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Early microstructure of white matter associated with infant attention

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ABSTRACT

Early infancy is characterized by rapid brain development that occurs alongside, and in response to, the development of cognitive and behavioral functions, including attention. Infants' ability to orient and sustain attention to stimuli develops in concert with refinement of the orienting network in frontoparietal regions of the brain. Infants (n = 97) underwent magnetic resonance imaging at one-month of age and data were fit to a diffusion tensor imaging model to calculate fractional anisotropy (FA) and radial diffusivity (RD), as well as to a neurite orientation dispersion and density imaging model to calculate intracellular volume fraction (ν_{ic}). Infant attention was assessed at six months of age using a dynamic puppet task (Cuevas and Bell, 2014). Infants with higher FA in the corpus callosum and anterior cingulum showed increased orienting behaviors. Our findings indicate that increased microstructure of the white matter tracts in the orienting network may play a role in the early neurodevelopment of attentional orienting behaviors.

1. Early microstructure of White matter associated with infant attention

Attention plays an important role in many cognitive tasks, including cognitive control, decision making, and planning (Colombo et al., 1991), and is vital for activities necessary for detecting and reacting to danger, obtaining resources, engaging with others, and regulating emotions (Colombo, 2001; Posner and Petersen, 1990; Putnam et al., 2008). Attentional difficulties are associated with cognitive and behavioral problems such as attention deficit hyperactivity disorder, anxiety disorders, and other inter- and intra-personal issues (Nigg and Nikolas, 2008; Pérez-Edgar et al., 2014). Given the importance of attention in many cognitive and behavioral outcomes, a better understanding of early attention is essential for targeting deficits in attentional processes early in life when they are most sensitive to insults and perhaps amenable to intervention (Pine et al., 2009).

1.1. Infant attention

The comparator model guided early theories of infant attention, and posited that visual looking behaviors are a proxy for encoding, or visual learning/attention. Infants' attention toward stimuli depends on whether they have an existing internal representation for the object they are encoding (Sokolov, 1963). Upon repeated exposures, the duration of looking toward the stimuli decreases, as the infant can readily access their constructed internal representation of the stimuli. Colombo et al. (1991) built on this and proposed that infants who can disengage and look away from the repeated stimuli sooner are more efficient and faster processors; they require less time to complete their internal representation of the stimulus presented. Referred to as visual habituation, this is a cornerstone of contemporary views of infant attention. Here, we conceptualize infant attention as infants' looking behaviors (both orienting towards the novel stimuli at initial presentation and also sustaining attention to the stimuli across the experimental trial). The procedure used was designed to elicit habituation to repeated stimuli (Colombo, 2001; Cuevas and Bell, 2014).

1.2. Infant neurodevelopment

Early infancy is characterized by rapid brain development (Stiles and

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Jernigan, 2010) that occurs alongside, and in response to, the development of cognitive and behavioral functions, including attention (Kagan and Herschkowitz, 2005). Increasingly, neuroimaging techniques, such as magnetic resonance imaging (MRI), have characterized the macro- and microstructural changes occurring during infancy (Gilmore et al., 2007; Mukherjee et al., 2001). This development follows a specific spatio-temporal pattern, with differing brain regions and networks showing distinct growth trajectories (Dean et al., 2017, 2018; Knickmeyer et al., 2008; Lebel et al., 2008; O'Muircheartaigh et al., 2014).

Attention is manifest from three complex networks which function in concert with, and influence the actions of, other brain networks (Petersen and Posner, 2012; Posner et al., 2006). The "alerting" network is sensitive to incoming information, allowing one to achieve and maintain an alert state. The "orienting" network is concerned with orienting and sustaining attention in space, priming the attentional system to respond to certain types of stimuli and to ignore others. Finally, the "executive control" network oversees a series of processes including selecting and switching goals, inhibiting inappropriate responses, and resolving behavioral conflicts.

The three attention networks develop in concert with the established spatio-temporal pattern, with the alerting and orienting networks, which are located in parietal and temporal areas, developing immediately after birth, while the executive control network, which is located more ventrally, is slower to mature (Fan et al., 2002; Posner et al., 2006).

