Week 5: Neonatal Neurology

Neonatal Neurology: Basic and Translational II

Thursday, July 30 4:30-6:00 pm EDT

Moderators
Karen Hussein
Sudhin Thayyil

EDT	Abstract	Title	Presenting Author
4:30 pm		Introduction & General Information	
4:35 pm	3379358	MSC derived extracellular vesicles reduce hypoxia-ischemia induced perinatal brain Injury	Claudia Sisa
4:45 pm	3381402	GABAergic disruption correlate with fluorothyl seizure susceptibility after neonatal hypoxic-ischemic brain injury in male mice.	Charles Lechner
4:55 pm	3378128	Administration of a Single Dose of Umbilical Cord Blood-Derived Non-Hematopoietic Stem Cells Improves Long-term Neurological Outcome in a Neonatal Rat Model of Severe Intraventricular Hemorrhage	Raghavendra Rao
5:05 pm	3381737	Cerebellar biochemistry, connectivity and neurobehavior in very preterm infants	Sudeepta Basu
5:15 pm	3381143	Term-Equivalent Functional Connectivity Relates to Motor Performance Across Childhood in Very Preterm Children	Peppar Cyr
5:25 pm	3378004	Risk for cerebral palsy (CP) may not be driven by early epigenetic factors in extremely low gestational age neonates (ELGANs)	An Massaro
5:35 pm	3378249	Brain Temperature and Metabolites – An in-vivo MR spectroscopy assessment of energy states, metabolism, neuronal maturation, and neurotransmission in infants with hypoxic-ischemic encephalopathy	Tai-Wei Wu
5:45 pm		Wrap Up	

Note: Schedule subject to change based on presenter availability.

CONTROL ID: 3379358

TITLE: MSC derived extracellular vesicles reduce hypoxia-ischemia induced perinatal brain Injury

PRESENTER: Claudia Sisa

AUTHORS (LAST NAME, FIRST NAME): Sisa, Claudia[1]; Naylor, Jordan E.[1]; Bruno, Stefania[2]; Camussi, Giovanni[2]; kholia, sharad[2]; Herrera Sanchez, Maria B.[2]; Lange, Sigrun[4]; Hristova, Mariya[3]; Deregibus, Maria Chiara[2]; Inal, Jameel[5]

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neurology: Translational

KEYWORDS: hypoxia-ischemia, brain injury, stem cells.

SESSION TITLE: Neonatal Neurology: Basic and Translational II |Neonatal Neurology: Basic and Translational II

SESSION TYPE: Webinar|Oral Poster Symposia

ABSTRACT BODY:

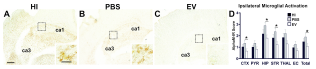
Background: Neonatal hypoxic-ischemic (HI) insult is a leading cause of disability and death in newborns, with therapeutic hypothermia being the only currently available clinical intervention. However, hypothermia has limited application and effectiveness. Thus, there is a great need for adjunct and novel treatments for enhanced or alternative post-HI neuroprotection. Extracellular vesicles (EVs) derived from mesenchymal stromal/stem cells (MSCs) have recently been shown to exhibit regenerative effects in various injury models. We hypothesize that intranasal application of MSC derived EV immediately following neonatal HI will prove neuroprotective.

Objective: We aimed to investigate the neuroprotective effects of MSC derived EVs in the Rice-Vannucci mouse model of severe HI-induced neonatal brain injury.

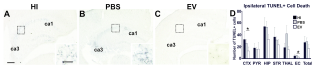
Design/Methods: MSC derived EVs were applied intranasally immediately post HI-insult and behavioral outcomes were assessed through negative geotaxis at 48 h post-treatment. Brains were thereafter excised and assessed for changes in glial response, cell death, and neuronal loss as markers of damage at 48 h post HI-insult.

Results: Brains of the MSC-EV treated group showed a significant decrease in microglial activation, cell death, and percentage tissue volume loss in multiple brain regions, compared to the control-treated groups. Furthermore, the negative geotaxis test showed improved behavioral outcomes at 48 h following MSC-EV treatment.

