Cerebral Blood Flow Velocity Asymmetry, Neurobehavioral Maturation, and the Cognitive Development of Premature Infants Across the First Two Years

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ABSTRACT: ***Objective:*** **Premature infants are at risk of adverse developmental outcomes even with no demonstrable neurological damage. Neonatal physiological measures that can serve as indicators of later development are therefore important for early evaluation and intervention.** ***Methods:*** **We followed the development of 51 low birth weight, premature infants across the first 2 years. Mean systolic cerebral blood flow velocity (CBFV) in the left and right middle cerebral arteries was measured at 37 weeks gestational age, neurobehavioral maturation was assessed with the Neonatal Behavior Assessment Scales (NBAS), and cognitive development was evaluated at 6, 12, and 24 months.** ***Results*****: Different patterns emerged for CBFV in the right versus left middle cerebral artery. Greater absolute values of right systolic CBFV were related to poorer performance on the habituation and orientation scales of the NBAS, whereas greater left systolic CBFV absolute values were related to better Mental Development Index (MDI) scores at 24 months. Right systolic CBFV asymmetry was related to poor neonatal orientation and low MDI score at 24 months. On the other hand, infants with left systolic CBFV asymmetry showed a more rapid increase in cognitive skills from 12 to 24 months and better cognitive performance at 2 years.** ***Conclusion:*** **Measurement of systolic CBFV in the neonatal period may assist in identifying infants at risk of poor developmental outcome.**

(*J Dev Behav Pediatr 28:*362–368, 2007) **Index terms:** cerebral blood flow velocity, neurobehavioral maturation, cognitive development, premature infants.

Premature infants are at risk of poor neurobehavioral, cognitive, and social emotional development across childhood and adolescence and such outcomes are observed even in infants with no overt neurological damage. Longitudinal studies have shown that premature infants exhibit delayed language development, lower intelligence scores, poor motor and academic skills, and neurological impairments during childhood and up to adolescence.[1–7] As such, physiological measures assessed in the neonatal period that can serve as indicators of later development are of clinical importance. The potential importance of such measures lies in their ability to identify individual differences that are otherwise clinically undetectable and can predict higher risk of developmental difficulties.

Several physiological measures that are assessed in newborns and predict later outcomes have been described, each addressing a different underlying mechanism. Such findings have been reported for cardiac vagal tone, which predicts cognitive development across infancy[8,9] and school age social competence.[10] Similarly, sleep-wake patterns in the neonatal period have been associated with emotion regulation[11] and cognitive development in preterm infants in the first year of life.[11–13]

An additional physiological measure that may be related to later development in premature infants is neonatal cerebral blood flow (CBF). Ojala and colleagues[14] examined the relationship between CBF in the first 24 hours and psychomotor development at 12 months in premature infants and found a relationship between low CBF and adverse psychomotor outcome. Rennie et al[15] examined the relationship between serial unilateral CBF velocity (CBFV) estimation in the first 3 days of life and neurological and developmental outcome at 18 months and found that infants with abnormal neurological signs or developmental delay at 18 months did not show the expected increase in CBFV during the first few days of life. The authors further suggested that bilateral measurements of CBFV in the middle cerebral arteries might provide an even better predictor of outcomes in such premature infants.

The possibility that CBFV asymmetry in the middle cerebral arteries may be related to individual differences in the infants' subsequent development is supported by findings on CBF asymmetry among adults and children. Among adults, greater right than left CBF was related to depression[16] and anxiety.[17] Among children, greater right CBF, as indicated by warmer right tympanic membrane, was associated with shyness and distractibility, while greater left CBF, as indicated by

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warmer left tympanic membrane, correlated with higher social competence.[18]