However, while several studies have characterized the attentional networks in the adult brain (Fan et al., 2002; Gao et al., 2009; Posner and Rothbart, 2007), comparatively fewer studies have examined these networks during early infancy (e.g., Posner et al., 2014). One of the few studies examining event related potentials (ERPs) and cortical source analysis in infants suggests that the ERP component associated with visual attention, known as the Negative central (Nc) component, is localized to inferior and superior regions of the prefrontal cortex and anterior cingulate (Reynolds et al., 2010; Reynolds and Richards, 2005; Reynolds and Romano, 2016). Moreover, over the course of the first year of life, this signal changes such that it becomes more localized within these brain regions (Reynolds et al., 2010). This refinement of the ERP signal suggests that the underlying neural systems responsible for attention undergo rapid development early in life. However, to our knowledge, no studies systematically examine infant neurodevelopment using advanced MRI techniques, particularly diffusion tensor imaging (DTI), and visual attention during early infancy. Given the integral role that neural networks play in subserving broader aspects of cognition, it is important to elucidate how early neurodevelopmental processes may be associated with the development of attentional mechanisms.

1.3. White matter microstructure

White matter subsists of bundles of myelinated nerve fibers necessary for the transmission of neural communication and organization of higher level cognitive functioning (Fields, 2008), of which early attention is a precursor (Lawson and Ruff, 2004). Diffusion tensor imaging (DTI) is a non-invasive quantitative MRI technique that is sensitive to the density and spacing of cellular membranes, cellular cytoskeleton, and the myelination of axons (Alexander et al., 2007, 2011). In particular, fractional anisotropy (FA) is a quantitative metric representing the direction and coherence of white matter fiber tracts, but it is susceptible to changes due to alterations in diffusivities along the axes of the diffusion tensor (Alexander et al., 2007; Jones et al., 2013). Radial diffusivity (RD) represents the average of the perpendicular diffusivities (Johansen-Berg, 2010) and is sensitive to alterations in myelin structure (Alexander et al., 2007; Beaulieu, 2002), though, like other DTI based measures, is not specific to myelin.

Neurite orientation dispersion and density imaging (NODDI; Zhang et al., 2012) is a diffusion MRI technique which estimates microstructural complexities of neurites and provides more specific markers of brain tissue microstructure than diffusion parameters such as FA or RD (Zhang et al., 2012). NODDI estimates the intracellular volume fraction parameter, ν_{ic}, a metric that is sensitive to the underlying neurite density. NODDI measures undergo rapid development during the first years of life and provide complementary information to that provided by DTI measures during early infancy (Dean et al., 2017).

1.4. The current study

Here, we examined the neurobiological foundation of infant attention by assessing relations between one-month infant white matter microstructure and orienting and sustained attention behaviors observed at six months of age. Infants rely on the orienting network to sustain attention to relevant and novel stimuli (Colombo et al., 1991; Rothbart et al., 2011); thus, we focused on six prominent bilateral white matter tracts that form connections with or pass closely by brain regions involved in the orienting network, specifically the cingulum, corpus callosum, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus (Fig. 1). FA was our focal measure.

We hypothesized that six-month-old infants who had higher FA in the selected tracts at age one-month would orient longer to the novel stimuli upon initial exposure, as infants prefer to look at novel stimuli (Colombo, 2001). Based on Colombo's work suggesting that infants who habituate toward stimuli are more efficient, we also predicted that infants with higher, more efficient FA would sustain attention to a lesser degree upon repeated exposure to the same stimuli. Of note, our hypotheses assume stability of individual differences in FA over the five-month interval between MRI and attention assessments.

Following initial analyses, we performed subsequent tests to consider the neurobiological *interpretation* that higher FA values reflected more myelination. First, to rule out the explanation that the association of higher FA in the selected tracts with attention simply reflected individual differences in overall brain maturation rather than specific effects of the selected tracts, we controlled for average whole brain FA measured from a whole brain white matter mask. Next, we examined the two additional diffusion imaging measures thought to be more sensitive to myelination than FA: radial diffusivity (RD) and the neurite orientation dispersion and density imaging (NODDI) measure, intracellular volume fraction (ν_{ic}).

2. Method

2.1. Participants

We analyzed data from a longitudinal study of 149 mother-infant

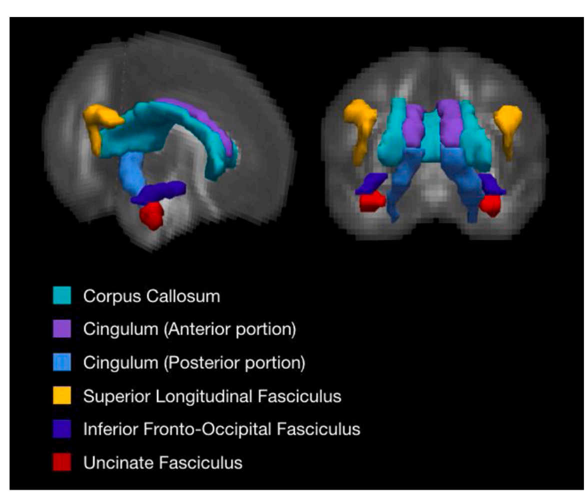

Fig. 1. Selected orienting network tracts.

