICC score of 0.987 (95% confidence interval = 0.911–0.999). Age-at-injury groups did not differ for number of SWI lesions detected, $F(2, 103) = 0.55$; $P = 0.58$. Distribution of SWI lesions is represented in Figure 2.

Pediatric TBI and Social Cognition

Middle childhood TBI

Control tasks. Groups did not differ on control tasks including feel inside (6-months: $t = -0.50$; $P = 0.62$; 24-months: $t = -1.55$; $P = 0.13$); direct belief (6-months: $t = 0.13$; $P = 0.90$; 24-months: $t = 1.34$; $P = 0.19$); direct intentions (6-months: $t = -1.05$; $P = 0.30$; 24-months: $t = -0.79$; $P = 0.43$); and literal truth (6 months: $t = -0.61$; $P = 0.54$; 24-months: $t = 0.16$; $P = 0.88$).

ToM tasks. As shown in Table II, the middle childhood TBI group demonstrated comparable performance to age-matched TD controls on all measures of conative and

affective ToM at 6-months ($P > 0.05$; Cohen’s $d = 0.01$ – 0.26) and 24-months post-TBI ($P > 0.05$; Cohen’s $d = 0.01$ – 0.26).

Late Childhood TBI

Control tasks. Groups did not differ on control tasks including feel inside (6-months: $t = -0.75$; $P = 0.46$; 24-months: $t = -1.92$; $P = 0.06$); direct belief (6-months: $t = 0.18$; $P = 0.86$; 24-months: $t = 0.16$; $P = 0.87$); direct intentions (6-months: $t = -1.2$; $P = 0.24$; 24-months: $t = -0.53$; $P = 0.60$) and literal truth (6 months: $t = -0.55$; $P = 0.58$; 24-months: $t = -0.29$; $P = 0.77$).

ToM tasks. At 6-months postinjury, these children showed comparable performance to TD controls on all measures of affective and conative ToM ($P > 0.05$; Cohen’s $d = 0.08$ – 0.33). At 24-months postinjury, these children were significantly less accurate for understanding ironic intentions, $t = -2.1$; $P = 0.05$ (2-tailed); Cohen’s $d = 0.62$, and showed worse performance for understanding Indirect Intentions involving irony and empathy, $t = -2.1$; $P = 0.04$ (2-tailed); Cohen’s $d = 0.63$.

Adolescent TBI

Control tasks. Groups did not differ on control tasks including feel inside (6-months: $t = -1.41$; $P = 0.17$;

Figure 2.

Probability distribution of brain lesions detected using SWI in the left lateral (A), left medial (B), right lateral (C), and right medial (D) hemispheres. Lesion distributions were created by aligning the individual T1 images to the Montreal Neurological Institute template using the nonlinear normalization procedure in Statistical Parametric Mapping 8 (SPM8). The lesion maps were normalized using the same transformations. The aligned lesion masks were averaged to produce a single image illustrating the distribution of lesions in the study population. Hotter colors indicate the colocation of lesions in multiple subjects. Lesions were most prominent in frontal regions (frontal only = 15 patients, frontal + extrafrontal only = 6, frontal + other regions [CC = 1, deep gray + CC = 1, cerebellum = 1, cerebellum + CC = 1]), followed by extrafrontal regions only ($N = 6$). A small number of patients (4) had lesions in several areas 6 (frontal + extrafrontal + cerebellum = 2, frontal + extrafrontal + deep gray = 1, frontal + extrafrontal + CC = 1). Very few patients had lesions solely in the CC (1), cerebellum (1) or deep gray (0) regions. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

24-months: $t = -0.95$; $P = 0.35$); direct belief (6-months: $t = -0.34$; $P = 0.73$; 24-months: $t = 0.17$; $P = 0.87$); direct intentions (6-months: $t = -1.20$; $P = 0.25$; 24-months: $t = -0.45$; $P = 0.66$); and literal truth (6 months: $t = -0.98$; $P = 0.34$; 24-months: $t = -0.15$; $P = 0.89$).

ToM tasks. At 6-months post-TBI, this group performed significantly worse than TD controls on affective ToM tasks including EEFT look on face, $t = -2.0$; $P = 0.04$; Cohen's $d = 0.77$; EEFT concealment information, $t = -2.7$; $P = 0.01$; Cohen's $d = 0.77$; and EEFT total score, $t = -2.8$; $P = 0.007$; Cohen's $d = 1.09$. Adolescents with TBI were also significantly poorer at understanding ironic inten-

tions, $t = -2.0$; $P = 0.04$; Cohen's $d = 0.74$, and understanding indirect intentions involving irony and empathy, $t = -2.2$; $P = 0.03$; Cohen's $d = 0.81$. Due to group differences in age at 6-month assessment, these analyses were repeated covarying to age at 6-month assessment, and this did not significantly alter the results.

