Week 5: Neonatal Neurology

Neonatal General: Brain

Friday, July 31 2:30-4:00 pm EDT

Moderators
Zachary Vesoulis
Subrata Sarkar

EDT	Abstract	Title	Presenting Author
2:30 pm		Introduction & General Information	
2:35 pm	3367905	Screening for Delirium in the Neonatal ICU – Prevalence and Associated Risk Factors	Elana Siegel
2:45 pm	3372303	Associations of body size and composition with brain volumes and white matter microstructure in very preterm infants	Katherine Bell
2:55 pm	3380282	Assessment of Cerebral Autoregulation in Extremely Low Gestational Age Newborns using Diffuse Correlation Spectroscopy and Signal Cross-Correlation	John Sunwoo
3:05 pm	3379815	Antibiotic exposure soon after birth is associated with altered auditory processing and discrimination responses in infants at one month of age	Marie Hickey
3:15 pm	3381652	Independent Value of Regional Brain Volumes at Term for Prediction of Motor Outcomes in Very Preterm Infants Without Severe Brain Injury	Maradith Skalak
3:25 pm	3381454	Independent Value of Brain Volumes at Term for Prediction of Cognitive Outcomes at 3 Years of Age in Very Preterm Infants	Maradith Skalak
3:35 pm	3377540	Chronic Lung Disease, Cry Acoustics, and Neonatal Neurobehavior in Infants Born Before 30 Weeks Gestation	Monika Martin
3:45 pm		Wrap Up	

Note: Schedule subject to change based on presenter availability.

CONTROL ID: 3367905

TITLE: Screening for Delirium in the Neonatal ICU – Prevalence and Associated Risk Factors

PRESENTER: Elana Siegel

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS: delirium, NICU, neonatal.

SESSION TITLE: Neonatal General: Brain |Neonatal General: Brain

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Delirium is a well-described complication of critical illness. Studies in the Pediatric Intensive Care Unit demonstrate prevalence rates of up to 20%. Infants in the highly medicalized NICU environment are likely at risk, yet there are only a handful of reports of NICU delirium. There have been no previous screening studies to quantify delirium prevalence in the neonatal population.

Objective: The objectives of our study were to assess feasibility of delirium screening, establish prevalence of delirium, and analyze risk factors for a positive delirium screen.

Design/Methods: All term or term-corrected (≥37+0 weeks) infants admitted to a level IV NICU were screened for delirium using the Cornell Assessment for Pediatric Delirium (CAPD) over eight study days; CAPD score≥9 was positive for delirium. Additional information collected included: gestational age at birth; recent exposure to opiates, benzodiazepines or steroids; respiratory support; recent surgery; and known neurological disorder potentially altering level of arousal/activity.

Results: Of 151 eligible infants, 147 (97.3%) were screened for delirium. Overall prevalence of a positive delirium screen was 33 (22.4%). Among infants without co-existing neurological disorder, prevalence was 13.3%. After controlling for neurological disorder, prevalence of delirium was significantly higher for those infants recently exposed to opiates, benzodiazepines or steroids, compared to those who were not (53.3% vs 6.9%, p<0.0001). Adjusted odds ratio for positive delirium screen was 7.25 (p = 0.0003) (Table).
Intubation/tracheostomy status was also associated with a positive delirium screen (15.2% vs 1.8%, p=0.0002). There was no evidence of association between delirium and babies born term/premature or recent surgery (Table).
For infants with a co-existing neurological disorder, delirium was not associated with use of opioids/benzodiazepines/steroids (66.7% vs 57.1%, p= 0.70). For infants without a co-existing condition, delirium was associated with use of opioids/benzodiazepines /steroids (53.3% vs 6.9%, p<0.0001), (Figure).

Conclusion(s): Screening for delirium is feasible in term-born and term-corrected age infants admitted to the NICU. More than 20% of such infants screen positive. Prevalence of positive delirium screen remains high when infants with underlying neurologic disorders are excluded. Respiratory support and medications known to be deliriogenic in older subjects were associated with a positive screen.

	Positive Delirium Screen	Negative Delirium Screen	Adjusted Odds Ratio [95% CI]*	p-value
All eligible babies (n=147)	33 (22.4%)	114 (77.6%)		
Babies with no history of neurological disorder (n=120)	16 (13.3%)	104 (86.7%)		
	n=33	**n=114**		
Gestational age at birth <37+0 weeks	yes – 15 (45.5%)	yes – 51 (44.7%)	1.19 [0.50, 2.87]	0.69
	no – 18 (55.5%)	no – 63 (55.3%)		
Recent opiate / benzo / steroid exposure (last 3 days)	yes – 14 (42.4%)	yes – 9 (9.3%)	**7.25 [2.48, 21.16]**	**0.0003**
	no – 19 (57.6%)	no – 88 (90.7%)		
History of surgery (<14 days)	yes – 7 (21.2%)	yes – 13 (11.5%)	1.80 [0.56, 5.73]	0.32
	no – 26 (78.8%)	no – 100 (88.5%)		
Respiratory support	23 (69.7%)	109 (95.6%)		**0.0002**
1. HFNC/LFNC/RA	5 (15.2%)	3 (2.6%)		**0.0002**
2. CPAP/SIMV	5 (15.2%)	2 (1.8%)		**0.0002**
3. intubated/trach				

