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# Uncovering the neuroanatomical correlates of cognitive, affective and conative theory of mind in paediatric traumatic brain injury: a neural systems perspective

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## Abstract

Deficits in theory of mind (ToM) are common after neurological insult acquired in the first and second decade of life, however the contribution of large-scale neural networks to ToM deficits in children with brain injury is unclear. Using paediatric traumatic brain injury (TBI) as a model, this study investigated the sub-acute effect of paediatric traumatic brain injury on grey-matter volume of three large-scale, domain-general brain networks (the Default Mode Network, DMN; the Central Executive Network, CEN; and the Salience Network, SN), as well as two domain-specific neural networks implicated in social-affective processes (the Cerebro-Cerebellar Mentalizing Network, CCMN and the Mirror Neuron/Empathy Network, MNEN). We also evaluated prospective structure–function relationships between these large-scale neural networks and cognitive, affective and conative ToM. 3D T1- weighted magnetic resonance imaging sequences were acquired sub-acutely in 137 children [TBI: $n = 103$; typically developing (TD) children: $n = 34$]. All children were assessed on measures of ToM at 24-months post-injury. Children with severe TBI showed sub-acute volumetric reductions in the CCMN, SN, MNEN, CEN and DMN, as well as reduced grey-matter volumes of several hub regions of these neural networks. Volumetric reductions in the CCMN and several of its hub regions, including the cerebellum, predicted poorer cognitive ToM. In contrast, poorer affective and conative ToM were predicted by volumetric reductions in the SN and MNEN, respectively. Overall, results suggest that cognitive, affective and conative ToM may be prospectively predicted by individual differences in structure of different neural systems—the CCMN, SN and MNEN, respectively. The prospective relationship between cerebellar volume and cognitive ToM outcomes is a novel finding in our paediatric brain injury sample and suggests that the cerebellum may play a role in

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the neural networks important for ToM. These findings are discussed in relation to neurocognitive models of ToM. We conclude that detection of sub-acute volumetric abnormalities of large-scale neural networks and their hub regions may aid in the early identification of children at risk for chronic social-cognitive impairment.

**Key words:** childhood; brain injuries; Theory of Mind; social cognition; magnetic resonance imaging

## Introduction

Childhood and adolescence coincide with rapid maturation of neural networks involved in complex social and affective processes, in particular, Theory of Mind (ToM). ToM is a multi-dimensional construct that allows individuals to ascribe a variety of psychological states, such as intentions or emotions, to others and thereby understand and subsequently predict behaviours (Blakemore, 2008; Chertkoff Walz *et al.*, 2010; Herbet *et al.*, 2013). Though deficits in ToM are a common consequence of neurological insults acquired in the first and second decade of life (Shaw *et al.*, 2004; Dennis *et al.*, 2012; Wolfe *et al.*, 2013; Stewart *et al.*, 2016), the specific neural correlates of these impairments remain unclear.

Recent neuroimaging and behavioural evidence supports a tripartite model that distinguishes between cognitive, affective and conative ToM (Dennis *et al.*, 2013a,b,c). *Cognitive ToM* is concerned with understanding others' beliefs, a skill that undergoes rapid maturation during infancy and early childhood, and is traditionally evaluated using false-belief tasks (Wellman *et al.*, 2001; Surian *et al.*, 2007; Sodian, 2011). Conversely, more complex forms of ToM can be divided into *conative ToM*, defined as the ability to understand how indirect speech acts involving irony and empathy are used to influence the mental or affective state of the listener; and *affective ToM*, concerned with understanding that facial expressions are often socially modulated to communicate emotions that we want others to think we feel (Hein and Singer, 2008; Dennis *et al.*, 2013c). In contrast to cognitive ToM, which emerges relatively early in development, complex ToM shows extended maturation through late childhood and adolescence (Wang *et al.*, 2006; Dumontheil *et al.*, 2010; Sebastian *et al.*, 2011), likely coinciding with the protracted development of fronto-temporal association areas (Sowell *et al.*, 2003; Gogtay *et al.*, 2004; Toga *et al.*, 2006; Blakemore *et al.*, 2007).

ToM is vulnerable to disruption in a number of childhood neurological conditions, including accidental traumatic brain injury (TBI); a common form of acquired disability caused predominantly by high-speed motor vehicle accidents and falls (Shaw *et al.*, 2004; Dennis *et al.*, 2012; Wolfe *et al.*, 2013; Stewart *et al.*, 2016). In TBI, forces occurring from impact and acceleration, deceleration and rotation of the brain inside the cranium induce focal and diffuse pathological changes that preferentially affect brain networks implicated in social behaviour (Yeates *et al.*, 2007). For instance, TBI is typically characterized by pathology in fronto-temporal brain regions implicated in ToM (Tasker *et al.*, 2005; Wilde *et al.*, 2005). In addition, traumatic axonal injury (TAI) is common in TBI, and may perturb connectivity within anatomically distributed networks that support ToM (Ryan *et al.*, 2015). Cross-sectional research shows that children with TBI display difficulty in recognizing emotions from facial expressions and prosody (Tonks *et al.*, 2007; Schmidt *et al.*, 2010; Tlustos *et al.*, 2011; Ryan *et al.*, 2013a,b), as well as deficits in complex forms of social cognition, including cognitive, affective and conative ToM (Snodgrass and Knott, 2006; Chertkoff Walz *et al.*, 2010; Dennis *et al.*, 2012, 2013a,b). While these findings suggest that ToM is vulnerable to the effects of TBI, the specific neural correlates of these deficits remain to be elucidated.

Complex social-affective processes such as ToM are likely supported by the coordinated and highly synchronised activity of several large-scale, domain-general neural systems—the salience network (SN), the default mode network (DMN) and the central executive network (CEN) (Menon, 2011). The SN is anchored in the anterior cingulate cortex (dACC) with extensive connectivity to cortical and subcortical areas, including the ventrolateral pre-frontal cortex (vlPFC), insula and amygdala (Seeley *et al.*, 2007). At the level of behaviour, the SN is involved in integrating salient internal and external events, including segregating emotional stimuli that may be necessary for understanding others' emotional states (Menon and Uddin, 2010; Menon, 2011). The SN exerts a modulatory influence on the DMN—another large-scale network anchored in the posterior cingulate cortex (PCC), inferior parietal lobule, ventromedial prefrontal cortex (vmPFC) and including widespread connections to the medial temporal lobe (MTL) (Buckner *et al.*, 2008; Menon, 2011). This network is activated by non-stimulus driven, self-related cognitive processes that likely support inferences about others' beliefs, intentions, and emotional states (Buckner *et al.*, 2008; Ahmed *et al.*, 2016). In contrast, the CEN links the dorsolateral prefrontal (dlPFC) and posterior parietal neocortices, as well as the thalamus and dorsal caudate (Koechlin and Summerfield, 2007), and is implicated in cognitive control processes (Menon and Uddin, 2010; Menon, 2011).

The role of domain-general neural systems in ToM processing is not well established; however recent reports suggest that the CEN supports ToM via cognitive control mechanisms, which 'bias' processing toward domain-specific neural networks involved in processing task-relevant social cues (Zaki *et al.*, 2010). For instance, fMRI evidence shows that when observers rely on non-verbal cues for ToM judgments, activation of the CEN is accompanied by biasing of neural activation toward brain areas involved in processing such cues, including premotor and parietal regions of the putative mirror-neuron-empathy network (MNEN) (Gallese and Goldman, 1998; Iacoboni and Dapretto, 2006; Iacoboni, 2008; Molenberghs *et al.*, 2009). In contrast, when observers consider contextual cues more relevant for ToM judgments, recruitment of CEN coincides with activation of brain areas implicated in understanding others' non-observable mental states (e.g. beliefs), including the medial prefrontal cortex (mPFC), superior temporal sulcus (STS), temporal pole and temporoparietal regions of the 'mentalizing network' (MN) (Fletcher *et al.*, 1995; Brunet *et al.*, 2000; Castelli *et al.*, 2000; Gallagher *et al.*, 2000; Vogeley *et al.*, 2001).