At 24-months postinjury, adolescents with TBI performed significantly worse than TD controls on affective ToM tasks including EEFT look on face, $t = -2.6$; $P = 0.01$; Cohen's $d = 1.07$; EEFT concealment information, $t = -2.6$; $P = 0.01$; Cohen's $d = 0.84$; and EEFT total score, $t = -2.5$; $P = 0.02$; Cohen's $d = 1.13$.

Associations Between Social Cognitive Deficits and Neuropathology

As expected, preliminary analyses at the group level ($n = 112$; injury age 5.0–15.0 years) revealed no significant brain-behavior relations at 6- or 24-months postinjury ($P > 0.05$).

Table III reports Pearson partial correlations between ToM and SWI lesions, covarying for age at assessment, SES, and gender. For the middle childhood TBI group, performance at 6- and 24-months postinjury was unrelated to the extent and number of SWI lesions ($P > 0.05$). For late childhood TBI, SWI lesions were related to 24-month outcomes only. Total lesion load was negatively correlated with measures of conative ToM, showing that individuals with more diffuse neuropathology were worse at understanding ironic and empathic intentions. Finally, in the adolescent TBI group, 6- and 24-month ToM outcomes were related to both the extent and number of SWI lesions. At 6-months postinjury, white matter load was negatively correlated with understanding empathic and ironic beliefs, showing that individuals with more diffuse white matter pathology had worse performance on these tasks. Similarly, gray matter load was negatively correlated with affective ToM, such that more diffuse gray matter pathology was associated with poorer performance on the EEFT task. Similarly, at 24-months post-TBI, total lesion load was negatively correlated with both conative and affective ToM, with more diffuse neuropathology linked to worse performance on these tasks. Further, number of SWI lesions was negatively correlated with understanding indirect beliefs and empathic beliefs and intentions at 24-months post-TBI.

SWI Pathology Location

Across all age-at-insult subgroups, there were no significant relationships between ToM outcomes and frontal or extrafrontal pathology, $P > 0.05$ (Table IV).

DISCUSSION

The purpose of the present prospective longitudinal study was to investigate the differential influence of age-at-insult

TABLE II. Affective and conative Theory of Mind (ToM) as a function of age-at-insult

Variable	Middle childhood (5–9 years)						Late childhood (10–11 years)						Adolescence (12–15 years)					
	6-months			24-months			6-months			24-months			6-months			24-months		
	Control M (SD)	TBI M (SD)		Control M (SD)	TBI M (SD)		Control M (SD)	TBI M (SD)		Control M (SD)	TBI M (SD)		Control M (SD)	TBI M (SD)		Control M (SD)	TBI M (SD)	
EEFT																		
LOOK	60.0 (24.2)	52.6(25.6)		57.5 (20.5)	54.7 (21.1)		58.9 (16.1)	62.9 (16.8)		56.9 (10.1)	63.2 (16.0)		68.6 (9.5)	60.0 (12.7)		71.1 (15.8)	52.4 (19.1)	
CON	60.6 (31.7)	57.2 (23.0)		63.9 (23.0)	56.9 (25.9)		82.1 (14.2)	81.1 (20.3)		75.4 (17.6)	76.4 (24.3)		92.7 (7.9)	80.0 (22.0)		94.4 (8.8)	78.3 (25.7)	
TOT.	59.3 (18.6)	54.2 (18.5)		65.4 (14.5)	61.5 (16.3)		67.5 (7.9)	68.3 (12.8)		69.8 (7.4)	71.7 (13.4)		76.8 (6.7)	67.3 (10.3)		81.9 (7.6)	66.7 (17.5)	
ICEP: ST																		
IB.	50.0 (34.1)	46.2 (32.2)		64.4 (17.6)	58.1(24.6)		72.0 (28.8)	67.6 (29.6)		70.5 (25.8)	72.2 (27.9)		81.1 (32.7)	71.8 (18.2)		69.4 (30.0)	64.9 (21.5)	
EB.	32.4 (28.9)	35.6 (32.3)		33.8 (23.1)	37.1 (30.5)		42.9 (31.8)	52.7 (27.5)		54.5 (21.4)	52.8 (29.7)		54.5 (38.6)	67.0 (16.9)		58.3 (27.6)	62.0 (22.4)	
II	25.9 (33.9)	29.3 (31.8)		46.3 (28.0)	38.8 (30.1)		50.0 (37.8)	48.0 (35.0)		69.9 (24.9)	51.0 (35.5)		74.2 (31.1)	49.7 (34.9)		59.3 (27.8)	53.3 (29.3)	
EI	53.2 (35.3)	48.4 (30.5)		75.5 (22.2)	72.4 (21.7)		71.4 (22.8)	72.1 (26.1)		79.5 (19.7)	74.0 (26.3)		73.5 (27.3)	61.8 (25.2)		70.4 (16.7)	67.8 (27.4)	
IEPT: CS																		
IC	38.0 (29.7)	37.7 (28.7)		55.3 (20.8)	48.4 (24.8)		61.0 (28.8)	57.8 (28.6)		70.2 (23.7)	61.6 (28.0)		77.7 (30.9)	60.8 (23.3)		64.4 (28.0)	59.1 (22.5)	
EP	42.8 (24.2)	42.0 (21.6)		54.6 (14.8)	54.7 (18.7)		57.1 (22.7)	62.4 (17.2)		67.0 (12.9)	63.4 (18.1)		64.0 (29.2)	64.4 (17.0)		64.4 (17.9)	64.9 (21.4)	
IB	41.2 (27.9)	40.9 (29.5)		49.1 (12.4)	47.6 (23.2)		57.4 (25.1)	60.1 (26.1)		62.5 (22.6)	62.5 (25.1)		67.8 (31.7)	69.4 (14.9)		63.9 (28.6)	63.4 (19.9)	
II	39.6 (27.9)	38.9 (22.7)		60.9 (20.1)	55.6 (18.9)		60.7 (23.5)	60.0 (19.4)		74.7 (15.7)	62.5 (22.7)		73.9 (21.9)	55.7 (23.1)		64.8 (16.7)	60.5 (23.7)	