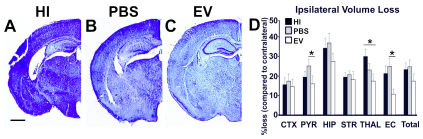
Conclusion(s): Our findings highlight the clinical potential of using MSC-derived EVs as a neuroprotective agent following neonatal hypoxia-ischemia



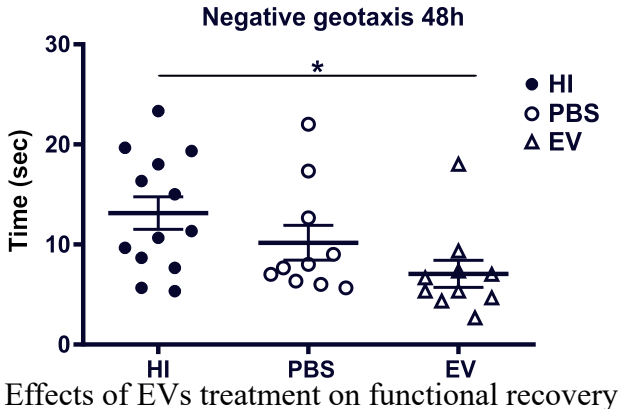
Effects of EVs treatment on microglia



Effects of EVs treatment on cell death



Effects of EVs treatment on tissue loss



Effects of EVs treatment on functional recovery

IMAGE CAPTION:
Effects of EVs treatment on microglia

Effects of EVs treatment on cell death

Effects of EVs treatment on tissue loss

Effects of EVs treatment on functional recovery

CONTROL ID: 3381402

TITLE: GABAergic disruption correlate with fluorothyl seizure susceptibility after neonatal hypoxic-ischemic brain injury in male mice.

PRESENTER: Charles Robert Lechner

AUTHORS (LAST NAME, FIRST NAME): Lechner, Charles R.[1]; McNally, Melanie[3]; Felling, Ryan J.[2]; Spahic, Harisa[1]; Northington, Frances J.[1]; Stafstrom, Carl E.[2]; Chavez-Valdez, Raul[1]

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CURRENT CATEGORY: Neurology

CURRENT SUBCATEGORY: Neonatal Neurology: Basic

KEYWORDS: GABA, Hippocampus, Seizures.

SESSION TITLE: Neonatal Neurology: Basic and Translational II |Neonatal Neurology: Basic and Translational II

SESSION TYPE: Webinar|Oral Poster Symposia

ABSTRACT BODY:

Background: Disruption of the hippocampal GABAergic network after neonatal hypoxia-ischemia (HI) in the mouse is characterized by lower numbers of parvalbumin (PV)+ interneurons (INs), simplified PV+ dendritic arbors, and decrease GAD65/67 8d after the insult. In this model, worse hippocampal HI injuries correlate with increased fluorothyl seizure susceptibility in male mice. Therapeutic hypothermia (TH) provides minimal protection against hippocampal injury, fluorothyl seizure susceptibility and GABA disruption

Objective: To test the hypothesis that GABAergic disruption correlate with fluorothyl seizure susceptibility in a sex-specific manner in a mouse model of neonatal HI.

Design/Methods:
C57BL6 mice injured with HI (Vannucci) at P10 were randomized to normothermia (NT, 36°C) or TH (31°C) for 4h, and exposed to fluorothyl at P18 to study seizure susceptibility prior to brain dissection for histology. Sham controls were anesthesia-exposed littermates. Using z-stack 3D imaging reconstruction (Zeiss L700), we evaluated in the pyramidal cell layer (Py) of the CA1 and CA3 subfields: i) the number of INs expressing PV, and calretinin (CAL), and ii) the % area of somatostatin (SST), GAD65/67, GABAB R1 and R2 and GABAR α1 subunit, expression. Correlation with seizure susceptibility (stage [S] 3 and 5) after fluorothyl exposure was then calculated. Non-parametric analysis was applied (SPSSv24.0).