*controlling for presence of co-existing neurological disorder

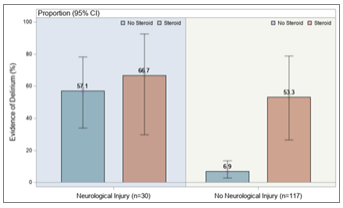

IMAGE CAPTION:

CONTROL ID: 3372303

TITLE: Associations of body size and composition with brain volumes and white matter microstructure in very preterm infants

PRESENTER: Katherine Bell

AUTHORS (LAST NAME, FIRST NAME): Bell, Katherine[1]; Matthews, Lillian G.[2]; Prohl, Anna K.[6]; Cherkerzian, Sara[3]; Inder, Terrie[4]; Warfield, Simon K.[6]; Onishi, Shun[7]; Belfort, Mandy B.[5]
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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS:

SESSION TITLE: Neonatal General: Brain |Neonatal General: Brain

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: For very preterm infants, birth to term equivalent age is a critical period for brain growth and development. Differentiating lean from fat mass describes the quality of physical growth during this period and may index brain growth and maturation. But, little is known about the relationships between body composition and regional brain growth or white matter maturation.

Objective: To assess associations of body size and composition with 1) total brain volume, 2) volumes of brain regions known to be sensitive to nutritional perturbations (hippocampus, cerebellum), and 3) white matter microstructure at term equivalent age among very preterm infants. We hypothesized greater lean mass—but not fat—would be associated with larger hippocampus and cerebellum volumes, and higher fractional anisotropy (FA) of early myelinating white matter tracts.

Design/Methods: Prospective observational study of 85 infants born <33 wks' gestation. At median postmenstrual age 39.3 wks, infants underwent air displacement plethysmography to measure body composition (from which we calculated Z-scores of lean and fat mass, weight, length, and body mass index) and brain magnetic resonance imaging (MRI). From MRI we assessed 1) total brain volume; 2) regional volumes from automated segmentation (MANTiS); 3) white matter microstructure using diffusion tensor imaging to calculate FA of 15 white matter tracts (listed in Table 2). We estimated associations of body size and composition with brain volumes and FA, using generalized estimating equations to adjust for covariates and account for multiple births.

Results: Infants were 57% male, median gestational age 29.1 wks (range 23.4, 32.9). Body size and lean mass were positively associated with volumes of most brain regions including the cerebellum, and with total brain size; whereas fat was not (Table 1). Body size and lean mass—but not fat—were also positively associated with FA in multiple white matter tracts (Table 2). Specifically, one unit increase in lean mass Z-score was associated with greater FA in: left cingulum 0.3%; left corticospinal tract 0.5%; and right posterior limb of the internal capsule 0.3%.

Conclusion(s): Greater lean mass—but not fat—at term equivalent age was associated with larger total brain and cerebellar volumes and alterations in white matter microstructure. Lean mass accrual may index brain growth and white matter development among preterm infants. Nutritional factors that promote lean mass accretion may also promote brain growth and maturation.

Table 1. Associations of body size and composition with total and regional brain volumes at term equivalent age among 85 very preterm infants.

	Estimated additional brain volume in cc (95% CI) per unit body composition or anthropometric Z-score.[1]											
	Total Brain Volume		**Cortical Gray Matter**		**Deep Gray Matter**		**White Matter**		**Hippocampus**		**Cerebellum**	
	Estimate	p	Estimate	p	Estimate	p	Estimate	p	Estimate	p	Estimate	p
Body Composition[2]												
Lean mass	**10.5 (4.0, 17.0)**	**0.001**	4.0 (-0.5, 8.5)	0.08	**0.5 (0.04, 0.9)**	**0.03**	**4.5 (1.0, 8.0)**	**0.01**	0.1 (-0.2, 0.4)	0.63	**1.2 (0.4, 2.0)**	**0.004**
Fat mass	3.8 (-4.0, 11.5)	0.34	0.3 (-3.6, 4.2)	0.89	0.2 (-0.2, 0.7)	0.29	2.9 (-0.6, 6.3)	0.10	0.001 (-0.3, 0.3)	0.99	0.3 (-0.7, 1.3)	0.55
Body fat percent	1.8 (-5.3, 9.0)	0.62	-0.3 (-3.9, 3.3)	0.87	0.2 (-0.3, 0.6)	0.45	1.8 (-1.4, 5.0)	0.26	0.002 (-0.3, 0.3)	0.99	0.1 (-0.8, 1.0)	0.81
Body Size[3]												
Weight	**17.2 (7.1, 27.3)**	**0.001**	4.6 (-2.6, 11.8)	0.21	**0.9 (0.2, 1.7)**	**0.02**	**9.6 (4.8, 14.3)**	**<0.001**	0.2 (-0.1, 0.4)	0.24	**1.6 (0.6, 2.7)**	**0.003**
Length	**19.7 (6.6, 32.8)**	**0.003**	**9.5 (0.7, 18.3)**	**0.03**	**1.1 (0.4, 1.9)**	**0.002**	**7.2 (0.4, 14.0)**	**0.04**	**0.4 (0.1, 0.7)**	**0.006**	**1.3 (0.1, 2.4)**	**0.04**
BMI	**14.0 (4.9, 23.2)**	**0.003**	3.1 (-2.7, 8.9)	0.30	0.7 (-0.1, 1.4)	0.07	**8.6 (3.8, 13.3)**	**<0.001**	0.001 (-0.3, 0.3)	0.99	**1.3 (0.4, 2.2)**	**0.006**

