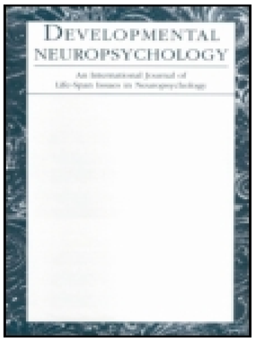

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Tracking the Neurodevelopmental Correlates of Mental State Inference in Early Childhood

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Between ages 4 and 6, children become better at inferring what others are thinking and feeling. However, the neural correlates of these advances are understudied. The current study investigated the relation between performance on a face-based mental state inference task and white matter characteristics. Two tracts of interest, the uncinate fasciculus (UF) and inferior longitudinal fasciculus, were analyzed due to their involvement in social–emotional and face processing, respectively. Findings demonstrate a significant relation between fractional anisotropy in the UF and task performance in 4- but not 6-year-old children. Findings have implications for typical and atypical populations.

Successful social interaction depends on making rapid inferences about what other people are thinking and feeling. Behavioral studies point to early childhood as an important period in the development of emotion recognition and mental state understanding (Wellman & Liu, 2004). For example, between 4 and 6 years of age, children gain the ability to discriminate between felt and expressed emotion and become more adept at inferring mental states when only looking at the eye region of faces (Peterson & Slaughter, 2009; Wellman & Liu, 2004). However, the mechanisms underlying the early development of mental state inference are understudied. Understanding of developmental neural factors involved in face-based mental state inference will provide insight into the development of social abilities in typical development as well as in populations with atypical social interaction and mentalizing abilities, such as populations with autism spectrum disorders (e.g., Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001).

Research with adults, and preliminary evidence from young children (Rice, Viscomi, Riggins, & Redcay, 2014), suggests an important early role of the amygdala in face-based mental state

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inference (i.e., judging emotions from the eye region of the face). Both functional neuroimaging studies (Castelli et al., 2010) and lesion studies (Adolphs, Baron-Cohen, & Tranel, 2002; Shaw et al., 2005) with adults have implicated the amygdala in inferring mental states from the eyes. Further, a recent study with children aged 4 and 6 (Rice et al., 2014) demonstrated a positive correlation between amygdala volume and face-based mental state inference ability. This relation between the amygdala and mental state inference could be due to the amygdala's role in guiding attention to the eye region of the face (Adolphs & Spezio, 2006), which may be an important first step in the process of interpreting the mental states of others.

While evidence supports a role of the amygdala in making mental state inferences from the eyes, the amygdala does not operate in isolation. Structural connections between the amygdala and prefrontal and temporal regions involved in social, emotional, cognitive, and perceptual processing may contribute to face-based mentalizing. Specifically, the uncinate fasciculus (UF) intersects the orbitofrontal cortex and the anterior and medial temporal lobes, including the amygdala (Ghashghaei, Hilgetag, & Barbas, 2007; Von Der Heide, Skipper, Klobusicky, & Olson, 2013)—regions that are involved in social–emotional processes such as theory of mind (Zahn et al., 2007), emotion recognition from faces (Fujie et al., 2008), and reward processing (Grabenhorst & Rolls, 2011). The inferior longitudinal fasciculus (ILF), a tract that connects the occipital lobe and posterior lingual and fusiform cortices to the lateral and medial temporal cortex near the amygdala and parahippocampal gyrus (Amaral & Price, 1984; Catani, Jones, & Donato, 2003; Latini, 2015), may play a more specific role in visual processing of faces. Patients with prosopagnosia, who have difficulty recognizing faces, show reduced tract integrity in the ILF and, for both patients and controls, face recognition ability is related to white matter characteristics in bilateral ILF (Thomas et al., 2009). Thus, the ILF and UF may play a role in the development of face-based mental state inference but this question has not been directly examined within early childhood.

Research investigating the development of these white matter tracts in early childhood is limited (review, Dennis & Thompson, 2013). The few studies that have examined age-related changes in white matter in very young children demonstrate linear and nonlinear effects of age on indices of myelin content (myelin water fraction; Dean et al., 2014), white matter volume (Giedd et al., 1999), and white matter microstructure, for example, fractional anisotropy (FA); (Bashat et al., 2007; Lebel et al., 2012; Walker et al., 2012). Cross-sectional studies from early childhood through adulthood demonstrate gradual development of frontal-temporal tracts including continued increase of FA within the UF past age 30 (Lebel et al., 2012) as well as increasing specificity of connectivity patterns from the amygdala with age (Saygin et al., 2015).