Results: In both sexes, the number of PV+INs was decreased in the CA1 and CA3 8d after HI (p=0.01 and 0.03 vs. sham, respectively). This effect was not documented in the M1 motor cortex and was not attenuated by TH. Only in males, latency to tonic seizures (S5) directly correlated with the number of PV+INs in CA1 (p=0.006) and CA3 (p=0.008). Unlike in non-fluorothyl exposed HI injured mice, GAD65/67 IR did not decrease and did not predicted seizure susceptibility. Similar to PV + INs, CAL+ INs were also decreased in CA1 and CA3 after neonatal HI. Conversely SST IR in the Py remained unchanged. Lastly, while GABAB R2 subunit was decreased 8d after neonatal HI, GABAB R1 was unchanged, and GABAR α1 was markedly increased in the Py 8d after HI in fluorothyl exposed mice.

Conclusion(s): Disruption of the hippocampal GABAergic network, specifically deficit of PV+INs after neonatal HI may explain seizure susceptibility in a sex-specific manner. Preservation of GAD65/67, SST+ boutons, GABAB R1 and overexpression of GABARα1 may be a compensation of the injured brain to the delayed seizures induced by fluorothyl.

(No Image Selected)

CONTROL ID: 3378128

TITLE: Administration of a Single Dose of Umbilical Cord Blood-Derived Non-Hematopoietic Stem Cells Improves Long-term Neurological Outcome in a Neonatal Rat Model of Severe Intraventricular Hemorrhage

PRESENTER: Raghavendra Rao

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neurology: Translational

KEYWORDS: Intraventricular hemorrhage, Umbilical cord blood stem cells, Neurological outcome.

SESSION TITLE: Neonatal Neurology: Basic and Translational II |Neonatal Neurology: Basic and Translational II

SESSION TYPE: Webinar|Oral Poster Symposia

ABSTRACT BODY:
Background: Intraventricular hemorrhage (IVH) occurs in 30-50% of extremely preterm (EPT, gestational age <28 wk) infants. Severe (grades 3 and 4) IVH is associated with long-term neurological deficits. Previous studies have demonstrated that administration of a single dose of human umbilical cord blood-derived stem cells (UCBSC) improves short-term outcomes in animal models of IVH.

Objective: To assess the effects of administration of a single dose of UCBSC on long-term neurological outcomes in a neonatal rat model of severe IVH.

Design/Methods: Unilateral grade 3-4 IVH was induced in postnatal day (P) 2 rat pups (brain development equivalent to that of human EPT infants) by injecting type VII collagenase, 0.75 μg in 2 μL normal saline into the right ganglionic eminence. A single dose of human nonhematopoietic UCBSC ($1x10^6$ cells in 0.2 mL vehicle) was injected intraperitoneally on either P4, P6 or P11. Motor function (unilateral body swing, forelimb placement and edge push resistance) and behavioral outcome (rearing and open field exploration) were assessed at 2-4 months of age (adulthood) and compared with the Control and untreated IVH groups (n=10-20/group).

Results: Survival rate was 100% (Control), 70% (untreated IVH) and 90% (IVH+UCBSC). Unilateral motor deficits and a hyperactive exploratory behavior were present in the untreated IVH group. UCBSC administration ameliorated these impairments, irrespective of the day of administration (Table 1 and Figure 1). Cavitary brain lesions were present in 75% in the untreated IVH group and in 43% in the UCBSC group (p<0.01).

Conclusion(s): Administration of a single dose of human nonhematopoietic UCBSC improved long-term neurological outcome in neonatal rats with severe IVH. The beneficial effects on functional recovery were greater than the effects on brain structure.

Table 1. Motor Deficits in Adult Rats after Neonatal Severe Intraventricular Hemorrhage

Group	N	Abnormal Body Swing	Deficient Forelimb Placement	Deficient Edge Push Resistance
Untreated IVH	5	100%	60%	100%
IVH + UCBSC on P6	8	12.5%	12.5%	12.5%
IVH + UCBSC on P11	6	0%	0%	0%

Values are percentage of rats in the group with motor deficit. Abbreviations: IVH, intraventricular hemorrhage; P, postnatal day; UCBSC, umbilical cord blood-derived nonhematopoietic stem cells.