In evaluating the neuroanatomical correlates of ToM in 65 children with mild complicated-severe TBI aged 8–13 years, Dennis et al. (2013a,b,c) used morphometric MRI to evaluate cross-sectional relationships between grey matter volumes of several large-scale neural networks and cognitive, affective and conative ToM in the chronic phase of injury. Contrary to expectations, these authors reported no significant cross-sectional relationships between volumes of domain-general (i.e. CEN, DMN, SN) or domain-specific neural networks (i.e. MN, MNEN) and cognitive or affective ToM, although they did find a significant relationship between network volumes and conative ToM, with specific correlations found

with the posterior cingulate and hippocampal formation. Given the increased need to identify early neuroanatomical markers of risk for social cognitive difficulties commonly documented in the child TBI population, prospective studies are needed to examine whether early volumetric abnormalities predict later social-cognitive problems in children with TBI.

Based on an emerging body of work in healthy adult populations, an extension of Dennis' neural network model might predict that post-injury social-cognitive dysfunction arises from disruption to cerebro-cerebellar networks shown to support cognitive ToM (Van Overwalle *et al.*, 2015a,b; Van Overwalle and Mariën, 2016). For instance, a recent meta-analytic connectivity modelling (MACM) study shows that cerebellar involvement in social-cognitive processing reflects distinct social mentalizing functionality, and that mentalizing regions of interest (ROIs) in the cerebellum show robust connectivity with the mentalizing network in the cerebrum, including the dmPFC, TPJ and temporal pole (Van Overwalle *et al.*, 2015b). Since the cerebellum has been largely overlooked in relation to social cognition in TBI research, despite abnormalities reported structurally in human and animal models (Spanos *et al.*, 2007; Calabrese *et al.*, 2014), further research is required to evaluate the potential link between the cerebro-cerebellar mentalizing network (CCMN) (Van Overwalle *et al.*, 2015b) and ToM in paediatric TBI.

Using paediatric TBI as a model disorder, this study investigated the sub-acute effect of brain injury on grey-matter volume of three large-scale, domain-general brain networks (the Default Mode Network, DMN; the Central Executive Network, CEN; and the Salience Network, SN), as well as two domain-specific neural networks implicated in social-affective processes (the Cerebro-Cerebellar Mentalizing Network, CCMN and the Mirror Neuron/Empathy Network, MNEN). We also aimed to evaluate prospective structure–function relationships between these large-scale neural networks and cognitive, affective and conative ToM.

Given the well-documented vulnerability of frontal, temporal and limbic areas to the acceleration-deceleration forces of paediatric TBI (Bigler *et al.*, 2013), we expected volumetric reductions in any or all of the five functional networks, which have frontal, temporal and limbic hub regions. In evaluating the neuroanatomical correlates of ToM, we had four hypotheses derived from previous literature (Dennis *et al.*, 2013c): (a) Cognitive ToM will be related to the CCMN; (b) Affective ToM will be related to the SN; (c) Conative ToM will be related to the MNEN network; and, (d) All three forms of ToM, which involve self-reflection and cognitive control mechanisms, will be related to the DMN and CEN.

## Materials and methods

### Participants

Participants included children with mild-severe TBI who were enrolled in the study at the time of injury, and represented consecutive admissions to The Royal Children's Hospital (RCH), Melbourne, Australia between 2007 and 2010. Typically developing control (TDC) children were recruited from the community, through local schools chosen to provide a range of socio-economic backgrounds.

For the TBI group, inclusion criteria were: (i) documented evidence of closed head injury, including a period of altered consciousness or presence of at least two post-concussive symptoms; (ii) medical records sufficiently detailed to determine injury severity, including the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974), and neurological and radiological findings; and, (iii) child and at least one parent fluent in English. Using emergency department (ED) records and information obtained from an in-house, non-standardized parent interview form administered upon study enrolment, the following exclusion criteria were applied: (i) non-accidental head injuries; (ii) diagnosed congenital, neurological, developmental, or psychiatric condition; (iii) prior intervention for social impairment; and (iv) previous TBI based on parent report. Sample items from the interview form used to assess study eligibility are provided in Supplementary Material S1.

One-hundred and twelve eligible children with TBI were enrolled in the study and were classified as: (i) mild TBI ($n = 57$): Glasgow Coma Score (GCS) 13–15, no evidence of mass lesion on CT or clinical MRI and no neurologic deficits; (ii) mild complicated TBI ($n = 14$): GCS 13–15, evidence of mass lesion on CT or clinical MRI; (iii) moderate TBI ($n = 26$): GCS 9–12, and/or mass lesion or other evidence of specific injury on CT/MRI, and/or neurological impairment; and, (iv) severe TBI ($n = 15$): GCS 3–8, and/or mass lesion or other evidence of specific injury on CT/MRI, and/or neurological impairment. The TDC group included 43 children group-matched to the TBI sample on age, sex and socio-economic status.

Tables 1 and 2 show participant demographic and injury information, including sex, socioeconomic status (SES) according to the ANZSCO (McMillan *et al.*, 2009), age at injury, cause of injury and MRI lesion location. There were no statistically significant group differences on any of the demographic variables. Since group differences for SES were approaching statistical significance ($P = 0.050$; Table 1), SES was included as a covariate in all analyses involving the primary outcome measures.

As shown in Table 2, the injury severity groups showed expected differences for lowest GCS, and for surgical involvement, such that the moderate and severe TBI groups were significantly more likely to require these interventions. Cause of injury was predominately falls/blows for the mild, mild-complicated and moderate TBI groups. For the severe TBI group, falls/blows and motor vehicle accidents (MVAs) were equally common.

### Pre-injury measures

At the time of injury, parents provided retrospective ratings of their child's pre-injury adaptive and social skills in the weeks preceding injury using the Adaptive Behaviour Assessment System-II (ABAS-II) (Harrison and Oakland, 2003), a parent questionnaire that examines functional skills necessary for daily living. The Global Adaptive Composite ($M = 100$, $s.d. = 15$) and Social Composite are reported in Table 1. No significant group differences were identified when estimates of pre-injury functioning were compared with ratings provided by TDC parents who completed these same questionnaires about their child at initial recruitment (Table 1).

### ToM outcomes

In line with the tripartite model of ToM (Dennis *et al.*, 2013c), children were administered three experimental measures of ToM, which have been previously validated in the child TBI population (Dennis *et al.*, 2012, 2013c; Robinson *et al.*, 2014). Performance of the TBI groups was compared to an age- and gender-matched typically developing control group ($n = 40$).

***Cognitive ToM.*** The Jack and Jill Task (Dennis *et al.*, 2012) was administered to assess cognitive ToM, reflected in children's understanding of false beliefs. Participants are shown three consecutive frames on a computer screen. Each frame includes a character (Jack and/or Jill), two hats (red and blue), and a ball.