dyads. We recruited mothers prior to or during the second trimester of pregnancy (<28 weeks gestation) through birth clinics, print advertisements, and other methods. Mothers were recruited based on several criteria, including: between 18 and 40 years of age, expecting singleton births, having no diagnosis of major psychiatric illnesses (i.e., schizophrenia, bipolar disorder, borderline personality disorder), having no pre-existing neurological conditions or major head trauma, having no autoimmune disease or infections during pregnancy, and having an uncomplicated childbirth. Additional exclusionary criteria included time spent in the neonatal intensive care unit (NICU) for medical interventions and if the infant did not go home with the mother at discharge. Mothers confirmed these criteria through interviews prior to enrollment and study team members verified them using medical history questionnaires obtained during the study.

Demographic measures indicated that 51.7 % (n = 77) infants were girls. Infants and mothers were primarily Caucasian (87.8 % and 90.5 %, respectively). Mothers were primarily middle class (median family income $80,001-$100,000). Many of the mothers had completed a graduate degree (50.0 %) or were college graduates (44.6 %). Mothers were 32.94 years old on average (SD = 3.83). Table 1 provides demographic information of the full sample.

We conducted statistical analyses on a subset (n = 97) of the full sample from whom both DTI and attention data were available (see Table 1 for sample size breakdown). One infant was removed from analyses due to excessive fussiness and inability to complete the attention behavior task. T-tests comparing the infants with useable data (n = 97) and those infants not in the study (n = 52) indicated that there were no differences in infant sex, family income, and maternal education levels among participants included and those participants not included in analyses. There were, however, significant differences in infant age at time of scan; infants included in the final sample (M = 32.91 days, SD = 6.03) were younger than those not included (M = 36.23 days, SD = 9.77); $t(72.396) = 2.24$, $p = 0.03$. As such, infant age at time of scan is included in all analyses as a covariate.

Table 1
Participant demographic characteristics.

Sample characteristics	Combined	Males	Females	*p* value
N			149	72
Mean ± standard deviation infant age at scan (days)			34.1 ± 7.7	33.1 ± 7.2
Mean ± standard deviation gestation (weeks)			39.6 ± 1.4	39.6 ± 1.3
Mean ± standard deviation birth weight (pounds)			7.7 ± 1.1	7.6 ± 1.1
Mean ± standard deviation birth length (inches)			20.2 ± 1.0	20.2 ± 1.1
Mean ± standard deviation head circumference (inches)			13.7 ± .6	13.7 ± .5
APGAR Score				
	1 min			
		Problematic (0−6)	14	6
		Satisfactory (7−10)	118	56
		Not Reported	17	10
	5 min			
		Problematic (0−6)	3	1
		Satisfactory (7−10)	129	61
		Not Reported	17	10
Mean ± standard deviation maternal age at birth (years)			32.9 ± 3.8	33.0 ± 4.0
Maternal racial background				
	African American/Black		3	0
	Asian		7	3
	Caucasian/White		134	68
	Native American Indian/Native Alaskan		3	0
	Other		1	0
	Not Reported		1	1
Maternal education				
	Some High School		1	1
	High School Graduate		1	0
	Trade School/Some College		6	3
	College Graduate/Graduate Training		66	28
	Graduate Degree		74	40
	Not Reported		1	0
1-Month MRI (*N*)			103	49
6-Months Attention Task (*N*)			141	69
Final Dataset (MRI + attention task) (*N*)			97	46

2.2. *Procedures and measures*

Infants underwent MRI at one-month of age and behavioral assessments at six-months of age. Subsequent testing occasions occurred at 12, 18, and 24 months but are not included in this study. The local Institutional Review board approved all study procedures, and experimenters obtained parental consent at each time point from each participating family.

