

Development of the mentalizing network structures and theory of mind in extremely preterm youth

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Abstract

Adolescents born preterm (<37 weeks of gestation) are at elevated risk for deficits in social cognition and peer relationships. Theory of Mind (ToM) is a complex form of social cognition important for regulating social interactions. ToM and the underlying mentalizing network continue to develop across adolescence. The present study recruited 48 adolescents (12–17 years old) who were either born extremely preterm (EPT; <28 weeks of gestation) or full-term (FT) at birth. Cortical thickness, gray matter volume and surface area were measured in four regions of the mentalizing network: the temporoparietal junction, anterior temporal cortex, posterior superior temporal sulcus and frontal pole (mBA10). We also assessed the adolescents' performance on a ToM task. Findings revealed both group differences and group-by-age interaction effects in the gray matter indices within the temporal lobe regions of the mentalizing network. The EPT group also performed significantly worse than the FT group on the ToM task. The cortical structural measures that discriminated the EPT and FT groups were not related to ToM performance. These results highlight altered developmental changes in brain regions underlying mentalizing functions in EPT adolescents relative to FT controls.

Key words: preterm birth; social cognition; adolescence; mentalizing network; MRI

Introduction

Preterm birth is categorized into moderate preterm (birth at a gestational age between 32 and 36 weeks), very preterm (28–31 weeks) and extremely preterm (EPT; <28 weeks) (Moutquin, 2003). Preterm birth is associated with a significant increase in rates of cognitive and emotional difficulties across development (Taylor, 2020), although mortality rates have improved substantially (Fanaroff et al., 2003). Preterm children face particular challenges in interacting with peers. They engage in fewer social activities, have smaller social networks, experience increased rates of social rejection and can become socially withdrawn (Ritchie et al., 2015; Montagna and Nosarti, 2016; Taylor, 2020). Existing research largely focuses on offspring born moderate or very preterm, although adverse neurodevelopmental outcomes are thought to be highest in EPT individuals. The present study assessed neurodevelopment in EPT youth. Cognitive and emotional impairments in social contexts may be a particular vulnerability for EPT youth relative to full-term (FT) controls (≥ 37 weeks), even after controlling for differences in IQ and physical disabilities (Taylor, 2020). We examined the behavioral and neural function of one specific social cognitive process referred to as Theory of Mind

(ToM). ToM, or mentalizing, involves understanding the thoughts, perceptions and experiences of other individuals independent of oneself. ToM ability emerges in early childhood and continues to develop into later childhood and adolescence (Burnett et al., 2011; Gweon and Saxe, 2013). ToM is thought to be instantiated in the coordinated activity across a network of brain regions, including the prefrontal cortex (PFC), temporoparietal junction (TPJ), superior temporal sulcus (STS) and temporal pole (Frith et al., 2003).

While compromised social functioning in preterm youth impairs quality of life across childhood, this is particularly detrimental during adolescence when integration with peers becomes an important facet of daily life. Social connections are a prominent source of identity and self-esteem. Moreover, vulnerability for mental health disorders is markedly increased during adolescence (Paus, 2005; Nelson et al., 2016), particularly in individuals such as preterm youth who do not integrate well with peers (Lindström et al., 2009). Understanding the factors that contribute to social functioning in preterm adolescents is thus important in identifying youth at risk for social difficulties and related mental health problems.

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Recent neuroimaging studies have focused on the ongoing elaboration of behavior and maturation of brain structure and function underlying ToM ability in adolescence (Burnett *et al.*, 2011; Mills *et al.*, 2014; Becht *et al.*, 2021). The mentalizing network, like many brain regions that support higher cognitive functions, undergoes protracted developmental maturation across adolescence and into early adulthood (Giedd, 2008; Mills *et al.*, 2014). The maturation of this network may underlie important cognitive and behavioral capabilities that facilitate peer integration in adolescence (Burnett *et al.*, 2011; Blakemore and Mills, 2014; Becht *et al.*, 2021). Conversely, differential development in this network may underlie compromised social capabilities.

To establish maturational norms, Mills *et al.* (2014) tracked structural changes in individuals between 7 and 30 years of age across four core regions in the mentalizing network [frontal pole (mBA10); TPJ, posterior STS (pSTS) and anterior temporal cortex (ATC)]. Cortical thickness (CT), gray matter volume (GMV) and surface area (SA), in all four regions, demonstrated age-related reductions across late childhood and early adolescence before stabilizing in early adulthood. These reductions are thought to represent age-related synaptic pruning, which, along with growth in white matter, are associated with cognitive development (Paus, 2005).

Previous studies have reported differences among preterm samples in CT, SA and GMV across several brain regions that intersect the mentalizing network, including regions of the temporal lobe and prefrontal cortex (Nosarti *et al.*, 2008; Nagy *et al.*, 2011; Lax *et al.*, 2013). The effects of preterm birth on age-related changes involving both increases and decreases in CT and GMV suggest effects on gray matter maturation during adolescence and into early adulthood. A study of age-related changes in brain structure during this period by Karolis *et al.* (2017) revealed global GMV reductions in the preterm samples but the volumetric reductions were particularly strong in medial temporal and subcortical regions with frontal regions being less affected. However, another study by Nam *et al.* (2015) found that preterm individuals had greater decreases in CT in the medial frontal, temporal and parietal regions from age 15 to 20 years relative to FT individuals.

The present study assessed developmental changes in the structures of the mentalizing network and ToM performance in EPT and FT adolescents. While previous studies have reported altered trajectories of brain development in preterm children and adolescents, none has specifically examined the mentalizing network or performance on a mentalizing task in EPT adolescents. A better understanding of the developmental changes in the cortical morphometry of the mentalizing network is needed to identify ways in which brain development is affected by EPT birth. Although previous studies have reported compromised ToM abilities in younger preterm children (Jones *et al.*, 2013; Williamson and Jakobson, 2014; Mossad *et al.*, 2017; Zmyj *et al.*, 2017), we also know little about the effect of EPT birth on ToM performance. The primary objectives of the present study were to examine the effect of group (EPT vs FT) and age on ToM performance, as well as on standard metrics of gray matter structure (CT, GMV and SA) in brain regions within the mentalizing network (Mills *et al.*, 2014; Becht *et al.*, 2021). We hypothesized that the EPT group would demonstrate impaired performance on the ToM task, as well as differential maturation of the mentalizing regions, compared to FT controls. In the event of a significant group-by-age effect on the structural measures, we aimed to conduct follow-up analyses to explore whether the structural indices that differentiated between the EPT group and FT controls were associated with levels of ToM performance.