**Table 1.** Baseline and demographic characteristics of enrolled sample

| | TD Control | Mild | Mild-complicated TBI | Moderate TBI | Severe TBI | $F/\chi^2$ | P |
|---|---|---|---|---|---|---|---|
| *Demographics* | | | | | | | |
| Total *n* | 43 | 57 | 14 | 26 | 15 | – | – |
| Male, *n* (%) | 24 (55.81) | 44 (77.19) | 8 (57.14) | 16 (61.54) | 8 (53.33) | 6.68 | 0.154 |
| SES, *M* (*s.d.*) | 1.26 (0.66) | 1.75 (1.14) | 2.08 (1.50) | 1.92 (1.19) | 1.57 (1.28) | 2.43 | 0.050 |
| Age at recruitment (years), *M* (*s.d.*) | 10.25 (3.04) | 10.67 (2.36) | 9.47 (2.44) | 10.33 (2.49) | 9.72 (3.01) | 0.80 | 0.528 |
| Age at research MRI (years), *M* (*s.d.*) | 10.41 (2.76) | 10.80 (2.33) | 9.57 (2.43) | 10.37 (2.58) | 10.41 (3.10) | 0.66 | 0.621 |
| Age at 24-month assessment (years), *M* (*s.d.*) | 11.50 (2.92) | 12.59 (2.31) | 11.21 (2.58) | 12.67 (2.50) | 12.02 (2.85) | 1.40 | 0.238 |
| Time: Injury to testing (years) | – | 1.98 (0.38) | 2.05 (0.12) | 2.03 (0.19) | 1.98 (0.15) | 0.249 | 0.862 |
| *Baseline functioning, M (s.d.)* | | | | | | | |
| ABAS Social | 10.44 (2.74) | 10.02 (3.37) | 9.46 (3.20) | 10.00 (2.08) | 9.86 (3.42) | 0.32 | 0.862 |
| ABAS GAC | 97.37 (15.38) | 97.26 (17.15) | 95.77 (16.15) | 98.32 (13.08) | 94.71 (15.75) | 0.14 | 0.965 |

*Note*: SES = Socio-Economic Status based on the ANZSCO.
Significant ($P < 0.05$) *post hoc* analysis comparing.
[a]TBI-Mild *vs* TBI-Moderate.
[b]TBI-Mild *vs* TBI-Severe.
[c]TBI-Mild-complicated *vs* TBI-Moderate.
[d]TBI- Mild-complicated *vs* TBI-Severe.
[e]TBI-Moderate *vs* TBI-Severe.

**Table 2.** Participant injury and global volumetric data

| | TD Control | Mild | Mild-complicated TBI | Moderate TBI | Severe TBI | $F/\chi^2$ | P |
|---|---|---|---|---|---|---|---|
| *Injury characteristics* | | | | | | | |
| Age at injury (years), *M* (*s.d.*) | – | 10.67 (2.36) | 9.47 (2.44) | 10.33 (2.49) | 9.72 (3.01) | 1.20 | 0.312 |
| Lowest GCS, *M* (*s.d.*) | – | 14.54 (1.04) | 13.93 (1.14) | 11.50 (1.98)[a,c] | 5.60 (2.20)[b,d,e] | 148.99 | <0.001 |
| Length of hospital stay (days), *M* (*s.d.*) | – | 0.48 (0.73) | 2.30 (1.82) | 4.75 (4.59)[a,c] | 17.7 (13.9)[b,d,e] | 38.83 | <0.001 |
| Surgical intervention, *n* (%) | – | 0 (0) | 0 (0) | 8 (31) | 7 (47) | 32.07 | <0.001 |
| *Cause of injury, n (%)* | | | | | | 33.60 | 0.001 |
| Motor vehicle accident (MVA) (car) | – | 1 (2) | 1 (7) | 5 (19) | 4 (27) | – | – |
| MVA (pedestrian/bike) | – | 3 (5) | 1 (7) | 5 (19) | 5 (33) | – | – |
| Fall (stationary) | – | 13 (23) | 4 (29) | 8 (31) | 2 (13) | – | – |
| Fall (moving) | – | 22 (39) | 7 (50) | 7 (27) | 3 (20) | – | – |
| Kicked/struck by object | – | 18 (32) | 1 (7) | 1 (4) | 1 (7) | – | – |
| *MRI Pathology, n (%)* | | | | | | | |
| Frontal | – | 13 (23) | 4 (29) | 14 (54) | 10 (67) | 27.46 | <0.001 |
| Extra-frontal | – | 6 (11) | 4 (29) | 9 (35) | 6 (40) | 20.56 | <0.001 |
| Sub-cortical | – | 2 (4) | 1 (7) | 4 (15) | 4 (27) | 16.27 | 0.003 |
| *Global volumes, $cm^3$ (s.d.)* | | | | | | | |
| Total brain volume | 1232 (118) | 1262 (116) | 1204 (86) | 1222 (113) | 1175 (103) | 1.752 | 0.142 |
| Intracranial volume | 1502 (138) | 1536 (144) | 1455 (119) | 1500 (121) | 1485 (180) | 0.731 | 0.573 |
| Total grey matter | 755 (71) | 779 (65) | 748 (44) | 750 (88) | 696 (59)[b,e] | 3.929 | 0.005 |
| Total white matter | 435 (49.91) | 439 (52.54) | 415 (45) | 433 (37) | 427 (74) | 0.349 | 0.845 |

Significant ($P < 0.05$) post-hoc analysis comparing.
[a]TBI-Mild *vs* TBI-Moderate.
[b]TBI-Mild *vs* TBI-Severe.
[c]TBI-Mild-complicated *vs* TBI-Moderate.
[d]TBI- Mild-complicated *vs* TBI-Severe.
[e]TBI-Moderate *vs* TBI-Severe.

In Frame A of each sequence, Jack is preparing to drop a ball into either a blue or red hat while Jill watches. In Frame B, Jack either moves the ball further into the blue hat (unswitched trials) or switches the ball to the red hat (switched trials). Jill is present in half of Frame B trials (witnessed trials) and absent in the other half (unwitnessed trials). In Frame C, participants decide whether Jill's belief about the location of the ball is correct or incorrect. Jill's judgment depends on what she believes about the ball's location, not its actual location: she will choose the original (Frame A) hat if she did not witness the switch. The ToM trials involve an unwitnessed switch of hat colour; control trials are those in which the switch was witnessed. Percentage of correct responses for switched, unwitnessed trials was the primary measure of cognitive ToM.

***Affective ToM.*** The Emotional and Emotive Faces Task (EFFT) (Dennis *et al.*, 2013a) was administered to assess affective ToM, or the child's understanding of the difference between emotional expression (how a character actually feels) and emotive communication (the emotion a character expresses socially,

which may be different from the felt emotion). Children were presented with short narratives that described a character in situations that were meant to evoke one of five basic emotions: happiness, sadness, disgust, fear and anger. In each vignette, a discrepancy existed between the emotion felt 'inside' and the character's facial expression. In keeping with the interpretative guidelines provided by the test developers (Dennis *et al.*, 2013a), each vignette involves (i) affective ToM trials, which ask the child how the character looked on his/her face ('look on face' condition) and (ii) otherwise identical control trials, which merely require the child to select the facial emotion display that matches the in-text description of how the protagonist was feeling ('feel inside' condition). 'Feel inside' control trials are considered distinct from affective ToM trials since they simply require the child to select the facial emotion display that matches the explicit in-text description of the protagonist's emotional state (Dennis *et al.*, 2013c). Sample items for both ToM and control trials are described in Supplementary Material S2a. Percent accuracy for emotive communication trials (i.e. 'look on face') was the primary measure of affective ToM.