[1]Estimates represent the difference in brain volume associated with one Z-score increase in body size or composition, adjusted using generalized estimating equations for gestational age at birth, sex, postmenstrual age at time of brain MRI, birthweight Z-score (except length and BMI Z-scores which are adjusted for length and BMI Z-scores at birth), and accounting for non-independence of infants born to the same mother. Bold text denotes statistically significant associations with p<0.05.
[2]Body composition Z-scores are calculated from reference charts for infants born full term.
[3]Anthropometric Z-scores are calculated from the Olsen reference charts.

Table 2. Associations of body size and composition with fractional anisotropy of white matter tracts at term equivalent age among 85 very preterm infants.

	Estimated increase in fractional anisotropy (expressed as %) per unit body composition or anthropometric Z-score. [1]															
	Left cingulum		**Right cingulum**		**Left corticospinal tract**		**Right corticospinal tract**		**Left posterior limb of the internal capsule**		**Right posterior limb of the internal capsule**		**Left uncinate fasciculus**		**Right uncinate fasciculus**	
	Estimate	p	Estimate	p	Estimate	p	Estimate	p	Estimate	p	Estimate	p	Estimate	p	Estimate	p
Body Composition[2]																
Lean mass	**0.3**	**0.02**	0.2	0.20	**0.5**	**0.02**	0.3	0.25	0.1	0.36	**0.3**	**0.04**	0.2	0.15	0.2	0.11
Fat mass	0	0.64	-0.003	0.98	0.2	0.32	0.3	0.25	0.1	0.24	0.1	0.31	0.2	0.22	0.1	0.33
Body fat %	0	0.78	-0.1	0.68	0.1	0.70	0.1	0.46	0.1	0.31	0.1	0.65	0.1	0.31	0	0.77
Body Size[3]																
Weight	**0.6**	**0.003**	0.4	0.12	**0.8**	**0.01**	0.6	0.16	**0.5**	**0.03**	0.4	0.09	**0.6**	**0.03**	0.3	0.07
Length	**0.4**	**0.03**	0.3	0.27	0.4	0.39	0.5	0.94	0.3	0.18	0.2	0.28	0.2	0.51	0.3	0.08
BMI	0.1	0.40	0.2	0.19	**0.6**	**0.006**	0.4	0.15	0.2	0.16	**0.3**	**0.02**	**0.4**	**0.006**	0.3	0.08

[1]Estimates represent the increase in fractional anisotropy associated with one Z-score increase in body size or composition, adjusted using generalized estimating equations for gestational age at birth, sex, postmenstrual age at time of brain MRI, birthweight Z-score (except length and BMI Z-scores which are adjusted for length and BMI Z-scores at birth), and accounting for non-independence of infants born to the same mother. Bold text denotes statistically significant associations with p<0.05. There were no statistically significant associations with any exposure variable and fractional anisotropy in the corpus callosum, anterior thalamic radiations, inferior longitudinal fasciculi, or optic radiations.
[2]Body composition Z-scores are calculated from reference charts for infants born full term.
[3]Anthropometric Z-scores are calculated from the Olsen reference charts.

IMAGE CAPTION:

CONTROL ID: 3380282

TITLE: Assessment of Cerebral Autoregulation in Extremely Low Gestational Age Newborns using Diffuse Correlation Spectroscopy and Signal Cross-Correlation

PRESENTER: John Sunwoo

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS: Cerebral autoregulation, Extremely low gestational age, Diffuse Correlation Spectroscopy.

SESSION TITLE: Neonatal General: Brain |Neonatal General: Brain

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Extremely low gestational age (ELGA, < 29 wks GA) newborns are at high risk to develop germinal matrix intraventricular hemorrhage (GM-IVH) within the first 3 days after birth. The GM-IVH results in poor neurodevelopmental outcomes. This risk relates to the immaturity of the vascular bed within the germinal matrix, which is particularly vulnerable to dysregulation of cerebral blood flow (CBF).

Objective: Therefore, optimal therapeutic strategies that maintain cerebrovascular stability is needed in ELGA; however, we lack a reliable continuous monitoring of CBF. To address this unmet need, we developed a diffuse correlation spectroscopy (DCS, 785nm) system and flexible optical sensors (Figure 1) to continuously monitor CBF in ELGA infants during their first three postnatal days.

