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## RESEARCH ARTICLE

# Altered resting-state functional connectivity within the developing social brain after pediatric traumatic brain injury

Carola Tuerk<sup>1</sup>  | Fanny Dégeilh<sup>1,2</sup>  | Cathy Catroppa<sup>3,4</sup> | Julian J. Dooley<sup>5</sup> | Michael Kean<sup>3</sup> | Vicki Anderson<sup>3,4</sup> | Miriam H. Beauchamp<sup>1,2</sup>

<sup>1</sup>Department of Psychology, University of Montreal, Montreal, Quebec, Canada

<sup>2</sup>Sainte-Justine Hospital Research Center, Montreal, Quebec, Canada

<sup>3</sup>Murdoch Children's Research Institute, The Royal Children's Hospital, Melbourne, Victoria, Australia

<sup>4</sup>Melbourne School of Psychological Science and Department of Pediatrics, University of Melbourne, Melbourne, Victoria, Australia

<sup>5</sup>Cuyahoga County Juvenile Court, Diagnostic Clinic, Cleveland, Ohio

## Correspondence

Miriam H. Beauchamp, Department of Psychology, University of Montreal, P.O. Box 6128, Downtown Station, Montreal, QC H3C 3J7, Canada.

Email: miriam.beauchamp@umontreal.ca

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## Abstract

Traumatic brain injury (TBI) in childhood and adolescence can interrupt expected development, compromise the integrity of the social brain network (SBN) and impact social skills. Yet, no study has investigated functional alterations of the SBN following pediatric TBI. This study explored functional connectivity within the SBN following TBI in two independent adolescent samples. First, 14 adolescents with mild complex, moderate or severe TBI and 16 typically developing controls (TDC) underwent resting-state functional magnetic resonance imaging 12–24 months post-injury. Region of interest analyses were conducted to compare the groups' functional connectivity using selected SBN seeds. Then, replicative analysis was performed in an independent sample of adolescents with similar characteristics (9 TBI, 9 TDC). Results were adjusted for age, sex, socioeconomic status and total gray matter volume, and corrected for multiple comparisons. Significant between-group differences were detected for functional connectivity in the dorsomedial prefrontal cortex and left fusiform gyrus, and between the left fusiform gyrus and left superior frontal gyrus, indicating positive functional connectivity for the TBI group (negative for TDC). The replication study revealed group differences in the same direction between the left superior frontal gyrus and right fusiform gyrus. This study indicates that pediatric TBI may alter functional connectivity of the social brain. Frontal-fusiform connectivity has previously been shown to support affect recognition and changes in the function of this network could relate to more effortful processing and broad social impairments.

## KEYWORDS

functional connectivity, neurodevelopment, resting-state fMRI, RRID: SCR\_009550, RRID: SCR\_001622, RRID: SCR\_007037, social brain, traumatic brain injury

## 1 | INTRODUCTION

Traumatic brain injury (TBI) sustained early in life has long-term consequences for development and ranks among the most common causes

of death and disability in children and adolescents (Araki, Yokota, & Morita, 2017). Pediatric TBI represents a particular risk for long-term impairments and interruption of normal development given the vulnerability of the developing brain to structural and functional disruption

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(Anderson, Spencer-Smith, & Wood, 2011; Crowe, Catroppa, Babl, & Anderson, 2012). Behavioral and social problems may be particularly debilitating for everyday functioning and interpersonal relations (Anderson et al., 2013; Beauchamp, Dooley, & Anderson, 2010; Beauchamp & Anderson, 2013). The extent of such difficulties has been shown to correlate with injury severity (Anderson et al., 2013; McDonald, 2013). Indeed, adolescents who sustain moderate to severe TBI may present elevated rates of clinically significant behavioral and social dysfunction, including aggressive (Dooley, Anderson, Hemphill, & Ohan, 2008) and socially inappropriate behaviors (Cole et al., 2008; Hicks et al., 2017), as well as sociocognitive impairments such as affect recognition deficits (e.g., impaired facial affect recognition) and reduced empathy (Tousignant et al., 2018). These problems can appear both in the acute and chronic stages post-injury, and may aggravate with time resulting in adverse adult outcomes, such as reduced social participation, social isolation and maladaptive behaviors (Beauchamp, Dooley, & Anderson, 2010; Catroppa et al., 2017).

The observation that TBI results in heterogeneous clinical outcomes supports the notion that long-term impairments, such as social problems, may be due to disruption of large-scale functional and anatomical neural networks (Ham & Sharp, 2012). Moderate to severe TBI is characterized by damage to white matter microstructure and diffuse axonal injury (Sharp, Scott, & Leech, 2014), resulting in disruption of large neural networks (Sharp et al., 2014). One such network is the social brain network (SBN), which has been shown to underlie social cognitive functions and may thus be implicated in social dysfunction following TBI (Johnson et al., 2005; Ryan, Catroppa, Beare, et al., 2016). It comprises the superior temporal sulcus (STS), fusiform gyrus, temporal pole, medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), amygdala, temporo-parietal junction (TPJ), and inferior parietal cortex (IPC; Beauchamp & Anderson, 2010; Johnson et al., 2005; Kennedy & Adolphs, 2012). Adolescence is a crucial time for social development during which the SBN undergoes profound changes and maturation (Blakemore, 2012). Thus, adolescents may be at particular risk for adverse social outcomes following TBI as they are in a developmental period where social skills are central to adequate social competence.

There is evidence from neuroimaging studies suggesting links between structural SBN disruptions and social impairments after TBI in children (Bigler et al., 2013; Levan, Baxter, Kirwan, Black, & Gale, 2015) and adolescents (Ryan, Catroppa, Beare, et al., 2016; Ryan, Catroppa, Cooper, Beare, Ditchfield, Coleman, Silk, Crossley, Beauchamp, et al., 2015; Ryan, van Bijnen, et al., 2016; Ryan et al., 2018). Such structural alterations may be linked to changes in functional connectivity between different nodes of the SBN through a disruption of neuronal function (Ansari, Oghabian, & Hossein-Zadeh, 2011). Resting-state functional magnetic resonance imaging (rsfMRI) is a powerful tool to explore the integrity of functional brain networks in both healthy and clinical populations (Fox & Raichle, 2007). By assessing correlations of fluctuations in the blood oxygen level-dependent (BOLD) signal between different nodes of the brain, rsfMRI allows for the investigation of large-scale functionally connected brain networks (Fox et al., 2005).

A line of research has begun to investigate the integrity of other well-established large-scale functional neural networks post-TBI. In

adults with moderate to severe TBI, abnormal functional connectivity (including both hypo- and hyper-connectivity) has been observed in resting-state networks subserving motor, memory, cognitive, and visual processing (Guo et al., 2019; Hillary et al., 2011, 2014; Rigon, Duff, McAuley, Kramer, & Voss, 2016; Rigon, Voss, Turkstra, Mutlu, & Duff, 2016, 2017; Shumskaya, van Gerven, Norris, Vos, & Kessels, 2017; Threlkeld et al., 2018). The most common findings points to functional connectivity abnormalities in the brain's default mode network (DMN) and salience network after adult TBI (Guo et al., 2019; Hillary et al., 2011; Threlkeld et al., 2018; Zhou et al., 2012).

Few studies have investigated altered functional connectivity following TBI in pediatric populations, especially in those with more severe injuries. Altered functional connectivity within the DMN, the dorsal attention network and motor networks have been found in three studies including children or adolescents with a range of TBI severities (Risen, Barber, Mostofsky, & Suskauer, 2015; Stephens et al., 2017, 2018). Closer to the current topic, one study in adolescents with moderate to severe TBI found reduced functional connectivity between the right anterior cingulate cortex (ACC) and amygdala, as well as between these regions, the medial prefrontal cortices and right temporal areas (Newsome et al., 2013). Given that the differences correlated with empathy ratings, the authors concluded that altered connectivity in these networks may be implicated in altered affective processing (Newsome et al., 2013). Together, these studies suggest that pediatric TBI may result in functional disruptions in functional networks related to behavioral and cognitive performance, with results indicating both stronger and lower connectivity when compared to typically developing peers.