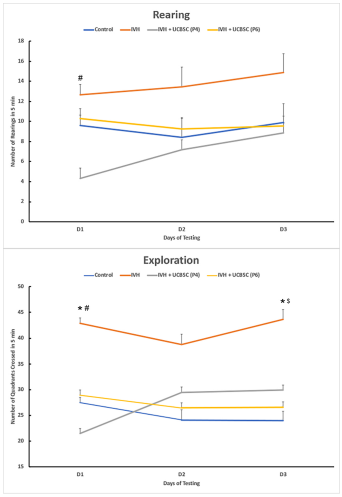

Figure 1. Behavioral outcome after neonatal intraventricular hemorrhage in adult rats. Values are mean±SEM; N=10-12 per group. Groups differ from each other in both tests ($p<0.05$, ANOVA). *$p<0.05$ vs. Control group; #$p<0.05$ vs. UCBSC (P4) group and $p=0.05 vs. UCBSC (P4) and UCBSC (P6) groups. Abbreviations: P, postnatal day; UCBSC, umbilical cord blood-derived nonhematopoietic stem cells.

IMAGE CAPTION:

Figure 1. Behavioral outcome after neonatal intraventricular hemorrhage in adult rats. Values are mean±SEM; N=10-12 per group. Groups differ from each other in both tests ($p<0.05$, ANOVA). *$p<0.05$ vs. Control group; #$p<0.05$ vs. UCBSC (P4) group and $p=0.05 vs. UCBSC (P4) and UCBSC (P6) groups. Abbreviations: P, postnatal day; UCBSC, umbilical cord blood-derived nonhematopoietic stem cells.

CONTROL ID: 3381737

TITLE: Cerebellar biochemistry, connectivity and neurobehavior in very preterm infants

PRESENTER: Sudeepta Kumar Basu

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CURRENT CATEGORY: Neurology

CURRENT SUBCATEGORY: Neonatal Neurology: Translational

KEYWORDS: Cerebellar metabolism, Resting state connectivity, Preterm brain injury.

SESSION TITLE: Neonatal Neurology: Basic and Translational II |Neonatal Neurology: Basic and Translational II

SESSION TYPE: Webinar|Oral Poster Symposia

ABSTRACT BODY:

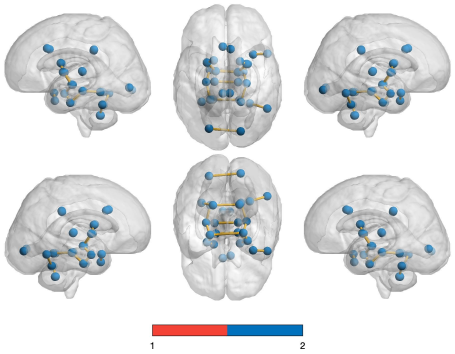
Background: Cerebellar injury is associated with cognitive and socio-behavioral impairments in preterm infants. Early-life metabolic and connectivity profiles may serve as important biomarkers for subtle microstructural alterations that predict long-term developmental outcomes.

Objective: To investigate the relationship between early ex-utero cerebellar metabolism, resting state connectivity, and neurobehavior in very preterm infants.

Design/Methods: We prospectively enrolled 25 very preterm infants (≤32 wks gestational age (GA) and ≤1500 g birth weight); excluding infants with brain injury or malformation on MRI or metabolic/genetic disorders. Early postnatal non-sedated MRI was performed to measure resting state functional connectivity strengths across 23 regions of interest (ROIs) per hemisphere. Connectivity strength was defined as Fisher-z transformed correlation (r_z) between blood oxygenation level dependent signals over time across all ROIs. Cerebellar metabolites from a 3 cm^3 voxel were measured using proton spectroscopy (^{1}H-MRS). The neonatal neurobehavioral scale (NNNS) evaluation was performed near term corrected age. Spearman correlation tests were used to investigate associations between cerebellar metabolites, connectivity strengths and NNNS scores.