Design/Methods: To date, we have enrolled 9 newborns (3 ELGA infants). We monitored them with DCS for 2-6 hours a day during the first few days after birth. We also co-recorded electrocardiogram, pulse oximetry, and when available invasive blood pressure, transcutaneous pCO_2, and regional cerebral oximetry. The presence of IVH was assessed from the head ultrasound on days 1, 3, 7, and 30 of life. We computed cross-correlation between CBF_i responses to fluctuation in mean arterial blood pressure (MAP) to quantify the degree of dysfunction in cerebral autoregulation (e.g., pressure passive events). A sliding window of 2.5 minutes was used to find a peak correlation (R) within 20 seconds of lag, and response time (Tr) was identified at the time of the peak correlation. A bootstrapped null distribution was used to test the significance of the correlation (Pr).

Results: This report summarizes the results of a pair of 23 wks GA twins. When baby A was compared to baby B, A had significantly higher probability of pressure passive events than baby B (p=0.046, Chi-square test, Table 1). Also, significantly shorter response time and unstable MAP had been detected in baby A than B, which suggests more reactive yet disruptive cerebral autoregulation. Although both babies developed Grade II IVH, while baby A had an ultrasound diagnosis of IVH at day 2 of life, IVH was not detected until day 7 of life in baby B.

Conclusion(s): We assessed cerebral autoregulation in ELGA infants using continuous CBF monitoring via DCS and signal cross-correlation. This can help clinicians to make informed decisions and foster the development of new interventions that can stabilize CBF and prevent IVH in ELGA infants.

Indices of pressure passive events in twin ELGA infants A and B

Indices \ ELGA	A	B	*P*-value
R	0.40 ± 0.2	0.14 ± 0.2	< 0.0001 *
Tr (sec)	1 (0-14)	9 (2-17)	0.008 ^
Pr	0.16 (0.03-0.43)	0.56 (0.15-0.81)	0.0001 ^
# (%) significant R (alpha=0.1)	23 (42%)	9 (23%)	0.046 *
Total # windows for correlation	55	40	
Day of life diagnosed with IVH	2	7	-

R: Correlation Coefficient; Tr: Response time at R; Pr: Bootstrap P-value of R; Mean ± Std; Median(IQR); * Two sample t test; ^ Wilcoxon rank sum test; * Chi-square test; Correlation window = 2.5 minutes; Peak correlation was found within-20 second lag;

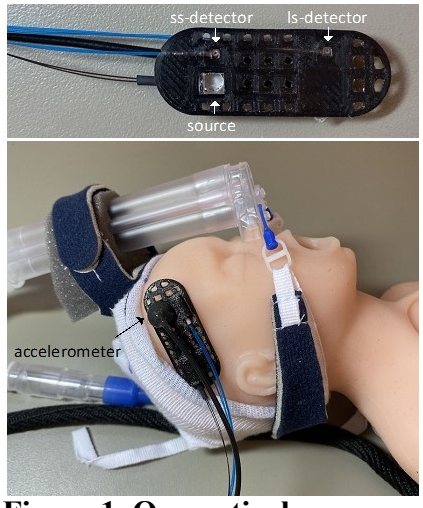

Figure 1. Our optical sensor prototype includes 5mm short (ss) and 20mm long (ls) separation channels and an accelerometer. The sensor is attached to the baby's head with

hydrogel to ensure skin integrity during the long monitoring sessions, and covered by a continuous positive airway pressure (CPAP) hat.

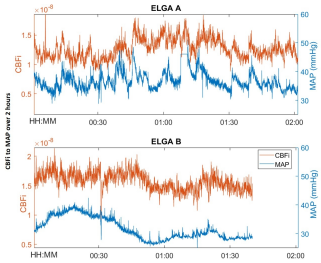

Figure 2. Two cases (2 twins, 23 wks GA) of CBFi responses to MAP measured at day 4 of life. Baby A and B were diagnosed with IVH at day 2 and 7 of life, respectively.

IMAGE CAPTION:

Figure 1. Our optical sensor prototype includes 5mm short (ss) and 20mm long (ls) separation channels and an accelerometer. The sensor is attached to the baby's head with hydrogel to ensure skin integrity during the long monitoring sessions, and covered by a continuous positive airway pressure (CPAP) hat.

Figure 2. Two cases (2 twins, 23 wks GA) of CBFi responses to MAP measured at day 4 of life. Baby A and B were diagnosed with IVH at day 2 and 7 of life, respectively.

CONTROL ID: 3379815

TITLE: Antibiotic exposure soon after birth is associated with altered auditory processing and discrimination responses in infants at one month of age

PRESENTER: Marie Hickey

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS:

SESSION TITLE: Neonatal General: Brain |Neonatal General: Brain

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Exposure to antibiotics, in the absence of infection, results in abnormal brain function in animals which is linked to changes in gut microbes. The hippocampus, a brain region important for recognition learning and memory, is a target of microbe-mediated effects on the brain. Studies in germ-free mice have shown that there is an early-life sensitive period for gut microbe effects on neurodevelopment.

Objective: To test the hypothesis that neonatal exposure to antibiotics affects recognition memory responses in human infants.

Design/Methods: Auditory recognition memory (mother-stranger voice paradigm) was assessed at 1 month of age in 15 infants born at term and exposed to antibiotics, but with negative cultures, and a subset of 57 term infants in the Mothers and Infants Linked for Health Growth (MILk) Study not exposed to antibiotics, using event-related potentials (ERPs).