Research in the field of electroencephalographic (EEG) asymmetry supports the hypothesis that asymmetry in CBFV may be related to infant development. Greater right than left frontal brain EEG activation at 9 months predicted continuity of inhibited temperamental pattern during the first 4 years.[19] Similarly, in newborns, greater relative right EEG activation was related to elevated levels of the stress hormone cortisol, a greater number of sleep/wake state changes, and less optimal performance on the Brazelton Neonatal Behavior Assessment Scales (NBAS). The authors concluded that newborns with greater relative right frontal EEG activation might be at greater risk of developmental problems than those with relative left frontal electroencephalographic activation.[20]

In light of the above, the goal of the present study was to examine the relationships between CBFV asymmetry in the left and right middle cerebral arteries, neurobehavioral maturation, and cognitive development during the first 2 years of life in premature infants. It was hypothesized that greater right than left CBFV would be related to poorer performance on the orientation and habituation scales of the NBAS and poorer cognitive development during the first 2 years of life.

METHODS

Participants

Fifty-one low birth weight, premature infants participated. The sample was drawn from a consecutive birth sample collected between March 1996 and December 1999 at the neonatal intensive care unit of Shaare Zedek Medical Center, a tertiary-care medical hospital in Jerusalem, Israel. To eliminate potential confounders, only mothers who were older than 20 years, married to the infant's father, and completed at least 12 years of schooling were included. The sample was considered to be middle class by Israeli standards.[21] Mothers were approached to participate in a developmental follow-up, and among those approached, eight mothers declined participation, citing time constraints as reason. Those mothers and infants did not differ on demographic or infant medical variables from the participating families. In the present study, infants who had cerebral blood flow velocity (CBFV) assessment at 37 weeks and met medical exclusion criteria were included. Exclusion criteria included grade 1–4 intraventricular hemorrhage, periventricular leukomalacia, perinatal asphyxia, metabolic or genetic disease, central nervous system infection, and an abnormal neurological examination results before discharge. The sample included 27 males and 24 females. Mean birth weight was 1265.31 g (SD = 369.02; range, 520–2450), and mean postmenstrual age was 30.23 weeks (SD = 2.65; range, 25–37). Infants were tested as part of a longitudinal follow-up of infant development in the neonatal intensive care unit. The study was approved by the Institutional Review Board and informed consent was obtained from one or both parents.

Measures and Procedures

CBFV measurement

CBFV were measured by Doppler velocimetry. The open fontanelles and sutures of the newborn provide unique windows for cranial ultrasound neuroimaging. Doppler measurements during ultrasonography provide information about the velocity of cerebral blood flow (CBF), and relative changes in these measurements of flow velocities have been shown to correlate with changes in global and regional CBF.[22] As Doppler ultrasonography is noninvasive and reproducible, it is standardly used to estimate blood flow in the cerebral vessels of preterm and term babies.[23]

CBFV was measured at a mean postmenstrual age of 37.14 weeks (SD = 0.79; range, 35.71–38.71) and at a mean of 48.02 days chronological age (SD = 19.59; range, 7–89). All infants were lying supine and were in a quiet awake state when examined. If an infant began to cry, an attempt was made to calm down the child before resuming the procedure. Flow velocity of the right and left middle cerebral arteries were assessed by pulsed Doppler ultrasonography (Hewlett Packard Image Point Ultrasound System, Andover, MA) with a transtemporal approach, using a 7.5-MHz transducer with an insonation angle close to 0 degrees, a sample volume of 1.5 mm and a 100-Hz high-pass filter to reduce noise. Peak systolic velocity, end-diastolic velocity, and velocity time integral were recorded. For each measurement, two consecutive high-quality waveforms were averaged. Three measurements were averaged for each infant.

Right mean systolic CBFV asymmetry score was calculated for each infant by subtracting the absolute values of left from right mean systolic CBFV. Positive values of right asymmetry scores indicate greater relative right mean systolic CBFV, while negative values indicate greater relative left mean systolic CBFV. Infants were ranked according to their right asymmetry scores and divided into fourths. One fourth of the infants (n = 13) with the lowest right asymmetry scores comprised Group 1, one half of the infants (n = 25) with median right asymmetry scores comprised Group 2, and another fourth (n = 13) of the infants, with the highest right asymmetry scores, comprised Group 3. As expected, left CBFV asymmetry was found in Group 1, no CBFV asymmetry was found in Group 2, and right CBFV asymmetry was found in Group 3.

