DEAKIN UNIVERSITY

Social Cognitive Dysfunction following Pediatric Arterial Ischemic Stroke: Evidence from a Prospective Cohort Study

AUTHOR(S)

Nicholas Ryan, M Greenham, A L Gordon, M Ditchfield, L Coleman, A Cooper, L Crowe, R W Hunt, P Monagle, M T MacKay, V Anderson

PUBLICATION DATE

01-05-2021

HANDLE

10536/DRO/DU:30149972

Downloaded from Deakin University's Figshare repository

Deakin University CRICOS Provider Code: 00113B

Stroke

ORIGINAL CONTRIBUTION

Social Cognitive Dysfunction Following Pediatric Arterial Ischemic Stroke

Evidence From a Prospective Cohort Study

Nicholas P. Ryan, PhD*; Mardee Greenham, PhD*; Anne L. Gordon, PhD; Michael Ditchfield, PhD; Lee Coleman, PhD; Anna Cooper, PhD; Louise Crowe, PhD; Rod W. Hunt, PhD; Paul Monagle, PhD; Mark T. Mackay, PhD; Vicki Anderson, PhD

BACKGROUND AND PURPOSE: Childhood and adolescence coincide with rapid maturation of distributed brain networks supporting social cognition; however, little is known about the impact of early ischemic brain insult on the acquisition of these skills. This study aimed to examine the influence of arterial ischemic stroke (AIS) on facial emotion recognition and theory of mind (ToM) abilities of children and adolescents initially recruited to a single-center, prospective longitudinal study of recovery following AIS.

METHODS: The study involved 67 participants, including 30 children with AIS (mean time since stroke=5 years) and 37 age-matched typically developing controls who were assessed on measures of cognitive ToM, facial emotion recognition, and affective ToM. Acute clinical magnetic resonance imaging, including diffusion-weighted imaging sequences, were used to evaluate prospective structure-function relationships between acute lesion characteristics (size, location, and arterial territories affected) and long-term social cognitive abilities.

RESULTS: Relative to age-matched typically developing controls, children with AIS showed significantly worse performance on measures of basic facial emotion processing, cognitive ToM, and affective ToM. In univariate models, poorer ToM was associated with larger infarcts, combined cortical-subcortical pathology, and involvement of multiple arterial territories. In multivariate analyses, larger lesions and multiterritory infants were predictive of ToM processing but not facial emotion recognition. Poorer cognitive ToM predicted less frequent prosocial behavior and increased peer problems.

CONCLUSIONS: Social cognitive skills appear vulnerable to disruption from early ischemic brain insult. In the first study to examine social cognition in a prospective cohort of children with AIS, our findings suggest that acute magnetic resonance imaging-based lesion characteristics may have predictive value for long-term social cognitive outcomes and may assist to identify children at elevated risk for social cognitive dysfunction.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: adolescent ■ child ■ emotion ■ social cognition ■ theory of mind

Social cognition is a multifaceted construct that involves the ability to encode and interpret a range of social cues, including language, intonation, and nonverbal cues (eg, facial expression, eye gaze, and gesture).[1,2] Although foundational social cognitive skills emerge within the first days of life,[3–5] complex aspects of social cognition show protracted maturation through to mid-to-late adolescence,[6–8] corresponding to the structural and functional maturation of distributed neural networks involving frontotemporal, limbic, and temporo-occipital brain regions.[9,10] Although neurological insult during critical periods of brain development has potential to perturb the acquisition of social cognitive skills,[11] little is known about

Correspondence to: Nicholas P. Ryan, PhD, Murdoch Children's Research Institute, Flemington Rd, Parkville, Victoria, 3052, Australia. Email nicholas.ryan@mcri.edu.au
*N.P. Ryan and M. Greenham contributed equally.
For Sources of Funding and Disclosures, see page xxx.
© 2021 American Heart Association, Inc.
Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

AIS	arterial ischemic stroke
MRI	magnetic resonance imaging
SDQ	Strengths and Difficulties Questionnaire
TDC	typically developing control
ToM	theory of mind

the influence of early ischemic brain injury on the acquisition of these competencies.

Arterial ischemic stroke (AIS) is a relatively rare cause of childhood disability with an incidence of 1.3 to 13.0 per 100 000 children and 1 per 1200 live births in neonates.[12,13] Pediatric AIS has been linked to a range of physical,[14,15] cognitive,[16] and behavioral impairments,[17–19] with evidence suggesting that early ischemic brain insults confer a heightened vulnerability to deficits in skills that are emerging or not yet fully developed at the time of stroke. With respect to social cognition, ischemic brain lesions have potential to disrupt connectivity within the putative social brain network; a distributed neural system characterized by complex interactions among frontotemporal, mesolimbic, temporo-occipital, and cerebro-cerebellar circuitry.[6,9,20,21] Although previous research suggests that social cognitive skills supported by this network may be vulnerable to the effects of diffuse childhood traumatic brain injury,[22–24] the long-term social cognitive consequences of pediatric AIS are poorly delineated.

To date, only one study has examined social cognition in children with a history of stroke. In this small retrospective pilot study, Lo et al[25] used functional magnetic resonance imaging (MRI) to evaluate the neural correlates of social cognition in 10 children diagnosed with hemorrhagic or ischemic stroke. Relative to typically developing controls (TDCs), the stroke group performed significantly worse on a tasks involving theory of mind (ToM); a complex social cognitive skill that involves the ability to infer another person's thoughts, beliefs, intentions, and feelings.[26–28] Contrary to predictions, the study found no significant association between reduced ToM performance and changes to resting-state connectivity within the default mode, salience, or mirror neuron empathy network.[25]

Although preliminary findings from Lo et al[25] are the first to suggest that childhood stroke may confer elevated risk for social cognitive dysfunction, the results raise several unresolved questions about the nature, correlates, and functional impact of poststroke social cognitive impairment. First, it remains unclear whether the presence of poststroke social cognitive deficits may underlie impairments in social behavior and functioning, which are consistently documented following child stroke.[17,29] Second, there are substantial limits to the generalizability of Lo et al's[25] small retrospective study of ToM in 10 child stroke cases. Given that AIS has potential to disrupt maturation of distributed neural circuitry supporting a range of distinct but overlapping social cognitive abilities, larger prospective studies are needed to identify stroke-related characteristics that may be predictive of long-term outcomes across multiple social cognitive domains, including basic social processing (eg, facial emotion recognition) and more complex forms of social understanding (eg, ToM).