***Conative ToM.*** *The Ironic Criticism and Empathic Praise task* (ICEPT) (Dennis *et al.*, 2013b) assesses conative ToM, or the child's understanding of how indirect speech acts are used to influence the mental or emotional state of the listener. Children were presented with six pictured scenarios involving two children, one of whom was engaged in an activity and another who commented on their performance of the activity. The pictures were presented alongside a narrative, and an audiotape of the speaker's utterances with neutral, ironic or empathic intonation. Children were told the goal of the child engaged in the activity (e.g. to build a tower), the outcome (e.g. 'the tower was . . . '), the speaker's character (e.g. 'she liked to cheer people up'), and what the speaker said (e.g. 'You made a great tower'). In line with the interpretative guidelines provided by the test developers (Dennis *et al.*, 2013c) each vignette involves (i) conative ToM trials requiring the child to identify the beliefs and intentions underlying referentially opaque communications involving irony and empathy, and (ii) otherwise identical control trials that have comparable domain-general cognitive demands but do not require conative ToM processing (Dennis *et al.*, 2013c). Control items are considered distinct from conative ToM items 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 ToM and control trials are described in Supplementary Material S2b. Percentage of correct responses for indirect speech acts, which reflected the understanding of belief and intent for empathic praise and ironic criticism conditions, was the primary measure of conative ToM.

## Structural MRI

***Image acquisition and processing.*** Children underwent a structural MRI research scan sub-acutely at 6-weeks post-injury ($M = 42.28$, $s.d. = 29.53$ days). MR images were acquired on a 3 Tesla Siemens Trio scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-Channel matrix head coil. High-resolution T1-weighted structural MR images were acquired for each participant (TR = 1900 ms, FA = 9°, FOV = 256 × 224, 176 slices, slice thickness = 1.0 mm, in plane resolution 0.5 × 0.5 mm). A susceptibility-weighted imaging (SWI) sequence was also acquired. For the transverse three-dimensional (3D) SWI sequences, we used TR/TE = 28/20 ms, FA = 15°, resolution 0.9 × 0.6 × 1.5 $mm^3$. The sequence, along with all image processing, was automated on the Siemens MR scanner platform based on the concepts of Haacke *et al.* (2004, 2009). SW images were created using the magnitude and phase raw data sets. A phase mask was created by setting all positive phase values (between 1° and 180°) to unity and by normalizing the negative phase values ranging from 0° to –180° to a grey scale of values ranging linearly from unity to zero, respectively. This normalized phase mask was multiplied four times against the original magnitude image and yielded images that enhanced the hypointensities of the region containing susceptibility properties (such as hemosiderin). Finally, a minimum intensity projection (mIP) over two sections was performed to display the processed data using contiguous sections of 4-mm thickness in the axial plane (Kao *et al.*, 2012). To visualize the SWI data, the mIP over the processed SW image is used. The effect of a mIP is to better show the connectivity of the veins, while the processed SWI, being a combination of the magnitude and phase images, shows a more complete venous structure than either magnitude or phase alone.

***Coding of neuroanatomical lesions.*** The location of neuroanatomical lesions was identified based on visual inspection of conventional MR and SWI sequences by a paediatric neuroradiologist and neuropsychologist blind to patients' clinical details. Scans were coded according to a modification of the Coffey system (Coffey and Figiel, 1991; Catroppa *et al.*, 2008) in order to determine the presence of lesions and haemorrhage, and their location and severity based on the extent of hyperintensities as seen on T1- or T2-weighted images. For this report, only basic information regarding neuroanatomical location is presented (Table 2).

***Morphometric analysis.*** T1 images were subjected to quality control using a qualitative rating system that involves visually ranking the quality of T1-weighted images taking into account motion, ringing and susceptibility (Backhausen *et al.*, 2016). Of the 155 scans acquired, 18 participants (TBI: $n = 9$; TD Control: $n = 9$) were excluded because of poor imaging data resulting from motion artefact, dental artefact or early termination of the scan sequence mostly from claustrophobia or non-compliance resulting in incomplete data.

The resulting MRI data for 137 participants was subjected to morphometric analysis using the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu.au), which automatically segments and parcellates cortical grey matter and subcortical structures. This approach has been utilized in previous adult (Warner *et al.*, 2010) and paediatric TBI research (Merkley *et al.*, 2008). Full details regarding the analysis steps are reported elsewhere (Dale *et al.*, 1999; Fischl *et al.*, 2002, 2004; Jovicich *et al.*, 2006).

In this study, FreeSurfer was used to extract total intracranial volume (TIV) and whole brain volume (WBV). Using a probabilistic labelling algorithm that relies on gyral and sulcal information, the cortex was parcellated into anatomical regions of interest (ROIs) based on the Desikan–Killiany atlas and projected back into each subject's native space. From this automated procedure, ROIs were computed by extracting the volumes for each ROI bilaterally. ROIs defined in Freesurfer variables (Desikan *et al.*, 2006) were assigned to domain-specific (CCMN, MNEN) and domain-general (DMN, SN, CEN) neural network packages defined by Dennis *et al.* (2013a,b,c) (Table 3), and

**Table 3.** Neural networks and associated Freesurfer regions

| Neural network | Freesurfer regions |
|---|---|
| *Default Mode Network (DMN)* | |
| Ventromedial prefrontal cortex (vmPFC) | Frontal pole + medial orbitofrontal cortex |
| Posterior cingulate cortex (PCC) | Posterior cingulate + cingulate isthmus |
| Inferior Parietal Lobule (IPL) | Inferior parietal lobe + precuneus |
| Hippocampal Formation (HF) | Hippocampus + entorhinal cortex + parahippocampal cortex |
| *Central Executive Network (CEN)* | |
| Dorsolateral prefrontal cortex (dlPFC) | Superior frontal cortex + caudal middle frontal cortex + rostral middle frontal cortex |
| Posterior parietal cortex (PPC) | Inferior parietal cortex + superior parietal cortex + precuneus |
| Caudate Nucleus (CN) | Caudate volume |
| Thalamus (TH) | Thalamus volume |
| *Salience Network (SN)* | |
| Ventrolateral prefrontal cortex (vlPFC) | Pars orbitalis |
| Insula (I) | Insula short volume + insula large ventral volume |
| Anterior cingulate cortex (ACC) | Rostral anterior cingulate + caudal anterior cingulate |
| Amygdala (A) | Amygdala volume |
| *Cerebro-cerebellar mentalizing network (CCMN)* | |
| Dorsomedial prefrontal cortex (dmPFC) | Caudal middle frontal cortex + rostral middle frontal cortex |
| Superior temporal sulcus (STS) | Superior temporal gyrus + bank superior temporal sulcus + middle temporal gyrus |
| Temporo-parietal junction (TPJ) | Supramarginal gyrus |
| Temporal pole (TP) | Temporal pole |
| Cerebellum | Cerebellum grey matter + cerebellum white matter |
| *Mirror Neuron Empathy Network (MNEN)* | |
| Premotor area (PMA) | Caudal middle frontal |
| Inferior parietal lobule (IPL) | Inferior parietal lobe + precuneus |
| Inferior frontal gyrus, pars opercularis (IPG, po) | Pars opercularis |
| Inferior frontal gyrus, pars triangularis (IFG, pt) | Pars triangularis |

*Note*: Adapted from Dennis et al. (2013c).

ROIs for each network were summed to calculate overall volume for each of the five neural networks of interest.

## Procedure

The RCH Human Research Ethics Committee and the Victorian Department of Education Ethics Committee approved this study. All parents gave their written, informed consent for children to participate in the study and for extraction of clinical data from medical records at the time of recruitment. For children older than 8 years, verbal assent was sought. Research MRI was conducted between 2 and 8 weeks post-injury. At 24-months post-injury, children participated in a direct assessment, which included completion of the ToM measures.