Method

Participants and procedures

Forty-eight adolescents ages 12–17 years participated in the study. Inclusion criteria were the absence of clinically identified neurological impairment or genetic cognitive conditions, normal or corrected vision, status as a native English speaker and no MRI contraindications. The EPT group consisted of 23 participants aged between 12 and 17 years who were born at a gestational age of <28 weeks. Usable structural data were not obtained for one EPT female. The final sample included 22 EPT children [11 females; mean age at MRI visit = 14.06 years, standard deviation (s.d.) = 1.80; mean gestational age (GA) = 25.96 weeks, s.d. = 1.30]. The EPT group consisted of 31.8% White, 59.1% Black or African American and 9.1% mixed race. Twenty-five FT adolescents participated as age- and sex-matched healthy controls (13 females; mean age at MRI visit = 14.00 years, s.d. = 1.61; mean GA = 39.08 weeks, s.d. = 1.12). Among the FT group, 64% were White, 16% Black or African American, 8% Asian and 12% mixed race. The racial distributions were not matched between groups ($P = 0.016$).

The full experimental protocol included sessions of about 2 h each for neuroimaging and administration of self-report and performance measures. The sessions were either completed on a single day or in two separate visits scheduled within 1 month of each other. Parents and adolescents provided written consent/assent. All procedures were approved by the Institutional Review Board at Nationwide Children's Hospital.

ToM measure

The Emotional and Emotive Faces task (EFFT; Dennis *et al.*, 1998, 2013a) was used to assess affective ToM. The task examines the participant's understanding of the discrepancy between emotional expression (how an individual actually feels) and emotive communication (the emotion that the individual expresses in social situations; Dennis *et al.*, 2013b). The experimenter reads the participant 15 vignettes about the main character (sex-matched with the participant) in different social situations with a friend, which were designed to elicit five basic emotional expressions: happiness, sadness, fear, disgust and anger. For each of the three scenarios and each emotion, the examiner asks the participant about the emotion that the main character would feel inside ('Feel Inside' question) and the emotion the character would 'show on their face' ('Look on Face' question). The participant responds by choosing a face from an array of faces displaying neutral, mild and strong emotion from the five types of expressions, with the questions 'Feel Inside' and 'Look on Face' counterbalanced across trials. To illustrate, a participant who was identified as a male is told a story about a birthday party at which the main character's friend bakes him a sloppily constructed birthday cake. He is then asked to point to both the face that reflects what he thinks about the cake ('Feel Inside') and the face that he would show to his friend ('Look on Face'). There is thus a discrepancy between the emotion that the story's protagonist felt 'inside' and the protagonist's facial expression.

The 'Feel Inside' and 'Look on Face' trials were scored in accordance with the test developers' guidelines (Dennis *et al.*, 2013b). The 'Look on Face' trials were the primary measure of affective ToM, as it taps into the capabilities of understanding the actual emotion the protagonist feels might be different from the emotion that s/he displays (Dennis *et al.*, 2013b; Robinson *et al.*, 2014; Ryan *et al.*, 2021). The 'Look on Faces' scores correlated with scores on other aspects of ToM in youth (Ryan *et al.*, 2021). 'Feel Inside'

trials simply require participants to select the facial emotion that matches the explicit descriptions of the protagonist's emotional state in the vignette (Ryan et al., 2021). For the 'Feel Inside' trials, participants were awarded 1 point for correctly identifying the actual emotion (e.g. 1 point for choosing the sad face for the sad vignette and 0 point for choosing other faces). For the 'Look on Face' trials, participants scored 2 points when selecting the contrasting facial emotion that masked the emotion felt inside (e.g. selecting the happy face for the sad vignette). One point was given if participants selected the neutral face or a milder expression of the emotion felt inside (e.g. 1 point for selecting a neutral or sad face in the sad vignette and 0 point for other faces). The total possible 'Feel Inside' score was 15 and 30 for 'Look on Face'. The total ToM score was the sum of 'Feel Inside' and 'Look on Face' scores (maximum 45). A linear regression model was conducted to examine the effect of age, group and their interaction effect on the ToM score.

Image acquisition

MRI data were acquired on a Siemens 3 Tesla scanner with 64-channel head coil arrays. Three-plane localizer scout images and an isotropic 3D T1-weighted anatomical scan covering the whole brain (MPRAGE) were obtained with repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, field of view (FOV) = 248 mm × 256 mm and voxel size = 1 × 1 × 1 mm³. The sagittal dimension of the T1-weighted scans was 176 slices.

Image processing

Postprocessing of the T1-weighted images was performed with FreeSurfer image analysis suite 6.0 (<https://surfer.nmr.mgh.harvard.edu>). Automated cortical reconstruction was performed using the recon-all pipeline. The procedures are detailed by Fischl and colleagues (Dale et al., 1999; Fischl et al., 1999, 2002, 2004a; Fischl, 2012). Briefly, the pipeline performs motion correction (Reuter et al., 2010), skull stripping (Ségonne et al., 2004), affine registration with Talairach space, intensity normalization (Sled et al., 1998), gray/white matter segmentation, construction of tessellated mesh to distinguish the gray/white matter boundary, topology correction, outward deformation of gray/white matter boundary and surface smoothing (Dale et al., 1999). Parcellation of the brain into gyrus- and sulcus-based regions was conducted using the Desikan-Killiany atlas (Fischl et al., 2004b; Desikan et al., 2006). All resulting segmentations were inspected to ensure adequate segmentation and parcellation.

Neuroimaging analysis

To focus on mentalizing structures, analyses were restricted to the four bilateral regions of interest (ROIs) of the mentalizing network characterized by Mills et al. (2014). Publicly available ROI masks from this study were used for the right and left mBA10 (or frontal pole), TPJ, pSTS and ATC. These ROIs, as described in greater detail by Mills et al. (2014), are displayed in Figure 1. The individual ROIs were combined into a single ROI label file separately for the left and right hemispheres. For completeness, whole-brain analysis was also performed.