Infant medical risk.

Infant medical risk was measured with the Clinical Risk Index for Babies.[24]

Neonatal Behavior Assessment Scales (NBAS)

At 37 weeks' gestational age, infants were examined with the NBAS[25] by a trained neonatologist blinded as to CBFV data. The habituation and orientation clusters of the NBAS[26] were included in this study, in light of findings correlating attention patterns in premature infants with cognitive outcomes up to adolescence.[27–31]

Cognitive development

Infants were tested with the Bayley Scales of Infant Development II[32] at 6, 12, and 24 months of age by trained and blinded psychologists. The Bayley Mental

Development Index (MDI) score was corrected for postmenstrual age.

Data Analysis

Analyses of variance (ANOVAs) were conducted to evaluate differences between the groups in performance on the habituation and orientation scales of the NBAS and on the MDI at 6, 12, and 24 months. A multivariate analysis of variance with repeated measures was conducted to evaluate differences between the groups in the course of mental development. To further understand the relationships between the variables, correlations were computed between absolute values of systolic CBFV in the right and left middle cerebral arteries, right-left CBFV asymmetry, habituation, orientation, and MDI scores at 6, 12, and 24 months. Finally, a hierarchical multiple regression was computed to predict cognitive development at 24 months from neonatal and socioeconomic measures.

RESULTS

Cerebral Blood Flow Velocity (CBFV) Asymmetry Groups

Medical and demographic information for infants in Group 1 (left asymmetry), Group 2 (no asymmetry), and Group 3 (right asymmetry) is presented in Table 1. As seen, no differences emerged between the groups in birth weight, postmenstrual age, Clinical Risk Index for Babies score, Apgar score at 1 and 5 minutes, ventilation days, chronological age at testing, or head circumference at 37 weeks. Similarly, no differences emerged between the groups in gender, maternal age or education, paternal age or education, or number of siblings.

Correlations were found between head circumference at 37 weeks and Mental Development Index (MDI) score at 6 months ($r = .34$, $p < .05$) and between postmenstrual age at birth and MDI score at 12 months ($r = .29$, $p < .05$). Number of ventilation days were related to performance on the habituation cluster of the Neonatal Behavior Assessment Scales (NBAS) ($r = -.46$, $p < .01$), MDI score at 6 months ($r = -.31$, $p < .05$), and MDI score at 12 months ($r = -.33$, $p < .05$). No additional correlations were found between medical or demographic measures and measures of infants' neurobehavioral maturation or mental development. Similarly, no correlations were found between medical or demographic measures and absolute values of systolic CBFV in the right or left middle cerebral artery or right-left CBFV asymmetry.

Means and SDs and the F value from the analysis of variance (ANOVA) for left and right systolic CBFV in Group 1 (left asymmetry), Group 2 (no asymmetry), and Group 3 (right asymmetry) and in the whole sample are presented in Table 2. As seen in Table 2, a significant difference between right and left CBFV was found in Group 1 (F[df = 1,24] = 16.73, $p < .001$), with greater relative left CBFV and in Group 3 (F[df = 1,24] = 4.66, $p < .05$), with greater relative right CBFV. No significant difference between right and left CBFV was found in Group 2 or in the whole sample.

Significant differences in absolute values of left systolic CBFV were found across groups (F[df = 2,48] = 10.36, $p < .001$). Bonferroni post hoc tests showed that left systolic CBFV was higher in Group 1 (left asymmetry) compared to Group 2 (no asymmetry) ($p < .01$) and Group 3 (right asymmetry) ($p < .001$). No significant difference was found between the groups in right systolic CBFV.