Current research has begun to explore how the early development of white matter tracts relates to individual differences in cognitive abilities in early childhood (e.g., phonological awareness: Saygin et al., 2013) and social abilities in infancy (Elison et al., 2013). Several studies in atypical development reveal differences in FA between children with autism and typically developing children in early childhood in frontal and temporal regions (e.g., Bashat et al., 2007; Walker et al., 2012). However, to our knowledge, no research has examined whether individual differences in social-cognitive ability are related to the typical development of UF or ILF within early childhood (i.e., 4–6 years of age).

The purpose of the current study was to close this gap in the literature by examining the development of structural characteristics of white matter tracts associated with amygdala connectivity (i.e., UF and ILF) and how they are related to behavioral measures of face-based mentalizing in typically developing 4 and 6 year olds. Our primary goal was to investigate the relation between white matter characteristics in the UF and ILF and performance on a face-based mental state inference task (Simplified Eye Reading Test (SERT); Peterson & Slaughter, 2009). In examining this relation, we also sought to identify age-related changes in brain structure and behavioral performance during this pivotal, yet understudied, time in the development of face and emotion processing.

We hypothesized that, compared to 4 year olds, 6 year olds would have higher scores on the SERT and greater FA values in the UF and ILF. We also hypothesized, controlling for age, that children with greater FA values in the UF and ILF would also have higher scores on the SERT. If supported, these findings would suggest that there is a connection between white matter characteristics in regions of the social brain and face-based mentalizing ability, clarifying the mechanisms underlying the well-documented advances in social and emotional ability between ages 4 and 6.

METHODS

Participants

Structural and diffusion-weighted data were collected from 59 children. Due to failure to finish the scan (1 child), motion artifacts (7 children), and technical difficulties (2 children), the final analyses include data from 49 children. Children were recruited from two non-continuous age groups: 4 year olds (n = 20, Mean Age = 4.48, SD = 0.31, 13 females) and 6 year olds (n = 29, Mean Age = 6.54, SD = 0.29, 15 females). These age groups were chosen based on past literature suggesting developmental differences in theory of mind abilities between 4 and 6 year olds (Peterson & Slaughter, 2009; Wellman & Liu, 2004).

Behavioral Measures/Assessments

Each child completed a battery of behavioral measures and assessments including the SERT (Peterson & Slaughter, 2009) and the Kaufman Brief Intelligence Test Second Edition (KBIT-2; Kaufman & Kaufman, 2004). While the SERT was the primary measure of interest, KBIT-2 scores were included as a covariate, as general intelligence may have influenced performance on the SERT and/or white matter characteristics.

Simplified Eye Reading Test

The SERT, a version of the Mind in the Eyes task (Baron-Cohen et al., 2001) designed for preschoolers, involved the child making mental state judgments about the eye region of black-and-white photographs. For each of the nine images, children were given a choice between two mental states (e.g., “serious” vs. “joking”) and scored one point for each correct response. The SERT has sound psychometric properties, including excellent test–retest reliability and satisfactory internal consistency (Peterson & Slaughter, 2009).

Image Acquisition and Processing

Images were collected on a 12-channel head coil on a Siemens 3T scanner (MAGNETOM Trio Tim System, Siemens Medical Solutions). The protocol included one three-dimensional T1 magnetization-prepared rapid gradient-echo (MPRAGE) sequence (176 contiguous sagittal slices, voxel size = 1.0 mm × 1.0 mm × 1.0 mm; repetition time/echo time/inversion time = 1900 msec/2.52 msec/900 msec; flip angle = 9º; pixel matrix = 256 × 256). The diffusion-weighted scan lasted for 6 minutes, 26 seconds and included three non diffusion-weighted volumes ($b = 0$) and 30 diffusion-weighted volumes (consisting of 30 directions, with 3 repetitions for each image). These images were acquired with non-collinear gradient directions ($b = 1000$ s/mm^2) at 128 × 128 base resolution and voxel resolution of 1.8 × 1.8 × 4.0 mm^3.