## Statistical analysis

All data were entered into SPSS Version 20.00 and screened for missing data and violations of normality. Normality plots indicated that ToM measures were normally distributed, and preliminary analysis indicated no violation of assumptions across analyses unless otherwise stated.

Group comparisons (TBI severity groups and TD controls) were conducted via ANOVAs for the following demographic and baseline functional variables: socio-economic status, ABAS, MRI age and age at 24-month assessment. Percentages and frequencies are reported for the following injury characteristics: cause of injury and evidence of pathology on acute CT, with chi-square or Fisher's exact tests to determine whether there were differences between injury severity groups.

For all analyses involving the primary outcome measures, we acknowledged factors previously shown to influence social outcomes after TBI, including injury severity group membership coded as three dichotomous dummy variables, sex, socioeconomic status and pre-injury social functioning assessed using the ABAS GAC (Taylor, 2010). Taking these factors into account, all regression analyses were performed with these variables entered as covariates, in addition to MRI age and estimated total intracranial volume (TIV) for imaging analyses. This approach enabled us to determine if brain structure measures are unique and therefore useful markers of post-injury ToM outcomes in children with TBI.

ToM data for the entire sample were analysed using multivariate analysis of covariance (MANCOVA) with Group Membership as the between subjects factor and ToM domain (cognitive *vs* affective *vs* conative) as the within subjects factors, with follow-up post-hoc pairwise comparisons using Bonferroni-correction. Effect sizes were calculated using partial eta squared ($\eta^2$; small effect $\eta^2 = 0.01$; medium effect $\eta^2 = 0.059$; large effect $\eta^2 = 0.138$).

Similarly, volumetric data for the entire sample were analysed using multivariate analysis of covariance (MANCOVA) with Group Membership as the between subjects factor and neural network (DMN *vs* CEN *vs* SN *vs* CCMN *vs* MNEN) and region of interest (entered into separate MANCOVAs as in Table 4) as the within subjects factors. For post-hoc pairwise comparisons, a Bonferroni-correction was used.

Multivariate regression analyses covarying for age, estimated total intracranial volume (TIV), pre-injury ABAS scores, sex, socioeconomic status, ToM control trial performance and injury severity group membership were conducted in the *TBI sample only* to examine the relationship of the five network volumes to the key ToM variables by hypotheses. Moderation analyses using hierarchical regression models were conducted to

**Table 4.** Group differences in volumes of neural networks and regions of interest

| Network volume $mm^3$ (*s.d.*) | TD control ($n = 34$) | Mild ($n = 53$) | Mild-complex ($n = 14$) | Moderate TBI ($n = 24$) | Severe TBI ($n = 12$) | F | *P* value | $\eta^2$ |
|---|---|---|---|---|---|---|---|---|
| *DMN* | 116 501 | 118 684 | 114 675 | 117 504 | 103 639[a,b,c,d] | 8.05 | <0.001 | 0.20 |
| vmPFC | 40 002 | 41 418 | 39 254[f] | 40 803 | 34 908[a,b,c,d] | 8.67 | <0.001 | 0.21 |
| PCC | 17 377 | 17 706 | 16 553 | 17 326 | 15 353[a,b,c,d] | 3.04 | 0.020 | 0.09 |
| IPL | 50 201 | 50 541 | 50 261 | 50 409 | 45 660[a,b,c,d] | 3.20 | 0.015 | 0.09 |
| Hip | 8921 | 9019 | 8607 | 8966 | 7718[a,b,c,d] | 5.72 | <0.001 | 0.15 |
| *CEN* | 171 479 | 177 105 | 172 502 | 174 454 | 158 440[a,b,c,d] | 4.65 | 0.002 | 0.13 |
| dlPFC | 83 690 | 88 404 | 85 137 | 86 545 | 77 555[a,b,c,d] | 4.13 | 0.004 | 0.11 |
| PPC | 63 713 | 64 252 | 63 871 | 64 321 | 58 771[a,b,c,d] | 2.58 | 0.041 | 0.08 |
| CN | 8087 | 8252 | 7982 | 7777 | 7462[b] | 1.62 | 0.174 | 0.05 |
| TH | 15 991 | 16 196 | 15 512 | 15 811 | 14 652[a,b,c,d] | 3.51 | 0.009 | 0.10 |
| **SN** | 52 546 | 53 997 | 51 845 | 53 012 | 48 561[a,b,c,d] | 4.53 | 0.002 | 0.12 |
| vlPFC | 3726 | 3831 | 3813 | 3851 | 3258[a,b,c,d] | 2.49 | 0.047 | 0.07 |
| I | 26 472 | 27 295 | 26 233 | 26 887 | 25 392[b] | 1.54 | 0.193 | 0.05 |
| ACC | 19 095 | 19 483 | 18 731 | 19 025 | 16 979[a,b,c,d] | 3.69 | 0.007 | 0.10 |
| A | 3253 | 3388 | 3068 | 3249 | 2932[a,b,d] | 3.06 | 0.019 | 0.09 |
| **CCMN** | 298 660 | 304 031 | 294 170 | 295 904 | 281 289[a,b,c,d] | 2.88 | 0.025 | 0.08 |
| dmPFC | 32 103 | 34 202 | 32 808 | 32 825 | 29 788[b,c,d] | 2.78 | 0.029 | 0.08 |
| STS | 65 893 | 67 429 | 65 650 | 66 711 | 59 230[a,b,c,d] | 4.52 | 0.002 | 0.12 |
| TPJ | 35 116 | 35 333 | 35 888 | 35 380 | 31 404[a,b,c,d] | 4.52 | 0.002 | 0.12 |
| TP | 12 790 | 12 684 | 11 951 | 12 892 | 10 207[a,b,c,d] | 7.67 | <0.001 | 0.19 |
| CB: Total | 152 759 | 154 382 | 147 872 | 148 096 | 150 661 | 0.69 | 0.599 | 0.02 |
| CB: WM | 29 685 | 29 008[g] | 28 277 | 27 482[e] | 29 931 | 3.50 | 0.010 | 0.10 |
| **MNEN** | 97 486 | 99 845 | 97 943 | 98 407 | 89 334[a,b,c,d] | 3.79 | 0.006 | 0.11 |
| PMA | 32 103 | 34 202 | 32 808 | 32 825 | 29 788[b,c,d] | 2.78 | 0.029 | 0.08 |
| IPL | 50 201 | 50 541 | 50 261 | 50 409 | 45 660[a,b,c,d] | 3.20 | 0.015 | 0.09 |
| iFG, po | 8310 | 8103 | 7972 | 8227 | 7580[a] | 1.22 | 0.307 | 0.04 |
| iFG, pt | 6873 | 7000 | 6902 | 6946 | 6307 | 0.81 | 0.520 | 0.03 |

Significant ($P < 0.05$) Bonferroni post-hoc analyses comparing.
[a]TDC *vs* TBI-Severe.
[b]TBI-Mild *vs* TBI-Severe.
[c]TBI-Mild-complicated *vs* TBI-Severe.
[d]TBI-Moderate *vs* TBI-Severe.
[e]TD *vs* TBI-Moderate.
[f]TBI-Mild *vs* Mild-complicated.
[g]TDC *vs* Mild-TBI.

determine the synergistic effects of neural network volume and injury severity on ToM in the TBI sample. Neural network volume and injury severity variables were transformed to z-scores and individually entered in block 1. The cross product of neural network volume and injury severity was computed and entered in block 2.