ST, subtests; IB, ironic belief; EB, empathic belief; II, ironic intent; EI, empathic intent; CS, composite scores; IC, ironic criticism; EP, empathic praise; IB, indirect belief; II, indirect intent.

Bold: Significant differences, $P < 0.05$.

TABLE III. Partial correlations between Theory of Mind outcomes and SWI variables, $r(p)$

FOB			SOI		ICEP composite scores				EEFT			
	Irony	Empathy	Irony	Empathy	Criticism	Praise	Ind. Belief	Ind. Intent	LOOK	CON	TOTAL	
Middle childhood TBI												
6 months	GM Ld.	0.31 (0.04)	0.38 (0.01)	0.03 (0.44)	0.20 (0.13)	0.20 (0.13)	0.42 (0.01)	0.38 (0.01)	0.16 (0.19)	-0.21 (0.13)	-0.09 (0.31)	-0.17 (0.18)
	WM Ld.	-0.06 (0.36)	-0.07 (0.34)	0.17 (0.17)	-0.05 (0.39)	0.06 (0.38)	-0.09 (0.31)	-0.08 (0.34)	0.09 (0.32)	0.06 (0.38)	0.07 (0.35)	0.00 (0.50)
	Tot. Ld.	0.08 (0.33)	0.10 (0.29)	0.15 (0.20)	0.04 (0.41)	0.13 (0.24)	0.10 (0.28)	0.10 (0.29)	0.13 (0.23)	-0.04 (0.41)	0.02 (0.25)	-0.07 (0.35)
	Total N	0.06 (0.36)	0.28 (0.06)	-0.05 (0.39)	0.08 (0.32)	0.01 (0.48)	0.27 (0.07)	0.19 (0.15)	0.02 (0.45)	-0.20 (0.14)	0.04 (0.41)	-0.15 (0.21)
24 months	GM Ld.	0.39 (0.02)	0.28 (0.08)	0.22 (0.14)	-0.05 (0.40)	0.35 (0.04)	0.22 (0.14)	0.37 (0.03)	0.15 (0.23)	-0.15 (0.23)	0.02 (0.46)	-0.13 (0.26)
	WM Ld.	0.14 (0.25)	0.15 (0.24)	0.19 (0.17)	-0.24 (0.12)	0.19 (0.17)	0.00 (0.50)	0.16 (0.22)	0.00 (0.50)	-0.22 (0.14)	-0.08 (0.35)	-0.03 (0.44)
	Tot. Ld.	0.28 (0.09)	0.23 (0.13)	0.25 (0.11)	-0.20 (0.16)	0.30 (0.07)	0.10 (0.32)	0.28 (0.08)	0.07 (0.38)	-0.23 (0.13)	-0.05 (0.40)	-0.08 (0.34)
	Total N	0.27 (0.10)	0.18 (0.20)	0.28 (0.09)	-0.27 (0.09)	0.31 (0.07)	0.04 (0.43)	0.24 (0.12)	0.08 (0.36)	-0.23 (0.13)	0.02 (0.47)	-0.24 (0.12)
Late childhood TBI												
6 months	GM Ld.	0.26 (0.07)	0.09 (0.31)	0.02 (0.46)	-0.12 (0.25)	0.15 (0.21)	-0.02 (0.47)	0.19 (0.14)	-0.06 (0.36)	0.16 (0.20)	0.12 (0.26)	0.21 (0.13)
	WM Ld.	0.23 (0.10)	0.15 (0.20)	-0.09 (0.31)	0.02 (0.47)	0.07 (0.35)	0.13 (0.23)	0.21 (0.12)	-0.08 (0.33)	0.10 (0.29)	-0.01 (0.48)	0.01 (0.48)
