White Matter Microstructure and Its Association with Visuospatial Processing Development During Early Infancy

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List of abbreviations: FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity; DTI, diffusion tensor imaging; NODDI, neurite orientation dispersion and density imaging; FICVF, intracellular volume fraction; ODI, orientation dispersion imaging; ITP, intensity of toy play.

Abstract

This study assessed relations between white matter microstructure at one month of age and visuospatial processing abilities at six months of age. Participants included ninety-one infants (n=48 female) born after singleton non-complicated pregnancy. The infants underwent MRI at one month of age and a behavioral assessment at six months of age. Results revealed that the intensity of toy play was associated with fractional anisotropy (FA) of the right (t=3.002, adjusted p=0.038) and left superior cerebellar peduncle (t=2.799, adjusted p=0.038) and right cingulate gyrus (t=2.908, adjusted p=0.0038) while Gaze Shifting was associated with mean diffusivity and axial diffusivity of the right superior cerebellar peduncle (t=3.099, adjusted p=0.048). No other correlations, including those studied interactions with biological sex, were significant after adjusting for multiple comparisons. The findings support the notion that developing white matter microstructure, as measured by diffusion MRI metrics, plays a role in the development of visuospatial processing. Future studies should explore how these relationships develop and predict visuospatial ability and working memory later in life.

Keywords: Visuospatial processing, cerebellum, biological sex, diffusion MRI, DTI, NODDI.

INTRODUCTION

Visuospatial processing is a fundamental nonverbal cognitive ability that involves interpreting perceptual stimuli and manipulating mental images, allowing individuals to understand spatial relationships and interact effectively with their environments. This ability is intricately linked to motor function, as it involves integrating various forms of spatial information necessary for motor responses, thereby playing a critical role in motor coordination[1]. As such, visuospatial processing is vital for performing various everyday tasks that require hand-eye coordination, such as picking up objects, writing, driving, and participating in sports.

Research indicates that visuospatial processing at one year of age can serve as a predictor of cognitive development later in life[2], and difficulties in visual processing are directly associated with academic and professional outcomes[3,4]. Unfortunately, delays in the development of visuospatial processing often remain undetected until school age, despite cognitive skills being more malleable during early childhood. The so-called "brain growth spurt" from 32 weeks of gestation to two years of age[5] is a critical period during which early intervention may lead to more positive developmental outcomes[6]. For instance, a recent meta-analysis found that early developmental interventions initiated before 12 months in preterm infants may improve cognitive outcomes in infancy and at preschool age but not at school age[7]. Despite the critical relevance of early visuospatial processing and developmental outcomes, as well as the significant impact of early intervention, there is no screening tool that can reliably predict or track the development of visuospatial processing in infancy. Notably, links between infant visual alertness and white matter microstructure have been associated with visuospatial processing at 6.5 years of age[8], highlighting the importance of identifying neural markers that could potentially serve as visuospatial processing outcome measures and inform relevant intervention or support strategies early in life.[5-7]

Previous work in both animal studies and with older children and adults has elucidated gray and white matter regions associated with visuospatial processing. In macaque monkeys, for instance, the fornix is associated with rapid visuospatial learning[9,10]. In adults born very preterm, a reduction in the volume of the fornix and cingulum is associated with a decline in visuospatial memory[11,12], while research on typically developing school-aged children suggests that an increase in fractional anisotropy (FA) of the corpus callosum and the superior longitudinal fasciculus positively correlates with visuospatial cognition after controlling for age[13,14]. Moreover, the corpus callosum plays an important role in unconscious visuomotor adaptation in individuals with unilateral damage to the primary visual cortex via recruitment from the intact hemisphere[15]. In another study of children with sensory processing dysfunction, the anterior limb of the internal capsule, superior longitudinal fasciculus, and cerebellar peduncle were associated with visuomotor processing[16]. However, limited data is available on neurobiological associations underlying visuospatial processing abilities[17] and even less is known about how these relationships emerge in the developing brain.