Results: 25 infants (16 female) at a mean GA of 28.4±1.9 wks underwent postnatal MRI at a mean of 30.8±2.1 wks postmenstrual age. Bilateral connectivity strengths between the right and left side of brain regions are depicted in Fig. 1 and Table 1; with bilateral cerebellar connectivity at r_z=0.7. Median connectivity of the cerebellum with other ROIs was 1.08 (IQR 0.29). Positive correlations were noted between cerebellar connectivity strength and N-acetylaspartate (Spearman correlation R=0.57, p value=0.017), choline (R=0.68, p=0.002) and creatine (R=0.46, p=0.06) (Table 2). Creatine levels correlated with quality of movement and stress (CNS and skin) components of the NNNS scores (Table 2).

Conclusion(s): For the first time we report that early ex-utero cerebellar metabolic profiles correlate with emerging functional connectivity and neurobehavior scores. We postulate that higher metabolite levels likely reflect increased neuronal density and maturation, which in turn correlate with higher connectivity and neurobehavioral scores at term. Altered cerebellar metabolism and connectivity may serve as an early biomarker for neurological impairment before irreversible injury is established.



Graphical representation of connectivity nodes reported in Table 1

Table 1: Top 20 whole brain connections in the early developing brain

ROI 1	ROI 2	r_z
Cingulate gyrus, posterior part-R	Cingulate gyrus, posterior part-L	0.91
Cingulate gyrus, anterior part-R	Cingulate gyrus, anterior part-L	0.84
THALAMUS-R	THALAMUS-L	0.78
AMYGDALA-L	Gyri parahippocampalis et ambiens anterior part-L	0.77
CAUDATE-L	LENTIFORM NUCLEUS-L	0.76
Anterior temporal lobe, medial part-L	Anterior temporal lobe, lateral part-L	0.74
OCCIPITAL LOBE-R	OCCIPITAL LOBE-L	0.74
HIPPOCAMPUS-L	Gyri parahippocampalis et ambiens anterior part-L	0.74
HIPPOCAMPUS-R	Gyri parahippocampalis et ambiens posterior part-R	0.74
SUBTHALAMIC NUCLEUS-L	LENTIFORM NUCLEUS-L	0.73
CAUDATE-R	LENTIFORM NUCLEUS-R	0.73
AMYGDALA-L	SUBTHALAMIC NUCLEUS-L	0.73
HIPPOCAMPUS-R	Gyri parahippocampalis et ambiens anterior part-R	0.72
CEREBELLUM-L	CEREBELLUM-R	0.72
CEREBELLUM-R	Lateral Occipital lobeipitotemporal and fusiformis	0.72
SUBTHALAMIC NUCLEUS-R	LENTIFORM NUCLEUS-R	0.71
Lateral Occipital lobeipitotemporal and	Medial and inferior temporal gyri posterior part-L	0.71
Gyri parahippocampalis et ambiens anterior	Gyri parahippocampalis et ambiens anterior part-R	0.71
SUBTHALAMIC NUCLEUS-R	SUBTHALAMIC NUCLEUS-L	0.70
HIPPOCAMPUS-L	Gyri parahippocampalis et ambiens posterior part-L	0.69

Table 1. Top 20 regional connectivity strengths in the developing preterm brain

Table 2: Early postnatal ^{1}H-MRS metabolic profile of the cerebellum is associated with resting state connectivity strengths and neurobehavioral scores in very preterm infants