	Tot. Ld.	0.27 (0.06)	0.14 (0.22)	-0.05 (0.40)	-0.05 (0.38)	0.12 (0.26)	0.07 (0.34)	0.23 (0.10)	-0.08 (0.32)	0.14 (0.22)	0.04 (0.42)	0.08 (0.32)
	Total N	0.00 (0.50)	0.09 (0.31)	-0.05 (0.40)	-0.17 (0.18)	-0.03 (0.44)	-0.05 (0.39)	0.05 (0.40)	-0.17 (0.18)	-0.15 (0.21)	-0.14 (0.22)	-0.25 (0.09)
24 months	GM Ld.	0.20 (0.15)	0.18 (0.17)	-0.01 (0.47)	-0.33 (0.04)	0.09 (0.32)	-0.09 (0.33)	0.22 (0.13)	-0.31 (0.05)	0.07 (0.35)	0.15 (0.21)	0.11 (0.29)
	WM Ld.	0.41 (0.01)	0.40 (0.01)	0.21 (0.14)	-0.24 (0.10)	0.33 (0.04)	0.16 (0.20)	0.46 (0.01)	0.02 (0.45)	0.03 (0.45)	0.08 (0.34)	0.01 (0.47)
	Tot. Ld.	0.34 (0.03)	0.32 (0.04)	0.11 (0.28)	-0.32 (0.04)	0.24 (0.10)	0.05 (0.41)	0.38 (0.02)	-0.10 (0.30)	0.05 (0.39)	0.13 (0.25)	0.07 (0.37)
	Total N	0.37 (0.03)	0.38 (0.02)	0.29 (0.07)	0.06 (0.38)	0.36 (0.03)	0.38 (0.02)	0.43 (0.01)	0.27 (0.08)	0.04 (0.41)	0.21 (0.14)	0.09 (0.32)
Adolescent TBI												
6 months	GM Ld.	-0.16 (0.22)	-0.34 (0.04)	0.12 (0.28)	-0.14 (0.25)	0.03 (0.45)	-0.28 (0.08)	-0.30 (0.07)	0.02 (0.45)	-0.43 (0.01)	-0.34 (0.04)	-0.55 (0.01)
	WM Ld.	-0.53 (0.01)	-0.24 (0.11)	-0.14 (0.25)	-0.02 (0.46)	-0.31 (0.06)	-0.15 (0.24)	-0.47 (0.01)	-0.13 (0.26)	0.25 (0.11)	0.08 (0.35)	0.18 (0.19)
	Tot. Ld.	-0.56 (0.01)	-0.34 (0.04)	-0.09 (0.32)	-0.07 (0.37)	-0.29 (0.07)	-0.23 (0.13)	-0.54 (0.01)	-0.11 (0.29)	0.10 (0.32)	-0.04 (0.43)	0.00 (0.50)
	Total N	0.01 (0.47)	-0.33 (0.05)	0.23 (0.13)	0.02 (0.46)	0.18 (0.19)	-0.16 (0.22)	-0.18 (0.19)	0.20 (0.16)	-0.07 (0.37)	-0.32 (0.06)	-0.29 (0.08)
24 months	GM Ld.	-0.46 (0.02)	-0.35 (0.06)	-0.08 (0.36)	-0.17 (0.24)	-0.26 (0.13)	-0.34 (0.07)	-0.48 (0.02)	-0.16 (0.26)	-0.27 (0.12)	-0.22 (0.17)	-0.39 (0.04)
	WM Ld.	-0.29 (0.10)	-0.32 (0.08)	-0.24 (0.15)	0.14 (0.28)	-0.30 (0.10)	-0.10 (0.33)	-0.37 (0.06)	-0.11 (0.33)	0.25 (0.15)	0.26 (0.14)	0.17 (0.23)
	Tot. Ld.	-0.45 (0.02)	-0.43 (0.03)	-0.26 (0.14)	0.06 (0.39)	-0.38 (0.05)	-0.23 (0.17)	-0.52 (0.01)	-0.16 (0.26)	0.12 (0.31)	0.15 (0.27)	0.01 (0.49)
	Total N	-0.51 (0.01)	-0.66 (0.01)	0.00 (0.50)	-0.15 (0.27)	-0.23 (0.17)	-0.53 (0.01)	-0.69 (0.01)	-0.09 (0.36)	0.04 (0.44)	-0.27 (0.14)	-0.17 (0.25)