2.2.1. *MRI data acquisition*

At one-month of age (M = 32.91 days, corrected for gestational age), infants underwent Magnetic Resonance Imaging (MRI) during natural, non-sedated sleep. Numerous techniques were utilized to enhance imaging data collection (blinded for review). Scans were scheduled during infant's normal naptimes and typically occurred after the infant was fed. Once asleep, experimenters took the infant into a darkened MRI scanner suite and positioned them into the MRI headcoil. Infants were swaddled using an infant MedVac vacuum immobilization bag (CFI Medical Solutions, USA) and foam cushions were placed around their heads to minimize intra-scan motion. To minimize acoustic noise from the MRI scanner, a foam insert was fit to the inside of the scanner bore, infants wore malleable ear plugs and MiniMuff® (Natus Medical Incorporated) neonatal noise-attenuating ear covers, while electrodynamic headphones (MR Confon, Germany) played white noise during the image acquisition. Imaging protocols were specially designed to limit the peak gradient slew-rates of the MRI pulse sequence to reduce the volume of the scan. A trained research staff member continuously monitored the child throughout the scan and mothers could remain in the scanner suite if they chose to do so.

A 3 T General Electric MR750 Discovery scanner using a 32 channel receive-only head RF array coil was used to obtain imaging data (Nova Medical, Wakefield, MA). During the MRI, structural T_1- and T_2-weighted images, resting state functional MRI, and a multi-shell diffusion weighted imaging were acquired. The total protocol acquisition took under an hour. Diffusion weighted images (DWIs) were acquired with a diffusion-weighted pulsed-gradient spin-echo sequence with EPI readout. 69 DWIs were acquired, 6 with no diffusion weighting (i.e., b-value = 0 s/mm^2) and 63 acquired along non-collinear diffusing encoding directions (b = 350 s/mm^2 [9 directions], b = 800 s/mm^2 [18 directions], and b = 1500s/mm^2 [36 directions]). Repetition time [TR] and echo time [TE] were 8400 ms and 94 ms, respectively. Imaging field of view [FOV] was 25.6 cm × 25.6 cm with an acquisition matrix of 128 × 128, providing a 2 mm × 2 mm in-plane resolution. Whole brain coverage was achieved through 60 sagittal-oriented contiguous slices with a slice thickness of 2.0 mm. DWIs underwent significant pre-processing, including manual assessment of individual images using an in-house processing pipeline that included correction for eddy-currents and motion (Jenkinson et al., 2002) and skull-stripping (3dSkullStrip tool; http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dSkullStrip.html). Diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI) models were fit to the diffusion weighted data and maps were normalized to a population specific template that was created using DTI-TK and a representative subset of the study sample (Zhang et al., 2006). The study enrolled and successfully matriculated 149 families for the MRI acquisition at one-month of age. However, due to motion artifacts or unsuccessful scans, $n = 103$ participants had complete DTI data.

White matter regions of the corpus callosum, anterior and posterior cingulum, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus were selected as these tracts have been suggested to be involved in orienting attention in older samples (Posner and Fan, 2008; Posner and Rothbart, 2007; Rothbart et al., 2011). The Johns Hopkins University (JHU) neonatal atlas (Oishi et al., 2011) was used to isolate these white matter tracts by first registering the JHU atlas to the study specific template and then inverse warping the white matter regions of interest to each individual's native space. Each individual's FA, RD, and ν_{ic} of specific tracts were calculated from native space. Whole brain average white matter FA, RD, and ν_{ic} were calculated from a subject-specific white matter mask that included all white matter voxels and was constructed from each subject's FA map. For additional descriptions of image preprocessing, brain template creation, and normalization, refer to Dean et al., 2017, 2018.

2.2.2. Infant attentional orienting behaviors

Of the original 149 families, $n = 142$ mothers and their infants returned to the laboratory at six-months of age for a battery of observed behavioral tasks eliciting mostly emotional behaviors. All laboratory assessments were video recorded for later review and coding. One task explicitly measured infant attention and is therefore the focus of the current investigation. We scored infant's orienting and sustained attention to enticing stimuli using an attention behavior task created by Cuevas and Bell (2014). The task comprised three trials, during which the experimenter presented the infant with two hand puppets adorned with large eyes and jingle bells. The experimenter presented the puppet stimuli for 60 s each trial; however, if infants diverted their attention away from the puppets for at least three seconds, the trial ended early.

To code infant attention behaviors, we counted the number of seconds during each 60 s trial that the infant attended to the puppets. We also scored shifts in attention and affective response across each of the three 60-second trials by dividing each trial into ten second epochs. During each ten second epoch, we coded whether the infant oriented to the puppet stimuli or not (0/1), the number of shifts in attention accrued in that epoch, and the infant's affective response on a Likert scale ranging from -3 (negative) to 3 (positive). The affective response variable was included in case infants responded negatively to the stimuli. In general, the mean affective response in the sample was 0.19 (SD = .32). As such, affective valence did not impact attentional orienting during the task; therefore, it is not included in analyses.