Cerebellar metabolites on preterm scan	**NAA (n=17)**	**Choline (n=17)**	**Creatine (n=17)**	**NAA/Cr (n=17)**	**Cho/Cr (n=17)**
Metabolite concentrations, in institutional units, median (IQR)	1.39 (1.18, 1.79)	1.73 (1.45, 2.20)	2.96 (2.46, 3.62)	0.48 (0.45, 0.51)	0.60 (0.56, 0.69)
Correlation of metabolites with connectivity Spearman Correlation R, p value					
Cerebellum	**0.57, 0.017**	**0.68, 0.002**	0.46, 0.06	0.41, 0.1	0.27, NS
Medial and inferior temporal gyrus-posterior part	0.05, NS	-0.20, NS	0.07, NS	0.21, NS	**-0.62, 0.008**
Medial and inferior temporal gyrus-posterior part	0.01, NS	-0.01, NS	0.12, NS	0.42, NS	**-0.52, 0.032**
Gyri parahippocampalis et ambiens	-0.05, NS	0.15, NS	-0.08, NS	-0.09, NS	**0.52, 0.032**
Correlation of metabolites with Neurobehavioral score Spearman Correlation R, p value					
Quality of movement	0.5, 0.064	0.33, NS	**0.65, 0.012**	-0.2, NS	-0.2, NS
Self-regulation	-0.15, NS	-0.39, NS	-0.18, NS	0.53, 0.06	-0.14, NS
Excitability	0.26, NS	0.31, NS	0.26, NS	-0.54, 0.052	0.26, NS
Stress CNS	-0.42, NS	-0.12, NS	-0.55, 0.052	0.01, NS	0, NS
Stress skin	-0.34, NS	0.39, NS	**0.59, 0.033**	-0.05, NS	-0.34, NS

Table 2. Relationship of cerebellar metabolites with early resting-state connectivity and term age neurobehavior scores

IMAGE CAPTION:
Graphical representation of connectivity nodes reported in Table 1

Table 1. Top 20 regional connectivity strengths in the developing preterm brain

Table 2. Relationship of cerebellar metabolites with early resting-state connectivity and term age neurobehavior scores

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CONTROL ID: 3381143

TITLE: Term-Equivalent Functional Connectivity Relates to Motor Performance Across Childhood in Very Preterm Children

PRESENTER: Peppar Cyr

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neurology: Translational

KEYWORDS: Prematurity, Functional Connectivity, Motor.

SESSION TITLE: Neonatal Neurology: Basic and Translational II |Neonatal Neurology: Basic and Translational II

SESSION TYPE: Webinar|Oral Poster Symposia

ABSTRACT BODY:
Background: Children born preterm are at high risk for motor impairments, but methods to predict which children will develop deficits, especially in the absence of brain injury, remain limited. Resting state-functional MRI (rs-fMRI) has been used to characterize the brain's intrinsic functional network architecture through investigations of spontaneous

neuronal activity. Prior research has shown correlation between the Somatomotor Network (SMN) and Default Mode Network (DMN), two canonical resting state networks, relates to motor performance in adolescents. However, the longitudinal nature of these associations throughout childhood has not been investigated.

Objective: To characterize longitudinal relationships between term-equivalent functional connectivity (FC) and childhood motor performance measures at ages 2, 5, and 9-10 years.

Design/Methods: Forty-three very preterm infants (VPT; birth gestational age 24-30 wks, mean 26.7 wks) without significant brain injury (e.g., grade II-IV intraventricular hemorrhage, cystic periventricular leukomalacia, moderate-severe cerebellar hemorrhage, cortical/deep nuclear gray matter injury) underwent rs-fMRI data collection on a 3T MRI scanner at term-equivalent age. Children were later assessed with the Bayley Scales of Infant and Toddler Development, 3rd edition at 2 years and Movement Assessment Battery for Children, 2nd edition (MABC-2) at 5 and 9-10 years. Median scores were compared with population norms using a Wilcoxon signed rank test (SPSS v.25). Whole-brain voxel-wise analysis was performed to relate neonatal FC to later motor measures.

Results: Motor scores were below population norms ($p<.001$) at all ages (Table 1), with 17% of VPT children scoring <80 on the Bayley Motor Composite at age 2 and 48% of VPT children scoring ≤5th percentile on the MABC-2 Total Standard Score at age 5 and/or 9-10.
Stronger term-equivalent FC measures between the medial prefrontal cortex (component of DMN) and motor cortex (component of SMN) correlated with higher motor scores (i.e., better performance) at ages 2, 5, and 9-10 ($p<.01$) (Figure 1).