Diffusion magnetic resonance imaging (MRI) non-invasively provides insights into the microstructural organization of the brain and is a powerful tool for investigating early brain development and associated behavioral outcomes[18]. Diffusion tensor imaging (DTI) is the most used method of diffusion MRI and provides quantitative metrics that describe tissue microstructure, including FA, and mean, axial, and radial diffusivity (MD, AD, and RD, respectively). These metrics can be used to probe neurodevelopment. FA is an index that describes the anisotropic properties of the diffusion tensor and provides information about the degree of directional dependence of the local water diffusion process. FA is a sensitive metric to white matter microstructure and tissue organization, with FA values increasing with age and within highly organized tracts[19,20]. AD and RD quantify properties of water diffusion parallel and perpendicular, respectively, to the axonal fibers and are often utilized as complementary measures of tissue microstructure[21,22], while MD represents the average diffusion occurring within a voxel. More recently, advanced biophysical diffusion MRI methods have been developed, including neurite orientation dispersion and density imaging (NODDI)[23] that allow for the estimation of more biologically meaningful metrics compared to those derived from DTI. NODDI metrics provide a more specific characterization of microstructural changes and estimates three microstructural metrics: the intracellular volume fraction (FICVF), reflecting axonal and dendritic packing density; the orientation dispersion index (ODI), quantifying angular variation of neurites; and the isotropic volume fraction (FISO), representing free water such as cerebrospinal fluid. In white matter, ODI quantifies the bending and fanning of axons. Fanning refers to axons diverging from a common origin (e.g., corona radiata), while bending describes axons curving along their trajectory. Both configurations increase ODI as neurites assume multiple orientations within a voxel[18,23,24].

In our previous study by Dowe et al., we investigated the association of DTI (FA, RD) and NODDI (FICVF) metrics at one month of age with infant's orienting and sustained attention using a dynamic puppet task[25] at six months of age and found that infants with higher FA in the corpus callosum and anterior cingulum had increased orienting behaviors[26]. The current study builds upon this previous work on orienting attention to examine behaviors that require visuospatial processing of objects within their immediate environment (the intensity of toy manipulation, changes in toy play, and gaze shifting) to infer the essential role of visuospatial processing in interpreting visual information, determining spatial orientation, and coordinating motor movements.

In this study, we examine the association between DTI and NODDI measures of early (one-month) infant microstructure and behavioral measures of later (six-month) visuospatial processing inferred from motor and attention tasks. We further investigate the role of biological sex in this association, as differences in visuospatial processing based on biological sex have been reported in multiple studies[27-29]. Sociocultural and biological explanations have been proposed for these differences[30]; however, the age at which these differences emerge, as well as the underlying neurobiological and environmental etiologies driving these differences, remain unclear[30,31]. Existing literature suggests conflicting findings regarding biological sex-based differences in the development of visuospatial processing. This has prompted us to investigate the role of biological sex as a moderator in brain-behavior associations. We hypothesize that early developing white matter microstructure supports the development of visuospatial processing behaviors in infancy, which could be different between biological sex groups.

	Total (*n* = 91)	Male (*n* = 43)	Female (*n* = 48)	*p*-value of mean sex differences.
Infant characteristics				
Gestational age at birth, weeks	39.5 (1.4)	39.4 (1.4)	39.6 (1.4)	0.498
Age at imaging, days	32.9 (6.1)	32.7 (5.7)	33.1 (6.4)	0.7548
Birthweight, pounds	7.7 (1.2)	7.6 (1.2)	7.7 (1.1)	0.6793
Birth length, inches	20.3 (1.2)	20.3 (1.1)	220.3 (1.2)	>0.9999
Head circumference, inches	13.7 (0.6)	13.8 (0.6)	13.6 (0.6)	0.1159
APGAR score at 1 min	8 (2)	8 (1)	8 (2)	>0.9999
APGAR score at 5 min	9 (1)	9 (1)	9 (1)	>0.9999
Maternal characteristics				
Maternal age, years	32.9 (3.8)	32.5 (4.1)	33.2 (3.5)	0.3821
Maternal education, years	17.6 (3.0)	17.9 (2.6)	17.3 (3.4)	0.3512
Race:				0.6128
White	83	40	43	
Black	1	0	1	
Other	7	3	4	
Family income at the time of birth, $:				0.1572
<40,000	4	2	2	
40,001-60,000	13	9	4	
60,001-80,000	16	10	6	
80,001-100,000	18	6	12	
100,001-200,000	33	14	19	
>200,000	6	1	5	
Marital status:				0.1966
Married to the child’s biological parent	80	36	44	
Married to the child’s stepparent	2	2	0	
Single and never married	2	2	0	
Separated/Divorced/Widowed/Other	7	3	4	