A master coder trained three other coders on the attention scoring. Once training reliabilities reached a Cohen's $\kappa = .80$ or higher, coders began to work independently. The master coder also double coded 20 % of all participants, and randomly checked reliabilities and performance of all coders to ensure coding stability and accuracy. No problems were detected during the coding process.

2.3. Data scoring and analysis

Attention variables used for data analysis included orienting and sustained attention. Descriptive statistics are shown in Table 2. In general, infants oriented to the puppets longest on the first trial (mean looking time 54 s), with decreasing looking times across the next two trials (50 and 42 s, respectively), though this pattern was not consistent across all infants. Correlations indicate that infants who oriented longer during the first trial also oriented longer for the remaining trials (Table 2). Further analyses use two variables calculated from the looking times: orienting and sustained attention. Orienting was defined as the amount of time the infant spent orienting towards the stimuli during Trial 1; sustained attention was a dichotomous variable, defined by an infant's orienting to the stimuli for greater than or equal to 45 of the allotted 60 s of the trial on two consecutive trials (i.e., they oriented at least 45 s to the stimuli on Trial 1 and Trial 2, and/or on Trial 2 and Trial 3).

Table 2
Partial correlations among infant attention variable, holding infant age and sex constant.

Infant Attention	1.	2.	3.
Trial One	———		
Trial Two	.339**	———	
Trial Three	.219**	.393**	———
Mean	54.553	49.801	41.809
S.D.	12.217	16.407	19.218

Note. * $p < 0.05$. ** $p < 0.01$.

2.4. Multiple regression analyses

Using multiple regression, we examined whether the underlying microstructure of selected white matter tracts at one-month of age as measured by FA would predict the attention variables at six-months of age, while controlling for family income at birth, infant sex, infant gestational age at time of scan, and the corresponding whole brain FA. Parallel regressions were subsequently conducted using radial diffusivity (RD) and intracellular volume fraction (ν_{ic}). In all analyses, we use a Bonferroni correction to adjust significance values for multiple comparisons ($p < .05/6$).

3. Results

3.1. Orienting network average FA in relation to later infant attentional behaviors

The first step in analyses was to examine whether the brain's orienting network (an average of all six orienting tracts of the brain) was related to attentional orienting and sustained attention behaviors at six months, using a single regression analysis. Though it did not withstand multiple comparisons correction, the regression revealed a positive relationship between one-month orienting network average FA and six-month orienting attention ($\beta = 258.594$, $p = .024$, adjusted $R^2 = .013$; see first row of Table 3). A similar relationship was not found for sustained attention. The intention of controlling for whole brain average FA was to discount the possibility that the finding was a result of general brain maturation rather than an effect due to FA in the six white matter tracts.

3.2. FA in specific white matter tracts in relation to later infant attentional behaviors

The next step in analyses was to determine whether specific white matter tracts were driving the observed relation between average orienting network FA and behavioral attention. We conducted six multiple regressions relating FA in the corpus callosum, anterior and posterior cingulum, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus to infant attentional orienting. Multiple regression analyses revealed that two of the six tracts were significantly related to six-month orienting attention (see Fig. 2). In particular, infants with higher FA in the corpus callosum ($\beta = 188.001$, $p = .002$, adjusted $R^2 = .064$) and anterior cingulum ($\beta = 238.247$, $p = .008$, adjusted $R^2 = .035$) at one-month of age showed significantly increased orienting at six-months of age. The posterior cingulum, uncinate fasciculus, superior longitudinal fasciculus, and inferior-fronto occipital fasciculus were not significantly related to infants' orienting, as shown in Table 3.

Consistent with the first analysis examining average orienting network FA and sustained attention, FA measures from the individual white matter tracts were not significantly associated with sustained attention.

Table 3
Beta Values for White Matter Microstructure Metrics Predicting Attention Variables.