A surface-based group-level vertex-wise analysis using FreeSurfer's glm-fit tool was performed on CT, GMV and SA metrics in the mentalizing regions. The thickness of the cortical ribbon was measured as the shortest distance between the pial

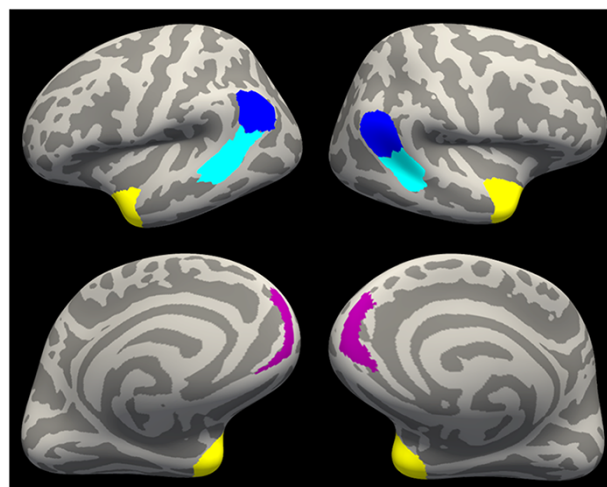


Fig. 1. The social brain ROIs. The ROI masks were obtained from Mills et al. (2014). The ROIs are medial Brodmann Area 10 (mBA10; purple), TPJ (dark blue), pSTS (aqua) and ATC (yellow).

and white matter surfaces. The GMV was measured as the volume between the pial and white matter surfaces. The SA was computed for the pial layer and calculated as the average of the area of the tessellated triangles touching the vertex on the gray matter surface. A general linear model was fit to examine the effects of group, age and group-by-age interaction effect on the CT, GMV and SA measures, respectively. To correct for multiple comparisons, a Monte Carlo permutation simulation was performed with an initial vertex-wise threshold of $P < 0.05$ using FreeSurfer's `mri_glmfit-sim` procedure (Hagler et al., 2006). Suprathreshold clusters were then tested against an empirical null distribution of maximum cluster size. We report clusters that survived the cluster-wise corrections ($P_{\text{cor}} < 0.05$, or clusters that were found in 95% of the permutation simulation iterations). Analyses on CT, GMV and SA were treated as independent tests (Mills et al., 2014). Thus, no additional statistical corrections were applied.

Further analyses used values extracted from the clusters that survived the corrected threshold of the group-by-age interaction effect. The exact values for individual participants were used to conduct Pearson correlations to investigate associations among clusters that showed a significant group-by-age interaction effect and the ToM score. We additionally conducted separate multiple regression analyses to examine the impact of age and the structural measure on ToM performance separately in the EPT and FT groups.

Results

The effect of group and age on ToM performance

The multiple regression examining the effect of age, group and age-by-group on the ToM performance revealed no age effect on ToM performance, $P = 0.62$. The group effect was significant, $B = -5.49$, $t = -2.99$, $P = 0.005$. The age-by-group interaction effect was not significant, $P = 0.50$. As shown in Figure 2A, the EPT group had lower ToM scores than the FT controls when controlling for age, $M_{\text{EPT}} = 27.77$, $s.d. = 6.25$, $M_{\text{C}} = 33.24$, $s.d. = 6.11$. Figure 2B displays group differences on the 'Feel Inside' and 'Look on Face' components of the ToM measure, with the group difference driven by the EPT group's lower scores on the 'Look on Face' component.

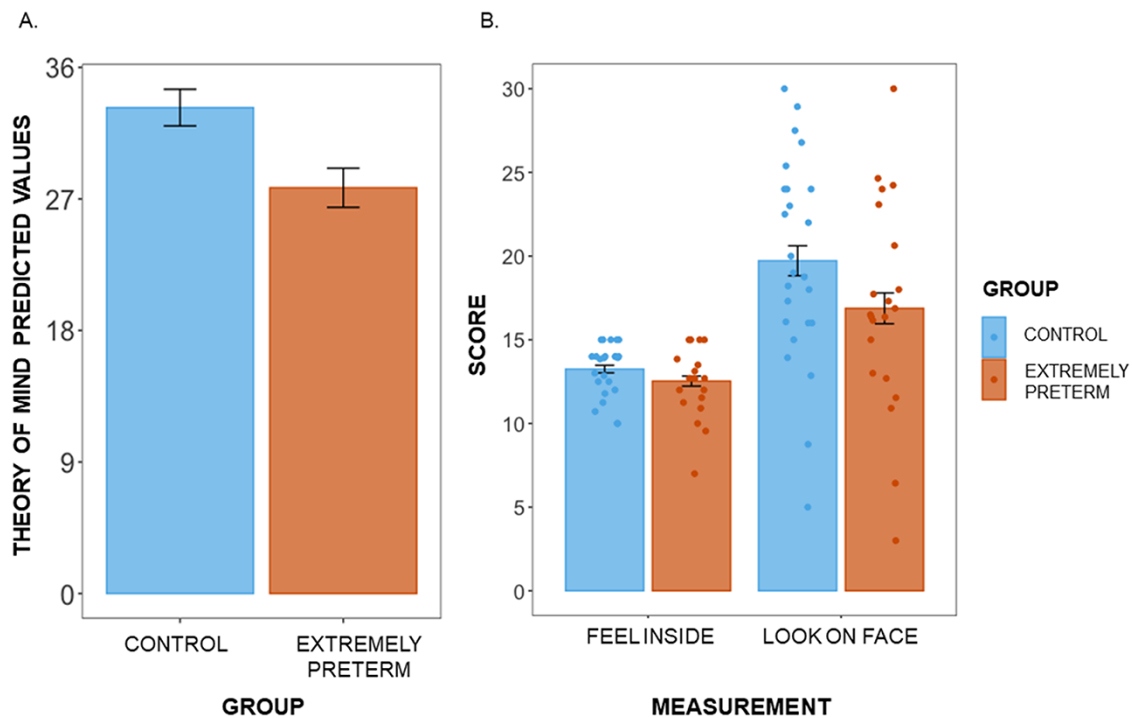


Fig. 2. Group differences in EFFT measures. A. Group differences in the ToM score controlling for age. The ToM score is the sum of 'Feel Inside' and 'Look on Face' scale scores. B. The mean 'Feel Inside' and 'Look on Face' scores for the EPT and control group.