RESULTS

Demographics

Infant and maternal demographic and clinical characteristics are presented in Table 1. The majority of the sample was White (83%) and belonged to the upper-middle socioeconomic class ($100-200K median household income). Demographic and clinical characteristics were evenly distributed between infant biological sex groups. Additional participant information can be found elsewhere[24,26,32-34].

Table 1. Infant and maternal demographic and clinical characteristics. Data presented as mean (standard deviation) and number of infants. *P*-value indicates non-significant differences between male and female infants.

Associations of white matter microstructure with visuospatial processing

The results of the main effect of the associations of DTI and NODDI metrics in different brain regions with ITP and Gaze Shifting that were not affected by biological sex are illustrated in Figures 1-2 and Supplemental Table 1.

FA of the Right and Left Superior Cerebellar Peduncle and Right Cingulate Gyrus at one month were positively associated with ITP scores at six months of age (Figure 1). Other associations of DTI and NODDI metrics with ITP did not withstand FDR correction (Supplemental Table 1).

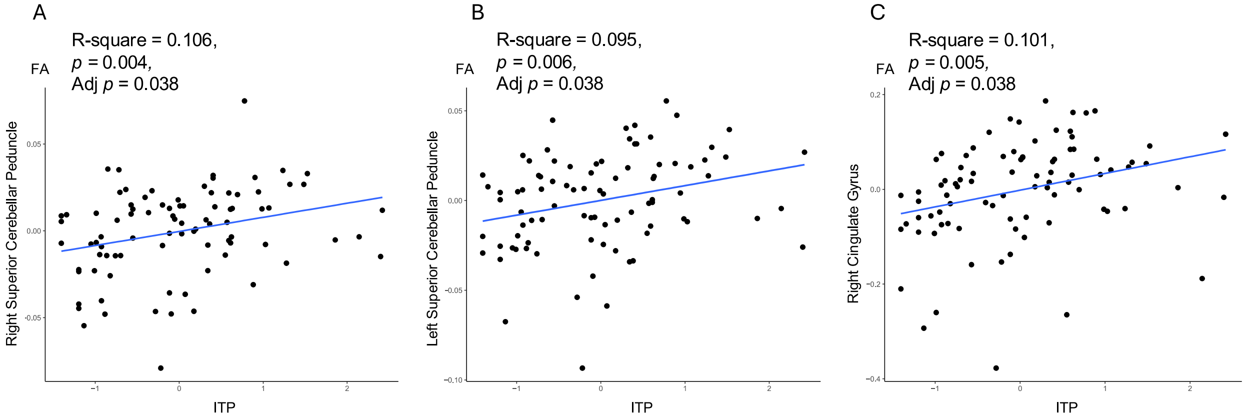

Figure 1. Associations of fractional anisotropy (FA) of Right and Left Superior Cerebellar Peduncle and Right Cingulate Gyrus at one month with Intensity of Toy Play (ITP) at six months of age.

MD of the Right Superior Cerebellar Peduncle at one month was significantly and positively associated with Gaze Shifting scores at six months of age, and this association withstood FDR correction. While other associations of Gaze Shifting did not survive FDR correction (Supplemental Table 1), the association of AD of the Right Superior Cerebellar Peduncle and Gaze Shifting was positive and close to maintaining significance after FDR corrections.