Despite efforts to understand network reconfigurations following TBI, the consequences of moderate to severe TBI and its impact on functional connectivity during development remain unclear. Investigation of the underlying neural mechanisms of social dysfunction after pediatric TBI is largely limited to structural methods, studies focusing on single brain regions, and a handful of task-related fMRI approaches (e.g., Newsome et al., 2010; Scheibel et al., 2011), none of which have yet focused on the SBN using a network-vision of social functioning. The present study aimed to investigate functional alterations within the SBN in adolescents with moderate to severe TBI using an exploration-replication approach. It was hypothesized that (a) adolescents with TBI would show alterations in functional connectivity between regions of the SBN when compared with typically developing controls (TDC), and (b) that alterations in functional connectivity would be related to impairments in social skills in the TBI group. No hypothesis concerning the direction of differences in connectivity was established *a priori* given the lack of previous literature supporting directionality.

## 2 | MATERIALS AND METHODS

### 2.1 | Exploration study

#### 2.1.1 | Participants

Participants ( $n = 30$ , 11–16 years) were recruited between 2007 and 2010 as part of a larger prospective, longitudinal study of pediatric

TBI and social skills (Anderson et al., 2013). Here, we report data from a subgroup of adolescent participants with mild complex, moderate or severe TBI and TDC participants who underwent rsfMRI within 12–24 months post-injury. The study was approved by the Royal Children's Hospital Human Research Ethics Committee, and the Victorian Department of Education Ethics Committee. All procedures were conducted in accordance with the Declaration of Helsinki. Parents gave their written, informed consent for children to participate in the study.

Adolescents with TBI were identified via admission records at the emergency department, screened for eligibility and recruited immediately post-admission. Age-matched TDC participants were recruited via local schools ensuring diversity in terms of socioeconomic backgrounds. Inclusion criteria were those of the original parent study: (a) age between 5 and 16 years at the time of injury; (b) closed head injury, including a period of altered consciousness or presence of at least two post-concussive symptoms; (c) medical reports of injury severity, including the Glasgow Coma Scale ([GCS]; Teasdale & Jennett, 1974), neurological and radiological findings; and (d) English speaking. The TDC group was required to meet criteria (a) and (d). Exclusion criteria were: (a) history of preinjury neurological or developmental disorder, nonaccidental injury, or previous TBI, and (b) prior intervention for social impairment.

TBI severity was determined based on medical records detailing GCS, as well as clinical neurological (i.e., presence of nausea, vomiting, drowsiness, memory or vision problems, confusion, impairment of proprioception, vertigo) and radiological findings (i.e., abnormalities on computed tomography [CT]/clinical MRI). Thus, classification was made as follows: (a) mild TBI: Lowest GCS 13–15, no evidence of mass lesion on CT/clinical MRI, no neurological deficits; (b) mild complex TBI: Lowest GCS 13–15, evidence of mass lesion on CT/clinical MRI; (c) moderate TBI: Lowest GCS 9–12, and/or mass lesion or other evidence of specific injury on CT/MRI, and/or neurological impairment; and (d) severe TBI: Lowest GCS 3–8, and/or mass lesion or other evidence of specific injury on CT/MRI, and/or neurological impairment.

About 12–24 months postinjury (mean [ $M$ ] = 15.75 months, [ $SD$ ] = 5.21 months), a subgroup of participants from the larger study completed a full MRI session including rsfMRI. The follow-up time frame of >1 year is based on reports that most social and behavioral difficulties after injury in individuals with TBI appear only in later stages of recovery (Anderson, 2004; Yeates et al., 2005). Participants were included in the present rsfMRI analyses if they met the following additional inclusion criteria: (a) mild complex, moderate or severe TBI, (b) useable rsfMRI imaging data (i.e., no excessive motion, see below), and (c) age 11–16 years at the time of the neuroimaging assessment. TDC participants were required to meet criteria (b) and (c). Participants with mild complex TBI were included in the analyses, as mild complex TBI is generally considered a more severe form of mild TBI given the presence of abnormalities on MRI/CT (Williams, Levin, & Eisenberg, 1990) and due to reports showing worse functional recovery that is similar to moderate–severe TBI (Temkin, Machamer, & Dikmen, 2003; Williams, Levin, & Eisenberg, 1990). After applying these inclusion criteria, 10 participants (5 TBI, 5 TDC) had to be excluded and 30 participants constituted the final sample (14 TBI, 16 TDC).

## 2.1.2 | Behavior

### *Demographic and injury characteristics*

Socioeconomic status (SES) was determined at the time of recruitment using the Australian and New Zealand Socioeconomic Classification of Occupations ([ANZSCO]; McMillan, Beavis, & Jones, 2009). The scale ranges from 0 to 100 with high scores reflecting higher occupational status for the primary caregiver. Cognitive abilities were measured using the Wechsler Abbreviated Scale of Intelligence ([WASI]; Wechsler, 1999) at 24 months post-injury. Full Scale Intelligence Quotient ([FSIQ];  $M = 100$ ,  $SD = 15$ ) is reported for descriptive purposes. For participants with TBI, the following details were collected at the time of recruitment via standard clinical report forms: GCS (injury severity), duration of loss of consciousness, neurological symptoms, surgical intervention, and cause of injury.

### *Child behavior*

The Child Behavior Checklist for ages 6–18 ([CBCL]/6–18) is a standardized parent report questionnaire with good psychometric properties and which documents behavioral and social problems over the previous six months (Achenbach & Rescorla, 2001). Items are rated by the primary caregiver and behaviors are reported according to two main scales: (a) Internalizing problems including Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints subscales; (b) Externalizing problems including Rule-Breaking and Aggressive Behavior subscales. Parents filled out the questionnaire at the time of the rsfMRI assessment. Given the social focus of the study, scores are also reported for subscales specifically related to social functioning (Aggressive Behavior, Rule-Breaking, Social Problems). Higher scores ( $T$ -scores,  $M = 50$ ,  $SD = 10$ ) on any of the scales indicate more behavioral or emotional problems (Achenbach & Rescorla, 2001).

## 2.1.3 | Magnetic resonance imaging

### *Image acquisition and preprocessing*

MR images were acquired on a 3 Tesla Siemens Trio scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-channel matrix head coil. For each participant, a high-resolution T1-weighted structural MR image was acquired using a three-dimensional T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (repetition time [ $TR$ ] = 1,900 ms, echo time [ $TE$ ] = 2.52 ms, flip angle [ $FA$ ] = 9°, slice thickness = 1.0 mm, voxel-size: 1.0 × 1.0 × 1.0 mm, field of view [ $FoV$ ] = 250 mm, 192 slices, GRAPPA = 2, duration = 4.24 min).

RsfMRI images were acquired with a 2D T2-star echo planar image (EPI) sequence ( $TR = 2,200$  ms,  $TE = 30$  ms,  $FA = 90^\circ$ , 32 slices, slice thickness = 3 mm, voxel-size 1.9 × 1.9 × 3.0 mm,  $FoV = 240$  mm, 280 volumes, GRAPPA = 2, duration = 10.24 min). The time-frame of 10 min is recommended for resting-state image acquisition in pediatric populations, as it reduces risk of motion artifacts and the participant falling asleep (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012). All participants were instructed to focus on a central white cross presented on a black screen, not to move and to rest during this sequence.