The impact of brain lesion characteristics on social cognitive skills has seldom been studied in childhood and adolescence; periods that coincide with rapid maturation of neural circuitry supporting social cognition.[7,8] Although the medial prefrontal and lateral temporal cortices are critical for social perceptual and cognitive processes,[30,31] lesions in these regions are unlikely to predict social cognitive dysfunction in children for whom these regions are undergoing rapid maturation and possess relatively limited functional specificity.[32,33] Consistent with this view, previous studies of diffuse childhood TBI suggest that, irrespective of lesion location, larger, and more diffuse lesions are predictive of higher-order cognitive outcomes, including ToM.[11,34] Given that social cognition is dependent on frontal-temporal, temporo-occipital, and cerebro-cerebellar circuitry that extends across multiple arterial territories,[35] a network paradigm of social cognitive disturbance would predict poorer outcomes to be documented in association with larger lesions and diffuse infarcts involving multiple arterial territories.[36] Although previous studies of child stroke populations have linked poorer executive functioning to large infarcts and combined cortical-subcortical lesions,[16,18,37–39] no existing studies have evaluated the predictive value of infarct characteristics for long-term social cognitive outcomes of children with AIS.

To address the dearth of literature concerning the effect of early ischemic brain insult on social cognitive abilities, this prospective cohort study aimed to characterize the nature, correlates, and functional impact of social cognitive dysfunction in children and adolescents with MRI-confirmed acute AIS. Specifically, we sought to disentangle the effects of pediatric AIS on cognitive ToM, concerned with understanding other's thoughts, intentions, and beliefs; affective ToM, which involves the ability to infer what others' are feeling based on specific social context[40] and basic facial emotion recognition, which involves the ability to recognize basic emotions from facial features. We also aimed to examine whether specific stroke characteristics (ie, lesion size, lesion location, and number of vascular territories affected) explain individual differences in social cognitive outcomes and explore the association between social cognition and everyday social functioning in children with AIS.

We expected the following: (1) compared with age-matched TDCs, children with AIS will display poorer ToM and facial emotion recognition; (2) lower scores on tests of

Stroke

ToM and facial emotion recognition would be associated with larger lesions, multiterritory infarcts, and combined cortico-subcortical pathology; (3) lower ToM and facial emotion recognition would correlate with less frequent prosocial behavior and increased peer problems on standardized parent-report measures of social functioning.

METHODS

Source data will not be made available since no patient approval was obtained for sharing anonymized data. However, detailed analytic methods and study materials, including output files of statistical analyses, will be made available to other researchers on request to the first author.

Participants

This study reports data from a 5-year follow-up of children enrolled in a larger prospective, longitudinal study[41] evaluating recovery in the first 12 months following MRI-confirmed acute ischemic parenchymal infarction corresponding to ≥1 arterial territories. Children were aged 0 to 18 years at recruitment and represented consecutive admissions to The Royal Children's Hospital Melbourne between December 2007 and January 2012. Exclusion criteria included previously diagnosed stroke, primarily hemorrhagic infarction, coexisting diffuse brain injury due to a traumatic or hypoxic-ischemic event, and birth before 36 weeks gestation. Children for whom English was a second language were also excluded. Ethics approval was obtained for this study from the Human Research Ethics Committee (HREC) of the Royal Children's Hospital Melbourne. Written consent was obtained by parents for their participation and that of their children.

Forty-one families were approached to participate in the 5-year follow-up. Three declined with no reason given and four families were untraceable. One participant was excluded due to unexplained developmental regression unrelated to the stroke. Two participants had substantial missing data, and 1 was 20-years of age at follow-up and did not have all social cognition measures administered. Therefore, this paper reports on the 5-year follow-up outcomes for 30 children with AIS and 37 TDCs recruited from the local community. Children were excluded from the TDC group if they had previous stroke, any neurological or psychological disorder, or English as a second language. Among those who underwent social cognitive testing at the 5-year follow-up, none of the children in the AIS or TDC groups had a comorbid neurodevelopmental or psychiatric diagnosis at the time of initial study enrollment or at the 5-year follow-up assessment.

Measures

Clinical MRI

Clinical brain MRI, including diffusion-weighted sequences, were conducted at the Royal Children's Hospital Melbourne on acute admission, using a standardized clinical protocol. Infarct characteristics (size, location, laterality, arterial territory) were rated by 2 neuroradiologists (M.D., L.C.) and the study Principal Investigator (A.G.), using a standardized coding system.[41,42] In keeping with our standardized coding system reported elsewhere,[41,43] lesion size was classified according to degree of vascular territory affected upon visual assessment. For example, infarcts were coded small when structures served by small perforating branches of arteries were affected (eg, discrete area of injury to structures supplied by lenticulostriate arteries). Infarcts were coded medium when a branch of a major cerebrovascular artery (eg, temporal arteries) was affected, and large denoted cases where an entire vascular territory was affected. Stroke location was qualitatively coded and categorized as cortical, subcortical (including white matter/subcortical nuclei/thalamus), combined cortico-subcortical, or cerebellar/brain stem. This coding system also allowed us to distinguish between children with supratentorial infarcts only (ie, cortical, combined cortico-subcortical, or discrete subcortical lesions) and those participants with infratentorial infarcts only (ie, cerebellar/brain stem lesions).

Neurological Function

Acute neurological impairment was assessed with the Pediatric Stroke Outcome Measure (PSOM),[44,45] a clinically administered tool that rates stroke severity from 0 (no deficits) to 10 (severe deficit). The PSOM is composed of 5 subscales (right sensorimotor, left sensorimotor, language production, language production, and cognition/behavior) that use ordinal scales ranging from 0 to 2 (0=none; 0.5=mild; 1=moderate; 2=severe). PSOM was administered within the first week after diagnosis by a pediatric occupational therapist. Consistent with the approach adopted in previous research,[17] we divided the stroke group into 2 groups; low severity and high severity, based upon the total PSOM score. The low severity group had a total PSOM score of 0 to 1.0; the high severity group had scores of ≥1.5.