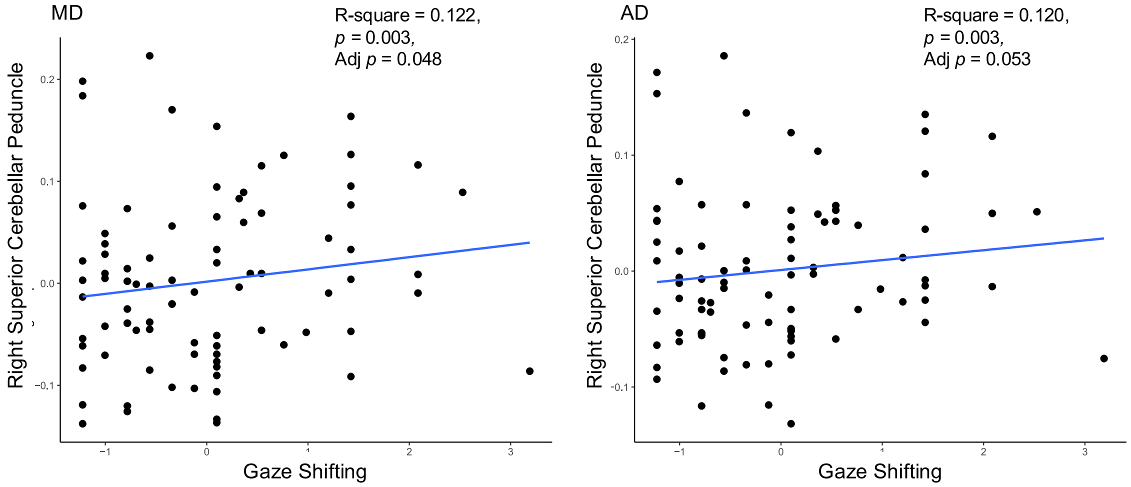

Figure 2. Associations of mean diffusivity (MD) and axial diffusivity (AD) of Right Superior Cerebellar Peduncle at one month with Gaze Shifting at six months of age.

Biological sex differences in associations between white matter microstructure and behavioral tests of visuospatial processing

Significant microstructure-by-sex interactions observed during the initial analysis did not withstand FDR correction. However, based on non-adjusted analyses, lower RD and MD of the Left Superior Cerebellar Peduncle and ODI of the Right Cingulate Gyrus were observed in one-month-old male infants with higher ITP scores at six months of age, which was not the case for female infants (Supplemental Figure 1). Additionally, one-month-old male infants with higher FICVF of the Left Superior Cerebellar Peduncle had higher ITP scores, which again was not true for female infants. One-month-old female infants with higher AD of the Right and Left Superior Cerebellar Peduncle had higher ITP scores at six months of age, which was not observed in male infants. Higher AD of the Right Superior Cerebellar Peduncle and AD of the Left Superior and Left Inferior Cerebellar Peduncle were identified in one-month-old male infants who had higher Gaze Shifting scores at six months of age, which was not the case for female infants. One-month-old male infants with lower FICVF of the Fornix had higher Gaze Shifting scores at six months of age, an association, which was again not observed in female infants. The uncorrected significance levels for the interactions with sex are provided in Supplemental Table 1.

DISCUSSION

This study investigated the association between white matter microstructure at one month of age and visuospatial processing behaviors at six months of age, as well as the role of biological sex in these associations. Our findings reveal significant associations of right and left superior cerebellar peduncle and right cingulate gyrus with ITP and right superior cerebellar peduncle with Gaze Shifting, suggesting that early white matter development plays a role in supporting visuospatial abilities.

Early White Matter Microstructure Predicts Later Visuospatial Processing Behaviors in Infancy

Visuospatial processing is an essential component of infants' engagement with their environment, operationalized here using ITP, a synthesis of the amount and intensity of toy play. An infant's engagement with toys depends on their perception of the visual stimuli from toys, assessment of spatial orientation in the quilt and eye-hand coordination to reach the toy. However, one might argue that while visuospatial processing is a crucial cognitive skill involved in toy play activities and gaze shifting after analyzing an object in space, individual differences in ITP and Gaze Shifting may not solely stem from variations in visuospatial processing and instead could result from a combination of skills including motor development and attention.