Structural magnetic resonance imaging (MRI) data were processed using a semi-automated processing stream using the default parameters in FreeSurfer 5.1.0 (Fischl, 2012), which created surface maps of grey and white matter as well as pial boundaries based on a probabilistic atlas. Importantly, this procedure has been validated for children as young as 4 years of age (Ghosh et al., 2010). Two independent, trained coders visually inspected surface maps, compared them to the original T1-weighted images for each participant, and edited segmentation where necessary. A third trained coder checked all segmentations after the edits.

Diffusion-weighted images were visually inspected for motion artifacts and processed using FreeSurfer's TRACULA (Yendiki et al., 2011). TRACULA uses Bayesian statistical methods to reconstruct probabilistic distributions of white matter tracts from each participant's native diffusion images using anatomical priors. This method has shown to be advantageous over traditional local and global tractography techniques. Local tractography requires manual labeling to isolate white matter tracts of interest, which has low reliability. Global tractography has challenges associated with the large solution space, which includes all possible connections between two brain regions (Yendiki et al., 2011). In addition to overcoming these limitations of past local and global tractography techniques, TRACULA is appropriate for child data (Ghosh et al., 2010; Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2014) and can accurately assess participant motion (Yendiki et al., 2014).

In addition to visual inspection, which resulted in the exclusion of two participants, participant data quality was assessed based on the outputs from eddy-current correction and the diffusion-weighted imaging (DWI) images using TRACULA's motion detection algorithm (Yendiki et al., 2014). For each participant, average volume-to-volume translation, volume-to-volume rotation, percentage of slices with excessive intensity drop-out, and average drop-out score for slices with excessive drop-out was calculated. Participants showing outlying values (i.e., 3 standard deviations or greater) on one or more of these measures were excluded from further statistical analyses ($N = 5$). Thus, no participant in the remaining dataset exceeded 1.08 mm translation, 0.01 degrees rotation, or 0.56% bad slices (the definition of a "bad slice" was based on drop-out scores >1, as described in Benner, Van der Kouwe, and Sorensen (2011)). Preprocessing included affine registration of the diffusion-weighted images to the b0 images to correct for misalignment that occurred due to motion and eddy-current distortions. Images were visually inspected for registration errors and no corrections were necessary. The T1-weighted scan was used to create the brain mask, which was obtained by first creating a white matter mask from Freesurfer's cortical parcellation and subcortical segmentation. Next, a mask of the cortex was created by mapping the cortical parcellation labels from Freesurfer to the volume and then growing the labels into the white matter by 2 mm. Next, the entire cortical parcellation and subcortical segmentation was binarized and dilated to create an anatomical brain mask. All three of these masks were then transformed (using intra- and inter-subject registrations) from individual T1 space to each individual's diffusion weighted image and then to MNI (Montreal Neurological Institute) template space using FSL's FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002).

FSL's DTIFIT estimated tensor fits at each voxel to produce FA images, and these were registered to the template space. Importantly, the tensor fits were only used in order to calculate FA values but were not used in the tractography algorithm. Rather, FSL's bedpostx (Behrens, Johansen-Berg, Jbabdi, Rushworth, & Woolrich, 2007) was used to fit the ball-and-stick model of diffusion to each individual's DWIs. The use of the ball-and-stick method over tensor fit to identify the tracts has several advantages, including that it can model multiple diffusion directions per voxel (up to two in this case). Pathway priors were then computed in template space by combining the atlas data with the individual's masks (i.e., atlas data, with manually labeled tracts and anatomical segmentations, were used to calculate *a priori* probabilities that each pathway intersects or neighbors the cortical parcellation and subcortical segmentation labels for each participant). The anatomical priors were then mapped back onto the participant's native DWI images. The local diffusion estimates from the ball-and-stick model and the individual's own cortical parcellations were used to estimate the posterior probability distribution of the location of each pathway in each individual and was estimated with a Markov Chain Monte Carlo (MCMC) algorithm. The tract volumes were then extracted and used to calculate averaged FA estimates from the tensor fit.

Statistical Methods

Behavioral Measures and Questionnaires

All analyses were conducted using R software (R Core Team, 2014). We performed nonparametric statistics on all analyses that included SERT scores in order to account for their ordered categorical nature (i.e., there are only 10 possible scores, ranging from 0 to 9), which could result in nonlinearities in the distance between response categories. To examine changes in mental state inference ability between ages 4 and 6, we conducted a Mann-Whitney U test to compare SERT scores in 4 and 6 year olds. Independent samples t-tests were conducted to determine whether the two age groups differed on Full-Scale IQ (FSIQ, as measured by the KBIT-2).