SWI variables: GM Ld., gray matter lesion load; WM Ld., white matter lesion load; Tot. Ld., total lesion load; Total N, total number of SWI lesions.

Bold: Association $p < .05$.

ToM variables: FOB, first-order beliefs; SOI, second-order intentions

TABLE IV. Partial correlations between Theory of Mind outcomes and lesion location, r (p)

	FOB			SOI			ICEP composite scores				EEFT		
	Irony	Empathy	Irony	Empathy	Criticism	Praise	Ind.Belief	Ind. Intent	LOOK	CON	TOTAL		
<i>Middle childhood TBI</i>													
6 months Frontal	0.13 (0.25)	-0.10 (0.30)	0.30 (0.05)	0.03 (0.44)	0.25 (0.08)	-0.06 (0.37)	0.01 (0.49)	0.25 (0.08)	-0.03 (0.44)	0.04 (0.41)	-0.08 (0.33)		
E-Frontal	0.37 (0.02)	0.40 (0.01)	0.10 (0.29)	-0.04 (0.41)	0.27 (0.07)	0.29 (0.05)	0.42 (0.01)	0.05 (0.40)	-0.23 (0.10)	-0.24 (0.09)	-0.24 (0.09)		
24 months Frontal	0.12 (0.28)	0.19 (0.19)	0.13 (0.27)	-0.13 (0.27)	0.14 (0.25)	0.09 (0.34)	0.19 (0.19)	0.03 (0.45)	-0.26 (0.11)	0.17 (0.20)	-0.03 (0.45)		
E-Frontal	0.32 (0.06)	0.05 (0.42)	0.14 (0.26)	0.13 (0.27)	0.26 (0.11)	0.12 (0.28)	0.20 (0.17)	0.25 (0.12)	0.27 (0.09)	0.05 (0.41)	0.23 (0.13)		
<i>Late childhood TBI</i>													
6 months Frontal	0.27 (0.07)	0.24 (0.10)	0.09 (0.32)	0.00 (0.50)	0.19 (0.15)	0.19 (0.15)	0.28 (0.06)	0.08 (0.33)	0.20 (0.13)	-0.03 (0.43)	0.08 (0.33)		
E-Frontal	0.19 (0.15)	0.18 (0.16)	0.04 (0.42)	0.05 (0.39)	0.12 (0.25)	0.19 (0.15)	0.21 (0.13)	0.07 (0.35)	0.02 (0.45)	0.00 (0.49)	-0.01 (0.49)		
24 months Frontal	0.31 (0.05)	0.27 (0.08)	0.09 (0.33)	-0.09 (0.33)	0.21 (0.13)	0.16 (0.20)	0.33 (0.04)	0.02 (0.47)	0.15 (0.21)	0.04 (0.43)	0.07 (0.35)		
E-Frontal	0.14 (0.23)	0.23 (0.11)	0.14 (0.24)	-0.30 (0.06)	0.16 (0.20)	-0.03 (0.45)	0.22 (0.13)	-0.07 (0.35)	-0.07 (0.35)	0.09 (0.33)	0.00 (0.50)		
<i>Adolescent TBI</i>													
6 months Frontal	-0.17 (0.21)	0.12 (0.28)	-0.03 (0.44)	0.37 (0.03)	-0.09 (0.33)	0.34 (0.04)	-0.04 (0.42)	0.19 (0.17)	0.10 (0.31)	0.14 (0.24)	0.15 (0.24)		
E-Frontal	-0.26 (0.10)	-0.23 (0.13)	0.18 (0.19)	-0.13 (0.26)	0.03 (0.44)	-0.22 (0.15)	-0.30 (0.07)	0.08 (0.35)	-0.15 (0.23)	-0.19 (0.18)	-0.19 (0.18)		
24 months Frontal	0.04 (0.44)	-0.13 (0.30)	-0.14 (0.29)	0.52 (0.01)	-0.07 (0.39)	0.26 (0.15)	-0.05 (0.42)	0.21 (0.19)	0.29 (0.11)	0.18 (0.23)	0.25 (0.15)		
E-Frontal	-0.32 (0.09)	-0.34 (0.08)	0.09 (0.35)	0.09 (0.36)	-0.10 (0.34)	-0.14 (0.28)	-0.37 (0.06)	0.12 (0.32)	0.09 (0.36)	0.08 (0.27)	0.13 (0.30)		

Frontal, evidence of frontal pathology on SWI; E-Frontal, evidence of extra frontal pathology on SWI.