## Results

### Effect of paediatric TBI on large-scale functional network volumes

As described in *Morphometric Analysis*, MRI for 137 of the 155 scanned participants were of sufficient quality for Freesurfer to produce volumetric data (34 TDC, 53 mild TBI, 14 mild-complicated TBI, 24 moderate TBI and 12 severe TBI). A sensitivity analysis was carried out between those with and without useable MRI, and revealed no significant differences on any pre-injury, demographic or injury-related variable. Groups did not significantly differ in estimated total intracranial volume (TIV) or whole brain volume (WBV; Table 2). Time interval between day-of-injury and research MRI scan was not significantly related to any measure of regional or global brain volume (all $P > 0.20$), and therefore MRI time interval was not included as a covariate in subsequent analyses.

Table 4 displays the group means and *s.d.*s for overall volumes of the five large-scale functional networks of interest. For network analyses, the overall MANCOVA was significant after controlling for SES, sex, MRI age and TIV, $F(5, 127) = 8.69$, $P < 0.001$, $\eta^2 = 0.255$. Group differences in network volume are presented in Table 4.

### ToM performance

One-hundred and twenty-four participants enrolled in the study (40 TDC, 43 mild TBI, 9 mild-complicated TBI, 21 moderate TBI and 11 severe TBI) completed all three behavioural ToM tasks at 24-months post injury. A sensitivity analysis was also carried out between those with and without complete ToM data, and revealed no significant differences on any pre-injury, demographic or injury-related variable.

Table 5 displays the group means and *s.d.*s for the Jack and Jill Task (JJT), Emotional and Emotive Faces task (EEFT) and Ironic Criticism and Empathic Praise task (ICEPT). Results for the ToM and control trials are reported as a function of injury severity group membership, controlling for SES, sex, age at testing and pre-injury ABAS scores (Table 5). Additional analyses of ToM trials are reported in the section that follows, with control trial performance entered as an additional covariate.

**Table 5.** Performance on theory of mind tasks according to group

| | TD M (s.d.) | Mild TBI M (s.d.) | Mild-complicated TBI M (s.d.) | Moderate TBI M (s.d.) | Severe TBI M (s.d.) | F | P value | $\eta^2$ |
|---|---|---|---|---|---|---|---|---|
| *JJT* | | | | | | | | |
| *ToM trials* | 85.63 (17.49) | 90.63 (11.26) | 86.46 (10.00) | 86.31 (14.87) | 83.81 (11.93) | 0.851 | 0.496 | 0.029 |
| *Control trials* | 88.54 (15.17) | 91.96 (10.71) | 87.04 (9.42) | 87.50 (14.13) | 87.12 (10.28) | 0.695 | 0.597 | 0.024 |
| *EEFT* | | | | | | | | |
| *ToM trials* | 70.56 (12.73) | 69.83 (13.78) | 60.83 (9.84)[a,b,c] | 63.93 (16.40)[d] | 72.05 (13.50) | 2.689 | 0.035 | 0.084 |
| *Control trials* | 87.00 (11.37) | 84.88 (13.34) | 78.89 (10.54) | 80.48 (16.58) | 79.09 (17.58) | 1.95 | 0.107 | 0.063 |
| *ICEPT* | | | | | | | | |
| *ToM trials* | 75.98 (10.68) | 77.80 (10.17) | 64.31 (10.78)[a,b,e] | 75.13 (11.62) | 73.00 (10.59) | 2.667 | 0.036 | 0.085 |
| *Control trials* | 83.33 (13.48) | 90.89 (9.24) | 84.26 (14.69) | 83.33 (22.20) | 90.15 (16.17) | 1.48 | 0.213 | 0.049 |

*Note:* EEFT, Emotional and Emotive Faces Task; ICEPT, Ironic Criticism and Empathic Praise Task; JJT, Jack and Jill Task.
Significant ($P < 0.05$) Bonferroni post-hoc analyses comparing.
[a]TDC *vs* TBI-Mild-complicated.
[b]TBI-Mild *vs* TBI-Mild-complicated.
[c]TBI-Severe *vs* TBI-Mild-complicated.
[d]TDC *vs* TBI-Moderate.
[e]TBI-Moderate *vs* TBI-Mild-complicated.

***Cognitive ToM***. As shown in Table 5, there was no significant main effect of injury severity group membership on cognitive ToM trials of the JJT. Results were unchanged when JJT control trial performance was entered as an additional covariate, $F(4, 124) = 1.510$, $P = 0.204$.

***Affective ToM***. There was a significant main effect of injury severity group membership on affective ToM trials of the EEFT (Table 5). Pairwise comparisons indicated that the moderate TBI group performed significantly worse than the TD control group. Moreover, the mild-complicated TBI group showed significantly poorer performance than the TD control and severe TBI group. Results were unchanged when EEFT control trial performance was entered as an additional covariate, $F(4, 124) = 2.526$, $P = 0.045$.

***Conative ToM***. As shown in Table 5, there was a significant main effect of severity on conative ToM trials of the ICEPT. Pairwise comparisons indicated that the mild-complicated TBI group showed significantly poorer performance than the TD control group, mild TBI group, and moderate TBI group. Results were unchanged when ICEPT control trial performance was entered as an additional covariate, $F(4, 124) = 3.345$, $P = 0.013$.

## Neuroanatomical correlates of ToM in the TBI sample

Multivariate regression analyses controlling for age, estimated total intracranial volume (TIV), pre-injury ABAS scores, sex, socioeconomic status, ToM control trial performance and injury severity group membership were conducted to examine the relationship of the five network volumes to the key ToM variables by hypotheses.

***Cognitive ToM***. The overall regression model was significant, $R^2 = 0.56$, $F(12, 77) = 6.75$, $P < 0.001$. As shown in Table 6, the only significant regressor was the CCMN ($P = 0.009$), such that smaller CCMN volume was associated with poorer cognitive ToM. We further explored the relation between cognitive ToM and specific regions of interest in the CCMN, the only network that was significantly related to function. Analyses of the five CCMN ROIs revealed that poorer cognitive ToM was related to reduced volume of the superior temporal sulcus ($\beta = 0.20$; $P = 0.035$), temporo-parietal junction ($\beta = 0.24$; $P = 0.012$) and cerebellum ($\beta = 0.31$; $P = 0.002$).

**Table 6.** Regression models predicting cognitive, affective and conative ToM based on volumetric data

| ToM domain | B | SE B | $\beta$ | P value | 95% CI |
|---|---|---|---|---|---|
| *Cognitive* | | | | | |
| DMN | −0.03 | 0.09 | −0.08 | 0.756 | [−0.20, 0.15] |
| CEN | 0.02 | 0.06 | 0.07 | 0.807 | [−0.11, 0.14] |
| CCMN | 0.07 | 0.03 | 0.50 | 0.009 | [0.02, 0.13] |
| *Affective* | | | | | |
| DMN | −0.15 | 0.16 | −0.31 | 0.347 | [−0.48, 0.17] |
| CEN | 0.12 | 0.11 | 0.37 | 0.249 | [−0.09, 0.34] |
| SN | 0.59 | 0.26 | 0.54 | 0.027 | [0.07, 1.10] |
| *Conative* | | | | | |
| DMN | −0.58 | 0.33 | −0.58 | 0.082 | [−1.24, 0.08] |
| CEN | −0.12 | 0.23 | −0.17 | 0.597 | [−0.57, 0.33] |
| MNEN | 1.10 | 0.38 | 0.97 | 0.005 | [0.34, 1.86] |

***Affective ToM***. The overall regression model was significant, $R^2 = 0.40$, $F(12,77) = 3.66$, $P < 0.001$. As shown in Table 6, the only significant regressor was the SN ($P = 0.027$), such that reduced SN volume was associated with poorer affective ToM. Analyses of the four SN ROIs revealed that poorer affective ToM was related to smaller insula ($\beta = 0.28$; $P = 0.009$) and amygdala volume ($\beta = 0.25$; $P = 0.026$).