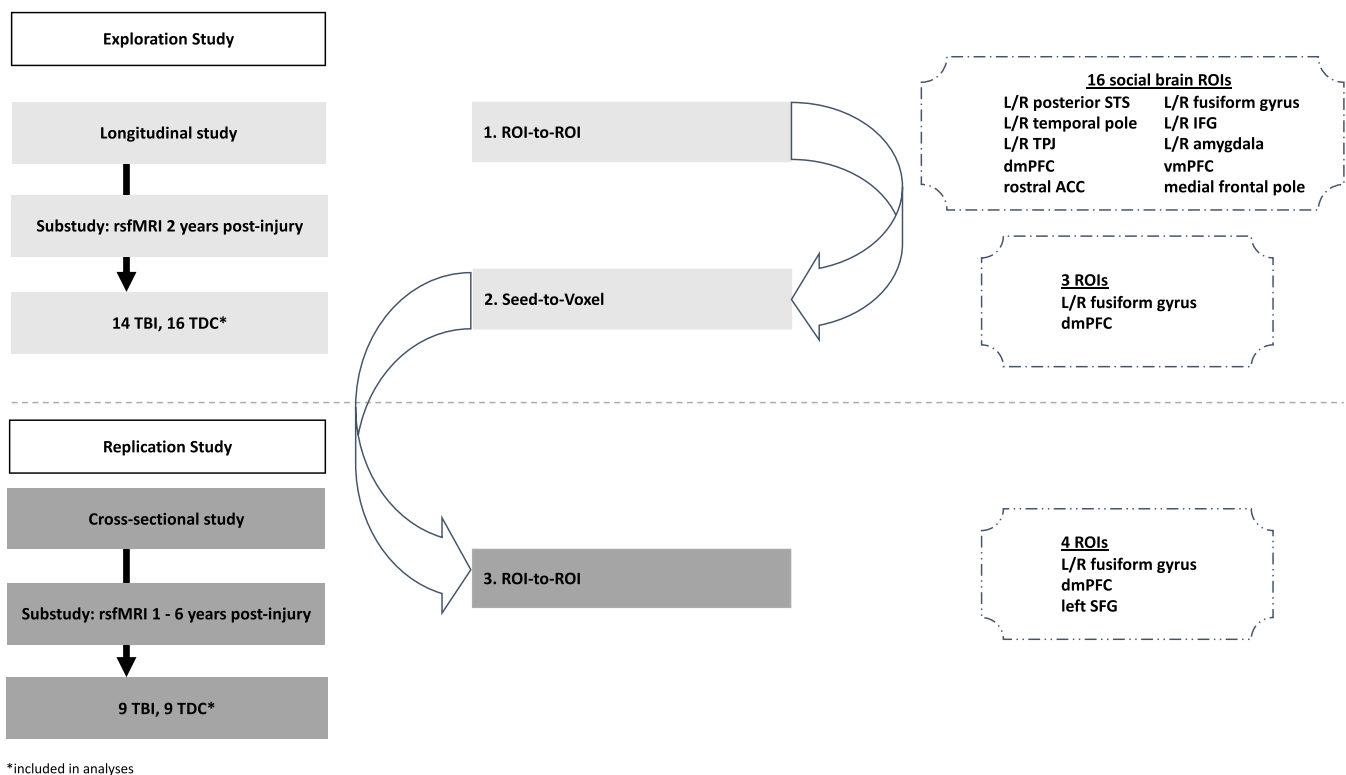
T1 and rsfMRI images were subjected to quality control by visual inspection (C.T., F.D.) for motion artifacts and image quality. Then, SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK; <https://www.fil.ion.ucl.ac.uk/spm>, RRID: SCR\_007037) and the CONN Functional Connectivity Toolbox version 17f (<http://www.nitrc.org/projects/conn>, RRID: SCR\_009550, Whitfield-Gabrieli & Nieto-Castanon, 2012) running on MATLAB version R2017b (MathWorks, Inc., Natick, MA, USA; <http://www.mathworks.com/products/matlab/>, RRID: SCR\_001622) were used for pre-processing and subsequent statistical analyses. Pre-processing steps in SPM12 included (a) slice timing correction of the EPI volumes and realignment to the first volume of the fMRI time series; (b) co-registration of the mean EPI (calculated during realignment) and the T1 images; (c) segmentation of tissues (gray matter [GM], white matter [WM] and cerebrospinal fluid [CSF]) and normalization using the T1 and an age-appropriate stereotaxic template (NIHPD 4.5–18.5 asymmetric: [www.bic.mni.mcgill.ca/ServicesAtlases/NIHPDobj1](http://www.bic.mni.mcgill.ca/ServicesAtlases/NIHPDobj1); Fonov et al., 2011); (d) spatial normalization of the co-registered T1 image and EPI volumes with a voxel size of  $2 \times 2 \times 2$  mm; and (e) smoothing of the normalized EPI images at 6 mm full width at half-maximum (FWHM).

The CONN toolbox was then used to run the noise reduction step (“denoising”) in order to remove unwanted motion, as well as physiological and other artefactual effects from the BOLD signal. This final step applies linear regression of nuisance variables using the anatomical principal component-based noise-correction “aCompCor” method (Behzadi, Restom, Liu, & Liu, 2007; Whitfield-Gabrieli & Nieto-Castanon, 2012) along with six movement parameters that were estimated during realignment. This was followed by band-pass filtering between 0.008 and 0.09 Hz in order to remove high-frequency noise. A threshold of 3 mm was applied for the six motion parameters, which none of the final sample surpassed. Mean frame-wise displacement was calculated according to Power et al. (2012). There was no difference between the two groups ( $p = .784$ ).

## 2.1.4 | Data analyses

### ROI-to-ROI resting-state fMRI analyses

Analyses steps are illustrated in Figure 1. Using the CONN toolbox and 16 regions of interest (ROI) from the SBN, ROI-to-ROI functional connectivity analyses were performed. ROIs were defined as 6 mm



**FIGURE 1** Overview of analyses steps. Analyses were conducted in a stepwise manner: First, ROI-to-ROI analyses were performed between 16 ROIs of the social brain in a first sample that was part of a larger longitudinal project (exploration study). Then, seed-to-voxel analyses were conducted to explore functional connectivity within the whole social brain in the same sample. In this step, only significant seeds (bilateral) from the ROI-to-ROI analyses were selected to test whether these seeds may be connected with other regions within the social brain that were not initially selected. These analyses served to define more specific ROIs to be tested in an independent replication sample: A ROI-to-ROI approach was applied to examine whether the results obtained in the exploration study would hold in an independent sample of participants that were recruited as part of a larger cross-sectional study (replication study). ACC, anterior cingulate cortex; dmPFC, dorsomedial prefrontal cortex; IFG, inferior frontal gyrus; L, left; R, right; ROI, region of interest; rsfMRI, resting-state functional magnetic resonance imaging; SFG, superior frontal gyrus; STS, superior temporal sulcus; TBI, traumatic brain injury; TDC, typically developing controls; TPJ, temporo-parietal junction; vmPFC, ventromedial prefrontal cortex

radius spheres around MNI coordinates derived from the social brain atlas described by Alcalá-López et al. (2018). This atlas is based on meta-analyses of neural activity related to social-cognitive processing involving almost 4,000 neuroimaging studies (Alcalá-López et al., 2018). The following ROIs were selected: Bilateral left posterior STS, fusiform gyrus, temporal pole, inferior frontal gyrus, TPJ, amygdala, as well as the dorsomedial PFC (dmPFC), the ventromedial PFC (vmPFC), the rostral ACC and the medial frontal pole. These brain regions have consistently been related to morphological abnormalities and to social difficulties following TBI (Ryan, Catroppa, Beare, et al., 2015, 2016; Ryan et al., 2017; Ryan, Catroppa, Cooper, Beare, Ditchfield, Coleman, Silk, Crossley, Rogers, et al., 2015; Ryan, Catroppa, Godfrey, et al., 2016; Ryan et al., 2018; see Table 1 for details on ROIs and MNI coordinates).