Table 1. Regions in the mentalizing network that showed a significant main effect of group (FT vs. EPT) and interaction effect of group and age on GMV and SA

Anatomical regions	Side	Peak value (t)	Size (mm ²)	MNI coordinates (x, y, z)	P cluster-wise corrected
GMV					
Group effect					
TPJ	L	3.32	359.90	-41, -63 34	0.008
ATC	R	3.26	457.40	52, 2, -19	0.001
Group-by-age effect					
TPJ	L	-3.24	311.9	-41, -63 34	0.02
ATC	R	-3.70	428.63	52, 2, -19	0.004
SA					
Group effect					
TPJ	L	3.29	564.98	-44, -64, 40	<0.001
TPJ	R	3.32	1074.16	56-51, 31	<0.001
ATC	R	2.74	721.46	49, -3, -22	<0.001
Group-by-age effect					
TPJ	L	-2.95	505.88	-44, -64, 39	<0.001
TPJ	R	-3.10	893.9	56-51, 31	<0.001
ATC	R	-2.77	637.1	51, -1, -18	<0.001

Note: No regions survived cluster-wise correction for CT; L = left; R = right.

The effects of group and age on cortical structures

The group-level analysis revealed a significant group (EPT and FT) and group-by-age interaction effect on GMV and SA in the TPJ and ATC ROIs (Monte Carlo simulation cluster $P < 0.05$). No significant group or group-by-age interaction effects were found for CT in any of the mentalizing ROIs. Results of the group-by-age interaction effects are displayed in Table 1 and Figure 3. Clusters for fully corrected results are presented. Table 1 shows that the clusters that showed significant group effect largely overlapped with those

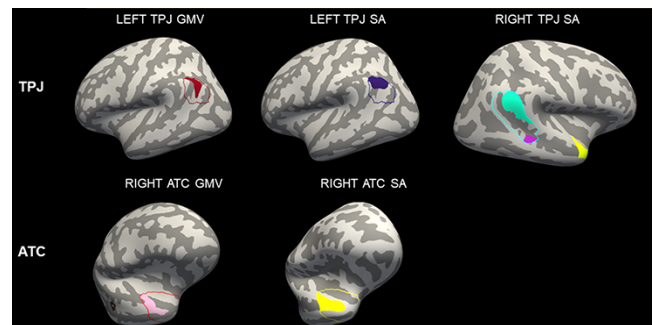


Fig. 3. Results of the interaction effect of group (EPT birth vs. FT birth) and age on GMV and SA. Significant cortical regions (corrected $P < 0.05$) were projected onto the inflated surfaces of the left and right hemispheres. The colored lines marked the ROIs (c.f. Figure 1).

that showed group-by-age interaction effect on the structural measures of the mentalizing ROIs. Figure 4 displays the scatterplots of the extracted values for the GMV and SA measures from the clusters that showed a significant group-by-age interaction effect.

There are significant group-by-age interactions on the GMV in the left TPJ and the right ATC. The interaction effect on the SA was significant in the bilateral TPJ and the right ATC. Supplementary Figure 1 presents the interaction effects with the exacted values of GMV and SA measures. Simple slope tests revealed that the EPT group displayed age-related increases in GMV at the left TPJ, $b = 0.14$, $t = 3.80$, $P < 0.001$, right ATC, $b = 0.12$, $t = 2.72$, $P = 0.01$, and the SA at the left TPJ, $b = 0.3$, $t = 3.08$, $P = 0.004$, right TPJ, $b = 0.4$, $t = 3.07$, $P = 0.004$, and right ATC, $b = 0.03$, $t = 2.52$, $P = 0.02$. The FT group showed reduced GMV at the ATC with age, $b = -0.10$, $t = -2.31$, $P = 0.03$, but no age-related changes for the other structural measures (all $P_s > 0.05$).

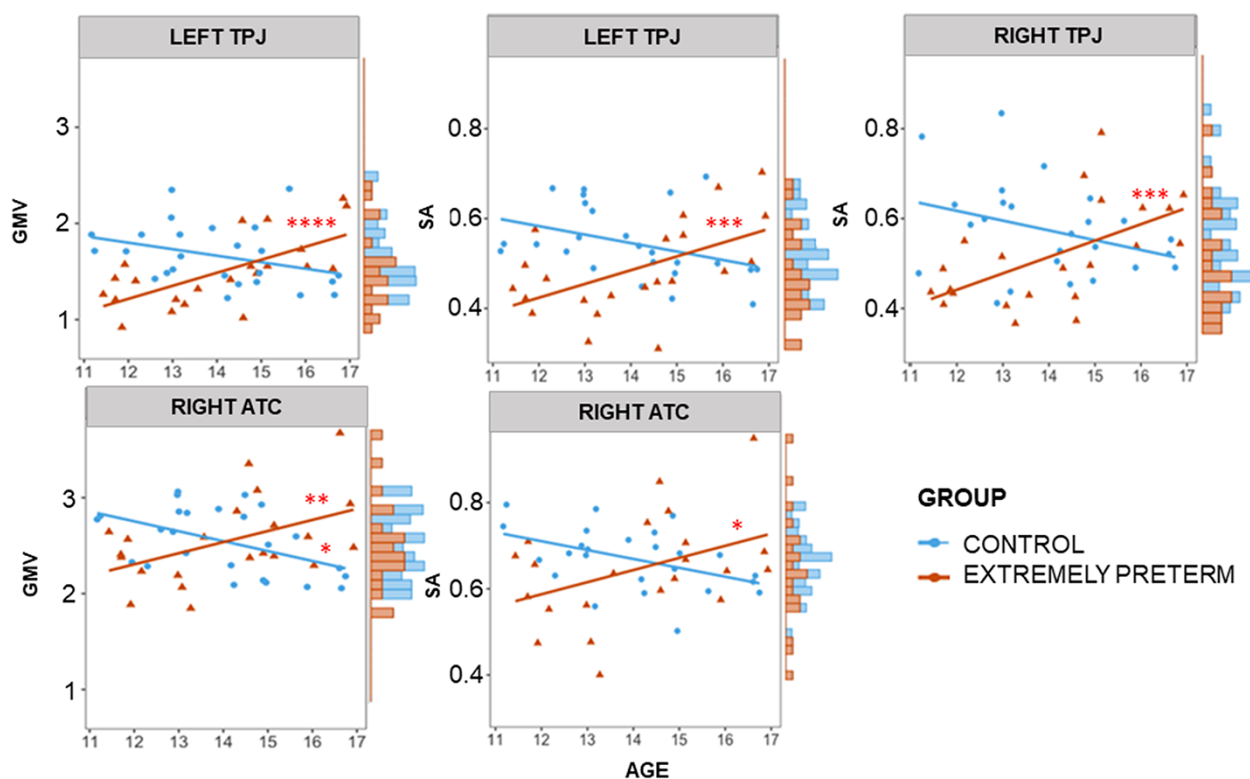


Fig. 4. The extracted values of GMV and SA measures from regions that showed the significant group (EPT and FT controls) and age interaction effect.