Brain Analyses

Statistical analyses were conducted on averaged FA from two tracts of interest that were selected due to their role in social cognition, including face and emotion processing: UF and ILF. FA is a measure of white matter tract characteristics, where values reflect tissue properties such as axonal ordering, axonal density, and degree of myelination (Jones, Knösche, & Turner, 2013). This particular diffusion measure was chosen based on past literature indicating that FA has a high signal to noise ratio, contrast to noise ratio, and robust ability to discriminate white and gray matter (Alexander, Hasan, Kindlmann, Parker, & Tsuruda, 2000; Hasan, Alexander, & Narayana, 2004). All analyses were conducted using a weighted average of FA over the entire path distribution. The weighted average calculation weights FA at each voxel by the probability that the voxel is part of the identified tract and thus reduces the contribution from activation in

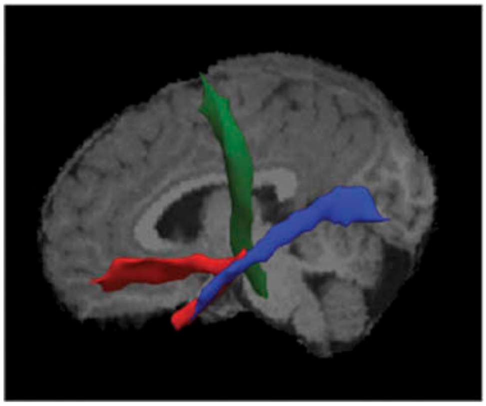

FIGURE 1 Illustration of the two tracts of interest, uncinate fasciculus (UF) (red) and inferior longitudinal fasciculus (ILF) (blue), and the control tract, CST (green). The tracts were estimated from an example participant's native diffusion space and are overlaid on the participant's anatomical image.

less probable voxels. The CST was included as a control tract in the regression analyses to examine the specificity of the relations between the tracts of interest and SERT scores, as we had no a priori hypotheses about the involvement of the CST in face-based mental state inference (Figure 1).

To investigate age-related differences in FA in the brain, we conducted linear regression models predicting FA in UF, ILF, and CST from age (in months). Given that participant sex may have been a confounding factor due to sex differences in amygdala structure (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997), function (e.g., Anderson et al., 2013; McClure et al., 2004), and UF microstructure (Hasan et al., 2009; Lebel & Beaulieu, 2011), we included sex as a covariate in all regression models. We also included FSIQ, amygdala volume, and participant motion parameters (translation and rotation) as covariates. From these models, we examined the main effects of age for all three tracts bilaterally. Finally, we conducted independent samples *t*-tests to determine whether 4- and 6-year-olds differed in the two motion parameters (translation and rotation).

Brain–Behavior Analyses

We used ordered logistic regression to test the main effect of age (in months), the main effect of FA in both tracts of interest, and the interaction of FA and age for each tract. In addition to sex, amygdala volume, and motion parameters, we included FSIQ score as a covariate in the model to rule out the possibility that IQ was driving the relation between white matter characteristics and SERT scores. We also conducted a confirmatory Bayesian analysis to ensure the robustness of the results (see Supporting Information).

RESULTS

Behavioral Measures and Questionnaires

Compared to 4 year olds, 6 year olds scored higher on the Simplified Eye Reading Test, but this numerical difference was not significant (Mann-Whitney $U = 199.5$, $p = .06$, $r = 0.27$, d = 0.52, *Med* (4 year olds) = 6, *Med* (6 year olds) = 7), and there was no difference in scores between males and females (Mann-Whitney $U = 256$, $p = .44$, $r = 0.11$, *Med* (males) = 6, *Med* (females) = 6.5). There were no effects of age or sex on FSIQ as measured by the KBIT-2 (*p*s > .05), although IQ scores are computed in relation to chronological age. Children's FSIQ significantly correlated with their SERT scores (tau = 0.23, $p = .03$, $r = 0.30$).