Table 1. Medical and Demographic Information in the Three Groups

	Group1 (Left Asymmetry) (n = 13)		Group 2 (No Asymmetry) (n = 25)		Group 3 (Right Asymmetry) (n = 13)		
	Mean	SD	Mean	SD	Mean	SD	F/χ^2
Postmenstrual age, wk	30.41	2.27	30.33	2.68	30.16	3.18	NS
Birth weight, g	1211.25	215.68	1303.83	391.86	1249.50	434.62	NS
CRIB score	3.5	3.06	2.6	3.53	3.25	3.16	NS
Apgar score							
1 min	7.53	1.80	7.47	1.60	7.36	2.29	NS
5 min	8.23	1.16	7.90	1.81	7.90	1.37	NS
No. of ventilation days	5.46	9.10	10.70	17.01	13.60	22.13	NS
Chronological age at testing, days	49.42	17.40	46.92	19.40	48.00	22.30	NS
Head circumference at 37 wk, cm	31.63	1.30	31.19	1.40	31.08	1.93	NS
Maternal age, yr	27.76	5.50	27.87	5.25	27	5.21	NS
Maternal education[a]	2.15	0.68	1.88	.78	1.92	0.64	NS
Paternal age, yr	32.46	7.18	31.00	6.11	30.46	6.72	NS
Paternal education[a]	2.08	0.99	1.63	.95	1.58	0.90	NS
No. of siblings	2.5	1.93	2.56	1.37	2.63	1.43	NS
Male/female ratio	4/9		16/9		7/6		NS

CRIB, Clinical Risk Index for Babies; NS, not significant. [a]1 = high school, 2, = professional school, 3 = university education.

Table 2. Right and Left Systolic Velocities in the Three CBFV Asymmetry Groups and in the Whole Sample

	Mean Systolic CBFV (cm/sec)				
	Right		Left		
	Mean	SD	Mean	SD	F
Group 1 (left asymmetry R<L) (n = 13)	49.69	12.85	69.2	11.41	16.73**
Group 2 (no asymmetry) (n = 25)	54.28	11.71	55.67	11.75	NS
Group 3 (right asymmetry R>L) (n = 13)	59.22	13.43	47.59	14.04	4.66*
Whole sample (n = 51)	57.06	14.40	54.37	12.67	NS

CBFV, cerebral blood flow velocity. *$p < .05$; **$p < .001$.

Developmental Differences Between Asymmetry Groups

All variables in the study, including NBAS scores and MDI scores at 6, 12, and 24 months were normally distributed and were checked for outliers. Means and SDs for habituation, orientation, and MDI scores at 6, 12, and 24 months are presented in Table 3. ANOVA computed for the NBAS habituation cluster yielded a marginally significant difference ($F[df = 2,48] = 2.84$, $p = .068$), indicating that infants with left CBFV asymmetry showed a somewhat better performance on visual and auditory habituation. A similar ANOVA computed for the orientation cluster showed no significant differences between groups ($F[df = 2,48] = 1.63$, $p > .10$). Similarly, no significant differences were found between groups in MDI at 6 months ($F[df = 2,48] = 1.02$, $p > .10$) or MDI at 12 months ($F[df = 2,48] = 0.77$, $p > .10$).

However, ANOVA for the effect of group on the MDI score at 24 months showed a significant difference between groups ($F[df = 2,48] = 4.62$, $p < .05$). Bonferroni post hoc tests showed that infants in Group 1 (left asymmetry) had significantly higher MDI scores at 24 months compared to infants in Groups 2 (no asymmetry, $p < .05$) and 3 (right asymmetry, $p < .05$).

A multivariate analysis of variance with repeated measures assessing MDI scores at 6, 12, and 24 months with group as a between-subject factor showed an interaction between time and group (Wilks' $F[df = 4,94] = 3.61$, $p < .01$), indicating differences in the developmental course of cognitive skills between the three groups. While no differences were found between MDI scores at 6, 12, and 24 months in Groups 2 (no asymmetry) and 3 (right asymmetry), a difference in MDI score across development was found in Group 1 (left asymmetry) ($F[df = 2,36] = 9.47$, $p < .001$). Bonferroni post hoc tests showed that MDI scores at 24 months were significantly higher in Group 1 than at 12 months. The mental developmental course of the three groups is presented in Figure 1.