Conclusion(s): These results demonstrate persisting relationships between neonatal FC and motor performance measures up to age 10 years in a longitudinal sample of VPT children. This suggests alterations in FC evident in the neonatal period in VPT infants may provide valuable prognostic information and inform targeted use of therapy services in children most likely to develop motor impairments.

Table 1

Measure (N)	Mean (SD)	Population Reference Mean
Sex (43)	17M, 26F	
GA at birth (wks) (43)	26.7 (1.7)	
Bayley Motor Composite - Age 2 (38)	87.3 (11.5)	100
% of Scores ≤ 80 on BMC	17%	6%
MABC Total Std Score - Age 5 (40)	6.25 (2.9)	10
MABC Total Std Score - Age 9-10 (25)	5.96 (3.1)	10
Scores ≤ 5th percentile on MABC Total Std Score - Age 5 or 9-10	48%	5%

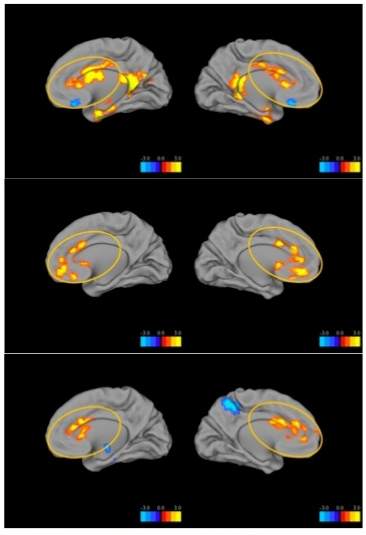

Figure 1 More positive functional connectivity between mPFC and motor cortex correlated with better motor scores at all time points.

IMAGE CAPTION:

CONTROL ID: 3378004

TITLE: Risk for cerebral palsy (CP) may not be driven by early epigenetic factors in extremely low gestational age neonates (ELGANs)

PRESENTER: An N. Massaro

AUTHORS (LAST NAME, FIRST NAME): Massaro, An N.[1]; Bammler, Theo K.[2]; MacDonald, James[2]; Perez, Krystle[2]; Comstock, Bryan A.[3]; Juul, Sandra E.[4]

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CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neurology: Translational

KEYWORDS: cerebral palsy, premature infant, epigenetics.

SESSION TITLE: Neonatal Neurology: Basic and Translational II |Neonatal Neurology: Basic and Translational II

SESSION TYPE: Webinar|Oral Poster Symposia

ABSTRACT BODY:

Background: Epigenetic modification via DNA methylation is a mechanism by which the ex-utero environment can impact cell specific gene expression. We reported pilot data that suggested a link between genomic differentially methylated regions (DMR) and risk for CP in preterm infants (Massaro et al, PAS 2017). Further investigation is needed to clarify the role of early epigenetic changes in the pathogenesis of CP.

Objective: To identify DMRs and associated differentially expressed genes that distinguish ELGANs with and without CP.

Design/Methods: We evaluated peripheral blood cell (PBC) specimens collected during a randomized trial of erythropoietin for neuroprotection in the ELGAN (PENUT, NCT# 01378273). DNA and RNA were isolated from PBC pellets collected on day 1 and 14. DNA methylation (Infinium MethylationEPIC BeadChip Assay; Illumina) and transcriptome data were generated (Human Clariom S Array; Affymetrix). Data were analyzed using R software (r-project.org). Bayesian models were used to compare a) CP vs no CP at day 1, b) the day 1 to 14 change for each diagnosis, and c) the day 1 to 14 change between CP vs no CP. Secondarily, iPathwayGuide meta-analyses were performed to identify genes and/or pathways that were unique to CP subjects across both methylation and gene expression datasets.