Bivariate Pearson's correlations between the mean BOLD signal time-courses of each pair of ROIs were calculated at the first level of analysis. This resulted in individual ROI-to-ROI functional connectivity maps for each participant ( $16 \times 16$ ) with positive correlation coefficients describing positive functional connectivity, and negative correlation coefficients describing negative functional connectivity (anti-correlation). The six motion parameters (three rotations, three translations) calculated during pre-processing were included as nuisance regressors. Finally, correlation coefficients were converted into normally distributed z-scores using Fisher's transformation for parametric testing.

At the second-level analysis, two-sample t-tests were performed to assess between-group differences in ROI-to-ROI functional connectivity for each ROI, controlling for age at rsfMRI acquisition, sex, SES, and total GM volume to account for the global presence of structural lesions. In addition, all analyses were masked using a GM mask

based on both TDC and TBI participants and involving GM, WM and CSF means from the normalized images. This was done in order to control for local effects of brain lesions. By also including TBI participants in the mask, the presence of focal atrophies was controlled for and analyses restricted only to those regions where it was expected to measure brain activation, that is, in brain regions with GM. This mask was calculated using the following formula:  $GM\ mask = (meanGM > meanWM) \cap (meanGM > meanCSF) \cap (meanGM > 0.3)$ .

A false discovery rate ([FDR]; Chumbley, Worsley, Flandin, & Friston, 2010) was used at a threshold of  $p < .05$  (two-tailed) at seed-level in order to control for Type I error.

#### Seed-to-voxel resting-state fMRI analyses

In a second step, the findings of the ROI-to-ROI analyses were tested in a less restrictive *a priori* analysis. Seed-to-voxel analyses were performed using bilateral seeds from the first ROI-to-ROI analyses that showed significant differences in resting-state functional connectivity between groups. This was done in order to explore whether the seeds from the first analyses would be connected with other regions of the social brain that were not initially selected.

In order to constrain analyses to the social brain and to further reduce Type I error given the number of comparisons, a social brain mask was applied which was based on anatomical areas from the Harvard-Oxford atlas included in CONN (Desikan et al., 2006; Fox et al., 2005). This social brain mask included bilateral STS, fusiform gyrus, temporal pole, mPFC, frontal pole, ACC, OFC, amygdala, TPJ, IPC, inferior frontal cortex, and insula.

For each participant, individual correlation maps throughout the social brain were created by extracting the mean resting-state BOLD time course from each of the selected seeds and by calculating

**TABLE 1** Selected regions of interest (ROI) for the connectivity analyses

Social brain ROI	Abbreviation	MNI coordinates		
		X	Y	Z
Left posterior superior temporal sulcus	pSTS_L	-56	-39	2
Right posterior superior temporal sulcus	pSTS_R	54	-39	0
Left temporal pole	TP_L	-48	8	-36
Right temporal pole	TP_R	53	7	-26
Left temporo-parietal junction	TPJ_L	-49	-61	27
Right temporo-parietal junction	TPJ_R	54	-55	20
Rostral anterior cingulate cortex	rACC	-3	41	4
Left fusiform gyrus	FG_L	-42	-62	-16
Right fusiform gyrus	FG_R	43	-57	-19
Dorsomedial prefrontal cortex	dmPFC	-4	53	31
Ventromedial prefrontal cortex	vmPFC	2	45	-15
Medial frontal pole	FP	1	58	10
Left inferior frontal gyrus	IFG_L	-45	27	-3
Right inferior frontal gyrus	IFG_R	48	24	2
Left amygdala	AM_L	-21	-4	-18
Right amygdala	AM_R	23	-3	-18

Note: 6 mm-ROIs selected from Alcalá-López et al. (2018).

correlation coefficients with the BOLD time course of each voxel throughout the social brain. The resulting Pearson's correlation coefficients between the time series of each seed and the individual voxels were Fisher's z-transformed in order to estimate maps of voxel-wise functional connectivity for each seed in the social brain for each participant. The resulting maps were then included in second-level analyses to evaluate between-group differences in seed-to-voxel connectivity using two-sample *t*-tests implemented in CONN, covarying for age, sex, SES and total GM volume. In addition, the GM mask calculated in the previous step was applied to account for local effects of brain lesions. Voxel-wise statistics within the social brain mask were performed at a threshold of  $p < .05$  (two-tailed) and corrected for multiple comparisons at cluster-level using the family-wise error (FWE); Nichols & Hayasaka, 2003), following the standard procedure as described in Whitfield-Gabrieli and Nieto-Castanon (2012). The more conservative FWE-correction was chosen as analyzing functional connectivity between each seed with a large number of voxels leads to an increased number of comparisons (Benjamini & Hochberg, 1995).

#### *Behavioral data analyses*

All data were first screened for violations of normality using SPSS statistical software (Version 25.0; Chicago, IL; <http://www-01.ibm.com/software/uk/analytics/spss/>, [https://www.ibm.com, RRID:SCR\\_002865](https://www.ibm.com, RRID:SCR_002865)). Group comparisons were performed using independent samples *t*-tests for data that were normally distributed and Mann-Whitney-*U* tests for those that were nonnormally distributed. An  $\alpha$ -level of  $p < .05$  was employed in order to determine significance.

Correlation analyses were performed to examine whether differences in functional connectivity between groups were related to social-behavioral functioning (CBCL scores) and to injury severity (GCS scores) in the TBI group. We extracted individual Fisher transformed correlation coefficients: (a) indicating significant group differences in ROI-to-ROI functional connectivity; and (b) for clusters of voxels indicating significant group differences in connectivity with SBN structures in seed-to-voxel analyses.

Two-tailed partial Pearson's correlation analyses were then performed between extracted functional connectivity scores and CBCL scores, covarying for SES (as CBCL T-scores already account for age and sex). GCS scores were correlated with functional connectivity scores covarying for age, sex and SES. Given the high number of comparisons ( $n = 6$ ), the threshold was lowered from  $p < .05$  to  $p < .01$  by applying Bonferroni correction ( $\alpha$ -value divided by number of comparisons).

## 2.2 | Replication study

### 2.2.1 | Participants

A replication analysis was conducted using a second independent sample of nine individuals with moderate to severe TBI (seven females) and nine TDC participants (three females) with available rsfMRI and behavioral (CBCL) data as described above. Participants

were ascertained as part of a separate cross-sectional research project on social reasoning in adolescents with TBI. TBI participants were retrospectively recruited one to six years after brain injury and were aged between 13 and 18 years. TDC participants were recruited through local schools using a random sampling strategy in order to include a broad range of socioeconomic backgrounds. Inclusion and exclusion criteria for both groups of participants were the same as those in the exploration study. The Mayo Classification System was used to determine injury severity retrospectively based on available positive clinical evidence (Malec et al., 2007).

### 2.2.2 | Behavior

#### *Demographics and injury characteristics*

In order to match the measures as closely as possible to those used in the exploration sample, the primary caregiver's education was used as a proxy for SES. Education was rated on a scale from one to eight according to the following categories: 1 = primary school, 2 = Year 10 or lower high school, 3 = Year 11, 4 = Year 12, 5 = technical and further education, 6 = university bachelor degree, 7 = university post-graduate, 8 = other diploma. Similar to the exploration study, cognitive abilities were measured for descriptive purposes using the FSIQ from the WASI. For participants with TBI, standardized clinical report forms were used to collect the data on injury severity (GCS) and cause of injury.

#### *Child behavior*

CBCL data were also available for the replication sample and the same subscores as in the exploration study were used for analyses.

### 2.2.3 | Magnetic resonance imaging

#### *Image acquisition and pre-processing*

MR images for this study were acquired on the same scanner as the exploration sample. Similarly, high-resolution structural T1 images were acquired following the same protocol. RsfMRI images were acquired with a 2D T2-star echo planar image sequence (TR = 2,000 ms, TE = 30 ms, FA = 90°, 32 slices, slice thickness = 3 mm, voxel-size 2.6 × 2.6 × 4.0 mm, FoV = 250 mm, 200 volumes, GRAPPA = 2, duration = 6.48 min). All participants had to focus on a central white cross presented on a black screen, were asked not to move and to rest during the sequence. Subsequent image preprocessing was conducted identical to the procedures described above. None of the participants surpassed the motion threshold of 3 mm, and no group difference was found for mean FD ( $p = .890$ ).