The cerebellum consists of a wide neural network that richly interconnects various parts of the brain and plays a crucial role in controlling movements, including visuomotor integration. The anatomy and functional connectivity of the visuomotor cerebellum has been previously described[35-37]. Although previously known for its role in motor functions, there is increasing scientific and clinical evidence of the cerebellum's importance for cognition. Evidence suggests that neuronal networks responsible for attention, as well as emotional, and sensorimotor regulation, map onto the cerebellum with topographic specificity. Posterior cerebellar lesions are associated with the cerebellar cognitive affective syndrome, which includes impairment in visuospatial processing and executive functioning.[38] A study of preterm-born adolescents revealed a significant association between fine motor skills, visual-motor integration, and the white matter microstructure of the cerebellar peduncle,[39] supporting our results. [39]Another study of children older than 7 years of age who underwent cerebellar resection due to low-grade astrocytoma demonstrated impairment in complex visuospatial processes, such as mental rotation of objects, visuospatial orientation, and planning, with no changes to sensory processing and perception[40]. A study using reversible inactivation of cerebellar regions in male monkeys highlighted the role of the posterior lateral cerebellum in learning new visuomotor tasks[41]. Additionally, a study examining neuronal activity in the cingulate motor area of monkeys during a behavioral task—specifically, reaching for a designated target with the instructed arm—revealed that the neurons in this area are involved in every phase of the activity. However, they demonstrate only modest selectivity regarding the spatial features of the visual signal[42].

Gaze shifting, operationalized as the frequency with which infants shift their gaze away from the presented object (i.e., the puppet), is an essential component of infant development (latency of gaze shifting was studied in our previous work[26]). It reflects the infant's ability to flexibly redirect attention in response to changes in the environment and indicates on infant's broadened interest and exploration. A longitudinal study of 20 infants between 6 and 26 weeks of age revealed that 6-week-old infants rarely looked away from the central to peripheral stimuli[43]. Gaze shifting was more likely to occur when the central stimulus was a video of the infant's mother's face with an abstract video as a peripheral stimulus, compared to the reverse condition, suggesting an infant's ability to recognize the mother's face and a shorter processing latency. This frequency of gaze shifting increased with age, and at 22 weeks, infants reliably shifted their gaze from central to the peripheral target under all stimulus combinations. These findings are consistent with another study of typically developing infants aged 1 to 9 months, which demonstrated significantly faster disengagement from central to peripheral targets in infants older than 4 months[44]. In contrast, visual fixation ability—rather than gaze shifting—has been linked to white matter maturation. Stjerna et al. found that newborn visual fixation, assessed at term-equivalent age in extremely preterm and full-term infants, correlated with widely increased FA across extensive white matter networks, suggesting that better visual fixation reflects more advanced brain microstructural development and predicts favorable long-term neurocognitive outcomes[45]. In our study FA of the right superior cerebellar peduncle was positively associated with ITP, while AD and MD of the same region were positively associated with Gaze Shifting. Since higher FA typically reflects more advanced white matter maturation, whereas elevated AD and MD indicate less mature microstructure, our findings suggest that Gaze Shifting is associated with earlier stages of brain development. Specifically, Dubois et al. hypothesized three stages of white matter development and showed that in earliest premyelination stage of white matter development, FA and AD can both increase together as axonal fibers become more directionally organized, before myelination begins[46]. The positive association between diffusivity measures (AD and MD) and Gaze Shifting demonstrated in our study may reflect the developmental stage at which this visual behavior emerges. In early infancy, gaze shifting relies predominantly on subcortical pathways which matures earlier than cortical attention networks.[47] The ability to disengage attention and shift gaze to a new target—particularly under competitive conditions—requires inhibitory cortical input from the frontal eye fields, a capacity that develops progressively during the first months of life[44]. Thus, newborns who demonstrate more frequent gaze shifting may be at a transitional developmental stage where subcortical-to-cortical connectivity is still maturing, reflected by higher diffusivity values indicative of less myelinated white matter.