Primary Outcomes

Social cognition was assessed across 3 domains using tasks from the Developmental NEuroPSYchological Assessment - Second Edition (NEPSY-II) Social Perception battery.[46]

Cognitive ToM

The NEPSY-II ToM Verbal Task was used to assess cognitive ToM, reflected in the child's understanding of others' beliefs and intentions. In this task, the child is read social stories or shown pictures depicting a variety of social scenes. The child is then asked questions about the protagonist's beliefs and intentions. In all the items, the child can answer very briefly; a word is often sufficient for a correct answer. The total number of correct responses is converted to a percentage accuracy score for statistical analyses, which adjust for child age.

Affective ToM

The NEPSY-II ToM Contextual Task was used to evaluate affective ToM, reflected in the child's understanding of others' emotions in social context.[47] In this task, the child is shown a series of drawings depicting children in a range of social contexts. In each drawing, there is a protagonist whose face is not shown. The child is provided with 4 photographs of different facial emotions and asked to select the face that depicts the protagonist's feeling in a specific social scenario. Thus, the child is required to infer the child's emotion based on social context, not their face. The total number of correct responses is converted to a percentage accuracy score for statistical analyses, which adjust for child age.

Stroke

Facial Emotion Recognition

The NEPSY-II Emotion Recognition Task evaluated the child's ability to process basic emotions from facial features. In this task, the child is asked to discriminate between basic facial expressions by comparing pictures of faces of children with typical facial expressions including joy, sadness, anger, disgust, fear, and a neutral expression. The child must decide if 2 expressions are similar or different, determine which faces have similar expressions among a series of faces, and identify 2 children with expressions similar to that of a third face. The child's performance is converted to a standard score for use in statistical analyses (mean=10; SD=3). Higher scores indicate better performance.

Social Functioning

Parents rated their child's social behavior using the Strengths and Difficulties Questionnaire (SDQ).[48] The SDQ is a parent-rated questionnaire that measures behavior and emotional symptoms across 5 domains: emotional symptoms, conduct problems, hyperactivity, peer problems, and prosocial behavior. Each of these 5 scales contains items on which parents rate their child on a 3-point scale according to how much an attribute applies to the child (0, 1, or 2 for each item). For the current study, social behavior was assessed using the Peer Problem and Prosocial Behavior scales, which are those that most directly assess social functioning.

Statistical Analysis

All analyses were entered into SPSS Version 25.0 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. For primary outcome analyses, performance for each of the 3 social cognitive tasks (facial emotion recognition, cognitive ToM, affective ToM) was examined separately. In addition to the individual task scores, performance on the cognitive and affective ToM tasks are summed to provide a ToM composite score, which provides an overall indicator of ToM.

Social cognition data for the entire sample were analyzed using multivariate ANCOVA (MANCOVA) with Group Membership (AIS versus TDC) as the between-subjects factor and social cognitive domain (facial emotion recognition versus cognitive ToM versus affective ToM) as the within-subjects factors, with follow-up post hoc pairwise comparisons. For all analyses involving the primary outcome measures, we acknowledged factors previously shown to influence social outcomes after acquired brain insult, including sex, socioeconomic status, and age. Taking these factors into account, all analyses were performed with these variables entered as covariates. Effect sizes were calculated using partial eta squared (η^2; small effect $\eta 2$=0.01; medium effect η^2=0.059; large effect η^2=0.138).

To examine the effect of lesion characteristics on different aspects of social cognition, data for the entire sample were analyzed using MANCOVA with lesion subgroup as the between-subjects factor and social cognitive task (facial emotion recognition versus cognitive ToM versus affective ToM) as the within-subjects factors, with follow-up post hoc pairwise comparisons. In these models, social cognitive abilities were examined in relation to the following neuroradiological factors: (1) lesion size (TDC versus medium infarcts versus large infarcts); (2) lesion location (TDC versus discrete subcortical/cerebellar versus combined cortico-subcortical lesions); and (3) number of arterial territories involved (TDC versus single territory versus multiterritory infarcts).

Finally, multivariable regression models were used to explore the independent contribution of all stroke characteristics (lesion size, location, number of arterial territories, and severity of acute neurological symptoms) to social cognitive outcomes. Exploratory analyses of the association between social cognition and everyday social function were conducted using multilinear regressions covarying for age, sex, and maternal SES.

RESULTS

Sample Characteristics

This article reports outcome data for 67 participants, including 30 individuals with pediatric AIS and 37 TDC children. As shown in Table 1, the AIS and TDC groups did not differ in age at assessment or sex. Maternal SES was higher in the TDC group and was used as a covariate in all analyses involving the primary outcome variable. None of the children in the stroke group had epilepsy or were taking seizure medication at the time of the 5-year follow-up assessment.

Table 2 presents the clinical and radiological findings of the stroke group at time of diagnosis. Infarcts were discrete subcortical in 9 children (30%), combined cortico-subcortical in 16 (53%), and discrete brain stem/cerebellar in 5 children (17%). Twenty-3 children had strokes involving a single arterial territory, whereas the remaining 7 children had multiterritory infarcts. Of note, age at stroke was not associated with lesion characteristics, including lesion size (*P*=0.279), number of vascular territories involved (*P*=0.737), or the presence of combined cortico-subcortical pathology (*P*=0.201). Eleven children (37%) had a cardioembolic cause, 3 children (10%) had Moya Moya syndrome, 2 children (7%) had cervical arterial dissection, 4 children (13%) had steno-occlusive arteriopathy,

Table 1. Sample Demographic Characteristics

	AIS	TDC	*F/X*^{2}	*P* value
No. of children	30 (12 neonatal)	37	…	…
Sex (male), n (%)	18 (60)	15 (40)	2.51	0.144
Maternal SES, mean (SD)	2.93 (1.11)	3.76 (1.04)	9.78	0.003
Age at assessment, y, mean (SD)	7.85 (3.12)	7.80 (2.79)	0.01	0.94

SES is socioeconomic status: 1=9th grade or less; 2=10th/11th grade; 3=high school graduate; 4=partial degree/professional qualification; 5=college/university graduate; 6=postgraduate degree. AIS indicates arterial ischemic stroke; SES, socioeconomic status; and TDC, typically developing control

Stroke American Heart Association.