	Orienting					Sustained Attention				
	Unstandardized β	95 % confidence interval for β		s.e.	*p*	Unstandardized β	95 % confidence interval for β		s.e.	*p*
		Lower Bound	Upper Bound				Lower Bound	Upper Bound		
Average Orienting Network FA	258.594	34.937	482.251	112.507	.024	6.122	−1.665	13.909	3.917	.122
Averaged Hemispheric FA										
Corpus Callosum	188.001	71.103	304.900	58.804	**.002**	4.496	.369	8.623	2.076	.033
Anterior Cingulum	238.247	63.321	413.173	87.994	**.008**	5.614	−.514	11.743	3.083	.072
Posterior Cingulum	−34.781	−242.419	172.857	104.449	.740	−2.124	−9.230	4.982	3.575	.554
Uncinate Fasciculus	118.981	−38.603	276.566	79.270	.137	3.252	−2.175	8.678	2.730	.237
Superior Longitudinal Fasciculus	154.538	−8.732	317.808	82.131	.063	2.631	−3.051	8.312	2.858	.360
Inferior Fronto-occipital Fasciculus	8.637	−155.611	172.885	82.622	.917	1.497	−4.123	7.118	2.827	.598
Averaged Hemispheric RD										
Corpus Callosum	−58995.554	−131113.623	13122.516	36277.896	.108	262.676	−2256.459	2781.811	1267.212	.836
Anterior Cingulum	−74611.290	−177748.510	28525.929	51881.606	.154	−1916.189	−5484.444	1652.067	1794.957	.289
Posterior Cingulum	−51668.591	−185205.168	81867.986	67173.540	.444	−390.328	−5000.918	4220.261	2319.287	.867
Uncinate Fasciculus	−13905.617	−84164.635	56353.401	35342.728	.695	522.705	−1894.790	2940.200	1216.084	.668
Superior Longitudinal Fasciculus	−40319.987	−98378.683	17738.709	29205.542	.171	−1604.929	−3595.485	385.628	1001.319	.113
Inferior Fronto-occipital Fasciculus	−76454.668	−175464.705	22555.370	49805.490	.128	574.198	−2877.335	4025.731	1736.241	.742
Averaged Hemispheric ν_{ic}										
Corpus Callosum	88.146	−64.594	240.886	76.833	.254	.516	−4.827	5.859	2.688	.848
Anterior Cingulum	167.966	−23.490	359.421	96.309	.085	.938	−5.823	7.700	3.401	.783
Posterior Cingulum	26.364	−153.858	206.586	90.658	.772	.796	−5.462	7.055	3.148	.801
Uncinate Fasciculus	−50.055	−152.293	52.183	51.429	.333	−1.967	−5.511	1.578	1.783	.273
Superior Longitudinal Fasciculus	156.888	39.291	274.485	59.155	.010	2.805	−1.399	7.010	2.115	.188
Inferior Fronto-occipital Fasciculus	135.608	−82.187	353.402	109.558	.219	−3.268	−10.865	4.330	3.822	.395

Note. Regression equations included family income at birth, infant gestational age at time of scan, infant sex, and Whole Brain measures of each respective metric as covariates (e.g., for regressions including FA metrics, including Whole Brain FA as a covariate). *p-values* withstanding Bonferroni multiple comparison corrections ($p < .05/6$) are bolded.

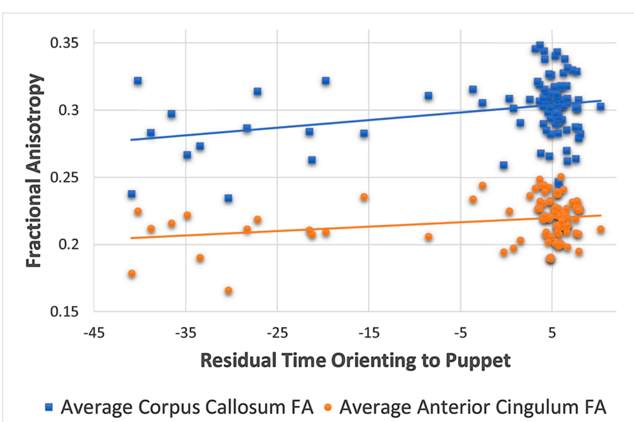

Fig. 2. Scatterplot of significant FA and Orienting regression findings.

3.3. RD and ν_{ic} in specific white matter tracts in relation to later infant attentional behaviors

FA is not specific to the underlying tissue microstructure (Jones et al., 2013; Jones and Cercignani, 2010). Therefore, follow-up analyses examined whether RD, which is more indicative of myelination, and ν_{ic}, which is a measure of neurite density, underlie observed associations between FA and orienting and sustained attention. Only 1 of the 24 regressions was significant at $p < .05$; regression analyses showed that higher ν_{ic} in the superior longitudinal fasciculus at one-month of age was related to increased orienting at six-months of age, but this did not withstand multiple comparisons correction. There were no significant results for ν_{ic} at one month and sustained attention at six months or RD at one month and either orienting nor sustained attention at six months (Table 3).