Brain Analyses

In linear regression models predicting FA in both left and right UF, ILF, and CST from age (in months), with FSIQ, amygdala volume, and participant motion parameters as covariates, the main effect of age was non-significant (*p*s > 0.05) (Figure 2). The two age groups did not differ on the motion parameters of translation and rotation (*p*s > .05). Descriptive statistics for FA values, SERT scores, and FSIQ can be found in Table 1.

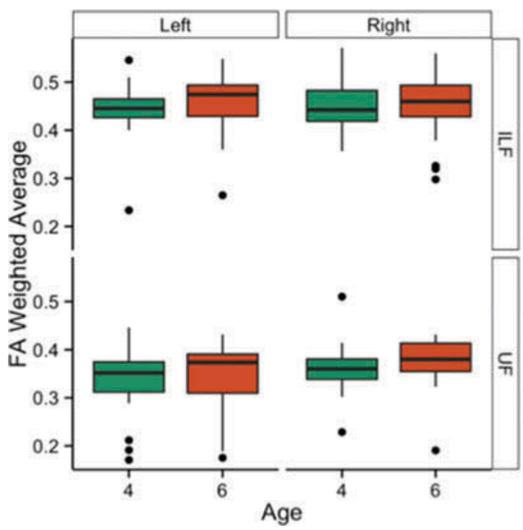

FIGURE 2 Fractional anisotropy (FA) values in uncinate fasciculus (UF), inferior longitudinal fasciculus (ILF), and corticospinal tract (CST; not pictured) did not differ significantly in 4 and 6 year olds (*p*s > .1). Age is displayed as a categorical variable for visualization purposes only. Upper and lower hinges correspond to the first and third quartiles, while upper and lower whiskers extend from the hinge to the highest (for upper whisker) and lowest (for lower whisker) values within 1.5 * IQR (interquartile range) of the hinge. Data beyond the whiskers (plotted as points) are extreme scores.

TABLE 1
Descriptive Statistics for FA Values, SERT Scores, and FSIQ

	4-year-old females		*4- year-old males*		*6-year-old females*		*6-year-old males*	
	Mean	*SE*	*Mean*	*SE*	*Mean*	*SE*	*Mean*	*SE*
Left UF FA	0.33	0.02	0.34	0.03	0.35	0.01	0.34	0.02
Right UF FA	0.36	0.01	0.36	0.03	0.38	0.01	0.38	0.02
Left ILF FA	0.43	0.02	0.46	0.02	0.46	0.01	0.45	0.01
Right ILF FA	0.45	0.01	0.45	0.02	0.46	0.01	0.44	0.02
SERT	6.00	0.39	5.29	0.36	6.53	0.46	6.43	0.33
FSIQ	114.50	2.40	114.40	5.04	117.60	3.53	114.90	3.35

Brain–Behavior Analyses

We used ordered logistic regression to predict face-based mental state inferences scores (SERT; Peterson & Slaughter, 2009) from FSIQ, sex, motion artifact (rotation and translation), amygdala volume, FA, age (in months), and the interaction between FA and age. We accomplished this using four models, one for each tract of interest (UF, ILF) within each of the hemispheres (left, right). In all four of these models, the FA of CST in the corresponding hemisphere, and its interaction with age, were also included as predictors to control for generalized increases in FA explaining or interacting with age to explain variability in SERT. For example, for the left UF, the model included ten predictors: sex, FSIQ, age, motion (translation, rotation), left amygdala volume, left UF FA, left CST FA, and the interactions between age and both FA measurements.

For each tract of interest, there were no main effects of FA (UF, ILF, or CST) on SERT scores, nor were there significant main effects of FSIQ. However, the model for left UF showed significant effects of age, sex, and an interaction between left UF FA values and age (beta = 0.65, $t(37) = 2.03$, $p = .05$; beta = −1.24, $t(37) = 2.06$, $p = .05$; beta = −0.85, $t(37) = 2.56$, $p = .02$) (Figure 3, Table 2). These data indicate that, while controlling for sex, FSIQ, motion, amygdala volume, and FA in a control tract (CST), left UF FA positively correlates with face-based mental state inferences significantly more strongly for 4 year olds than for 6 year olds. These findings hold with or without amygdala volume in the model. Follow-up ordinal correlation analyses within the 4- and 6-year old age groups suggest that, whereas the correlation between left UF FA and SERT is significantly positive in 4 year olds (tau = 0.50, $p < .01$, $r = 0.63$), this is not the case in 6 year olds (tau = −0.06, $p = .68$, $r = 0.08$). This pattern was not observed in right UF or either ILF. Results from the additional Bayesian analysis were consistent with this age-dependent relation between FA and face-based mentalizing (see Supporting Information).