Table 2. Clinical and Neuroradiological Characteristics

	AIS group: n=30
Age at diagnosis, median (IQR)	1.45 (4.04)
Time since diagnosis, y, mean (SD)	5.26 (0.76)
Lesion characteristics	
Lesion size	
Large, n (%)	6 (20)
Medium, n (%)	24 (80)
Small, n (%)	0 (0)
Vascular territory	
Full MCA, n (%)	1 (3)
Partial MCA, n (%)	13 (43)
PCA, n (%)	5 (17)
Vertebrobasilar, n (%)	4 (13)
Multiterritory, n (%)	7 (23)
Location	
Combined cortico-subcortical, n (%)	16 (53)
Discrete subcortical, n (%)	9 (30)
Discrete cerebellar/brain stem, n (%)	5 (17)
Laterality	
Left n (%)	9 (30)
Right n (%)	10 (33)
Bilateral n (%)	6 (20)
Infratentorial only n (%)	5 (17)
Acute PSOM total score, median (IQR)	0.75 (2.0)
Acute PSOM high severity, n (%)	11 (37)
Acute PSOM low severity, n (%)	19 (63)

IQR indicates interquartile range; MCA, middle cerebral artery; PCA, posterior cerebral artery; and PSOM, Pediatric Stroke Outcome Measure.

Stroke

1 child (3%) had multiple probable causes, and 9 children (30%) had unknown risk factors. On acute neurological examination, most stroke participants (63%) had mild-moderate deficits based on the PSOM total score; the median total PSOM score was 0.75 (interquartile range, 2.0).

Social Cognition 5 Years Poststroke

Table 3 displays the means and SDs for the AIS and TD groups for each social cognitive task. The overall MANCOVA was significant after controlling for SES, sex, and age, F=3.88, P=0.01, η^2=0.170. There was a significant main effect of group on all social cognition measures. As shown in Table 3, children with stroke performed significantly worse than TDCs on the ToM composite measure. Group differences also reached statistical significance when cognitive and affective ToM tasks were examined separately, such that children with stroke displayed significantly poorer cognitive and affective ToM. Compared with TDCs, the stroke group also displayed significantly poorer facial emotion recognition abilities (Table 3).

Predictors of Social Cognition: Univariate Models

Preliminary analyses involving the entire sample (AIS and TDC) were used to examine whether infarct characteristics (size, location, and number of arterial territories involved) were related to social cognitive performance. Each of the lesion subgroups did not differ from TDCs on age at assessment or maternal SES (all P>0.10).

Impact of Lesion Size

The overall MANCOVA was significant after controlling for SES, sex, and age, F=4.26, P=0.009, η^2=0.110. Lesion size was significantly associated with affective ToM, F(2,66)=6.13, P=0.004, such that children with large-sized lesions performed significantly worse than both the TDC group (P=0.001) and children with medium-sized lesions (P=0.005). There was no main effect of lesion size on any other measure of social cognition (η^2 effect size range: 0.04–0.09).

Impact of Lesion Location

The overall MANCOVA was significant after controlling for SES, sex, and age, F=5.47, P=0.002, η^2=0.12. There was a significant main effect of lesion location on affective ToM (F[2,66]=6.16, P=0.004), cognitive ToM (F[2,66]=7.52, P=0.001), and ToM composite scores (F[2,66]=7.97, P=0.001). In all these models, pairwise comparisons revealed that children with combined cortico-subcortical lesions had significantly worse scores than both the TDC group (all P<0.01) and children with discrete subcortical/cerebellar lesions (all P<0.01). There was no main effect of lesion location on facial affect recognition (F[2,66]=2.38, P=0.10).

Impact of Number of Arterial Territories

The overall MANCOVA was significant after controlling for SES, sex, and age, F=4.10, P=0.01, η^2=0.17. There was a significant main effect of arterial territory on affective ToM (F[2,66]=4.94, P=0.010), cognitive ToM (F[2,66]=5.69, P=0.005), and ToM composite scores (F[2,66]=5.91, P=0.005). In all these models, pairwise comparisons revealed that children with multiterritory infarcts had significantly worse scores than both the TDC group (all P<0.01) and children with single territory infarcts (all P<0.05). There was no main effect of lesion location on facial affect recognition (F[2,66]=2.14, P=0.13).

Predictors of Social Cognition: Multivariate Models

As shown in Table 4, multiple regression models were performed to evaluate the relative contribution of various stroke-related factors to social cognition outcomes. Age, sex, and maternal SES were also added to the models as covariates. Multicollinearity between variable sets was checked by examining the variance inflation factor of the variables within regression models. None of the variance

Table 3. Effect of AIS on Social Cognition

	AIS	TDC	*F*	*P* value	η^2
Basic social processing					
Emotion recognition, M (SD)	9.87 (2.24)	10.95 (2.11)	4.65	0.035	0.07
Complex social processing					
Cognitive ToM, M (SD)	61.21 (21.74)	72.35 (17.63)	9.59	0.003	0.14
Affective ToM, M (SD)	66.67 (26.26)	76.56 (16.86)	5.09	0.028	0.08
ToM composite, M (SD)	62.38 (21.11)	72.19 (15.94)	8.72	0.005	0.13

AIS indicates arterial ischemic stroke; M, mean; TDC, typically developing control; and ToM, Theory of Mind.

inflation factors exceeded a conservative cutoff of 2, suggesting that multicollinearity was not problematic.[49]

For the ToM composite, the overall model including all predictors was significant, $F(6,29)=8.302$, $P<0.001$, $R^2=0.725$. As shown in Table 4, multiterritory infarcts uniquely predicted poorer ToM performance. Similarly, the overall model for the Cognitive ToM was also significant, $F(6,29)=7.007$, $P<0.001$, $R^2=0.690$. Multiterritory infarcts independently predicted poorer cognitive ToM, but lesion location, lesion size, and severity of acute neurological symptoms did not. For affective ToM, the overall model was significant, $F(6,29)=3.931$, $P=0.006$, $R^2=0.556$. Large-sized lesions and multiterritory infarcts uniquely predicted poorer affective ToM processing.