### 2.2.4 | Data analyses

#### *ROI-to-ROI resting-state fMRI analyses*

Following the analyses in the exploration study, which served to define more specific ROIs, ROI-to-ROI analyses were applied to the replication sample to test the results in an independent sample of adolescents. The ROI-to-ROI approach was chosen to replicate the results

from the exploration study as closely as possible, therefore limiting the number of seeds and target regions and maintaining adequate statistical power given the smaller sample size. ROIs were chosen based on seeds and clusters showing significant group differences in the exploration sample. If not otherwise indicated, ROIs were selected bilaterally.

At the first level of analysis, individual ROI-to-ROI functional connectivity maps ( $4 \times 4$ ) were calculated for each participant including the six motion parameters calculated during the realignment step as nuisance regressors. Correlation coefficients were converted into Fisher's  $z$ -scores. Then, two-sample  $t$  tests were applied to evaluate between-group differences in ROI-to-ROI functional connectivity for each seed, controlling for age at rsfMRI testing, sex, years of parental education, and total GM

volume. Results were thresholded at  $p < .05$  using FDR-correction method (two-tailed) to control for multiple comparisons and a GM mask was applied to all analyses following the same procedure as in the exploration sample to control for the presence of focal lesions.

#### Behavioral data analyses

As for the exploration sample, data were screened for violations of normality and group comparisons were performed using independent samples  $t$ -tests for data that were normally distributed and Mann-Whitney  $U$  tests for nonnormally distributed data. Significance was determined using an  $\alpha$ -level of  $p < .05$ . Given the small sample size, partial correlation analyses of functional connectivity scores and CBCL scores or injury severity were not performed in this sample

**TABLE 2** Participant characteristics (exploration sample)

	TBI, $n = 14$ M (SD)	TDC, $n = 16$ M (SD)	Statistic	$p$
<b>Demographics</b>				
Sex male ( $n, \%$ )	11 (78.57)	9 (56.25)	$\chi^2(1) = 1.67$	.20
Age (years)	13.09 (1.42)	13.59 (1.68)	$t(28) = .87$	.39
SES (ANZSCO)	49.94 (21.30)	74.21 (18.21)	$t(28) = 3.37$	.002*
FSIQ (WASI-2)	96 (11.11), $n = 11$	106.07 (9.74), $n = 15$	$t(24) = 2.45$	.02*
<b>Injury characteristics</b>				
Age at injury (years)	11.77 (1.57)	—	—	—
Time since injury (months)	15.75 (5.21)	—	—	—
GCS (lowest)	10.86 (3.44)	—	—	—
Neurological symptoms ( $n, \%$ )	4 (28.57)	—	—	—
Surgical intervention ( $n, \%$ )	3 (21.43)	—	—	—
<b>LOC (<math>n, \%</math>)</b>				
No LOC	3 (21.43)	—	—	—
<5 min	9 (64.29)	—	—	—
>5 min, <24 hr	1 (7.14)	—	—	—
<b>Cause (<math>n, \%</math>)</b>				
MVA	4 (28.57)	—	—	—
Fall/blow	9 (64.29)	—	—	—
Kicked/struck by object	1 (7.14)	—	—	—
<b>CBCL subscales</b>				
Aggressive <sup>a</sup>	56.64 (10.08)	51.38 (1.82)	$U = 81.50$	.19
Social <sup>a</sup>	55.79 (8.14)	52.00 (3.86)	$U = 84.50$	.22
Internalizing	56.43 (6.63)	49.44 (8.12)	$t(28) = 2.60$	.02
Externalizing <sup>a</sup>	53.21 (8.47)	49.44 (6.89)	$U = 70.50$	.08
Rule-breaking	56.21 (7.28)	50.69 (1.08)	$t(28) = 2.82$	.01

Notes:  $p$ -values are calculated using independent samples  $t$ -tests for continuous variables and chi-square ( $\chi^2$ ) tests for categorical variables between groups. For group comparisons on CBCL scores, the significance level was adjusted to  $p = .01$ . CBCL scores represent  $T$ -scores.

Abbreviations: ANZSCO, Australian and New Zealand Socioeconomic Classification of Occupations; CBCL, Child Behavior Checklist; FSIQ, Full-Scale Intelligence Quotient; GCS, Glasgow Coma Score; LOC, loss of consciousness; M, mean; MVA, motor vehicle accident; SES, socioeconomic status; TBI, traumatic brain injury; TDC, typically developing controls; WASI-2, Wechsler Abbreviated Intelligence Scale-2.

<sup>a</sup>For nonnormally distributed data, Mann-Whitney  $U$  tests were used.

\*Significant at  $p < .05$ .

which is not recommended as it significantly reduces statistical power (Cohen, 1988).

### 3 | RESULTS

#### 3.1 | Exploration study

##### 3.1.1 | Participant characteristics

Participant demographic and injury characteristics including neuro-radiological reports are summarized in Tables 2 and 3. There were no group differences for sex or age at the 24-month follow-up assessment. However, the two groups differed significantly with respect to SES, indicating higher SES for the TDC group ( $p = .002$ ). Consequently, SES was included as a covariate in all analyses. In addition, a significant difference was found for IQ between the two groups

( $p = .02$ ). Of note, a repeated-measures ANOVA showed that IQ remained stable over time from 6 to 24 months for both groups ( $F [1,24] = 26.19, p = .52$ ).

Group differences were found on the CBCL Internalizing subscale, indicating higher scores and thus more internalizing problems for the TBI compared to the TDC group ( $p = .02$ ), as well as for the Rule-Breaking subscale indicating more problems for the TBI group ( $p = .01$ ; Table 2). No other significant group differences were found on any other CBCL subscale.

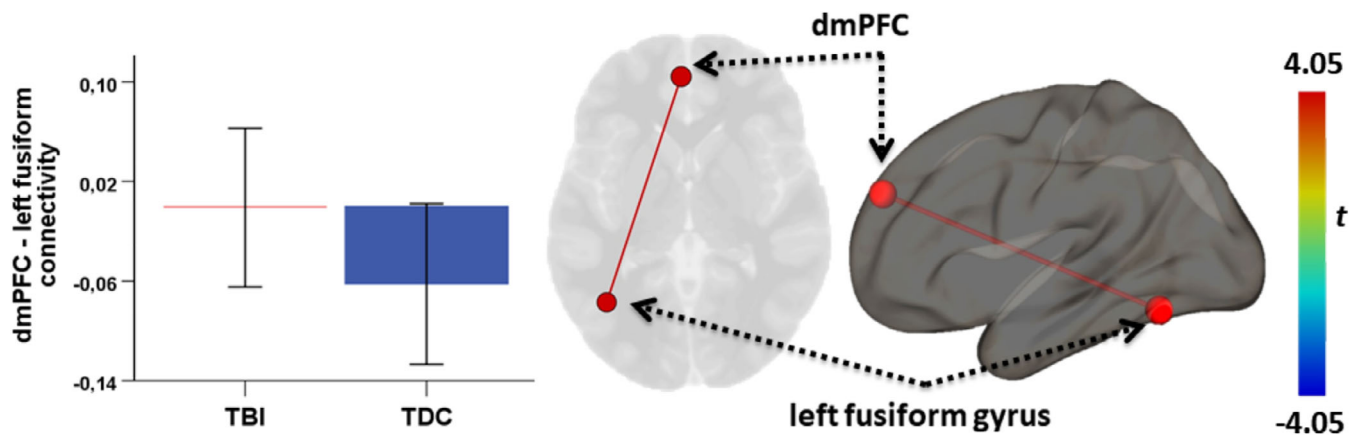
##### 3.1.2 | ROI-to-ROI functional connectivity