DISCUSSION

Between ages 4 and 6, children become better at making inferences about what others are thinking and feeling based on their facial expressions (Peterson & Slaughter, 2009; Wellman & Liu, 2004). While there is some evidence from lesion, functional, and structural neuroimaging

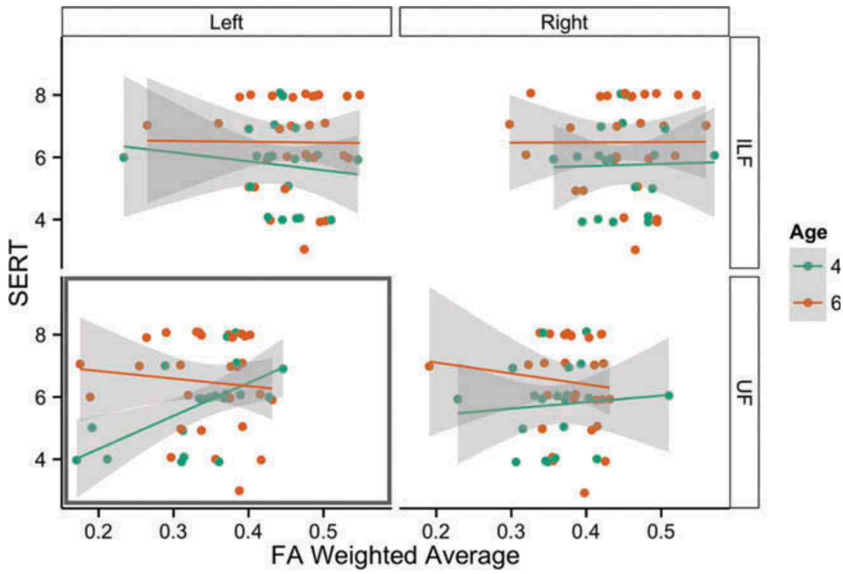

FIGURE 3 Fractional anisotropy (FA) in left uncinate fasciculus (UF) positively correlates with face-based mental state inferences (as indexed by the Simplified Eye Reading Test; SERT) for 4 year olds but not 6 year olds (outlined in dark grey). This pattern was not observed in right UF or either ILF. Standard error ribbons (+/− 1 SE) are depicted in grey for each region and age group. Age is displayed as a categorical variable for visualization purposes only.

studies that the amygdala is involved in face-based mental state inference (Adolphs et al., 2002; Gordon et al., 2013; Rice et al., 2014; Shaw et al., 2005), only one previous study has examined this question in early childhood (Rice et al., 2014) and none have investigated this early development of mental state inference abilities from a brain connectivity perspective.

The current study demonstrated a significant difference between 4- and 6-year-old children in the relation between white matter characteristics (measured by FA) in the UF, a tract that intersects the amygdala and orbitofrontal cortex (OFC), and performance on the SERT, a measure of face-based mentalizing. This relation between white matter characteristics and mind-reading ability held after controlling for IQ, sex, amygdala volume, and participant motion, and was specific to the UF. This indicates that the UF, but not ILF, may be especially important for facilitating mental state inference from the eyes early in development. The specificity of the brain–behavior relation to UF suggests that the face processing abilities that the ILF supports (Philippi, Mehta, Grabowski, Adolphs, & Rudrauf, 2009; Thomas et al., 2009) may be separable from those involved in the recognition of emotions and mental states from faces. Additionally, our finding that left, but not right, UF FA was related to SERT performance in 4-year-olds was consistent with previous literature on left-lateralization of this task (Rice et al., 2014; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). However, the models for left and right UF were not significantly different from each other and thus it is difficult to say anything for certain about laterality due to the small sample size.

TABLE 2
Descriptive statistics from an ordered logistic regression model predicting scores on the Simplified Eye Reading Test (SERT) from age and uncinate fasciculus (UF) and inferior longitudinal fasciculus (ILF) fractional anisotropy (FA), controlling for sex, Full-Scale IQ (FSIQ), amygdala volume (AMY), motion, and FA in a control tract, the corticospinal tract (CST). Age is displayed as a categorical variable for visualization purposes only. Results show a main effect of age and sex in the model for left UF and a significant interaction between left UF FA values and age, such that the relationship between left UF FA and SERT scores decreased as age increased.