Biological Sex Differences in the Relationship between White Matter Microstructure and Visuospatial Processing in Infancy

Numerous studies have demonstrated sex differences in brain development. In a study of children and adolescents, females exhibited slower age-related developmental brain changes compared to males, as evidenced by a decrease in gray matter volume and an increase in white matter and corpus callosum volume[48]. Additionally, in a study of adults, males showed greater parietal surface area, which was advantageous, while females showed greater gray matter volume in the parietal lobe, which was disadvantageous for spatial abilities[49]. Moreover, extensive research on the effects of prematurity on brain development indicate that these effects are less severe and have a more significant impact on white matter tissue in female infants compared to males[50], This finding suggests that the male brain may be more vulnerable to developmental abnormalities caused by prematurity[50,51]. Our analyses examining biological sex as a moderator of brain-behavior associations did not survive FDR correction; however, uncorrected results suggested that associations were more pronounced in male infants. These preliminary findings are consistent with prior work demonstrating that middle cerebellar peduncle and cingulum FA predict cognitive outcomes in preterm infants[52,53], and that cerebellar white matter tracts exhibit significant sex-by-age interactions during development, with males showing prolonged maturation compared to females[54,55]. Such sexually dimorphic developmental patterns may contribute to the observed differences in brain-behavior relationships. Larger studies are warranted to further elucidate potential sex-specific effects.

Limitations

This work is not without limitations. First, we employed two behavioral tasks that tap into visuospatial processing, which are also used to assess motor and attentional abilities. Thus, we infer effects on visuospatial processes but are unable to pinpoint specific visual processes. Second, our sample was not highly powered for the study of interactions, and many interactions lost significance after correcting for multiple comparisons. This lack of statistical power would be remedied by studying a larger sample. Finally, although we benefit from using two time points to infer developmental association (one-month MRI and six-month behavior), true longitudinal designs that incorporate multiple repeated assessments would provide a more accurate understanding of the neurobehavioral development of visuospatial processing in infancy and childhood.

Future Directions/Implications

Research is needed to investigate further neuroradiographic differences between male and female infant white matter tracts and how these differences evolve with age. Additionally, future studies could incorporate additional methods, such as eye tracking, which enables highly precise quantification of spatial and temporal gaze patterns and provides a direct window into visual perception and attention, offering complementary insights to behavioral data on visuospatial processing. Still, findings from our sample suggest that diffusion MRI methods early in infancy may provide limited evidence for early recognition of neurocognitive development differences as early as one month of age. With additional support, these tools could be a valuable component of screening for early risk. Thus, future investigations are sorely needed to identify risk factors associated with visuospatial processing differences at an early age.

METHODS

Ethics approval

All methods and experimental protocols used in this study were approved by the Institutional Review Board (IRB) of the University of Wisconsin (ID: 2013-1537, PI: Richard Davidson) and carried out in accordance with relevant guidelines and regulations. The work was adherent to the tenets of the Declaration of Helsinki. Parental consent was obtained at each assessment occasion.

Participants

Data were collected from 2014 to 2018 as part of a longitudinal study on early brain and behavioral development. Enrollment criteria are detailed in our previously published studies, which had different goals and hypotheses from those of the current paper [26,33]. Briefly, pregnant women between 18 and 40 years of age expecting a singleton birth after a non-complicated pregnancy were recruited for this study at <28 weeks of gestation. We conducted statistical analyses on a subset (N = 91) of the full sample, which provided DTI/NODDI metrics and completed behavioral tasks for visuospatial processing, including the “Quilt” and “Attention Puppet” tasks. Institutional review board approval was obtained.