***Conative ToM***. The overall regression model was also significant, $R^2 = 0.51$, $F(12,77) = 5.55$, $P < 0.001$. The only significant regressor was the MNEN ($P = 0.005$), such that smaller MNEN volume was associated with poorer conative ToM (Table 6). Analyses of the four MNEN ROIs revealed that poorer conative ToM was associated with reduced volume of the premotor area ($\beta = 0.32$; $P = 0.003$), inferior parietal lobule ($\beta = 0.30$; $P = 0.006$) and pars opercularis ($\beta = 0.26$; $P = 0.024$).

## Interaction effects in the TBI sample

Moderation analyses using hierarchical regression models revealed no significant interactions between neural network volume and injury severity on ToM for CCMN ($\beta = -0.05$, $P = 0.55$), MNEN ($\beta = -0.06$, $P = 0.60$) or SN ($\beta = 0.03$, $P = 0.80$). Similarly, there were no significant interactions between neural network

volume and age on ToM for CCMN ($\beta = -0.01$, $P = 0.93$), MNEN ($\beta = 0.01$, $P = 0.99$), or SN ($\beta = -0.01$, $P = 0.89$).

## Discussion

This study aimed to evaluate the sub-acute effect of paediatric TBI on brain structure of three large-scale, domain-general neural networks (the Default Mode Network, DMN; the Central Executive Network, CEN; and the Salience Network, SN), as well as two domain-specific neural networks implicated in social-affective processes (the Cerebro-Cerebellar Mentalizing Network, CCMN; and the Mirror Neuron/Empathy Network, MNEN). We also aimed to evaluate prospective relationships between large-scale neural networks and ToM outcomes in chronic phase TBI. In keeping with expectations, we found that severe paediatric TBI is associated with volumetric reductions in each of the five large scale neural networks and their putative hub regions as early as 2-months post-injury. Moreover, we found that cognitive, affective and conative ToM were associated with volumes of different neural systems—the CCMN, SN and MNEN, respectively.

### Vulnerability of large-scale neural networks in paediatric TBI

In keeping with the anticipated vulnerability of fronto-temporal limbic regions to acceleration-deceleration forces of paediatric TBI (Wilde *et al.*, 2005; Bigler *et al.*, 2010; McAllister, 2011; Bigler, 2013; Bigler *et al.*, 2013), severe TBI was associated with sub-acute volumetric reductions of the SN, DMN, CEN, MNEN and MNEN. While generalized structural brain differences are documented in the chronic-phase of severe paediatric TBI (Wilde *et al.*, 2005; Spanos *et al.*, 2007; Fearing *et al.*, 2008; Merkley *et al.*, 2008; Bigler *et al.*, 2010; Wu *et al.*, 2010; Beauchamp *et al.*, 2011a,b; Levin *et al.*, 2011), the nature and extent of volumetric differences in the sub-acute phase is poorly understood. In addressing this substantial gap in current knowledge, the current findings suggest that neuroanatomical abnormalities may be detectable as early as 2-months post-severe TBI, and are reflected in volumetric differences in large-scale neural systems anchored in fronto-temporal limbic regions.

The pattern of sub-acute volumetric differences in large-scale neural networks likely reflects the initial neuropathological consequences of primary and secondary injury mechanisms, which interact dynamically in the pathogenesis of grey-matter tissue loss. Since many of the frontal, temporal and limbic hub regions of these networks are highly susceptible to surface contusions, biomechanical shearing and compressive injuries, focal injuries to these regions likely cause brain tissue deformation and induce neuroinflammatory reactions that compromise cerebral perfusion, thereby affecting cellular degradation and apoptosis (Xu *et al.*, 2010). Previous studies of adults have shown that severe TBI is associated with diffuse pathological changes throughout the brain, including dynamic patterns of primary-injury induced cell death that occurs within hours of injury and continues beyond 2-years post injury (Blatter *et al.*, 1997; Adams *et al.*, 2011; Bigler, 2013). While the current findings converge with previous adult data to suggest that the initial neuropathological consequences of injury may be apparent as early as 2-months post-injury, robust associations between these volumetric abnormalities and post-injury social behaviour have not previously been established.

### Neuroanatomical correlates of ToM in the immature brain

***Cognitive ToM.*** In support of expectations, poorer cognitive ToM was associated with smaller grey matter volume of the CCMN and its putative hub regions, including the temporo-parietal junction, superior temporal sulcus, and cerebellum. These findings overlap with previous lesion-deficit and functional neuroimaging studies showing that understanding others' beliefs recruits a highly circumscribed 'mentalizing network' (MN), comprising the medial prefrontal cortex (Amodio and Frith, 2006), bilateral temporal parietal junction (Samson *et al.*, 2004; Saxe, 2009; Young *et al.*, 2010) and superior temporal sulcus (Apperly *et al.*, 2005; Blakemore *et al.*, 2007). In contrast to the mPFC, which is activated when processing many kinds of information about people (Mitchell *et al.*, 2005; Ochsner *et al.*, 2005; Amodio and Frith 2006) functional imaging data show that, over the course of middle to late childhood, the TPJ demonstrates increasing specialization from responding to *any* facts about a person to responding exclusively to information about others' mental states (Saxe *et al.*, 2009). This evidence for late-emerging cortical selectivity of ToM regions may account for null findings in a previous cross-sectional study of chronic phase paediatric TBI, which found no significant relationship between cognitive ToM and volumes of the MN in a younger sample of children with TBI (Dennis *et al.*, 2013c). In contrast, we identify a robust link between cognitive ToM and regions of the CCMN in older children and adolescents for whom higher-order association regions involved in ToM are likely undergoing rapid functional specialization (Sowell *et al.*, 2003; Gogtay *et al.*, 2004; Toga *et al.*, 2006; Saxe *et al.*, 2009).

Evidence for an association between cognitive ToM and CCMN volume in the TBI group was documented together with the finding that individual differences in cerebellar volume prospectively predict cognitive ToM outcomes in children with TBI. These results are novel in the TBI literature but broadly consistent with an emerging body of functional neuroimaging data which highlight the domain-specific role of the cerebellum in social mentalizing processes (Van Overwalle *et al.* 2015b; Van Overwalle and Mariën, 2016). For instance, using meta-analytic connectivity modelling (MACM), Van Overwalle *et al.* (2015b) reveal that cerebellar involvement in social information processing reflects distinct social mentalizing functionality, and that mentalizing ROIs in the cerebellum show robust connectivity with the mentalizing network in the cerebrum, comprising the dmPFC, TPJ and temporal pole. Extending on this emerging body of work, evidence linking the cerebellum to cognitive ToM is a novel finding in a paediatric brain injury population, and might suggest that the cerebellum plays a role in the neural systems important for cognitive ToM.