Linear regression analysis, with adjustment for covariates such as birth mode, gestational age at birth, and sex, was employed to compare groups with respect to ERP features that represent early stimulus processing and discrimination (P2 amplitudes) between mother and stranger voices.

Results: Infants exposed to antibiotics exhibited smaller overall mean P2 amplitudes for both mother and stranger voice conditions ($p = 0.001$), with the greatest reduction (more negative beta coefficients in bold) observed in response to mother's voice in right and left frontal and right central scalp regions (Table). In addition, infants exposed to antibiotics showed larger P2 amplitudes to stranger's as compared to mother's voice, a reversal of the typical response exhibited by infants not treated with antibiotics (Figure, compare mother to stranger response change within each infant treatment group). In an exploratory analysis within the group of infants exposed to antibiotics, abnormal ERP responses did not correlate with increased inflammatory cytokine concentrations (tumor necrosis factor alpha, interleukin-1-beta, interleukin-6, interleukin-8, and interferon gamma).

Conclusion(s): Otherwise healthy infants born at term gestation and exposed to antibiotics soon after birth demonstrated altered auditory processing and discrimination responses at one month of age, supporting the presence of a microbiota-gut-brain axis in humans during very early life.

Association of antibiotic exposure with mean P2 amplitude by lead grouping

Condition	Region	B (SE)	p
Mother voice	Left frontal	-2.585 (0.844)	0.003
	Right frontal	-3.054 (0.829)	0.0005
	Left central	-0.497 (0.735)	0.50
	Right central	-1.288 (0.606)	0.037
Stranger voice	Left frontal	-2.035 (0.883)	0.024
	Right frontal	-1.251 (0.846)	0.14
	Left central	-1.511 (0.752)	0.049
	Right central	-0.842 (0.669)	0.21

Adjusted for sex, gestational age at time of ERP and delivery mode. B, Beta coefficient. SE, standard error.

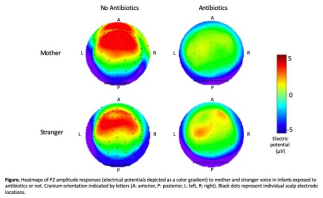

Figure. Heatmaps of P2 amplitude responses (electrical potentials depicted as a color gradient) to mother and stranger voice in infants exposed to antibiotics or not. Cranium orientation indicated by letters (A: anterior, P: posterior, L: left, R: right). Black dots represent individual scalp electrode locations.

IMAGE CAPTION:

CONTROL ID: 3381652

TITLE: Independent Value of Regional Brain Volumes at Term for Prediction of Motor Outcomes in Very Preterm Infants Without Severe Brain Injury

PRESENTER: Maradith Skalak

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS: Neurodevelopmental outcomes , MRI, Prediction.

SESSION TITLE: Neonatal General: Brain |Neonatal General: Brain

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Very preterm infants are at high risk for motor impairments. Qualitative brain imaging is commonly used to assess risk, however accurate prediction remains elusive especially in infants without severe brain injury.

Objective: To determine whether automatically-quantified brain volume measurements on term MRI are independent predictors of motor outcomes in preterm infants, above and beyond known clinical risk factors and semi-quantitative structural MRI readings.

Design/Methods: Prospective cohort of preterm infants born ≤31 weeks gestation from four level III NICUs in Columbus, Ohio of 94 infants without severe injury or motion artifacts using 3T MRI scanner (1mm^3 resolution) at term-equivalent age. Motor testing was performed using the Bayley Scales of Infant and Toddler Development, Third Edition at two years corrected age. Automated volumetric analysis was performed using the Developing Human Connectome Project pipeline. Structural MRI scans were reviewed by a three pediatric neuroradiologists and global brain abnormality score per Kidokoro et al. (2013) was assigned by first author. Biometric measurements were done by first author and demonstrated high intra-rater reliability (n=20, intra-class coefficients 0.82 – 0.99). We used multivariable regression to evaluate the independent value of relative brain volumes (adjusted for total tissue volume) above clinical predictors and Kidokoro score (Table 1) for predicting motor outcomes.

Results: 75 of the 94 infants (80%) returned for developmental testing (Table 2). Several regional volumes were significantly associated with motor outcomes in univariate analyses (Table 3). For motor impairment (Bayley Motor<80), the area under the receiver operating characteristic curve (AUC) for clinical predictors and Kidokoro score was 0.91; with the addition of brain volumes, it improved to 0.96 (Table 4). Similarly, addition of brain volumes to clinical predictors and Kidokoro score improved the adjusted R^2 value for the Bayley Motor score from 0.33 to 0.55, with several regional volumes showing significance or trend towards significance in predicting motor scores (Table 4).

Conclusion(s): : In our regional cohort, objectively-quantified regional brain volumes at term independently improved the accuracy of predicting motor outcomes beyond existing clinical and structural imaging predictors in very preterm infants without severe brain injury. External validation in a large sample of infants is needed.

Table 1. Baseline characteristics of clinical predictors of motor development and the Kidokoro global brain abnormality score at term-equivalent age in very preterm infants.