For completeness, we conducted a whole-brain analysis to examine the impact of group, age and group-by-age interaction effect. The results are depicted in Supplementary Table S1. Clusters that survived the whole-brain corrections were outside the predefined ROIs. However, there were temporal regions adjacent to the study-defined ROIs that displayed significant group effects for GMV and SA and a significant group-by-age effect for SA.

The relation between cortical structural measures and ToM performance

Finally, a follow-up analysis was conducted to assess the degree to which group differences in the development of the mentalizing network and ToM performance covaried. We examined the correlations among the structural measures for clusters that displayed significant group-by-age interaction and ToM performance. The correlation results are displayed in Table 2. While there were significant correlations among TPJ and ATC regions that showed significant interaction effects on GMV and SA, none of the structural measures correlated with the ToM score across participants. Furthermore, multiple regression analyses showed that age did not moderate the relation between the structural measure and ToM score in either the EPT or control group, $P_s > 0.13$. For completeness, the correlations among clusters that showed significant group effects on GMV and SA, and the ToM scores are presented in Supplementary Table S2. The structural measures of clusters that showed significant group effects were not related to ToM performance across all participants, $P_s > 0.11$. Age did not moderate the relation between the structural measure and ToM performance in either the EPT or control group, $P_s > 0.13$.

Table 2. Correlations of clusters that showed group-by-age interaction effect on CT, GMV and SA with the ToM performance

	1. L TPJ GMV	2. L TPJ SA	3. R TPJ SA	4. R ATC GMV	5. R ATC SA
0					
2. L TPJ SA	0.83 ^{***}				
3. R TPJ SA	0.47 ^{***}	0.52 ^{***}			
4. R ATC GMV	0.47 ^{***}	0.37 ^{**}	0.37 ⁺		
5. R ATC SA	0.32 ⁺	0.41 ^{**}	0.41 ^{**}	0.85 ^{***}	
6. ToM	0.09	0.05	0.16	0.11	0.23

Note: L = left; R = right.
* $P < .05$, ** $P < .01$, *** $P < .001$.

Discussion

The present study compared behavioral performance on a ToM task and maturational changes in the cortical structures of the mentalizing network in a group of EPT and FT adolescents. The EPT adolescents performed significantly worse on the ToM task compared to the FT controls. Findings also revealed group differences in age-related changes in the GMV and SA of TPJ and ATC regions of the mentalizing network (Mills et al., 2014; Becht et al., 2021). Although several previous studies have reported compromised social functioning in youth with preterm birth (Montagna and Nosarti, 2016), this is the first study to systematically assess both cognitive performance on a ToM task and maturational changes in the mentalizing network in preterm-born adolescents.

The impaired ToM ability associated with EPT birth may have negative impacts on the development of adaptive social functioning and, in turn, increase risks for downstream psychiatric outcomes. Preterm children showed an increased likelihood of meeting diagnostic criteria for psychiatric disorders, including

autism spectrum disorder, attention deficit hyperactivity disorder, anxiety and depression (Johnson and Marlow, 2011; Treyvaud et al., 2013). ToM is a social cognitive function crucial for the development of adaptive social functioning (Slaughter et al., 2015; Devine and Apperly, 2022). Impaired ToM functioning is implicated in the development of psychiatric outcomes associated with preterm birth (Happé and Frith, 2014). Research has shown that EPT-born children displayed poorer ToM, which was associated with less adaptive social functioning (Marleau et al., 2021). The present study was guided by the theoretical model (Montagna and Nosarti, 2016) that describes the developmental cascade from preterm birth to neural alterations in the social brain network, which, in turn, perturbs key social cognitive functions, such as ToM, and leads to socioemotional problems. The maladaptive pathway gives rise to increased risks for psychiatric disorders.

The EPT adolescents were particularly challenged with affective ToM, measured with the 'Look on Face' items of the EFFT. These items tested the understanding of the discrepancy between the emotion that the character felt 'inside' and the 'appropriate' emotion to display in social situations. Higher functioning of affective ToM requires individuals to understand both social norms and the potential impact that one individual's expression may have on another. 'Feel Inside' merely examined the participants' ability to select the facial emotion that matched the protagonist's emotional state (Dennis et al., 2013a; Ryan et al., 2021). The current ToM assessment is sensitive to individual differences in ToM (Dennis et al., 2013a; Hoskinson et al., 2019; Ryan et al., 2021). The finding builds on prior evidence indicating that preterm youth have difficulty with the attribution of intentionality and 'mental states' in childhood (Williamson and Jakobson, 2014; Zmyj et al., 2017). The study provides initial evidence that EPT birth is associated with difficulties in the affective aspect of ToM, a skill that is likely to play a critical role in developing social competence and establishing peer networks in adolescence (Burnett et al., 2011; Blakemore and Mills, 2014; Becht et al., 2021).

Contrary to expectations, we did not find age-related improvements in the ToM performance in either group, nor did we observe group-by-age interactions in ToM performance. While previous research has found age-related improvement in ToM abilities in childhood (Hughes and Devine, 2015; Lecce et al., 2017), the present results failed to confirm age-related changes across adolescence. One possibility is that different components of ToM follow different developmental time courses, and the affective aspect of ToM assessed in the EFFT may show a developmental plateau by early adolescence (Hughes and Devine, 2015). Future studies would benefit from using multiple ToM assessments (Hoskinson et al., 2019; Ryan et al., 2021) in a longitudinal design. In contrast to ToM performance, there were group differences in developmental changes in cortical structures in key regions of the mentalizing network, including the TPJ and ATC regions (Mills et al., 2014). Previous studies have found age-related decreases in gray matter structural measures in the mentalizing network in typically developing adolescents (Mills et al., 2014; Becht et al., 2021). In contrast, our findings indicated that EPT birth was characterized by age-related GMV and SA increases in the bilateral TPJ and the right ATC, whereas the FT group displayed expected age-related GMV and SA reductions in these regions (Mills et al., 2014). Thus, EPT birth was associated with an altered pattern of maturational change in the gray matter structures of key mentalizing regions.