For facial emotion recognition, the overall model was not statistically significant, $F(6,29)=.45$, $P=0.84$, $R^2=0.106$, with no independent predictors of outcome (Table 4).

Associations Between Social Cognitive Task Performance and Parent-Reported Social Functioning

As shown in Table 5, multiple linear regressions were performed to evaluate the independent contribution of social cognition to everyday social functioning in the stroke group. After covarying for age, sex, and maternal SES, poorer cognitive ToM was predictive of more frequent peer problems based on parent reports. Similarly, poorer cognitive ToM was associated with less frequent prosocial behavior as rated by parents.

DISCUSSION

Despite a growing body of research linking pediatric AIS to increased risk of neurodevelopmental dysfunction,[19,50] little is known about the impact of early focal ischemic brain injury on social cognitive functions. In the first prospective study to quantify the effect of pediatric AIS on facial emotion recognition and ToM, this study sought to evaluate nature, correlates, and functional impact of social cognitive dysfunction in a consecutive sample of children with MRI-confirmed AIS. As expected, we found that relative to TDCs, children with AIS displayed poorer social cognitive abilities across measures of cognitive ToM, basic facial emotion processing, and affective ToM. Poorer social cognitive outcomes were documented in association with combined cortico-subcortical lesions, multiterritory infarcts, and large-sized

Stroke

Table 4. Multivariate Regression Models Predicting Social Cognition From Stroke Characteristics

	Emotion recognition			Cognitive ToM			Affective ToM			ToM composite		
	B	SE	*P* value	B	SE	*P* value	β	SE	*P* value	β	SE	*P* value
Lesion Size												
Medium	(ref)			(ref)			(ref)			(ref)		
Large	−0.69	1.23	0.581	−0.302	1.57	0.849	−1.55*	0.621*	0.02*	−1.86	1.83	0.322
Lesion location												
Discrete subcortical/cerebellar	(ref)			(ref)			(ref)			(ref)		
Combined cortico-subcortical	0.51	1.22	0.679	−2.53	2.06	0.231	−0.25	0.69	0.718	−2.78	2.47	0.271
Vascular territory												
Single territory infarct	(ref)			(ref)			(ref)			(ref)		
Multiterritory infarct	−1.26	1.41	0.381	−4.26*	1.58*	0.013*	−1.35*	0.623*	0.041*	−5.61	1.84	0.006*
Acute PSOM total score												
Low severity	(ref)			(ref)			(ref)			(ref)		
High severity	0.19	0.21	0.361	1.84	1.24	0.151	0.4	0.488	0.42	2.24	1.44	0.134

Covariates in all models: age, sex, maternal socioeconomic status. β indicates unstandardized beta coefficient; PSOM, Pediatric Stroke Outcome Measure; and ToM, theory of mind.

*$P<0.05$.

Table 5. Multilinear Regressions Predicting Everyday Social Functioning From Social Cognition

	SDQ prosocial behavior			SDQ peer problems		
	β	SE	*P* value	B	SE	*P* value
Facial emotion recognition	−0.036	0.139	0.797	−0.018	0.11	0.868
Cognitive ToM	0.182	0.087	0.047	−0.158	0.07	0.033
Affective ToM	0.125	0.227	0.587	−0.18	0.184	0.337
ToM composite	0.136	0.072	0.071	−0.126	0.058	0.038

Covariates in all models: age, sex, maternal socioeconomic status. SDQ indicates Strengths and Difficulties Questionnaire; and ToM, theory of mind.

lesions. As predicted, we also found that poorer cognitive ToM was associated with less frequent prosocial behavior and increased peer problems reported on standardized parent-report measures.

Although impairments in social cognition are recognized as one of the most profound and disabling sequelae in children with traumatic brain injury,[11,51] these outcomes have seldom been studied in children with AIS. To address the dearth of research in this area, our first aim was to quantify the long-term impact of pediatric AIS on basic and complex social cognitive abilities. In line with predictions, we found that relative to TDCs, children with AIS displayed significantly worse performance on measures of cognitive ToM, basic facial emotion processing, and affective ToM. These findings are broadly consistent with previous findings from a small retrospective pilot study, which provided the first evidence for ToM impairment in a sample of 10 children with hemorrhagic or ischemic stroke.[25] Overall, findings from our prospective consecutive cohort add to an emerging body of evidence suggesting that social cognitive abilities are vulnerable to the effects of early ischemic brain insult[25] and suggest that social cognitive impairments are evident many years postdiagnosis following stabilization of neurological functioning.

Our second aim was to assess whether specific stroke characteristics accounted for individual differences in social cognitive abilities. Univariate analyses revealed that when examined in isolation, poorer ToM abilities were associated with larger lesions, a combined cortico-subcortical lesion pattern, and multiterritory infarcts. Although this pattern of results is broadly consistent with previous studies of other poststroke cognitive outcomes,[16,18,37–39] we found that lesion characteristics were predictive of ToM, but not basic facial emotion-processing abilities. Although unexpected, this pattern of results is likely explained by developmental factors.[32] Specifically, a critical period model[52] would hypothesize that, in contrast to complex ToM which shows protracted maturation into mid-late adolescence,[6] basic facial emotion-processing skills are likely to be relatively well established at the time of ischemic insult and, therefore, less vulnerable to persisting, long-term disruption.[11] Overall, our findings suggest that, at least for higher-order social cognitive skills, such as ToM, early clinical MRI-based indicators, may have some prognostic value for long-term social cognitive outcomes in children with AIS.