Although Group 1 (left asymmetry), which had the highest MDI scores at 24 months and the best mental development course, had the least number of ventilation days, the difference between groups in days of ventilation was not significant. Furthermore, when ANOVA for the effect of group on MDI score at 24 months and multivariate analysis of variance for the effect of group on mental development course were repeated with number of ventilation days as a covariate (analysis of covariance), the effects for group on the MDI score at 24 months remained significant ($F[df = 2,46] = 3.84$, $p < .05$), as did the effect of group on mental development course (Wilks' $F[df = 4,90] = 3.76$, $p < .01$). No effect was found for number of ventilation days on MDI at 24 months ($F[df = 1,46] = 0.23$, $p > .10$) or on mental development course (Wilks' $F[df = 2,45] = 0.79$, $p > .10$).

Correlations Between CBFV, Neurobehavioral Maturation, and Cognitive Development

The relationships between right CBFV absolute values, left CBFV absolute values, right CBFV asymmetry, left CBFV asymmetry, NBAS habituation and orientation, and

Table 3. Means and Standard Deviations for Neonatal Behavioral Assessment Scales Habituation and Orientation, and Mental Development Index at 6, 12, and 24 Months in the Three Asymmetry Groups

	Group 1 (Left Asymmetry) (n = 13)		Group 2 (No Asymmetry) (n = 25)		Group 3 (Right Asymmetry) (n = 13)		
	Mean	SD	Mean	SD	Mean	SD	F
Habituation	6.53	0.87	6.31	0.61	5.79	1.1	2.48*
Orientation	6.19	0.90	5.81	0.78	5.58	0.98	NS
MDI score							
At 6 mo	95.23	5.62	91.78	7.42	91.27	10.53	NS
At 12 mo	86.92	10.11	90.92	9.88	88.53	9.07	NS
At 24 mo	103.76	12.57	91.46	14.34	87.97	15.41	4.62**

MDI, Mental Development Index. *$p < .10$; **$p < .05$.

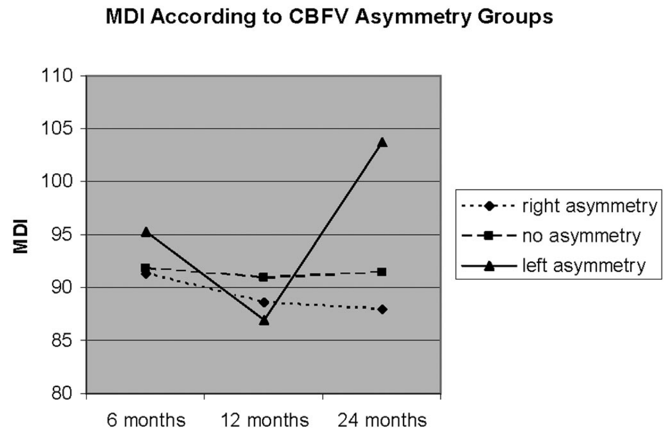

Figure 1. Mental Development Index (MDI) scores at 6, 12, and 24 months according to cerebral blood flow velocity (CBFV) asymmetry groups.

MDI scores at 6, 12, and 24 months were examined with Pearson correlations and are presented in Table 4. As seen in Table 4, a greater absolute value of right systolic CBFV was related to poorer neonatal habituation and orientation. A greater absolute value of left systolic CBFV was related to a better MDI score at 24 months. Greater right CBFV asymmetry was related to poor neonatal orientation and a poorer MDI score at 24 months, whereas the mirror variable of greater left CBFV asymmetry was related, as expected, to better neonatal orientation and a better MDI score at 24 months.