We evaluated whether functional connectivity between selected ROIs from the SBN differed between the TBI and TDC groups. The results revealed positive connectivity between the dmPFC and left fusiform

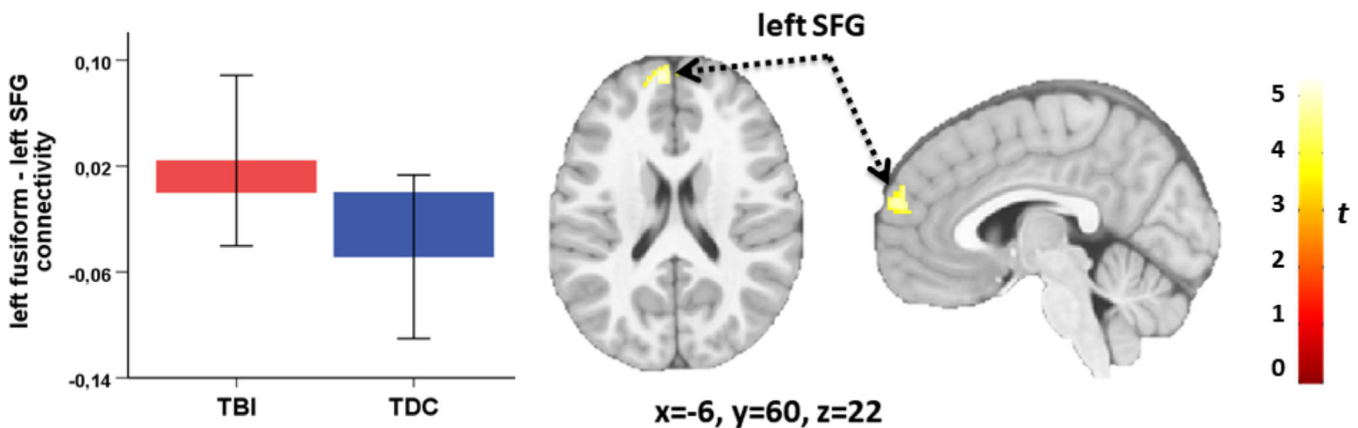
**TABLE 3** Neuropathology on clinical CT/MRI for TBI participants (exploration sample)

	Sex	Injury type	Age at injury	GCS	CT/MRI findings	Skull fracture
TBI_E1	M	Fall	10.5	8	L frontal extradural hematoma; L multifocal frontal GM/WM hemorrhage and gliosis	—
TBI_E2	M	Kicked/ struck by object	14.0	15	R posterior frontal WM gliosis	—
TBI_E3	M	Fall	11.0	13	R frontal parenchymal and cortical hemorrhagic contusions; L occipito-parietal cortical contusion; B frontal GM/WM hemorrhage and gliosis; B temporal, occipital, parietal GM gliosis; R temporal hemorrhage; multifocal GM/WM hemorrhage and gliosis	—
TBI_E4	F	Fall	11.8	15	B multifocal anterior frontal WM gliosis; scalp edema in L occipital region	—
TBI_E5	M	Fall	10.9	11	R inferior frontal extradural hemorrhage contusion; R inferior frontal GM/WM gliosis; B encephalomalacia	Complex fracture R frontal lobe, ethmoid and spheroid bones, superior and medial orbital walls
TBI_E6	M	MVA	10.5	10	Small L hemorrhagic cortical contusion and small extra axial hematoma; L anterior frontal hemorrhage; B multifocal frontal WM petechial hemorrhage and gliosis; L temporal multifocal WM hemorrhage and gliosis + anterior callosal hemorrhage	Undisplaced linear fracture L fronto-parietal bone
TBI_E7	M	MVA	9.2	8	NA	—
TBI_E8	F	Fall	12.3	15	Intra-axial bleeding; B petechial frontal hemorrhage	—
TBI_E9	M	Fall	11.4	11	R occipital GM/WM hemorrhage	—
TBI_E10	M	MVA	11.7	3	Scalp edema in L frontal region; subarachnoid hemorrhage	—
TBI_E11	M	Fall	14.8	8	Scalp edema in L parietal region; L temporal and L frontal GM/WM hemorrhage; diffuse axonal injury; edema; mass effect	Undisplaced linear fracture L parietal bone
TBI_E12	F	MVA	10.6	10	Scalp edema in R frontal region; globus pallidus calcification	—
TBI_E13	M	Fall	12.3	14	Subdural bleed	—
TBI_E14	M	Fall	13.9	11	NA	—

Abbreviations: B, bilateral; CT, computed tomography; F, female; GCS, Glasgow Coma Score (lowest); GM, gray matter; L, left; M, male; MRI, magnetic resonance imaging; MVA, motor vehicle accident; NA, not available; R, right; TBI, traumatic brain injury; WM, white matter.



**FIGURE 2** ROI-to-ROI functional connectivity analysis in the exploration sample. A significant group difference in ROI-to-ROI functional connectivity between the TBI and the TDC groups was found between the dorsomedial prefrontal cortex (dmPFC) and left fusiform gyrus, indicating positive connectivity in the TBI as compared to the TDC group, which showed negative dmPFC-left fusiform connectivity. Error bars represent standard errors [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**FIGURE 3** Seed-to-voxel functional connectivity analyses in the exploration sample. A significant group difference in seed-to-voxel functional connectivity between the TBI and the TDC groups was found between the left fusiform gyrus and left superior frontal gyrus (SFG), showing positive connectivity for participants with TBI and negative connectivity for TDC participants. Error bars represent standard errors [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

gyrus in participants with TBI as compared to TDC participants who showed negative connectivity between these two regions ( $t[24] = 4.05, p = .004, \text{FDR-corrected}$ ; Figure 2).

### 3.1.3 | Seed-to-voxel functional connectivity

The aim of these seed-to-voxel analyses was to highlight regions that showed group differences in the ROI-to-ROI analyses and to test the connectivity of these seeds with other regions that were not initially selected in a less restrictive *a priori* analyses. Based on the results of the ROI-to-ROI analyses, the bilateral fusiform gyrus and dmPFC were used as seeds in seed-to-voxel analyses. Significant differences between the two groups were found between the left fusiform gyrus and left superior frontal gyrus ( $k = 483, x = -6, y = 60, z = 22; p = .001, \text{FWE-corrected at cluster-level}$ ), indicating positive connectivity for the TBI group and negative connectivity for the TDC group. No differences were found for the dmPFC seed or for the right fusiform gyrus seed. Results are summarized in Figure 3.

### 3.1.4 | Correlations with CBCL and injury severity

Partial correlation analyses between functional connectivity and CBCL scores and injury severity revealed no significant associations in the TBI group after correction for multiple comparisons.

## 3.2 | Replication study

### 3.2.1 | Participant characteristics

Table 4 presents participant demographic and injury characteristics for the replication study. There were no group differences on any of the demographic variables. Nevertheless, in order to replicate the analyses performed on the exploration sample as closely as possible, parent education (as a proxy for SES) in addition to age and sex were included as covariates in all analyses. Information on injury and neuro-pathology based on CT and clinical MRI in the TBI participants is summarized in Table 5. No significant group differences were found on any of the CBCL scores (Table 4).