***Conative ToM.*** In line with predictions, poorer conative ToM was associated with reduced volume of the MNEN and its putative hub regions, including the premotor area, inferior parietal lobule and pars opercularis. Simulation models of social cognition suggest that the MNEN mediates ToM via imitation of what the actor is feeling, such that the neural networks of the observer are recruited as if he/she were feeling or behaving as the actor (Iacobini, 2008; Goldman, 2009; Corradini and Antonietti, 2013). This hypothesis is supported by evidence that MNEN regions involved in understanding others' emotions comprise the same neural circuitry recruited when we ourselves subjectively experience these same emotions (Decety and Chaminade, 2003; Lawrence *et al.*, 2006; Schulte-Rüther *et al.*, 2007; Pfeifer *et al.*,

2008; Molenberghs *et al.*, 2016). Although evidence linking MNEN volume to conative ToM is a novel finding in a brain injury population, the mechanism underlying this association remains to be established. However, since our conative ToM paradigm requires the child to infer speaker intent from referentially opaque social interactions that likely impose greater demands on simulation processes (Schulte-Rüther *et al.* 2007; Corradini and Antonietti, 2013; Molenberghs *et al.*, 2016), poorer post-injury conative ToM may be associated with abnormal simulation mechanisms.

***Affective ToM.*** In keeping with expectations, our results show that poorer affective ToM is associated with reduced volume of the SN and its putative hub regions, including the amgydala. These findings are broadly consistent with previous studies which implicate the SN in orienting to and integrating impending affective stimuli into decision making models (Menon and Uddin, 2010; Wiech *et al.*, 2010). For instance, one study found that, compared with affective ToM judgments made in the absence of facial emotion displays, the presence of facial emotional cues was associated with increased activation of SN hub regions, in particular, the amygdala. Although the current findings establish a novel link between affective ToM and neuroanatomical differences in the SN in a paediatric population, the mechanism of this relation remains to be established. Affective ToM difficulties may occur in part because of failure of the SN to orient to and integrate salient facial emotional stimuli into judgments about others' emotional states (Menon and Uddin, 2010).

## Theoretical and clinical implications

Our findings are broadly consistent with neuroimaging studies of ToM in the healthy adult population, which indicate that different types of ToM involve unique brain areas. In a series of activation likelihood estimation meta-analyses on 144 datasets, Molenberghs *et al.* (2016) showed that abstract cognitive theorizing about others' non-observable mental states (i.e. beliefs) is reliably associated with activation of the putative mentalizing network (mPFC, TPJ and STS). In contrast, the neural correlates of affective ToM appear to depend on specific task demands (Molenberghs *et al.*, 2016). Activation of pars opercularis and premotor regions is consistently observed in affective ToM paradigms involving pictures or videos of dyadic interactions without much context, thereby imposing greater demands on the observer's capacity for simulation (Keysers and Gazzola, 2007; Molenberghs *et al.*, 2016). On the other hand, affective ToM tasks requiring integration of static facial emotion cues with story-based, contextual cues likely impose less demand on simulation mechanisms, and are more closely tied to SN regions that support detection and integration of these salient emotion cues into affective ToM judgments (Schmitgen *et al.*, 2016). In line with this evidence, our results suggest that ToM is associated with various neural routes, which may depend on the extent to which a task imposes demands on simulation mechanisms (i.e. conative ToM), detection and integration of salient facial emotional stimuli (i.e. affective ToM) or abstract cognitive theorizing about others' beliefs (i.e. cognitive ToM).

From a clinical standpoint, our findings provide novel prospective links between sub-acute volumetric deficits in large-scale neural systems and ToM outcomes in chronic-phase paediatric TBI. In particular, we show that ToM hub regions identified from previous adult functional imaging studies are susceptible to the effects of paediatric TBI, and that individual variation in these brain structures may provide markers of vulnerability to poorer ToM outcomes in the long-term post injury.

Though our current findings underscore the potential prognostic value of early neuroanatomical abnormalities, limited evidence for reduced ToM in the severe TBI group is perhaps surprising and contrasts with evidence for a dose–response relationship between injury severity and ToM assessed via these same experimental measures in previous cross-sectional TBI studies involving children of comparable age, injury severity and time post-injury (Dennis *et al.*, 2013c; Robinson *et al.*, 2014). More specifically, although mean percentage accuracy of the mild uncomplicated, moderate and TD control groups was comparable to previous studies (Dennis *et al.*, 2013b,c), the severe TBI group performed better than expected, and did not significantly differ from TD controls and children with milder injuries on measures on conative and affective ToM. Several potential factors may account for this surprising pattern of findings. First, the unexpected findings might reflect substantial heterogeneity in the nature and extent of higher cortical injury in children diagnosed with severe TBI based on initial clinical indicators. More specifically, initial clinical indicators used to assign injury severity group membership lack sensitivity to detect structural abnormalities in frontal-temporal-limbic brain regions (Dennis *et al,.* 2012), which appear to have prognostic significance for chronic ToM outcomes in the current sample. Second, chronic ToM difficulties may be more apparent among children with mild-complicated and moderate injuries because, unlike children with severe TBI, they are less likely to have sufficient access to rehabilitation services and support for school reintegration. It is also possible that poorer affective and conative ToM in the mild-complicated and moderate TBI group at least partly reflects the contribution of proximal environmental risk factors (e.g. poorer parent mental health/family functioning), which although not measured in the current study, are shown to influence both social cognitive and behavioural outcomes in chronic paediatric TBI (Rosema *et al.*, 2012; Li and Liu, 2013; Ryan *et al.*, 2013a).

## Limitations and future directions

Since we relied on structural imaging data collected at a single, sub-acute time-point to evaluate the prospective relationship between large scale neural network volumes and chronic ToM outcomes, casual relationships between these variables cannot be established, and the extent of chronic structural brain abnormalities in this TBI group are unknown. Additionally, since structural MRI was acquired during the acute/sub-acute recovery period when children with TBI are medically unstable and therefore valid and reliable estimates of ToM and other cognitive abilities cannot be obtained, we were unable to compare the cross-sectional and prospective impact of sub-acute volumetric differences on ToM outcomes. Moreover, despite the inclusion of a parent-report measure of pre-injury adaptive functioning, it was not possible to account for pre-injury ToM abilities or brain volumes, and therefore the exact contribution of the TBI to either of these outcomes is unclear.

While our results help identify large-scale neural networks that may be important for conative, affective and cognitive ToM in the developing brain, the precise mechanisms underpinning these relationships are unclear, and require further investigation using task-based functional neuroimaging paradigms. Importantly, while each ToM domain was robustly associated with a single neural system, successful attribution of mental states on these tasks likely relies on coordinated activity

between the default-mode and other task-relevant networks (Bonnelle *et al.*, 2012). Functional imaging investigations are therefore warranted to determine whether ToM difficulties are associated with a failure to deactivate the DMN in synchrony with engagement of task-relevant networks such as the SN.

## Conclusions

In one of the largest studies to investigate the sub-acute effect of paediatric TBI on brain structure, we provide new evidence that neuroanatomical abnormalities of large-scale functional networks are detectable as early as 2-months post-severe TBI, and may prospectively predict later social cognitive outcomes. In addressing the paucity of research examining the neural correlates of ToM in the injured brain, we identify several large-scale neural networks that may be important for cognitive, affective and conative ToM in the developing brain. More specifically, evidence for a link between the cerebellum and ToM is a novel finding from our paediatric clinical sample and suggests that the cerebellum may play a role in the neural networks important for cognitive ToM. Moreover, evidence for robust prospective brain-behaviour relationships in the TBI sample suggests that sub-acute volumetric abnormalities of large-scale neural networks may represent valuable prognostic markers for early identification of children at elevated risk for poorer ToM outcomes.

## Ethical considerations

The RCH Human Research Ethics Committee and the Victorian Department of Education Ethics Committee approved this study. All parents gave their written, informed consent for children to participate in the study and for extraction of clinical data from medical records at the time of recruitment.

## Access to data

Authors N.R. and S.H. had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## Supplementary data

Supplementary data are available at *SCAN* online.

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