Predicting Cognitive Development at 24 Months

A hierarchical multiple regression model was used to predict infants' cognitive outcomes at 24 months from infant medical risk, maternal education, and left and right CBFV absolute values. Predictors were entered in three blocks. In the first block, infant medical risk was entered as the sum of the standardized scores of birth weight and gestational age to partial out variance related to the main risk factors in premature infants. In the second block, maternal education was entered since parental education serves as the best proxy for socioeconomic status in the Israeli population.[21] In the third block, the infant's mean left and right systolic CBFVs were entered. The regression model is presented in Table 5.

As seen in Table 5, the only measure with a unique contribution to the prediction of mental development at 24 months is the left CBFV absolute value, which remained significant after controlling for infant medical risk and maternal education. A greater absolute value of left mean systolic CBFV was related to better MDI score at 24 months.

DISCUSSION

This study is the first to systematically examine the relationships between cerebral blood flow velocity (CBFV) in the middle cerebral arteries measured in the neonatal period and neurobehavioral status and mental development in premature infants during infancy. Differential results were obtained for CBFV in the right and left middle cerebral arteries. Greater right CBFV absolute values were related to poorer performance on the habituation and orientation scales of the Brazelton Neonatal Behavior Assessment Scales (NBAS), whereas greater left CBFV absolute values were predictive of better Mental Development Index (MDI) scores at 24 months. Right CBFV asymmetry was related to both poor neonatal orientation and low MDI scores at 24 months. Infants with left CBFV asymmetry showed an increase in MDI scores from 12 to 24 months and had better MDI scores at 24 months compared to infants with right CBFV asymmetry or no CBFV asymmetry. Taken together, these findings suggest that, similar to previously reported findings for frontal electroencephalography, asymmetry in the direction of increased right hemispheric activity is related with worse developmental outcomes, while asymmetry in the direction of increased left hemispheric activity is associated with better developmental outcomes.

Attention patterns in premature infants were previously reported to be closely linked with cognitive development. Visual-following and auditory-orienting composites derived from the Einstein Neonatal Neurobehavioral Assessment Scale were related to MDI scores at several time points. Infants born preterm who showed a deviant

Table 4. Correlations Between Cerebral Blood Flow Velocity, Neonatal Behavioral Assessment Scales Habituation and Orientation, and Mental Development Index Scores at 6, 12, and 24 Months

	Right CBFV (Absolute Value)	Left CBFV (Absolute Value)	Right CBFV Asymmetry (Right-Left)	Left CBFV Asymmetry (Left-Right)	Habituation	Orientation	MDI		
							6 Mo	12 Mo	24 Mo
Right CBFV (absolute value)	—	0.59***	0.33*	−0.33*	−0.32*	−0.41**	−0.01	0.01	0.07
Left CBFV (absolute value)		—	−0.55**	0.55**	−0.06	−0.08	0.06	−0.03	0.38**
Right CBFVasymmetry (right-left)			—	−1***	−0.25	−0.32*	−0.09	0.05	−0.37**
Left CBFV asymmetry (left-right)				—	0.25	0.32*	0.09	−0.05	0.37**
Habituation					—	0.36**	−0.01	0.12	0.20
Orientation						—	−0.08	−0.15	0.00
MDI score at 6 mo							—	0.32*	0.30*
MDI score at 12 mo								—	0.30*

CBFV, cerebral blood flow velocity; MDI, Mental Development Index; NBAS, Neonatal Behavioral Assessment Scales. *$p < .05$; **$p < .01$; ***$p < .001$.