The EPT group may experience a maturational delay as the age-related increase in GMV and SA may be more similar to the pattern of cortical growth in FT youth prior to the initiation of

the pruning process (Nam et al., 2015). Future neuroimaging studies are needed to understand the mechanisms underlying the maturational differences in the mentalizing regions. The developmental differences in the mentalizing network might be rooted in preterm-related early deviations from normative development in cortical structural maturation (Dimitrova et al., 2021), impairments in domain-general functions, such as attentional control (Telford et al., 2016), and biological motion perception (Williamson et al., 2015) and domain-specific challenges like altered functional connectivity in the face-processing network (Sato et al., 2021). Impaired social cognition might be related to lower intellectual abilities and executive functions. However, studies have found preterm-related differences in social cognition functioning after controlling for the general cognitive functions (e.g. Marleau et al., 2021). The brain networks underlying social cognition may thus be particularly vulnerable to developmental abnormalities following preterm birth.

The regional variations in the group-related structural differences are particularly noteworthy. Mentalizing abilities have been described as dependent on integrated network functionality across regions (Mills et al., 2014; Becht et al., 2021). The present findings suggest that EPT birth has more pronounced effects during adolescence on the development of the TPJ and ATC than on the development of the pSTS and frontal pole. ToM is likely to emerge from the complex interaction of a number of smaller-scale networks (Schaafsma et al., 2015). The recent meta-analysis suggests that the TPJ subserves the ability to shift attention to other individuals and maintain the abstract concept of false beliefs (Schurz et al., 2017). The ATC plays an important role in semantic knowledge, developing social scripts and understanding person-specific knowledge (Olson et al., 2013; Schurz et al., 2014). These social cognitive functions are important for the development of social competence and psychosocial health in adolescence (Paus et al., 2008; Blakemore and Mills, 2014). Future studies are warranted to examine the functional implications associated with the EPT-related differential structural development of the TPJ and ATC.

We did not find significant group differences or group-by-age interaction effects on CT in any of the mentalizing regions. This is consistent with Becht et al.'s (2021) finding indicating that individual differences in developmental changes of CT in these regions were less prominent relative to changes in SA (Becht et al., 2021). The study found greater interindividual variability for the SA compared to the CT measure of the mentalizing network. Given the relatively small sample size of our study, we thus may have had more power to detect between-group differences for the SA and GMV indices than for the CT measure.

An additional finding was the absence of associations between ToM scores and the GMV and SA of the TPJ and ATC that displayed significant group effect and group-by-age interaction effect. As the mentalizing function might not be a unified construct (Schurz et al., 2014, 2021), the functions subserved by the TPJ and ATC might be different from regions associated with the ToM function measured in our ToM assessment. The findings that EPT adolescents demonstrate performance deficits on ToM tasks and, independently, alterations in the developmental patterns of mentalizing brain structures likely reflect a complex and multifaceted profile of socio-cognitive functioning in EPT youth. It is important to note that the present study focused on examining EPT-related structural differences restricted to the mentalizing ROIs that have been identified in typically developing youth (Mills et al., 2014). Our whole-brain analysis indicated that there were group differences and group-by-age interaction effects in structural measures

of regions outside the mentalizing network. EPT youth may show structural differences in wider neural networks that are associated with a range of cognitive functions (Hadaya and Nosarti, 2020). It is also possible that EPT birth may lead to a cascade of impacts on the development of wider neural networks (Thomas and Karmiloff-Smith, 2002). The 'neuroplastic' framework suggests that EPT youth may have undergone functional remapping of functions that underlie ToM, including those outside the mentalizing network (Nosarti, 2013). An important future direction is to identify EPT-related differences in both neural structures and functions underlying ToM and examine the impacts of these differences on the cognitive functions of ToM and social functions at the behavioral level.

Limitations of the present study should be noted. First, the cross-sectional study cannot reveal within-subject longitudinal changes in cortical structures within the mentalizing network or the causal relation between changes in the cortical structures and ToM performance. Maturation of brain circuits may be impacted by environmental experience, and an altered trajectory of social brain regions could reflect impoverished opportunities for social interaction. Hence, an important future direction is to understand the reciprocal influences of structural development in the mentalizing network and social functioning in EPT youth. Second, a more comprehensive assessment of social cognitive capabilities may be useful in specifying the nature of social cognition deficits in EPT adolescents. It is possible, for example, that these adolescents may have more difficulties in cognitive components (e.g. mental perspective-taking) or affect-cognitive components of ToM than in emotion perception or empathy (Schurz et al., 2014, 2021). Such findings in future studies may help pinpoint specific functional impairments where intervention might be most beneficial. Third, the EPT and FT adolescents were not matched on distributions of ethnicity. Future investigations would benefit from including a larger sample of EPT and FT youths from diverse backgrounds with matched ethnicity distributions and socioeconomic status.

In summary, our findings are consistent with many previous studies indicating that EPT adolescents demonstrate a pattern of altered brain morphology (e.g. Nam et al., 2015; Karolis et al., 2017), including in the temporal lobe regions (Nosarti et al., 2008). The current findings extend the current literature by documenting altered patterns of age-related changes in cortical structures in regions that comprise the mentalizing network in EPT compared to FT adolescents. The results suggest that age-related differences are more pronounced in the temporal lobe (particularly TPJ and ATC). The findings provide further support that EPT birth increases the susceptibility to disturbances in cortical maturational processes (Nosarti, 2013) and is characterized by sustained alterations in gray matter morphology (Hadaya and Nosarti, 2020). We also found that EPT birth is associated with reduced ToM performance in adolescence. Future longitudinal investigations are needed to better characterize the trajectory of developmental changes in the mentalizing regions for EPT individuals and to determine if EPT birth alters the timing of structural development (delayed and/or accelerated) or places EPT individuals on a different developmental pathway.