4. Discussion

This study evaluated relations between infant white matter neurodevelopment in preselected orienting network tracts at one-month of age and observable attention behaviors at six-months of age. In doing so, we hope to bridge research traditions on infant cognition and underlying microstructural neurodevelopment of circuit components to promote a richer understanding of the complex relations between brain and behavior in infancy.

4.1. FA and neurite density in the orienting network

Consistent with the adult literature (Posner and Rothbart, 2007), FA in specific orienting network tracts are important in later attention behaviors. Specifically, our results indicated that infants with higher FA in tracts associated with attention as early as one-month of age orient to enticing stimuli for longer periods of time in middle infancy even after controlling for whole brain FA. Importantly, this association does not simply reflect a general individual difference in the trajectory of brain development, which would have been indicated if behavioral measures of attention had been associated with higher FA in regions that are not functionally linked to attention.

These analyses focused on six prominent bilateral white matter tracts that form connections to or pass by frontoparietal regions thought to be implicated in the orienting network in infancy; namely, the anterior and posterior cingulum, the corpus callosum, the superior longitudinal fasciculus, the inferior fronto-occipital fasciculus, and the uncinate fasciculus (Posner and Fan, 2008; Posner and Rothbart, 2007; Rothbart et al., 2011). We found that increased FA in the anterior but not the posterior cingulum related to attentional orienting. The cingulum bundle is an important white matter tract in the brain that connects frontal, parietal, and temporal structures. Due to its size, researchers often segment the cingulum into anterior and posterior portions (Wu, Sun, Wang, Wang, et al., 2016). The anterior portion plays a role in decision making, emotion, and other executive functioning skills, while the posterior portion is implicated in other cognitive functioning. We only identified relevant tracks in early infancy; it is possible that the posterior cingulum would be related to later developing cognitive skills, or that as the posterior cingulum develops that it will, in future, relate to attention. Future work could follow developmental trends in the cingulum to better understand how this white matter tract relates to behavioral attention skills.

The corpus callosum, where FA values were also significantly associated with orienting, is the largest white matter tract in the brain, connecting the left and right hemispheres and allowing for cognitive and emotional functioning and communication between hemispheres (Constable et al., 2008). Earlier research has found FA reductions in the corpus callosum of children with ADHD, suggesting that the corpus callosum plays a key role in attentional monitoring (Gazzaniga, 2000; Langevin et al., 2014); our findings suggest that these functions may start developing as early as one-month of age.

Though FA is highly sensitive to microstructural changes, it lacks specificity as a biomarker of microstructural architecture (Alexander et al., 2007). Regression analyses conducted using measures of neurite density did not withstand multiple comparisons corrections. Before correction, the superior longitudinal fasciculus, when measured both via FA and ν_{ic}, appeared to relate to attentional orienting behaviors at six-months of age. The superior longitudinal fasciculus is large in size and projects to frontal, occipital, parietal, and temporal lobes, and it plays a role in regulating behavior during motor tasks. It is involved in focusing spatial attention and regulating selection and retrieval of spatial information (Schmahmann et al., 2008). The trending significance of higher FA and neurite density in the superior longitudinal fasciculus may suggest that the underlying *neurite* microstructure in this tract is an important component of neural underpinnings of infant attentional behaviors.

The uncinate fasciculus is a white matter tract connecting limbic structures to more frontal structures. Among all tracts selected, the uncinate fasciculus is the slowest tract to develop when assessed via FA (von Der Heide et al., 2013), and thus perhaps not ideal to include in studies of very young (one-month-old) infants. Indeed, in a sample of older infants imaged at six-months of age, (Elison et al., 2013) found that increased FA in the uncinate fasciculus predicted joint attention when measured later at nine-months of age. The inferior fronto-occipital fasciculus is a fiber bundle connecting frontal, occipital, and temporal areas, and is involved in the processing of visuospatial information, reading, and attention (Catani and De Schotten, 2008; Schmahmann et al., 2008; Wu et al., 2016a, 2016b). Though the microstructure of these tracts develops and forms connections throughout the brain during pre- and post-natal stages of development (Dubois et al., 2014), these tracts are still relatively immature at one-month of age. Results here suggest that one-month of age may be too early for the neurite microstructure to predict further neural development that influences orienting behaviors at six-months of age. Future work with a larger sample or different timepoints of measurement may be able to elucidate stronger relations.