Table 5. Prediction of Cognitive Development at 24 Months

	β	R^2 Change	F Change	*df*
Medical risk	−.03	.00	0.27	1,49
Maternal education	.04	.01	0.63	1,48
Left systolic velocity	.51**			
Right systolic velocity	−.24	.16	4.66*	2,46

R^2 total =.18; F(4,46) = 2.59; $p < .05$. * $p < .05$; ** $p < .01$.

performance on both visual-following and auditory-orienting composites showed significantly lower cognitive test scores at 1 and 6 years and were more likely to be classified as subaverage at 6 years.[31] In addition, long total fixation time in premature infants was related to low IQ scores at 5,[27] 8,[31] 12,[29] and 18[28] years. At both 12 and 18 years, infants' attention was predictive of tasks thought to tap information processing and the capacity to inhibit prepotent responses in tasks requiring analogical and strategic thinking.[28,29] In the present study, no relationships were found between attention patterns, as measured by the NBAS habituation and orientation, and cognitive development, possibly because of the small sample size and its homogeneity due to the inclusion criteria.

The middle cerebral arteries supply parts of the temporal, parietal, and frontal lobes.[33] Thus, the effects of CBFV asymmetry on neurobehavioral maturation and cognitive development may be related to deferential activation in each of these areas. Consistent with the present findings, greater relative right frontal electroencephalographic (EEG) activation has been previously associated with poor neurobehavioral maturation in newborns.[20] Moreover, factors that were related to greater relative right frontal EEG activation correlated with poor neurobehavioral maturation and cognitive development, whereas factors related to lower relative right frontal EEG activation were associated with improved neurobehavioral development. Maternal anxiety, depression, and anger during the second trimester of pregnancy, for instance, were found to predict newborns' greater right frontal activity asymmetry and were also related to less optimal performance on the NBAS.[34] In a different study, Jones and colleagues[35] found that a withdrawn maternal interactive style, typical of maternal depression, was related to both greater infant right frontal EEG activity asymmetry and to lower Bayley MDI scores at 1 year. Finally, massage therapy, which was found to attenuate right frontal EEG asymmetry in 1-month-old infants of depressed mothers,[36] was also related to better performance on the orientation scale in full-term infants[37] and better performance on the habituation scale in premature infants.[38] These findings point to links between hemispheric asymmetry, neurobehavioral maturation, and cognitive outcomes during infancy, and the present findings demonstrate that the links between neonatal cerebral blood flow asymmetry and neurodevelopment follow the same pattern.

Infants with left CBFV asymmetry showed an increase in MDI score from 12 to 24 months and had a better MDI score at 24 months compared to infants with right CBFV asymmetry or no CBFV asymmetry. In addition, greater left CBFV absolute values were predictive of better MDI at 24 months. It is possible that neonatal left CBFV serve as a precursor to processes that unfold during the second year of life and involve left hemisphere activity and language development. In a longitudinal sample of infants seen monthly from 13 to 22 months, it was found that orienting to the right member of a pair of identical pictures increased monotonically in the second year of life, and the correlation between this orientation bias and language development increased until 20 months of age. It was suggested that the acceleration of vocabulary and maturational changes in the central nervous system that occur between 16 and 22 months are associated with a special excitatory state in the temporal cortex of the left hemisphere.[39] Since the middle cerebral arteries supply parts of the temporal lobe,[33] it is possible that high left CBFV in the neonatal period facilitates the high excitatory state of the left hemisphere in the second year of life and thus also the increase in MDI score from 12 to 24 months. Our findings, demonstrating a different developmental course of infants who exhibit left CBFV asymmetry, suggest that this measure may tap an important mechanism related to individual differences in brain maturation across infancy.

To summarize, right CBFV were negatively related to neurobehavioral maturation, particularly to neonatal attention, whereas left CBFV were positively related to the course of infants' mental development during infancy. Consequently, the measure of CBFV asymmetry, which indicates the balance of right and left CBFV, was related to both neonatal attention and infants' mental development. The mechanisms that underlie these relationships are still not fully understood and the present findings, therefore, provide a first step. The number of infants in each group was small, and this is clearly a study limitation. Future research with larger samples and more in-depth assessment of a variety of outcomes is required to further investigate the mechanisms linking CBFV, attention, and cognitive development.

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