	Coefficient	*SE*	t *value*	p *value*
Model predicting SERT Scores from Left UF				
FSIQ	0.62	0.32	1.96	0.06
Sex	−1.24	0.60	2.06	0.05*
Translation	−0.63	0.71	0.88	0.38
Rotation	1.42	0.72	1.96	0.06
Age	0.65	0.32	2.03	0.05*
Left UF	−0.16	0.32	0.51	0.61
Left CST	0.31	0.32	0.97	0.33
Left AMY	0.02	0.31	0.07	0.95
Age × Left UF	−0.85	0.33	2.56	0.02*
Age × Left CST	0.32	0.32	1.00	0.32
Age × Left AMY	0.60	0.37	1.62	0.11
			Pseudo R^2	0.144
Model predicting SERT Scores from Right UF				
FSIQ	0.47	0.28	1.68	0.10
Sex	−0.99	0.56	1.75	0.09
Translation	−0.95	0.68	1.40	0.16
Rotation	1.65	0.72	2.30	0.03*
Age	0.60	0.31	1.94	0.06
Right UF	−0.51	0.29	1.74	0.09
Right CST	0.62	0.30	2.02	0.05*
Right AMY	0.05	0.32	0.16	0.89
Age × Right UF	−0.67	0.34	1.96	0.06
Age × Right CST	0.58	0.34	1.71	0.10
Age × Right AMY	0.48	0.33	1.46	0.15
			Pseudo R^2	0.134
Model predicting SERT Scores from Left ILF				
FSIQ	0.58	0.30	1.95	0.06
Sex	−1.08	0.60	1.79	0.8
Translation	−0.84	0.72	1.16	0.25
Rotation	1.47	0.74	1.98	0.06
Age	0.56	0.32	1.75	0.09
Left ILF	0.09	0.31	0.30	0.77
Left CST	0.11	0.034	0.33	0.74
Left AMY	0.06	0.31	0.18	0.86
Age × Left ILF	0.25	0.37	0.69	0.50
Age × Left CST	−0.16	0.29	0.55	0.59
Age × Left AMY	0.47	0.37	1.27	0.21
			Pseudo R^2	0.102
Model predicting SERT Scores from Right ILF				
FSIQ	0.48	0.30	1.57	0.13

(*Continued*)

TABLE 2
(*Continued*)

	Coefficient	*SE*	t *value*	p *value*
Sex	−1.06	0.57	1.84	0.07
Translation	−0.88	0.72	1.23	0.23
Rotation	1.60	0.76	2.10	0.04*
Age	0.52	0.31	1.69	0.10
Right ILF	0.13	0.32	0.39	0.70
Right CST	0.20	0.32	0.62	0.54
Right AMY	0.06	0.32	0.20	0.85
Age × Right ILF	0.24	0.32	0.76	0.45
Age × Right CST	0.20	0.35	0.56	0.58
Age × Right AMY	0.47	0.34	1.38	0.18
			Pseudo R^2	0.109

Note. *P*-values were approximated by calculating area under the curve more extreme than the observed *t*-value with degrees of freedom penalized for all coefficients in each model, including the cutpoints for the SERT latent variable.
$*p < 0.05$.

Although we do not know the exact mechanism by which individual differences in structural connections in the brain might relate to mental state inference abilities, the UF may act as a bridge between the amygdala—which plays a role in guiding fixations to the eye region of the human face (Adolphs & Spezio, 2006)—and the frontal cortices, which evaluate the meaning behind the facial expression (Frith & Frith, 2003). The current paradigm, however, cannot disambiguate whether higher FA at age 4 directly leads to better mentalizing (e.g., by improving amygdala-OFC communication during the SERT) or whether higher FA values at age 4 instead reflect a developmental history of increased social attention to faces, which could produce increased mentalizing skills. Studies that combine functional neuroimaging with diffusion-weighted imaging (DWI) in a longitudinal design could provide more compelling evidence for the links between the developmental relation between fractional anisotropy in a white matter tract, brain function, and emerging behavioral abilities.