Clinical Variable	Very Preterm Infants with Follow-up (N=75)
Sex, male n (%)	31 (41.3)
Birth weight (grams), median (range)	1075 (445 – 2340)
Gestational age (weeks), median (range)	28.6 (23.7 – 31.9)
Disadvantaged socioeconomic status, n (%)	40 (53.3)
Severe bronchopulmonary dysplasia, n (%)	22 (27.5)
Severe retinopathy of prematurity, n (%)	8 (10)
Intra-uterine growth restriction	7 (8.8)
White matter or cerebellar injury on head ultrasound after 35 weeks corrected age	12 (15)
Kidokoro score, n (%) No brain abnormality Mild brain abnormality Moderate brain abnormality Severe brain abnormality	 44 (58.7) 20 (26.7) 9 (12.0) 2 (2.7)

Table 2. Bayley Scales of Infant and Toddler Development, third edition (Bayley III) motor subscale results

Motor outcome	Very Preterm Infants with Follow-up (N=75)
Motor impairment, n (%)	10 (13.3)
Bayley III Motor Scale score, median (range)	94 (46 – 112)

Table 3. Regional relative brain volumes significantly associated with motor outcomes in univariate analyses.

Outcome measure	Regional volume	P value
Motor impairment		
	Cerebrospinal fluid	0.030
	Superior temporal gyrus posterior part white matter	0.046
Bayley III Motor score		
	Superior temporal gyrus posterior part white matter	0.000
	Superior temporal gyrus white matter (merged region)	0.000
	Superior temporal gyrus middle part white matter	0.007
	Temporal lobe white matter	0.013
	Anterior temporal lobe lateral part gray matter	0.034
	Anterior temporal lobe medial part white matter	0.039
	Temporal lobe gray matter (merged region)	0.045
	Cerebrospinal fluid	0.047
	Cingulate gyrus white matter	0.047

Table 4. Final model for prediction of motor outcomes measured on the Bayley-III at 2 years corrected age in very preterm infants.

Outcome	Predictor	Coefficient (SE)	P value	AUC* or Adjusted R2
Motor impairment				0.96
	Kidokoro score	1.51 (0.98)	0.123	
	Sex	-2.7 (1.23)	0.028	
	Gestational age	-1.19 (0.64)	0.064	
	Severe BPD	2.79 (1.2)	0.021	
	Socioeconomic status	-2.01 (1.08)	0.063	
	Birth weight	0.01 (0)	0.083	
	Cerebrospinal fluid	26.72 (14.45)	0.065	
	White matter	234.03 (96.79)	0.016	
	Cerebellum	207.86 (116.42)	0.074	
Bayley III motor score				0.55
	Kidokoro score	0.16 (1.78)	0.928	
	Severe ROP	-10.03 (3.91)	0.013	
	Injury on head ultrasound	-12.08 (3.6)	0.001	
	Intrauterine growth restriction	-13.09 (4.7)	0.007	
	Superior temporal gyrus posterior part white matter	291135 (160328.61)	0.074	
	Superior temporal gyrus white matter (merged region)	-295591.91 (160068.94)	0.069	
	Superior temporal gyrus middle part white matter	295168.24 (159933.39)	0.070	
	Anterior temporal lobe lateral part gray matter	-4153.27 (1740.67)	0.020	
	Cingulate gyrus white matter	3042.54 (910.11)	0.001	

*AUC: Area under the receiver operating characteristic curve; BPD; bronchopulmonary dysplasia; ROP: retinopathy of prematurity

IMAGE CAPTION:

CONTROL ID: 3381454

TITLE: Independent Value of Brain Volumes at Term for Prediction of Cognitive Outcomes at 3 Years of Age in Very Preterm Infants

PRESENTER: Maradith Skalak

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS: Neurodevelopmental outcomes , MRI, Prediction.

SESSION TITLE: Neonatal General: Brain |Neonatal General: Brain

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Very preterm infants are at risk for cognitive impairment. Standard imaging tools, including head ultrasound and qualitative brain MRI, do not reliably predict cognitive outcomes. Regional brain volumes at term have shown conflicting prognostic value and have not been adequately compared with existing predictors or cognitive outcomes beyond 2 years corrected age.

Objective: To determine whether automated brain volume measurements on term MRI improves ability to predict cognitive outcomes at 3 years corrected age, independent of clinical predictors and structural MRI.

Design/Methods: Prospective cohort of 110 very preterm infants (31 weeks gestation) were enrolled from 4 level III NICUs in Columbus, Ohio. Brain MRI was done at term-equivalent age using 3T scanner (1 mm^3 resolution). General conceptual score (GCA) on the Differential Ability Scales (DAS)-II was our primary outcome. Automated volumetric analysis was successful in 94 subjects (subjects excluded for severe brain injury or motion artifacts) using the Developing Human Connectome Project pipeline to yield more than 200 regional brain volumes. Structural MRI scans were read by 3 pediatric neuroradiologists and biometric measurements were obtained by the first author with high intra-rater reliability (n=20; ICC 0.82 – 0.99) to yield a global brain abnormality score per Kidokoro et al. (2013). We used multivariable regression to assess independent value of relative brain volumes (divided by total tissue volume) over and above known clinical predictors and Kidokoro score for predicting cognitive outcomes (Table 1).