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Conflict of interest

The authors declared that they had no conflict of interest with respect to their authorship or the publication of this article.

Supplementary data

Supplementary data are available at SCAN online.

References

- Becht, A.I., Wierenga, L.M., Mills, K.L., et al. (2021). Beyond the average brain: individual differences in social brain development are associated with friendship quality. *Social Cognitive and Affective Neuroscience*, **16**(3), 292–301.
- Blakemore, S.-J., Mills, K.L. (2014). Is adolescence a sensitive period for sociocultural processing? *Annual Review of Psychology*, **65**, 187–207.
- Burnett, S., Sebastian, C., Kadosh, K.C., Blakemore, S.-J. (2011). The social brain in adolescence: evidence from functional magnetic resonance imaging and behavioural studies. *Neuroscience and Biobehavioral Reviews*, **35**(8), 1654–64.
- Dale, A.M., Fischl, B., Sereno, M.I. (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. *NeuroImage*, **9**(2), 179–94.
- Dennis, M., Barnes, M.A., Wilkinson, M., Humphreys, R.P. (1998). How children with head injury represent real and deceptive emotion in short narratives. *Brain and Language*, **61**(3), 450–83.
- Dennis, M., Agostino, A., Taylor, H.G., et al. (2013a). Emotional expression and socially modulated emotive communication in children with traumatic brain injury. *Journal of the International Neuropsychological Society: JINS*, **19**(1), 34–43.
- Dennis, M., Simic, N., Bigler, E.D., et al. (2013b). Cognitive, affective, and conative theory of mind (ToM) in children with traumatic brain injury. *Developmental Cognitive Neuroscience*, **5**, 25–39.
- Desikan, R.S., Ségonne, F., Fischl, B., et al. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, **31**(3), 968–80.
- Devine, R.T., Apperly, I.A. (2022). Willing and able? Theory of mind, social motivation, and social competence in middle childhood and early adolescence. *Developmental Science*, **25**(1), e13137.
- Dimitrova, R., Pietsch, M., Ciarrusta, J., et al. (2021). Preterm birth alters the development of cortical microstructure and morphology at term-equivalent age. *bioRxiv*, **2021**(2006), 118488.
- Fanaroff, A.A., Hack, M., Walsh, M.C. (2003). The NICHD neonatal research network: changes in practice and outcomes during the first 15 years. *Seminars in Perinatology*, **27**(4), 281–7.
- Fischl, B., Sereno, M.I., Dale, A.M. (1999). Cortical surface-based analysis: II: inflation, flattening, and a surface-based coordinate system. *NeuroImage*, **9**(2), 195–207.