Interestingly, when all stroke-related factors were examined together in multivariate regression models, multiterritory infarcts and larger lesions were unique predictors of ToM, even after adjusting for acute neurological symptoms as measured by the PSOM. Given that ToM is dependent on distributed frontal-temporal, temporo-occipital, and cerebro-cerebellar circuitry that is irrigated by middle cerebral artery, posterior cerebral artery, and vertebrobasilar circulation,[35] it is perhaps not surprising that poorer ToM was documented in association with infarcts in multiple arterial territories. In contrast, and despite the critical role of cortical brain regions in social cognitive processes,[30,31] the presence of cortical pathology did not independently contribute to poorer ToM in multivariate regression models. Overall, the pattern of structure-function relationships in our stroke sample converges to suggest that, irrespective of lesion location, variation in complex social cognitive outcomes is at least partly explained by the amount of structural brain pathology to distributed neural networks involved in complex social cognitive skills.[11,34]

Our third and final aim was to explore the independent contribution of social cognitive abilities to everyday social functioning in children with AIS. Although social cognitive impairments are linked to worse social adjustment in adult stroke survivors,[53,54] these associations remain largely unexplored in pediatric stroke populations. In keeping with expectations, we found that poorer cognitive ToM was predictive of less frequent prosocial behavior and increased peer problems on standardized parent-report measures. Overall, these findings suggest that social cognitive dysfunction may be one of several factors that underpins everyday social and behavioral impairments commonly documented in children with AIS.[17,29] Since social cognitive dysfunction appears to be a risk factor for poorer social functioning in our sample, social cognitive screening may be a valuable supplement to routine clinical neuropsychological assessments, which are often used to evaluate post-stroke recovery and help guide intervention planning in this high-risk population.

Stroke

Although the current study represents the largest prospective investigation of long-term social cognitive outcomes of children with AIS, our analyses were constrained by small sample size. For instance, due to the small number of patients with cerebellar involvement, we did not have adequate statistical power to evaluate social cognitive outcomes of this subgroup separately. Although our lesion location groupings (ie, combined cortico-subcortical versus discrete lesions) are consistent with the broader literature that distinguishes between outcomes of diffuse versus focal developmental lesions,[55] further research in larger samples is needed to examine whether cerebellar involvement may differentially affect social cognitive development in children with AIS. Similarly, due to small number of participants in the neonatal and childhood-onset AIS subgroups, further research is needed to examine whether the magnitude of the effect of AIS on social cognitive abilities differs as a function of developmental stage at stroke.

Moreover, although our study is the first to highlight the prognostic value of acute clinical MRI for long-term social cognitive outcomes, the study is limited by its sole reliance on a standardized coding system for clinically acquired images. This standardized coding protocol has been reported previously[41,43] and involves visual assessment of lesion size coded independently by 2 pediatric neuroradiologists. Further research is, therefore, needed to evaluate the prognostic value of other quantitative measures of lesion size, including infarct volumes. Further studies using advanced structural brain imaging methods (eg, diffusion tensor imaging/tractography, voxel-based morphometry) are also needed to evaluate whether neuroanatomical changes within social cognitive neural networks may assist to explain individual variation in social cognitive outcomes after child stroke.

CONCLUSIONS

To our knowledge, this study is the first to examine social cognition and its correlates in a prospectively recruited sample of children with AIS. Our findings show that, relative to their typically developing peers, children with stroke display significantly poorer performance on measures of basic and complex social processing. Moreover, assessment of brain-behavior relationships revealed that multiterritory infarcts and larger lesions prospectively predicted poorer social cognition 5 years poststroke. Overall, these findings suggest that clinical MRI has potential to unlock prognostic markers that may aid identification of children at elevated risk for long-term social cognitive dysfunction. Evidence of robust relationships between social cognition and parent-reported social functioning underscores the potential value of social cognitive screening in pediatric stroke populations.

ARTICLE INFORMATION

Received October 5, 2020; final revision received December 17, 2020; accepted January 26, 2021.

Affiliations

Clinical Sciences, Murdoch Children's Research Institute, Melbourne, Australia (N.P.R., M.G., L.C., A.C, L.C., R.W.H., P.M., M.T.M., V.A.); School of Psychology, Deakin University, Geelong, Australia (N.P.R.); Department of Paediatrics, The University of Melbourne, Australia (N.P.R., A.C., R.W.H., P.M., M.T.M., V.A.); Paediatric Neuroscience Department, Evelina London Children's Hospital, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom (A.L.G.); Department of Population Health Sciences, Kings College London, United Kingdom (A.L.G.); Paediatric Imaging, Monash Children's Hospital, Melbourne, Australia (M.D.); Department of Radiology and Paediatrics, Monash University, Melbourne, Australia (M.D.); Department of Medical Imaging (L.C.), Department of Neonatal Medicine (R.W.H.), Department of Haematology (P.M.), and Department of Neurology (M.T.M.), and Department of Psychology (V.A.), The Royal Children's Hospital, Melbourne, Australia.

Acknowledgments

This work was supported by the Victorian Government Operational Infrastructure Support Program. The funding bodies did not play a role in the design of the study, collection, analysis, and interpretation of the data, or writing of the article.

Sources of Funding

This research received funding and infrastructure support from the Murdoch Children's Research Institute and Royal Children's Hospital, Melbourne.

Disclosures

Dr Mackay received funding outside the submitted work from the National Health and Medical Research Council (Grant ID APP1065794). The other authors report no conflicts.

American Stroke Association. A division of the American Heart Association.