Regardless of the precise mechanism linking higher FA in UF to mentalizing in 4 year olds, 6 year olds do not show the same pattern. Structural connectivity between amygdala and OFC may be more important for mentalizing at age 4—a time of emergence of explicit theory of mind abilities (Wellman & Liu, 2004). In fact, evidence from lesion studies suggests that developmentally early, but not late, amygdala damage negatively impacts theory of mind performance (Shaw et al., 2004; Spunt et al., 2015), emphasizing that the role of the amygdala and related brain networks changes over time. These findings are also consistent with evidence from both human and animal studies suggesting a differential role of the amygdala in early development (Gabard-Durnam et al., 2014; Saygin et al., 2015; Thomas et al., 2001). Additionally, evidence from functional magnetic resonance imaging (fMRI) studies of older children and adults (review, Schurz et al., 2014) suggests that amygdala-prefrontal networks may play less of a role in mental state inference from the eyes later in development. Finally, a recent study with late-onset amygdala lesion patients showed intact behavioral performance and normative cortical network activation during a theory of mind task (i.e., false belief reasoning; Spunt et al., 2015), providing evidence that connections between the amygdala and cortical networks may not be necessary for typical theory of mind abilities by adulthood. The hypothesis that amygdala-prefrontal networks may play an important role in the emergence, but not maintenance, of theory of mind is consistent with the skill learning hypothesis (Johnson, 2001), which suggests that different neural substrates may be involved in the acquisition of a particular skill and the use of that skill. However, future longitudinal studies will be needed to directly test this theory and to test the causal relation between FA and improved mentalizing.

In spite of age-related changes in the relation between face-based mentalizing and white matter characteristics, we did not find evidence of age-related changes in FA within the UF or ILF in the current study. Given evidence that the UF and ILF exhibit a protracted development (Lebel & Beaulieu, 2011), it is possible that the window between ages 4 and 6 was too narrow to capture the gradual change in tract development. Indeed, previous studies have found age-related changes in early childhood within these tracts when examining a wider age range (e.g., Lebel & Beaulieu, 2011; ages 5–10). Future research investigating age-related changes in tract FA within the narrow age range of the present study would benefit from a longitudinal investigation, particularly given that there is large variability in brain development within each age group.

Finally, it is important to note that this study had three limitations related to data acquisition and data interpretation. First, the number of non-collinear directions in our scanning protocol (30) is on the lower end of the number of directions needed to accurately reconstruct white matter tracts (Jones et al., 2013); however, this was a necessity due to the young age range of our sample and the need to minimize acquisition time. Second, the use of FA to examine developmental changes in white matter is a limitation, given that FA relies on a tensor fit, which makes it difficult to determine the primary direction of crossing fibers in complex anatomical regions of the brain. However, TRACULA circumvents some of these concerns by using a tensor-based metric, which identifies tracts using a ball-and-stick model, and with the use of anatomical priors mapped to each individual's own anatomy. We also model up to two crossing fibers in our tractography analyses. A final limitation is that the biological mechanisms underlying diffusion anisotropy measures remain unclear; thus we are unable to make conclusions about underlying anatomy, although there is some evidence that FA values reflect tissue properties such as axonal ordering, axonal density, and degree of myelination (Jones et al., 2013).

CONCLUSION

The current study suggests a role of the left UF, a white matter tract intersecting the amygdala and orbitofrontal cortex, in the development of face-based mental state inference abilities. Specifically, we found evidence for differential involvement of the UF at age 4 versus 6. This differential relation with age is consistent with a small but growing body of literature documenting a changing role of the amygdala throughout development (e.g., Adolphs, 2010; Spunt et al., 2015) and highlights the importance of assessments of brain–behavior relations throughout typical development, as neural circuits supporting behaviors in older children and adults may not always reflect the developmental emergence of those behaviors (see Johnson, 2001). Diffusion tensor imaging is a promising technique to investigate these questions in young children and clinical populations as participants are not required to perform tasks while in the scanner and can view videos of their choice. Thus, the use of child-friendly brain imaging techniques, such as DWI, with concurrent behavioral indices of social development in a longitudinal design promises to significantly advance our understanding of the early typical and atypical development of social cognition.

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SUPPLEMENTAL MATERIAL

Supplemental material for this article can be accessed at http://www.tandfonline.com/hdvn.

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