- Fischl, B., Salat, D.H., Busa, E., et al. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, **33**(3), 341–55.
- Fischl, B., Salat, D.H., van der Kouwe, A.J.W., et al. (2004a). Sequence-independent segmentation of magnetic resonance images. *NeuroImage*, **23**, S69–S84.
- Fischl, B., van der Kouwe, A., Destrieux, C., et al. (2004b). Automatically parcellating the human cerebral cortex. *Cerebral Cortex*, **14**(1), 11–22.
- Fischl, B. (2012). FreeSurfer. *NeuroImage*, **62**(2), 774–81.
- Frith, C.D., Wolpert, D.M., Frith, U., Frith, C.D. (2003). Development and neurophysiology of mentalizing. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, **358**(1431), 459–73.
- Giedd, J.N. (2008). The teen brain: insights from neuroimaging. *Journal of Adolescent Health*, **42**(4), 335–43.
- Gweon, H., Saxe, R. (2013). Developmental cognitive neuroscience of theory of mind. *Neural Circuit Development and Function in the Brain*, **3**, 367–77.
- Hadaya, L., Nosarti, C. (2020). The neurobiological correlates of cognitive outcomes in adolescence and adulthood following very preterm birth. *Seminars in Fetal & Neonatal Medicine*, **25**(3), 101117.
- Hagler, D.J., Saygin, A.P., Sereno, M.I. (2006). Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. *NeuroImage*, **33**(4), 1093–103.
- Happé, F., Frith, U. (2014). Annual research review: towards a developmental neuroscience of atypical social cognition. *Journal of Child Psychology and Psychiatry*, **55**(6), 553–77.
- Hoskinson, K.R., Bigler, E.D., Abildskov, T.J., et al. (2019). The mentalizing network and theory of mind mediate adjustment after childhood traumatic brain injury. *Social Cognitive and Affective Neuroscience*, **14**(12), 1285–95.
- Hughes, C., Devine, R.T. (2015). Individual differences in theory of mind from preschool to adolescence: achievements and directions. *Child Development Perspectives*, **9**(3), 149–53.
- Johnson, S., Marlow, N. (2011). Preterm birth and childhood psychiatric disorders. *Pediatric Research*, **69**(8), 11–8.
- Jones, K.M., Champion, P.R., Woodward, L.J. (2013). Social competence of preschool children born very preterm. *Early Human Development*, **89**(10), 795–802.
- Karolis, V.R., Froudast-Walsh, S., Kroll, J., et al. (2017). Volumetric grey matter alterations in adolescents and adults born very preterm suggest accelerated brain maturation. *NeuroImage*, **163**, 379–89.
- Lax, I.D., Duerden, E.G. Lin, S.Y., et al. (2013). Neuroanatomical consequences of very preterm birth in middle childhood. *Brain Structure & Function*, **218**(2), 575–85.
- Lecce, S., Bianco, F., Devine, R.T., Hughes, C. (2017). Relations between theory of mind and executive function in middle childhood: a short-term longitudinal study. *Journal of Experimental Child Psychology*, **163**, 69–86.
- Lindström, K., Lindblad, F., Hjern, A. (2009). Psychiatric morbidity in adolescents and young adults born preterm: a Swedish National Cohort Study. *Pediatrics*, **123**(1), e47.
- Marleau, I., Vona, M., Gagner, C., Luu, T.M., Beauchamp, M.H. (2021). Social cognition, adaptive functioning, and behavior problems in preschoolers born extremely preterm. *Child Neuropsychology*, **27**(1), 96–108.
- Mills, K.L., Lalonde, F., Clasen, L.S., Giedd, J.N., Blakemore, S.-J. (2014). Developmental changes in the structure of the social brain in late childhood and adolescence. *Social Cognitive and Affective Neuroscience*, **9**(1), 123–31.
- Montagna, A., Nosarti, C. (2016). Socio-emotional development following very preterm birth: pathways to psychopathology. *Frontiers in Psychology*, **7**(80), 1–23.
- Mossad, S.I., Smith, M.L., Pang, E.W., Taylor, M.J. (2017). Neural correlates of ‘Theory of Mind’ in very preterm born children. *Human Brain Mapping*, **38**(11), 5577–89.
- Moutquin, J.-M. (2003). Classification and heterogeneity of preterm birth. *BJOG: An International Journal of Obstetrics and Gynaecology*, **110**, 30–3.
- Nagy, Z., Lagercrantz, H., Hutton, C. (2011). Effects of preterm birth on cortical thickness measured in adolescence. *Cerebral Cortex*, **21**(2), 300–6.
- Nam, K.W., Castellanos, N., Simmons, A., et al. (2015). Alterations in cortical thickness development in preterm-born individuals: implications for high-order cognitive functions. *NeuroImage*, **115**, 64–75.
- Nelson, E.E., Jarcho, J.M., Guyer, A.E. (2016). Social re-orientation and brain development: an expanded and updated view. *Developmental Cognitive Neuroscience*, **17**, 118–27.
- Nosarti, C., Giouroukou, E., Healy, E., et al. (2008). Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. *Brain*, **131**(Pt 1), 205–17.
- Nosarti, C. (2013). Structural and functional brain correlates of behavioral outcomes during adolescence. *Early Human Development*, **89**(4), 221–7.
- Olson, I.R., McCoy, D., Klobusicky, E., Ross, L.A. (2013). Social cognition and the anterior temporal lobes: a review and theoretical framework. *Social Cognitive and Affective Neuroscience*, **8**(2), 123–33.
- Paus, T. (2005). Mapping brain maturation and cognitive development during adolescence. *Trends in Cognitive Sciences*, **9**(2), 60–8.
- Paus, T., Keshavan, M., Giedd, J.N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews Neuroscience*, **9**(12), 947–57.
- Reuter, M., Rosas, H.D., Fischl, B. (2010). Highly accurate inverse consistent registration: a robust approach. *NeuroImage*, **53**(4), 1181–96.
- Ritchie, K., Bora, S., Woodward, L.J. (2015). Social development of children born very preterm: a systematic review. *Developmental Medicine and Child Neurology*, **57**(10), 899–918.
- Robinson, K.E., Fountain-Zaragoza, S., Dennis, M., et al. (2014). Executive functions and theory of mind as predictors of social adjustment in childhood traumatic brain injury. *Journal of Neurotrauma*, **31**(22), 1835–42.
- Ryan, N.P., Anderson, V.A., Bigler, E.D., et al. (2021). Delineating the nature and correlates of social dysfunction after childhood traumatic brain injury using common data elements: evidence from an international multi-cohort study. *Journal of Neurotrauma*, **38**(2), 252–60.
- Sato, J., Safar, K., Vandewouw, M.M., et al. (2021). Altered functional connectivity during face processing in children born with very low birth weight. *Social Cognitive and Affective Neuroscience*, **16**(11), 1182–90.
- Schaafsma, S.M., Pfaff, D.W., Spunt, R.P., Adolphs, R. (2015). Deconstructing and reconstructing theory of mind. *Trends in Cognitive Sciences*, **19**(2), 65–72.
- Schurz, M., Radua, J., Aichhorn, M., Richlan, F., Perner, J. (2014). Fractionating theory of mind: a meta-analysis of functional brain imaging studies. *Neuroscience and Biobehavioral Reviews*, **42**, 9–34.
- Schurz, M., Tholen, M.G., Perner, J., Mars, R.B., Sallet, J. (2017). Specifying the brain anatomy underlying temporo-parietal junction activations for theory of mind: a review using probabilistic

- atlases from different imaging modalities. *Human Brain Mapping*, **38**(9), 4788–805.
- Schurz, M., Radua, J., Tholen, M.G., et al. (2021). Toward a hierarchical model of social cognition: a neuroimaging meta-analysis and integrative review of empathy and theory of mind. *Psychological Bulletin*, **147**(3), 293.
- Ségonne, F., Dale, A.M., Busa, E., et al. (2004). A hybrid approach to the skull stripping problem in MRI. *NeuroImage*, **22**(3), 1060–75.
- Slaughter, V., Imuta, K., Peterson, C.C., Henry, J.D. (2015). Meta-analysis of theory of mind and peer popularity in the preschool and early school years. *Child Development*, **86**(4), 1159–74.
- Sled, J.G., Zijdenbos, A.P., Evans, A.C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Transactions on Medical Imaging*, **17**(1), 87–97.
- Taylor, H.G. (2020). Neurodevelopmental origins of social competence in very preterm children. *Seminars in Fetal & Neonatal Medicine*, **25**(3), 101108.
- Telford, E.J., Fletcher-Watson, S., Gillespie-Smith, K., et al. (2016). Preterm birth is associated with atypical social orienting in infancy detected using eye tracking. *Journal of Child Psychology and Psychiatry*, **57**(7), 861–8.
- Thomas, M., Karmiloff-Smith, A. (2002). Are developmental disorders like cases of adult brain damage? Implications from connectionist modelling. *Behavioral and Brain Sciences*, **25**(6), 727–50.
- Treyvaud, K., Ure, A., Doyle, L.W., et al. (2013). Psychiatric outcomes at age seven for very preterm children: rates and predictors. *Journal of Child Psychology and Psychiatry*, **54**(7), 772–9.
- Williamson, K.E., Jakobson, L.S., Saunders, D.R., Troje, N.F. (2015). Local and global aspects of biological motion perception in children born at very low birth weight. *Child Neuropsychology*, **21**(5), 603–28.
- Williamson, K.E., Jakobson, L.S. (2014). Social attribution skills of children born preterm at very low birth weight. *Development and Psychopathology*, **26**(4pt1), 889–900.
- Zmyj, N., Witt, S., Weitkämper, A., Neumann, H., Lücke, T. (2017). Social cognition in children born preterm: a perspective on future research directions. *Frontiers in Psychology*, **8**(455), 1–7.