Results: Of the 94 very preterm infants with successful imaging, 80 (81%) returned for DAS-II testing at 3 years corrected age (Table 2). In univariate analyses, several relative regional volumes were significantly correlated with the DAS-GCA score (Table 3). Some volumes remained significant in multivariable analysis, independent of Kidokoro score and injury on head ultrasound. Addition of volumes to prediction model improved performance of prediction of cognitive impairment (Table 4).

Conclusion(s): In our regional cohort, objectively-quantified regional brain volumes improved performance of prediction model for cognitive impairment. This data suggests that there may be a role for brain volumes in prediction of cognitive outcomes of preterm infants, especially those without severe brain injury.

Table 1. Baseline characteristics of clinical predictors of cognitive outcomes and the Kidokoro global brain abnormality score in very preterm infants.

Clinical Variable	Very Preterm Infants with Follow-up (N=80)
Sex, male n (%)	32 (40)
Birth weight (grams), median (range)	1075 (445 – 1900)
Gestational age (weeks), median (range)	29.1 (23 – 31.9)
Disadvantaged socioeconomic status, n (%)	46 (57.5)
Severe bronchopulmonary dysplasia, n (%)	22 (27.5)
Severe retinopathy of prematurity, n (%)	8 (10)
Intra-uterine growth restriction, n (%)	7 (8.8)
Injury on head ultrasound after 35 weeks corrected age, n (%)	12 (15)
Kidokoro score, n (%) No brain abnormality Mild brain abnormality Moderate brain abnormality Severe brain abnormality	 47 (58.8) 21 (26.3) 9 (11.3) 3 (3.8)

Table 2. Cognitive testing with the Differential Ability Scales, second edition (DAS-II) at 3 years corrected age results.

DAS-II Outcome	Very Preterm Infants with Follow-up (N=80)
General conceptual ability Median (Range)	90 (36 – 128)
Nonverbal subtest Median (Range)	92 (39 – 132)
Verbal subtest Median (Range)	89 (35 – 132)
Cognitive impairment N (%)	18 (22.5)

Table 3. Regional relative brain volumes significantly associated with cognitive outcomes in univariate analyses.

Outcome measure	Relative regional brain volume	P value
DAS-GCA		
	Cerebral Spinal Fluid (CSF)	0.005
	Thalamus low intensity in T2	0.012
	Hippocampus	0.013
	Hippocampi and amygdala	0.021
DAS Nonverbal subtest		
	CSF	0.003
	Thalamus low intensity in T2	0.008
	Hippocampus	0.020
	Hippocampi and amygdala	0.021
DAS Verbal subtest		
	CSF	0.016
	Hippocampus	0.037
	Cingulate gyrus anterior part white matter	0.048
	Thalamus low intensity part in T2	0.050
Cognitive Impairment		
	CSF	0.000
	Cingulate gyrus anterior part white matter	0.023
	Cingulate gyrus anterior part gray matter	0.023
	Superior temporal gyrus posterior white matter	0.024
	Gyri parahippocampalis et ambien posterior part white matter	0.034
	Brainstem	0.050

Table 4. Final models for prediction of cognitive outcomes

Outcome	Number of predictors	Parameter	Parameter estimate (standard error)	P value	Adjusted R2 or AUC
DAS-GCA	10				0.46
		Kidokoro score	-5.91 (2.59)	0.026	
		Gestational age	3.77 (1.41)	0.010	
		Socioeconomic status	15.09 (3.38)	<.0001	
		Injury on head ultrasound	-11.52 (5.15)	0.029	
		IUGR	-17.72 (7.09)	0.015	
		Birth weight	-0.02 (0.01)	0.089	
		White matter	-272.51 (138.26)	0.053	
		Cerebellum	-388 (248.66)	0.123	
		Deep gray matter	-727.33 (476.1)	0.1312	
		Occipital lobe white matter	776.11 (493.07)	0.1201	
Cognitive impairment	7				0.93
		Kidokoro score	0.94 (0.61)	0.124	
		Severe BPD	1.35 (0.56)	0.017	
		Injury on head ultrasound	1.68 (0.7)	0.017	
		Birth weight	0.01 (0)	0.031	
		CSF	32.4 (10.59)	0.002	
		Brainstem	1614.19 (557.74)	0.004	
		Thalamus low intensity in T2	-5272.9 (2251.61)	0.019	

AUC – Area under receiver operating characteristic curve. IUGR - intra-uterine growth restriction. BPD - bronchopulmonary dysplasia. CSF - cerebral spinal fluid.

IMAGE CAPTION:

CONTROL ID: 3377540

TITLE: Chronic Lung Disease, Cry Acoustics, and Neonatal Neurobehavior in Infants Born Before 30 Weeks Gestation

PRESENTER: Monika Martin

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal General

KEYWORDS:

SESSION TITLE: Neonatal General: Brain |Neonatal General: Brain

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:
Background: Chronic lung disease (CLD) is a significant risk factor for developmental delays in children born preterm. Most studies assessing preterm infants with CLD have performed neurodevelopmental exams at or after 12 months of age, with no known studies in patients prior to discharge from the NICU.