ToM variables: FOB, first-order beliefs; SOI, second-order intentions.

Note: No significant relationships identified.

on high-level social cognition following TBI sustained across middle childhood to adolescence. Moreover, in approaching the neuropathological bases of social cognitive impairment after pediatric TBI, we aimed to examine whether ToM impairments at 6- and 24-months postinjury were related to the neuroanatomical location, extent, and number of micro-hemorrhagic lesions detected using SWI. In line with the critical period model [Anderson et al., 2010, 2011; Crowe et al., 2012; Dennis, 1989; Dennis et al., 2014; Kolb et al., 2004], adolescent TBI was associated with impairment in conative and affective ToM at 6- and 24-months post-TBI, and these difficulties were related to more diffuse neuropathology and a greater number of SWI lesions. In contrast, at both time points, the middle childhood TBI group demonstrated ToM performance that was comparable to TD controls and unrelated to neuropathology, while in the late childhood TBI group we found a time-dependent emergence of social cognitive impairment by 24-months postinjury, linked to more diffuse neuropathology. These findings suggest that diffuse cerebral damage adversely impacts the acquisition and establishment of high-level social cognitive skills, and that the long-term social consequences of diffuse damage may not be realized until the associated skills reach maturity.

Consistent with expectations, although middle childhood TBI was associated with performances comparable to TD controls and unrelated to the number and extent of brain lesions, the adolescent TBI group showed persisting social cognitive dysfunction that was related to more diffuse neuropathology. Although younger age at insult has traditionally been associated with increased risk for cognitive impairment [Anderson and Moore, 1995; Donders and Warscahussy, 2007; Hebb, 1942], our findings suggest that, for high-level social cognition, previous assumptions of a linear relationship between age and injury and outcome may not be appropriate. Rather, social cognitive outcomes may be dependent on neurological and cognitive development at the time of injury [Anderson et al., 2010; Dennis et al., 2014]. While evidence shows that false belief understanding matures rapidly during infancy and early childhood [Sodian et al., 2007; Surian et al., 2007; Wellman et al., 2001], there is recent support for protracted maturation of complex cognitive-affective ToM into midadolescence and adulthood [Choudhury et al., 2006; Dumontheil et al., 2010], corresponding to structural and functional development of anterior brain regions critically involved these high-level functions [Blakemore, 2008; Choudhury et al., 2006; Giedd et al., 1999; Shaw et al., 2008]. It may be that, for adolescents with TBI, diffuse disruption to white matter connections compromises structural connectivity between anatomically distributed “social brain” regions that, by adolescence, may have developed functional specificity that more closely approximates the adult brain [Johnson, 2001; Johnson et al., 2005]. Furthermore, since it appears that adolescent TBI may disrupt protracted maturation and refinement of social cognitive neural networks, we speculate that adolescence may coincide with a critical

period for the acquisition and establishment of high-level social cognitive skills.

Consistent with expectations, late childhood TBI was associated with a time-dependent emergence of high-level social cognitive impairment. At 6-months postinjury, this group showed comparable performance to TD controls, but by the 24-month time point these children demonstrated a highly circumscribed impairment in conative ToM that was significantly associated with more diffuse neuropathology. Evidence for significant group differences in conative but not affective ToM for the late childhood groups is broadly consistent with previous evidence for protracted maturation of complex cognitive-affective behavior into midadolescence [Choudhury et al., 2006; Dumontheil et al., 2010], and may suggest that affective ToM was equally difficult for both the clinical and control groups. Overall, the present findings converge with studies of pediatric TBI in mice, indicating that the social consequences of early diffuse brain insult may not become apparent until adolescence when high-level social cognitive skills are expected to reach maturity [Blakemore, 2008; Choudhury et al., 2006; Dumontheil et al., 2010].

Our results may explain the null findings of previous cross sectional studies that have examined social cognitive outcomes in younger children with TBI [Walz et al., 2009]. This study suggests that developmental factors may mask impairments in skills that are emerging or not yet fully established at the time of insult, and that high-level social cognitive dysfunction does not become apparent until later in development when relative to TD peers, these children fail to make age-appropriate developmental gains. Thus, it may be that poor long-term outcomes after pediatric TBI stem from a failure to acquire high-level social cognitive skills required to meet the normative developmental demands of adolescence.