Imaging Acquisition and Processing

At one month of age (corrected to a 40-week gestation length), infants underwent MRI during natural, non-sedated sleep[20,56]. A 3.0 Tesla General Electric MR750 Discovery scanner equipped with a 32-channel receive-only head RF array coil was used to obtain imaging data (Nova Medical, Wakefield, MA). Diffusion-weighted images (DWIs) were acquired using a three-shell diffusion-weighted pulse-gradient spin-echo sequence. Parallel imaging was used to reduce image acquisition time and distortions from magnetic field inhomogeneities. Sixty-nine DWIs were acquired, including 6 with no diffusion encoding (i.e., b-value=0 s/mm2), 9 directions with b=350 s/mm2], 18 directions with b=800 s/mm2, and 36 directions with b=1500 s/mm2. Additional imaging parameters consisted of the following: repetition time [TR]=8400 ms, echo time [TE]=94 ms, and bandwidth=3906 Hz/pixel, imaging field of view [FOV]=25.6 cm×25.6 cm, and 2mm×2mm in-plane resolution. Coverage across the whole brain was achieved using 60 sagittal-oriented contiguous slices with a slice thickness of 2.0 mm. Total acquisition time using strategies to reduce acoustic noise was approximately 10 minutes.[24]

DWIs were processed using an in-house processing pipeline that included manual assessment of individual images, denoising[57], Gibbs ringing removal[58], eddy current and motion correction [59] 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 subsequently fit to the diffusion-weighted data. Maps were normalized to a population-specific template created using DTI-TK and a representative subset of the study sample[60]. Given the known high specificity of NODDI metrics to white matter microstructural changes, we studied both DTI and NODDI metrics. The Johns Hopkins

University neonatal atlas[61] was used to delineate the infant brain into white matter regions by spatially aligning the atlas to the population specific template using ANTs and nearest neighbor interpolation. The normalized neonatal atlas was then transformed into the native space of each subject by applying the inverse of the spatial transformation. Alignment of atlas to native space FA maps was manually assessed. A total of 10 white matter tracts (Genu of the Corpus Callosum, Fornix, Superior Cerebellar Peduncle, Inferior Cerebellar Peduncle, Anterior Limb of the Internal Capsule, Posterior Limb of the Internal Capsule, Sagittal Striatum, Cingulate Gyrus, Superior Longitudinal Fasciculus, and Uncinate Fasciculus) are involved in visual and sensorimotor functioning, as previously shown in the literature[9-13,16,62-66].

Behavioral Assessment of Visuospatial Processing

At six months of chronological age, infants participated in two observational paradigms designed to assess their interest and attention by simulating everyday scenarios they might encounter: (a) the “Quilt” task from the Prelocomotor version of the *Laboratory Temperament Assessment Battery* (Lab-TAB[67], and (b) the “Attention Puppets” task adapted from Cuevas et al[25] These tasks were selected due to the known role of visuospatial processing in motor functions, such as skilled reaching, grasping, eye movements, and other motor response[68]. The tasks were recorded and later coded for attentional salience.

During the “Quilt” task, the infant was placed in a prone position at the center of a quilt, within arm’s reach of several colorful, textured, and enticing toys. The experimenter directed the infant’s attention to the toys and then left the room for 3 minutes. Two behaviors were scored from this task: bouts of toy play and the intensity of toy manipulation. For bouts of toy play, the number of toys the infant touched during the task, which indicates interest and the ability for visuospatial orientation, planning, and eye-hand coordination, was counted. The infant’s intensity of manipulating the toys was scored on a 5-point Likert scale (0 = No manipulation to 4 = extremely high manipulation) every 10 seconds. Scores were then averaged across the entire task to reflect the Intensity of Toy Manipulation. The approximate total duration of the “Quilt” task was 3 minutes. Originally designed to assess activity level and interest, this task was included as an indicator of the visuospatial processing necessary to engage with, find, and manipulate toys. The processing streams involved in motor responses depend on different classes of spatial information. For example, motor responses like skilled reaching and grasping require precise coordinate computations to locate visual targets relative to the body or its parts, known as allocentric-egocentric spatial processing[68,69].