Stroke

REFERENCES

1. McDonald S. New frontiers in neuropsychological assessment: assessing social perception using a standardised instrument, The Awareness of Social Inference Test. *Aust Psychol.* 2012;47:39–48.
2. Beauchamp MH, Anderson V. SOCIAL: an integrative framework for the development of social skills. *Psychol Bull.* 2010;136:39–64. doi: 10.1037/a0017768
3. Leppänen JM, Nelson CA. The development and neural bases of facial emotion recognition. *Adv Child Dev Behav.* 2006;34:207–246. doi: 10.1016/s0065-2407(06)80008-x
4. Rajhans P, Jessen S, Missana M, Grossmann T. Putting the face in context: body expressions impact facial emotion processing in human infants. *Dev Cogn Neurosci.* 2016;19:115–121. doi: 10.1016/j.dcn.2016.01.004
5. Grossmann T, Johnson MH. The development of the social brain in human infancy. *Eur J Neurosci.* 2007;25:909–919. doi: 10.1111/j.1460-9568.2007.05379.x
6. Dumontheil I, Apperly IA, Blakemore SJ. Online usage of theory of mind continues to develop in late adolescence. *Dev Sci.* 2010;13:331–338. doi: 10.1111/j.1467-7687.2009.00888.x
7. Choudhury S, Blakemore SJ, Charman T. Social cognitive development during adolescence. *Soc Cogn Affect Neurosci.* 2006;1:165–174. doi: 10.1093/scan/nsl024
8. Yurgelun-Todd D. Emotional and cognitive changes during adolescence. *Curr Opin Neurobiol.* 2007;17:251–257. doi: 10.1016/j.conb.2007.03.009
9. Blakemore SJ. The social brain in adolescence. *Nat Rev Neurosci.* 2008;9:267–277. doi: 10.1038/nrn2353
10. Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, Greenstein D, Clasen L, Evans A, Rapoport JL, et al. Neurodevelopmental trajectories of the human cerebral cortex. *J Neurosci.* 2008;28:3586–3594. doi: 10.1523/JNEUROSCI.5309-07.2008
11. Ryan NP, Catroppa C, Cooper JM, Beare R, Ditchfield M, Coleman L, Silk T, Crossley L, Beauchamp MH, Anderson VA. The emergence of age-dependent social cognitive deficits after generalized insult to the developing brain: a longitudinal prospective analysis using susceptibility-weighted imaging. *Hum Brain Mapp.* 2015;36:1677–1691. doi: 10.1002/hbm.22729
12. Mallick AA, O'Callaghan FJ. The epidemiology of childhood stroke. *Eur J Paediatr Neurol.* 2010;14:197–205. doi: 10.1016/j.ejpn.2009.09.006