The absence of significant findings with RD may not be surprising given the age of the infants when scanned. Myelination follows a protracted spatiotemporal pattern of development; structures such as the cerebellum, pons, and internal capsules undergo myelination before others (Deoni et al., 2011; Dubois et al., 2008). However, myelination in these structures proliferates around three-months of age and myelination of the frontoparietal structures selected for analysis in this study would begin around four- to six-months of age (Deoni et al., 2011). Therefore, the orienting network white matter tracts delineated here may be relatively unmyelinated at such an early age (Kinney et al., 1988), and thus myelination of the tracts at one-month of age would not predict attentional processes five months later. Nonetheless, the inclusion of RD and ν_{ic} analyses in the current study provide additional information about the neurobiological mechanisms involved, and assessment of alternative white matter imaging metrics may help provide further insight into the relationships at hand.

5. Limitations and conclusions

The infant attention literature has not yielded a consensus on how to define and measure attention. Infant attention has been operationally defined and assessed in a multitude of ways; methods and definitions have focused on visual fixation, preference, discrimination, encoding, habituation, and processing speeds, among other characteristics (Colombo, 2002). These aspects of infant attention have considerable overlap, and further parsing is necessary to have a clear understanding of what infant visual attention entails. In this work, we defined sustained attention as looking towards the stimuli for at least 45 of the 60 s allotted in two consecutive trials, with the intention of tapping into processes that reflect Colombo's (2001) distinction between fast and slow visual processors. Importantly, our results did not become significant after relaxing the sustained attention threshold from 45 s to 30 s, indicating our measure of sustained attention may not be fine-tuned enough to detect differences associated with neuroimaging parameters. In addition, in their original study, Cuevas and Bell (2014) allowed the infant to orient and sustain attention to puppet stimuli for as long as the infant wanted; there was no cap on the time possible for each trial. We limited each trial to 60 s, and infants only completed the three trials on one occasion, restricting our ability to examine the test-retest reliability of our attention task. As such, our slightly altered procedure may have limited measured variability in attentional behaviors or not fully capture sustained attention.

The developmental timeframe of our results deserves careful consideration. Most MRI studies assess behavior concurrently with the MRI scan. Our study design, which was a compromise among competing priorities, did not assess infant behavior at one-month of age, partially because an infant's behavioral repertoire at one-month of age is quite limited for the types of attentional behaviors that we wished to study. Thus, we assessed behavior at six-months of age. This five-month interval between MRI and behavior allows us to examine trajectories of putative MRI-to-behavior relationships, but without fully understanding concurrent relationships. The interpretation of our results would be clearer if we had been able to add an MRI assessment at six-months of age.

Infant neuroimaging studies face practical obstacles. First, these studies are dependent on the participant's ability to lie still in the scanner. An arduous task for a child or adult is even more of a challenge when involving infants. However, scanning procedures tailored to an infant population, including using noise-reducing ear-muffs, a vacuum-inflated swaddle, and slowing down scan times to decrease the acoustic sounds, resulted in high scan success. Second, DTI scans are particularly susceptible to artifact; images can be noisy and of comparatively poorer resolution than structural MR images (Cascio et al., 2007). However, diffusion imaging data underwent significant pre-processing and manual assessment, with the removal of images with significant artifacts. Moreover, our region-of-interest (ROI) approach is likely less sensitive to motion artifacts as we average data within a defined ROI, rather than performing a voxel-wise analysis (blinded for review).

Neuroimaging studies often segment structures into subdivisions; for example, researchers often subdivide the cingulum into anterior, medial, and posterior portions, while the superior longitudinal fasciculus is often subdivided into four distinct portions (Schmahmann et al., 2008;Wu et al., 2016a, 2016b). The only structure readily segmented in our study was the cingulum. We cannot exclude the possibility that our results would be altered if we had been able to subdivide the tracts under investigation.

An additional consideration is that white matter development during infancy is yet to be well documented or understood. On the whole, prediction from a one-month DTI scan to six-month behavior would seem to face notable obstacles: the tracts are still rapidly developing and there is evidence for the relative stability, or lack thereof, of FA measurements in relation to white matter structure. Hermoye et al. (2006) charted the development of FA along with the shape and size of white matter tracts. In general, Hermoye et al. (2006) noted rapid change during the first year of life, slow change during the second year, and relative stability after the second year. These results suggest that FA associations with attention might not generalize over developmental periods and render our significant findings with FA and later orienting attention more notable.

Nonetheless, our findings indicate that increased structural integrity of the white matter tracts related to the orienting network may play a role in the early neurodevelopment of attentional orienting behaviors. Because impaired attentional abilities are commonly noted in many neurodevelopmental conditions, their understanding should be a research priority.

Declaration of Competing Interest

None.

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