**TABLE 4** Participant characteristics (replication sample)

	TBI, <i>n</i> = 9 M (SD)	TDC, <i>n</i> = 9 M (SD)	Statistic	<i>p</i>
Demographics				
Sex male ( <i>n</i> , %)	7 (77.78)	3 (33.33)	$\chi^2(1) = 3.60$	.06
Age (years)	16.82 (.81)	15.75 (1.29)	$t(16) = 2.10$	.05
SES	5.56 (1.74)	5.00 (2.00)	$t(16) = .63$	.54
FSIQ (WASI-2)	106.22 (14.57)	100.50 (15.31), <i>n</i> = 8	$t(15) = .79$	.44
Injury characteristics				
Age at injury (years)	13.33 (2.00)	—	—	—
Time since injury (years)	3.48 (1.69), 1.35–6.28	—	—	—
GCS (lowest)	11.00 (2.83)	—	—	—
Cause ( <i>n</i> , %)				
MVA	4 (44.44)	—	—	—
Fall/blow	5 (55.56)	—	—	—
CBCL subscales				
Aggressive <sup>a</sup>	54.22 (5.40)	54.11 (4.81)	$U = 39.50$	.927
Social <sup>a</sup>	53.67 (6.34)	51.11 (2.62)	$U = 29.50$	.283
Internalizing	49.44 (14.02)	48.11 (10.34)	$t(16) = .23$	.821
Externalizing	50.33 (9.15)	51.89 (5.44)	$t(16) = .44$	.667
Rule-breaking	55.56 (6.65)	53.56 (2.51)	$t(16) = .84$	.418

Notes: *p*-values are calculated using independent samples *t* tests for continuous variables and chi-square ( $\chi^2$ ) tests for categorical variables between groups. For group comparisons on CBCL scores, the significance level was adjusted to  $p = .01$ . CBCL scores represent *T*-scores.

Abbreviations: CBCL, Child Behavior Checklist; FSIQ, Full-Scale Intelligence Quotient; GCS, Glasgow Coma Score; M, mean; SES, socioeconomic status; TBI, traumatic brain injury; TDC, typically developing controls; WASI-2, Wechsler Abbreviated Intelligence Scale-2.

<sup>a</sup>For nonnormally distributed data, Mann–Whitney *U* tests were used.

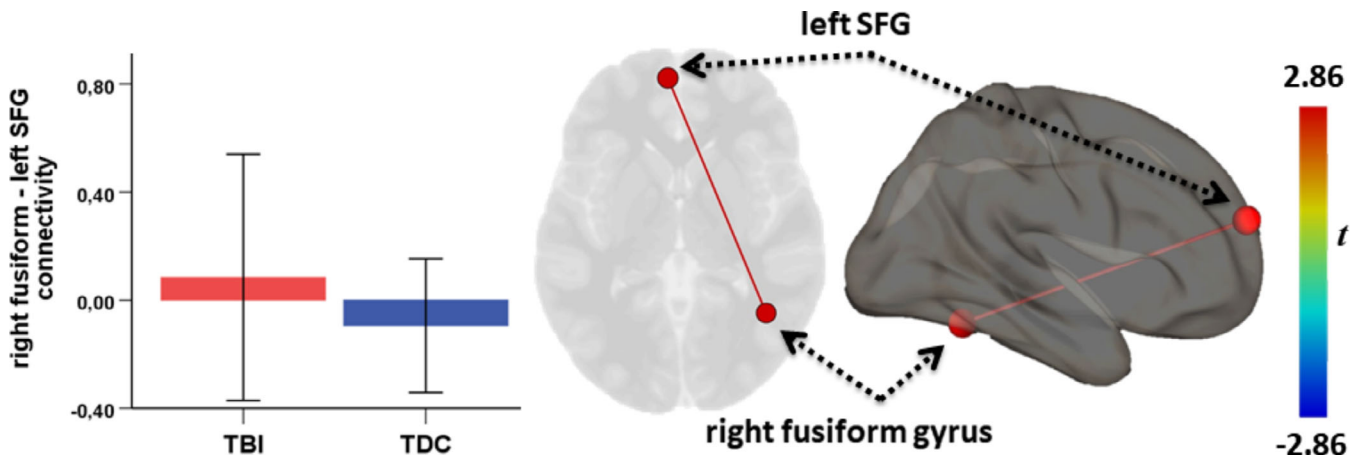
**TABLE 5** Neuropathology on clinical CT/MRI for TBI participants (replication sample)

	Sex	Injury type	Age at injury	GCS	CT/MRI findings	Skull fracture
TBI_R1	F	MVA	15.27	NA	Parietal hematoma; subdural hematoma; generalized edema	Undisplaced parietal
TBI_R2	M	MVA	14.70	12	NA	Frontal bone (craniotomy)
TBI_R3	M	Fall	14.95	13	B temporal hemorrhage; small extradural collection over the lateral aspect of the L occipital lobe	—
TBI_R4	F	Fall	14.32	NA	R temporo-occipital hematoma; B fronto-temporal hemorrhagic contusions	—
TBI_R5	M	MVA	9.70	12	NA	NA
TBI_R6	M	MVA	13.62	6	NA	NA
TBI_R7	M	Fall	11.75	12	R frontal and anterior temporal contusion; intraparenchymal hemorrhage; small R frontal traumatic subarachnoid hemorrhage	R parietal
TBI_R8	M	Fall	14.63	13	L frontal cortical contusion	B occipital
TBI_R9	M	Fall	11.05	13	R frontal cortical contusion; L occipito-parietal cortical contusion	R frontal

Abbreviations: B, bilateral; CT, computed tomography; F, female; GCS, Glasgow Coma Score (lowest); L, left; M, male; MRI, magnetic resonance imaging; MVA, motor vehicle accident; NA, not available; R, right; TBI, traumatic brain injury.

The two TBI groups did not show any difference in IQ ( $p = .09$ ), sex ( $p = .96$ ), SES ( $p = .23$ ), or GCS ( $p = .93$ ). All age-related variables showed significant differences, including age at rsfMRI acquisition

( $p < .001$ ), injury age ( $p = .049$ ), and time since injury ( $p < .001$ ). In particular, the TBI group in the replication sample was older (difference score [years] = 3.73), had an overall older age at injury (difference



**FIGURE 4** ROI-to-ROI functional connectivity analyses in the replication sample. A significant group difference in ROI-to-ROI functional connectivity between the TBI and the TDC groups was found between the right fusiform gyrus and left superior frontal gyrus (SFG), showing positive connectivity for the TBI group and negative connectivity for the TDC group. Error bars represent standard errors [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

score [years] = 1.56), and underwent brain imaging a longer time after injury (difference score [years] = 2.17) than the exploration sample.

A comparison of demographical variables between the two TDC groups (exploration and replication) showed no difference in IQ ( $p = .37$ ), sex ( $p = .27$ ), or SES ( $p = .15$ ), but the two TDC groups differed for age, with those in the replication study being older than those in the exploration study (difference score [years] = 2.16,  $p = .003$ ).

### 3.2.2 | ROI-to-ROI functional connectivity

In the replicative ROI-to-ROI analyses, the left and right fusiform gyrus, dmPFC and left superior frontal gyrus were used as seed regions, based on the results of the exploration study. For the left superior frontal gyrus, an additional 6 mm spherical ROI was defined using peak coordinates from the significant cluster from the exploration study. Given that the bilateral fusiform gyrus showed differences in seed-based functional connectivity between groups in both analyses, the right fusiform gyrus was also included in the analyses in order to explore functional connectivity within and across hemispheres. Consistent with the analyses in the exploration sample, results revealed positive connectivity between the left superior frontal gyrus and right fusiform gyrus in participants with TBI, compared to TDC participants who showed negative connectivity between those two ROIs ( $t[12] = 2.86$ ,  $p = .04$ , FDR-corrected; Figure 4). None of the other ROIs showed significant functional connectivity differences.

## 4 | DISCUSSION

This study aimed to investigate alterations of functional connectivity within the SBN following TBI associated with skull fracture and/or intracranial lesions in two independent adolescent samples. Given the inconsistencies across existing studies of functional connectivity in terms of methodology and sample constitution, and the lack of

replication in previous studies, we applied an exploratory exploration-replication approach and two different types of ROI-analyses. Analyses in the two samples revealed similar patterns of altered functional connectivity within the SBN: Positive frontal-fusiform functional connectivity in adolescents with TBI compared to their non-injured peers.