Though our findings establish a link between impaired ToM and diffuse neuropathology, we found that ToM impairment was unrelated to pathology location. This finding is in keeping with recent studies reporting that lesion location and laterality are not predictive of social outcome after early brain insult [Greenham et al., 2010; Ryan et al., 2014], and suggest that the structural integrity of an anatomically distributed network of social brain regions and their connections may be necessary for the development of social cognitive processes in childhood [Kennedy and Adolphs, 2012; Semple et al., 2012].

Recent evidence suggests that diffuse axonal dysfunction associated with pediatric white matter injury is a greater burden to adaptive plasticity and recovery than is neuronal loss of cortical injury [Follett et al., 2009]. More specifically, this research shows that diffuse white matter injury interferes with the activity-dependent gain and loss of synapses, and introduces substantial variability into the system. In applying this model of brain recovery to the immature social brain network, our findings suggest that diffuse TAI may disrupt these neuronal processes, and

adversely impact the acquisition and establishment of high-level social cognitive skills.

Our results also support the long-term prognostic utility of SWI. While SWI is superior at detecting hemorrhagic lesions, as well as significantly smaller lesions relative to other imaging modalities [Beauchamp et al., 2011a,b; Chastain et al., 2009; Sigmund et al., 2007; Tong et al., 2003, 2004], in previous studies, relationships between SWI and cognitive outcomes have been limited to global measures of intellectual functioning [Beauchamp et al., 2013; Tong et al., 2004]. Our results extend on these findings to support the prognostic value of SWI for long-term social cognitive outcomes. Moreover, while structural imaging techniques including volumetric brain morphometry (VBM) and diffusion-weighted imaging (DWI) are widely used to investigate the neuropathological bases of high-level cognitive impairments in TBI [Dennis et al., 2013c; Kinnunen et al., 2011], our results suggest that SWI can be used to generate an clinically useful index of macrostructural damage that does not require reference to a control group, and is related to long-term social cognitive outcomes after pediatric TBI.

Some methodological limitations weakened the strength of our findings. The first limitation pertains to the scope of the longitudinal follow-up. Further follow-up at 30- and 60-months postinjury will be required to elucidate the full extent to which childhood TBI is associated with a time-dependent emergence of high-level social cognitive impairment. It is likely that for participants in the middle and late childhood subgroups, high-level social cognitive skills were emerging or not yet fully established at the 24-month time point. On this basis, we speculate that the present findings represent a conservative estimate of social cognitive impairment. Moreover, since it is unlikely that early recovery processes had stabilized at 6-months postinjury, we cannot fully exclude the possibility that the social cognitive impairments are at least partly attributable to deficits in domain general abilities. However, based on evidence for a differential impact of TBI on social cognitive but not nonsocial cognitive control variables, we suggest that children and adolescents in our TBI sample demonstrate domain specific, high-level social cognitive deficits.

Further studies using microstructural neuroimaging techniques such as diffusion-weighted imaging and tractography are required to determine whether our findings generalize to other domains of social cognition that illustrate comparable developmental trajectories to ToM, and are mediated by similar, overlapping social cognitive neural circuits.

Our findings are consistent with a critical period model, suggesting that high-level social cognitive outcome after pediatric TBI is dependent on neurological and cognitive development at the time of injury [Anderson et al., 2010; Crowe et al., 2012; Dennis et al., 2014]. Moreover, while we show that high-level social cognitive impairment is

associated with diffuse damage to multiple component brain regions, evidence for a time-dependent emergence of high-level social cognitive impairment in adolescence suggests that the social consequences of diffuse cerebral insult may not be realized until the associated skills are expected to reach maturity. To our knowledge, this is the first human study to document the emergence of age-dependent social cognitive deficits after generalized insult to the developing brain; suggesting that diffuse cerebral damage may irreversibly disrupt processes of myelination and gray matter synaptic pruning that are critical for activity-dependent interregional refinement of anatomically distributed brain regions that underlie ToM [Johnson et al., 2005].

Our findings accord with a network paradigm of social cognitive disturbance, by suggesting that the integrity of a distributed network of brain regions and their connections is necessary for the development of social cognitive processes in childhood. This type of approach should prompt neuropsychological researchers to consider structural connectivity (rather than an over simplistic, location-centered paradigm) when interpreting cognitive impairments in children, especially in the domain of social cognition [Herbet et al., 2014; Kennedy and Adolphs, 2012].