Objective: To determine whether CLD severity in preterm infants is associated with atypical neurobehavior and cry acoustics prior to hospital discharge.

Design/Methods: Infants born <30 weeks post-menstrual age (PMA) were enrolled in the multicenter Neonatal Neurobehavior and Outcomes in Very Preterm Infants (NOVI) Study. The NICU Network Neurobehavioral Scale (NNNS) was administered at discharge, and risk profiles and summary scores calculated. Maximum likelihood factor analysis was performed on cry acoustics. Generalized estimating equations examined the associations of CLD severity with NNNS scores and cry factors adjusting for site, maternal and neonatal complications, and PMA at birth and NNNS.

Results: Of 709 enrolled NOVI infants, 676 had complete medical and NNNS data; 177 (26.2%) had moderate/severe (mod/sev) CLD, and 163 (24.1%) had mild CLD. Maternal and infant characteristics differed by CLD severity (Table 1). Factor analysis of cry data (n=418) revealed two factors that explained the greatest proportion of variation: frequency/energy (loudness) and hyperphonation (high pitch). Cry factors were not associated with CLD. Infants with mod/sev CLD were 3 times more likely to have an overall atypical NNNS risk profile when compared to infants without CLD (OR=3.09; 95% CI:1.02, 9.37). Comparisons for individual NNNS summaries indicated that mod/sev CLD was associated with lower NNNS attention scores and increased lethargy. Mod/sev CLD was also associated with lower quality of movement compared to mild CLD, and with lower arousal compared to no CLD (Table 2).

Conclusion(s): Severity of CLD in preterm newborns at the time of hospital discharge was associated with specific neurobehavioral patterns. Identification of targeted neurobehavioral problems by administering the NNNS in these at-risk newborns prior to NICU discharge may lead to earlier initiation of specific therapeutic interventions with potential to improve long-term outcomes.

Table 1. Maternal and Infant Characteristics

N % or Mean SD	No CLD (n=336)		Mild CLD[1] (n=163)		Moderate/Severe[2] CLD (n=177)		p
Maternal Characteristics							
Maternal Age at childbirth	29.0	6.3	30.0	6.9	28.4	6.1	0.324
Pre-pregnancy BMI	28.0	7.7	28.5	7.3	27.1	7.0	0.376
SES Hollingshead index, neonatal	35.2	12.9	37.1	13.0	35.3	12.7	0.938
Minority race or ethnicity	190	57.8 %	94	57.7%	92	52.9	0.541
Infant Characteristics							
Post Menstrual Age (PMA) at Birth	28.0	1.5	26.2	1.8	26.0	1.9	<0.001
PMA at NNNS Exam	37.3	2.4	40.0	2.6	42.5	3.1	<0.001
Sex of Infant, male	188	56.0%	93	57.1%	95	53.7%	0.809
Birth Weight (grams)	1087.7	264.0	846.1	227.5	797.8	230.4	<0.001
Total Length of Stay (days)	70.6	25.0	102.8	25.4	123.6	48.3	<0.001
Maternal risks							
Maternal Hypertension, Chronic or Pregnancy-Induced	75	22.3%	44	27.2%	51	29.0%	0.208
Diabetes mellitus	27	8.1%	9	5.5%	9	5.1%	0.35
Infection, pregnancy	46	13.7%	8	4.9%	15	8.5%	0.006
Asthma	24	7.2%	14	8.6%	15	8.5%	0.804
Infant risks							
NEC or Sepsis	38	11.3%	33	20.2%	46	26.0%	<0.001
Severe ROP [a]	4	1.2%	15	9.2%	21	11.9%	<0.001
Antenatal Steroids	309	92.0%	141	86.5%	146	83.0%	0.008
Bassler Brain Injury [b]	29	8.7%	20	12.3%	39	22.0%	<0.001

1 Requiring mechanical/nasal ventilation or oxygen via high flow nasal cannula (HFNC)] at 36 weeks post menstrual ag[illegible]MA)
2 Requiring oxygen via nasal cannula or room air via HFNC at 36 weeks PMA
a Severe ROP=retinopathy of prematurity, Stages 4-5 or laser/cryotherapy
b Brain Index adapted from Bassler et al., 2009; periventricular leukomalacia, ventricular dilatation, parenchymal echodensity

Table 2. CLD severity by NNNS summary scores

	Adjusted Means*							
	No CLD (1)		Mild CLD (2)		Moderate/Severe CLD (3)		Multiple Comparison p-v	
	Mean	SE	Mean	SE	Mean	SE	(1) vs (2)	(1) vs (3)
Attention	5.220	0.222	5.041	0.224	4.702	0.230	0.178	0.004
Quality of movement	4.497	0.088	4.582	0.094	4.436	0.097	0.305	0.648
Arousal	3.705	0.099	3.672	0.101	3.517	0.100	0.648	0.032
Lethargy	5.117	0.314	5.077	0.323	5.830	0.341	0.851	0.010

*Adjusted for site, PMA at birth, maternal hypertension, maternal diabetes, infection during pregnancy, necrotizing enterocolitis/sepsis, severe ROP, antenatal steroids and brain injury

IMAGE CAPTION:

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