For the “Attention Puppets” task, the infant sat in the mother’s lap while the experimenter stood behind a divider, wearing puppet gloves on their hands. The puppet gloves featured bells, glitter, and fun faces for the infant to see above the dividing wall. The experimenter’s face and body were not visible to the infant. A loud handclap prompted the infant to attend to the puppet on 4 different occasions. The number of times the infant looked away from the puppets for more than three seconds, or gaze shifting, was coded for each of the 4 administrations of this task, and the average number of times the infant looked away was counted. The approximate total duration of the "Attention Puppets" task was 4-5 minutes. Gaze shifting, when an infant redirects attention from an object, is a key aspect of visuospatial processing, crucial for developing visual attention and spatial awareness [68] [68,69]

Statistical Analyses

Correlations among variables from behavioral tasks for visuospatial processing (Intensity of Manipulation, Toy Play, and Gaze Shifting) are presented in Table 3. A positive correlation between "Intensity of Manipulation" and "Toy Play" led to these two variables being standardized and then averaged into an "Intensity of Toy Play (ITP)".

Table 2. Correlation among three variables from behavioral tasks for visuospatial processing ("Quilt" and "Attention Puppets" tasks).

	Toy Play	Intensity of Manipulation
Intensity of Manipulation	**0.624** **(<.001)**	
Gaze Shifting for <3 sec.	-0.004 (.974)	0.100 (.364)

Note. Spearman correlation computed using listwise deletion to handle missing data. Variables converted to Z-scores for comparison.

To determine whether to examine the left and right hemispheric regions of interest independently, we first compared hemispheric differences between 8 bilateral white matter tracts (Superior and Inferior Cerebellar Peduncle, Anterior and Posterior Limb of the Internal Capsule, Sagittal Striatum, Cingulate Gyrus, Superior Longitudinal Fasciculus, and Uncinate Fasciculus), while controlling for multiple comparison via the Benjamini-Hochberg procedure (Supplemental Table 2). Fornix and Genu of the Corpus Callosum were analyzed without lateralization due to their anatomical midline orientation and the DTI and NODDI mapping templates used for the study. Significant left and right lateralization was demonstrated for nearly all analyzed white matter tracts across DTI and NODDI metrics. Consequently, the right and left hemispheric white matter tracts were analyzed separately.

To address our aims, a series of multiple regressions examined whether the microstructure of the selected white matter tracts at one month of age, measured via DTI and NODDI metrics, would predict the behavioral outcomes of visuospatial processing at six months of age, measured by ITP and Gaze Shifting. To enhance comparability among variables of different measurement units, all continuous variables (DTI and NODDI metrics and behavioral test scores) were standardized via mean-centering. In addition, we examined the potential interaction effect of infant biological sex and controlled for age at the time of imaging. For nonsignificant microstructure-by-sex interactions, the main effect model was tested. Correction for multiple comparisons was performed via the Benjamini-Hochberg procedure to control the false discovery rate (FDR; $p < 0.05$). All analyses were conducted using R and RStudio, R version 4.3.3 (2024-02-29).

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Consent statement: Parental consent was obtained prior to each study appointment.

Disclosure statement: The authors report no conflict of interest.

Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Figure Legends:

Figure 1. Scatter plot showing the interactions of the median Fractional Anisotropy (FA) of Right and Left Superior Cerebellar Peduncle and R Cingulate Gyrus and Intensity of Toy Play (ITP) scores while controlling for age at the time of imaging. Vertical axis shows diffusion tensor imaging (DTI) metrics, horizontal axis behavioral tests. Both variables were mean-centered. Values presented on top of each panel are t-value, p-value and p-value FDR adjusted for multiple comparison.

Figure 2. Scatter plot showing the interactions of the median Mean (MD) and Axial Diffusivity (AD) of Right Superior Cerebellar Peduncle and Gaze Shifting while controlling for age at the time of imaging. Vertical axis shows diffusion tensor imaging (DTI) metrics, horizontal axis behavioral tests. Both variables were mean-centered. Values presented on top of each panel are t-value, p-value and p-value FDR adjusted for multiple comparison.

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