More specifically, in the exploration sample, group differences in ROI-to-ROI functional connectivity within the SBN were found, indicating positive connectivity between the dmPFC and left fusiform gyrus in those with TBI compared to negative connectivity between these two regions in controls. Then, consistent with the findings of the ROI-to-ROI analyses, seed-to-voxel analyses revealed differences in functional connectivity, indicating positive connectivity in the TBI group and negative connectivity in the TDC group between the left fusiform and left superior frontal gyri. This confirmed altered frontal-fusiform connectivity in the TBI group. No significant associations between functional connectivity scores and behavior were found. The replication study revealed a similar pattern of altered connectivity between the right fusiform gyrus and left superior frontal gyrus, indicating positive functional connectivity in adolescents with TBI, and negative functional connectivity in non-injured adolescents.

Increased functional connectivity patterns have also been found in other rsfMRI studies of moderate to severe TBI in children and adults, indicating higher resting-state functional connectivity in the DMN (Bonnelle et al., 2011; Xiao, Yang, Xi, & Chen, 2015) and task-fMRI studies in adolescents with TBI revealing increased activation in the fusiform gyrus and PFC in relation to social cognition tasks involving theory of mind and affect recognition (Newsome et al., 2010; Rigon et al., 2018; Scheibel et al., 2011). Increased functional connectivity could possibly be explained using the “cortical inefficiency model”, developed in the field of schizophrenia research (Manoach, 2003), according to which additional resource allocation is required in order to maintain task performance. Consistent with this hypothesis, previous TBI studies report alterations in brain activity, whereby more extensive cerebral activation patterns have been observed in relation

to task performance, suggesting neuroplastic mechanisms following TBI (see Levin, 2003 for a review). For example, in an fMRI study involving participants with moderate–severe TBI, Christodoulou and colleagues found higher and more widespread activation in the frontal lobes during a working memory task in participants with TBI compared to noninjured controls (Christodoulou et al., 2001). Such recruitment of the frontal lobes is in line with the present finding and may indicate changes in functional activity as a result of TBI. Importantly, higher functional connectivity has also been linked to neuropathology after moderate to severe TBI in adults (e.g., Scheibel et al., 2009). Conversely, Rigon et al. (2017) found lower functional connectivity between bilateral fusiform gyri and frontal brain regions, in particular in the mPFC, in a sample of adults with moderate to severe TBI, compared to TDC. However, the contrasting findings may be due to the age of the participants, as this study included adolescents and the study by Rigon et al. (2017) was conducted in an adult sample. In sum, higher levels of functional connectivity in the TBI group as observed in our study (i.e., positive connectivity involving frontal brain regions), may reflect a failure in decoupling anterior brain areas indicative of more effortful processing (Price & Friston, 2002; Sharp et al., 2011).

From a developmental perspective, SBN regions, including prefrontal brain regions and the fusiform gyri, have been shown to undergo protracted structural and functional changes and specialization throughout infancy and into late childhood and adolescence (Blakemore, den Ouden, Choudhury, & Frith, 2007; Burnett, Bird, Moll, Frith, & Blakemore, 2009). In addition, such developmental changes are often paralleled by a valence switch of functional connectivity patterns, from positive to negative connectivity in brain areas involved in regulatory functions, including the PFC (Gabard-Durnam et al., 2014; Gee et al., 2013). Such changes in functional connectivity valence have been interpreted as a neurobiological mechanism for the development of regulatory functions, including inhibition and emotion regulation (Gabard-Durnam et al., 2014; Gee et al., 2013). This assumption finds further support in a study by Stephens et al. (2018) who found that children with TBI had less negative (i.e., anti-correlated) functional connectivity between the DMN and right Brodmann Area 40, associated with poorer response inhibition. Negative functional connectivity may be required for an optimal level of cognitive functioning, similarly to the present findings. It may thus be hypothesized that similar mechanisms might be at play with respect to frontal-fusiform connectivity patterns, and adolescents with TBI show more immature (positive) functional connectivity, whereas their uninjured counterparts may display more adult-like (negative) functional connectivity.

The fusiform gyrus, as well as several brain regions in the frontal lobe, have previously been shown to play a crucial role in affect recognition and processing, in particular facial affect recognition (Ganel, Valyear, Goshen-Gottstein, & Goodale, 2005). Socio-cognitive functions such as affect recognition have been shown to be impaired following moderate to severe TBI (McDonald, 2013; Ryan, Catroppa, Cooper, Beare, Ditchfield, Coleman, Silk, Crossley, Beauchamp, et al., 2015) and may therefore contribute to more general social dysfunction after TBI (Neumann, McDonald, West, Keiski, & Wang, 2016;

Rosenberg, Dethier, Kessels, Westbrook, & McDonald, 2015). However, given no socio-cognitive tasks were included in the present study, any association between the resting-state fusiform findings and altered affect recognition remains speculative. While this study suggests that abnormal functional connectivity within the SBN, and specifically frontal-fusiform connectivity, is present after TBI, future studies are needed to investigate any postulated associations with social functioning by using combined neuroimaging and behavioral designs.

#### 4.1 | Strengths and limitations

The present study is the first to examine resting-state functional connectivity alterations within the SBN after moderate to severe pediatric TBI and contributes to our understanding of social impairment after TBI, a problem that is increasingly recognized but for which the neural mechanisms remain obscure. This research is novel in that it focused specifically on the social brain and used two ROI-based analyses in two different samples of adolescents with TBI. Largely consistent results in both samples illustrate the robustness of the findings. Using two different samples enhances the generalizability of the findings and all data were acquired on the same scanner, excluding scanner bias. We further controlled for age, sex, total GM volume and SES in both samples, in addition to selecting only few ROIs for the analyses, thus applying a conservative approach.

Nonetheless, some limitations need to be considered. Using different samples introduced some heterogeneity and potential bias. RsfMRI did not take place in the same time span post-injury and the TBI replication sample was slightly older. It is possible that different neural reorganization mechanisms were underway in the two samples and conclusions regarding functional connectivity at different injury stages are not possible. However, consistent frontal-fusiform associations in both groups support the observation that similar aberrant functional connectivity within the SBN is present independent of these age variables. Age was included as a covariate in all analyses to control for possible age effects on the results.

The lack of significant associations between functional connectivity and behavior may be a result of the small sample sizes and therefore the lack of statistical power to detect potential brain-behavior correlations. The absence of such associations may also be due to the general measure of behavior/social skills that was used (parent questionnaire, CBCL). Using direct child-measures would facilitate testing of specific social impairments.

Last, the two groups differed significantly in terms of SES. While SES was controlled for in all analyses, it is possible that preexisting differences may partly explained functional connectivity differences. Longitudinal studies are needed to explore such a link more specifically and how functional connectivity evolves over time.

Future research could expand on the present findings using more systematic studies on SBN alterations following TBI and larger, more homogeneous samples in longitudinal studies to determine how functional connectivity evolves over time and to explore putative associations with social skills.

## 5 | CONCLUSION

The study brings to light alterations in both intra- and interhemispheric connections within the SBN after TBI involving the fusiform gyrus bilaterally. Failure to deactivate frontal areas may be associated with more effortful and inefficient processing after TBI. In addition, differences in functional connectivity could point to altered developmental mechanisms following TBI. Despite the lack of association between altered functional connectivity and behavior in this study, the present findings suggest that abnormal frontal-fusiform connectivity after moderate to severe TBI in adolescence may reflect differences in facial affect recognition, emotion dysregulation and more global social difficulties as reported in other studies. The findings provide a basis for future efforts to establish the utility of resting-state functional connectivity as a potential marker of social dysfunction following TBI and to disentangle the complex mechanisms involved in adverse social functioning using combined neuroimaging-behavioral designs that investigate associations with social skills.

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## CONFLICT OF INTEREST

The authors report no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## ORCID

Carola Tuerk  <https://orcid.org/0000-0002-0910-846X>

Fanny Dégeilh  <https://orcid.org/0000-0002-5802-4975>

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