13. Dunbar MJ, Kirton A. The incidence of perinatal stroke is 1: 1200 live births: a population-based study in Alberta Canada. *Stroke*. 2020;51:A51–A51.
14. Husson B, Hertz-Pannier L, Renaud C, Allard D, Presles E, Landrieu P, Chabrier S; AVCnn Group. Motor outcomes after neonatal arterial ischemic stroke related to early MRI data in a prospective study. *Pediatrics*. 2010;126:912–918. doi: 10.1542/peds.2009-3611
15. Cooper AN, Anderson V, Hearps S, Greenham M, Ditchfield M, Coleman L, Hunt RW, Mackay MT, Monagle P, Gordon AL. Trajectories of motor recovery in the first year after pediatric arterial ischemic stroke. *Pediatrics*. 2017;140:e20163870.
16. Hajek CA, Yeates KO, Anderson V, Mackay M, Greenham M, Gomes A, Lo W. Cognitive outcomes following arterial ischemic stroke in infants and children. *J Child Neurol*. 2014;29:887–894. doi: 10.1177/0883073813491828
17. Lo W, Gordon A, Hajek C, Gomes A, Greenham M, Perkins E, Zumberge N, Anderson V, Yeates KO, Mackay MT. Social competence following neonatal and childhood stroke. *Int J Stroke*. 2014;9:1037–1044. doi: 10.1111/ijs.12222
18. Everts R, Pavlovic J, Kaufmann F, Uhlenberg B, Seidel U, Nedeltchev K, Perrig W, Steinlin M. Cognitive functioning, behavior, and quality of life after stroke in childhood. *Child Neuropsychol*. 2008;14:323–338. doi: 10.1080/09297040701792383
19. Greenham M, Gordon A, Anderson V, Mackay MT. Outcome in childhood stroke. *Stroke*. 2016;47:1159–1164. doi: 10.1161/STROKEAHA.115.011622
20. Adolphs R. The social brain: neural basis of social knowledge. *Annu Rev Psychol*. 2009;60:693–716. doi: 10.1146/annurev.psych.60.110707.163514
21. Van Overwalle F, Baetens K, Mariën P, Vandekerckhove M. Social cognition and the cerebellum: a meta-analysis of over 350 fMRI studies. *Neuroimage*. 2014;86:554–572. doi: 10.1016/j.neuroimage.2013.09.033
22. Dennis M, Simic N, Agostino A, Taylor HG, Bigler ED, Rubin K, Vannatta K, Gerhardt CA, Stancin T, Yeates KO. Irony and empathy in children with traumatic brain injury. *J Int Neuropsychol Soc*. 2013;19:338–348. doi: 10.1017/S1355617712001440
23. Dennis M, Simic N, Bigler ED, Abildskov T, Agostino A, Taylor HG, Rubin K, Vannatta K, Gerhardt CA, Stancin T, et al. Cognitive, affective, and conative theory of mind (ToM) in children with traumatic brain injury. *Dev Cogn Neurosci*. 2013;5:25–39. doi: 10.1016/j.dcn.2012.11.006
24. Ryan NP, Catroppa C, Beare R, Silk TJ, Hearps SJ, Beauchamp MH, Yeates KO, Anderson VA. Uncovering the neuroanatomical correlates of cognitive, affective and conative theory of mind in paediatric traumatic brain injury: a neural systems perspective. *Soc Cogn Affect Neurosci*. 2017;12:1414–1427. doi: 10.1093/scan/nsx066
25. Lo W, Li X, Hoskinson K, McNally K, Chung M, Lee J, Wang J, Lu ZL, Yeates K. Pediatric stroke impairs theory of mind performance. *J Child Neurol*. 2020;35:228–234. doi: 10.1177/0883073819887590
26. Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a "theory of mind"? *Cognition*. 1985;21:37–46. doi: 10.1016/0010-0277(85)90022-8
27. Wellman HM. *The Child's Theory of Mind*. The MIT Press; 1992.
28. Perner J. *Understanding the Representational Mind*. The MIT Press; 1991.
29. Anderson V, Gomes A, Greenham M, Hearps S, Gordon A, Rinehart N, Gonzalez L, Yeates KO, Hajek CA, Lo W, et al. Social competence following pediatric stroke: contributions of brain insult and family environment. *Soc Neurosci*. 2014;9:471–483. doi: 10.1080/17470919.2014.932308
30. Adolphs R. The neurobiology of social cognition. *Curr Opin Neurobiol*. 2001;11:231–239. doi: 10.1016/s0959-4388(00)00202-6
31. Saxe R. Uniquely human social cognition. *Curr Opin Neurobiol*. 2006;16:235–239. doi: 10.1016/j.conb.2006.03.001
32. Johnson MH, Griffin R, Csibra G, Halit H, Farroni T, de Haan M, Tucker LA, Baron-Cohen S, Richards J. The emergence of the social brain network: evidence from typical and atypical development. *Dev Psychopathol*. 2005;17:599–619. doi: 10.1017/S0954579405050297
33. Johnson MH. Functional brain development in infants: elements of an interactive specialization framework. *Child Dev*. 2000;71:75–81. doi: 10.1111/1467-8624.00120
34. Power T, Catroppa C, Coleman L, Ditchfield M, Anderson V. Do lesion site and severity predict deficits in attentional control after preschool traumatic brain injury (TBI)? *Brain Inj*. 2007;21:279–292. doi: 10.1080/02699050701253095
35. Tatu L, Moulin T, Vuillier F, Bogousslavsky J. Arterial territories of the human brain. In: *Manifestations of Stroke*. Paciaroni M, Agnelli G, Caso V, Bogousslavsky J (eds). Karger Publishers; 2012:99–110.
36. Kennedy DP, Adolphs R. The social brain in psychiatric and neurological disorders. *Trends Cogn Sci*. 2012;16:559–572. doi: 10.1016/j.tics.2012.09.006
37. Hetherington R, Tuff L, Anderson P, Miles B, deVeber G. Short-term intellectual outcome after arterial ischemic stroke and sinovenous thrombosis in childhood and infancy. *J Child Neurol*. 2005;20:553–559. doi: 10.1177/08830738050200070201
38. Westmacott R, Askalan R, MacGregor D, Anderson P, Deveber G. Cognitive outcome following unilateral arterial ischaemic stroke in childhood: effects of age at stroke and lesion location. *Dev Med Child Neurol*. 2010;52:386–393. doi: 10.1111/j.1469-8749.2009.03403.x
39. Long B, Anderson V, Jacobs R, Mackay M, Leventer R, Barnes C, Spencer-Smith M. Executive function following child stroke: the impact of lesion size. *Dev Neuropsychol*. 2011;36:971–987. doi: 10.1080/87565641.2011.581537
40. Sebastian CL, McCrory EJ, Cecil CA, Lockwood PL, De Brito SA, Fontaine NM, Viding E. Neural responses to affective and cognitive theory of mind in children with conduct problems and varying levels of callous-unemotional traits. *Arch Gen Psychiatry*. 2012;69:814–822. doi: 10.1001/archgenpsychiatry.2011.2070
41. Gordon AL, Anderson V, Ditchfield M, Coleman L, Mackay MT, Greenham M, Hunt RW, Monagle P. Factors associated with six-month outcome of pediatric stroke. *Int J Stroke*. 2015;10:1068–1073.
42. Leventer RJ, Phelan EM, Coleman LT, Kean MJ, Jackson GD, Harvey AS. Clinical and imaging features of cortical malformations in childhood. *Neurology*. 1999;53:715–722. doi: 10.1212/wnl.53.4.715
43. Cooper AN, Anderson V, Hearps S, Greenham M, Hunt RW, Mackay MT, Monagle P, Gordon AL. The pediatric stroke outcome measure: a predictor of outcome following arterial ischemic stroke. *Neurology*. 2018;90:e365–e372. doi: 10.1212/WNL.0000000000004906
44. deVeber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol*. 2000;15:316–324. doi: 10.1177/088307380001500508
45. Kitchen L, Westmacott R, Friefeld S, MacGregor D, Curtis R, Allen A, Yau I, Askalan R, Moharir M, Domi T, et al. The pediatric stroke outcome measure: a validation and reliability study. *Stroke*. 2012;43:1602–1608. doi: 10.1161/STROKEAHA.111.639583
46. Korkman M, Kirk U, Kemp S. *NEPSY®—Second Edition*. Harcourt Assessment; 2007.
47. Sebastian CL, Fontaine NM, Bird G, Blakemore SJ, Brito SA, McCrory EJ, Viding E. Neural processing associated with cognitive and affective Theory of Mind in adolescents and adults. *Soc Cogn Affect Neurosci*. 2012;7:53–63. doi: 10.1093/scan/nsr023
48. Goodman R. The strengths and difficulties questionnaire. *J Child Psychol Psychiat*. 1997;38:581–586.
49. Craney TA, Surles JG. Model-dependent variance inflation factor cutoff values. *Quality Engineering*. 2002;14:391–403.
50. O'Keeffe F, Stark D, Murphy O, Ganesan V, King J, Murphy T. Psychosocial outcome and quality of life following childhood stroke - A systematic review. *Dev Neurorehabil*. 2017;20:428–442. doi: 10.1080/17518423.2017.1282052
51. Rosema S, Crowe L, Anderson V. Social function in children and adolescents after traumatic brain injury: a systematic review 1989-2011. *J Neurotrauma*. 2012;29:1277–1291. doi: 10.1089/neu.2011.2144
52. Dennis M. Language and the young damaged brain. In: Boll T, ed. *Clinical Neuropsychology and Brain Function: Research, Measurement and Practice*. American Psychological Association 1988:85–124.
53. Stiekema AP, Nijsse B, de Kort PL, Spikman JM, Visser-Meily JM, van Heugten CM. The relationship between social cognition and participation in the long term after stroke. *Neuropsychol Rehabil*. 2021;31:278–292.
54. Nijsse B, Spikman JM, Visser-Meily JMA, de Kort PLM, van Heugten CM. Social cognition impairments are associated with behavioural changes in the long term after stroke. *PLoS One*. 2019;14:e0213725. doi: 10.1371/journal.pone.0213725
55. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*. 2011;134(pt 8):2197–2221. doi: 10.1093/brain/awr103

Stroke