Moreover, to more accurately predict the trajectory of social cognitive outcome after pediatric brain insult, the present findings indicate that less reliance should be placed on clinical classifications made at the time of insult. In our sample, 11 patients originally clinically classified as “mild TBI” were reclassified as “mild complicated” according to SWI, and the extent of lesions identified in this neuroimaging modality were related to long-term social cognitive outcomes. Based on these results, we suggest that clinicians should exercise caution when prognosticating based on early clinical indicators, and that SWI may be a useful alternative to identify children and adolescents at elevated risk for long-term social cognitive impairment.

Our results have several important implications for clinical practice. While we show that adolescent TBI is associated with elevated risk for poor social cognitive outcome, our results also suggest that injury at a younger age confers elevated risk for a time-dependent emergence of social cognitive impairment. Because ToM impairments are likely to remain undetected by routine neuropsychological assessments post-TBI, our results indicate that social cognition test batteries may be a valuable supplement to neuropsychological assessment protocol, and would assist to identify children who may “grow into” social cognitive deficits over time.

Since high-level social cognitive skills are likely a critical prerequisite to achieve normative adolescent goals, children and adolescents with TBI may benefit from social cognitive remediation interventions designed to improve social skills. Since recent evidence suggests that the immature social brain is particularly amenable to early environmental inputs [Belsky and de Haan, 2011; Ryan et al.,

2014; Sengpiel, 2007], interventions designed to optimize the environment may assist to maximize recovery of social cognitive and communicative functions, and thus reduce risk for long-term social difficulties.

CONCLUSIONS

Our study provides support for the vulnerability of the immature social brain network to disruption from TBI. Adolescents with TBI showed persisting social cognitive dysfunction at 6- and 24-months post-TBI; suggesting that outcome and recovery of high-level social cognition is dependent on neurological and cognitive development at the time of insult. Moreover, while our results show that diffuse structural damage to multiple component brain regions adversely impacts the acquisition and establishment of high-level social cognitive skills, evidence for a time-dependent emergence of social cognitive deficits in adolescence suggests that the social consequences of diffuse cerebral insult may not be realized until the associated skills reach maturity. Furthermore, while our findings converge to suggest that the structural integrity of an anatomically distributed network of brain regions and their connections is necessary for the establishment of high-level social cognitive skills, further research using both structural and functional MR techniques is required to elucidate the neuroanatomical bases of both typical and atypical social cognitive development following childhood TBI.

APPENDIX

THE EMOTIONAL AND EMOTIVE FACES TASK Sample Item

Children are read the following scenario; “Terry is watching a scary movie with her friends and feels really afraid (Dennis et al., 2013c). Terry doesn’t want to show how she feels because her friends will think she’s a baby. Participants were asked how Terry felt inside (Emotion Identification) and how she looked on her face (Emotive communication) by selecting a face from the display. The ToM condition is the Emotive Communication score (“Look on Face” questions), which measures the emotion on the face as a deceptive representation of what is felt inside. The control condition is the Emotional Expression score (“Feel Inside” questions), which measures the emotion on the face as a transparent read-out of the emotion experienced.

CRITICISM AND EMPATHIC PRAISE TASK Sample Item

Two social dyads are shown in each vignette that involves simultaneous presentation of a picture, a narrative, and an audiotape of the speaker’s utterances recorded with neutral, ironic, or empathic intonation (Dennis et al., 2013c). In one of the vignettes, Sally tells John he has done a good job fixing the bicycle. In the Literal Truth scenario, this matches the actual job. In the Ironic Criticism scenario,

Sally believes John has done a poor job and her intent is to convey a negative evaluation. In the Empathic Praise scenario, Sally believes John has done a poor job but her intent is to convey a positive, comforting evaluation. Participants were told the task goal (e.g., to repair a bicycle), shown the outcome (e.g., "the bicycle was . . ."), and informed about the speaker's character (e.g., "she liked to chat and talk to people"; "she liked to bug and annoy people"; "she liked to cheer people up") and what the speaker said to the hearer (e.g., "You did a great job"). Questions probed beliefs (what the speaker thought about the event, what the speaker thought about the hearer) and intentions (what the speaker wanted the hearer to think about the event, what the speaker wanted the hearer to think about him- or herself). The key measures are Literal Truth (control task), Ironic Criticism (conative ToM task, with an opaque relation between words and meaning, and a negative second-order intention toward the hearer), and Empathic Praise (conative ToM task, with an opaque relation between words and meaning, and a positive second-order intention toward the hearer).

ACKNOWLEDGEMENTS

This work was supported by a grant from the Victoria Neurotrauma Initiative, Australia and the Victorian Government Operational Infrastructure Support Program. The funding bodies did not play a role in the design of the study, collection, analysis and interpretation of the data, or writing of the manuscript.
All authors report no disclosures.

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