Results: DNA methylation data were generated from 94 PENUT subjects (n=35 CP vs n=59 Control). Gene expression data were generated from a subset of subjects with adequate RNA (RIN>5); 56 subjects (n=29 CP vs n=27 Control) on day 1 and 23 subjects (n=12 CP vs n=11 Control) on day 14. Only one DMR was identified for the day 1 to 14 change between CP vs no CP (chr15: 40861240-40861791, associated gene: RNA Pseudouridine Synthase Domain Containing 2), without evidence for differential gene expression (log_2 fold change -0.016; p=0.994). iPathwayGuide meta-analyses identified only 2 genes, and no relevant pathways, that were differentially expressed between day 1 and 14 only in CP cases, observed consistently across both DNA methylation and gene expression datasets (Figure 1). These genes and functional information are summarized in Table 1.

Conclusion(s): Genome wide DNA methylation and whole transcriptome analyses from PBC specimens demonstrate limited evidence for early epigenetic factors that relate to later CP in ELGANs. Further investigation is needed to determine whether epigenetic modifications in alternative tissue types or later in life contribute to CP risk.

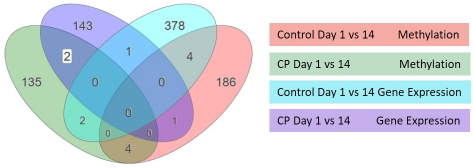

Figure 1. iPathwayGuide meta-analysis of DNA methylation and gene expression data identified 2 genes (highlighted in white) unique to CP that demonstrate evidence of differential methylation and gene expression

Gene Symbol	Name	Methylation Log_2 Fold Change; P-value	Gene Expression Log_2 Fold Change; P-value	Functional Information
CSRP1	Cysteine and Glycine Rich Protein 1	-0.209; p=1.000e-6	+0.270; p=0.015	Gene regulation, cell growth and somatic differentiation
USP44	Ubiquitin Specific Peptidase 44	+0.015; p=1.000e-6	+0.261; p=0.036	Deubiquitinating enzyme; regulates spindle assembly checkpoint by preventing anaphase onset

Table 1. Gene information from iPathwayGuide meta-analysis

IMAGE CAPTION:
Figure 1. iPathwayGuide meta-analysis of DNA methylation and gene expression data identified 2 genes (highlighted in white) unique to CP that demonstrate evidence of differential methylation and gene expression

Table 1. Gene information from iPathwayGuide meta-analysis

CONTROL ID: 3378249

TITLE: Brain Temperature and Metabolites – An in-vivo MR spectroscopy assessment of energy states, metabolism, neuronal maturation, and neurotransmission in infants with hypoxic-ischemic encephalopathy

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CURRENT CATEGORY: Neonatology

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SESSION TITLE: Neonatal Neurology: Basic and Translational II |Neonatal Neurology: Basic and Translational II

SESSION TYPE: Webinar|Oral Poster Symposia

ABSTRACT BODY:
Background: Therapeutic hypothermia (TH) reduces the risk of death and disability in neonates with hypoxic-ischemic encephalopathy (HIE). The mechanism underlying neuroprotection by controlled cooling of brain structures has not been fully elucidated and the impact of temperature on brain metabolites is unclear.

Objective: To determine the relationship between brain temperature and brain metabolites in infants with HIE.

Design/Methods: This is a prospective observational study. Infants with HIE were enrolled. We excluded infants with congenital anomalies, sepsis, or stroke. MRI was obtained *during* and *after* TH. Brain temperatures, derived by MR spectroscopy based on chemical shift differences, were correlated with brain metabolite concentrations at injury-prone regions, Fig.1. Brain metabolites representative of cellular energy state (phosphocreatine-**PCr** --an energy reservoir able to transfer phosphate to generate ATP from ADP and result in creatine-**Cr**, by creatine kinase), membrane metabolism (**choline**), neuronal/axonal maturation (N-acetyl-aspartate-**NAA**), neurotransmission (**glutamate**), and anaerobic metabolism (**lactate**) were analyzed. Normality of data was determined and correlation between temperature and metabolites were analyzed using Pearson's correlation.

Results: A total of 541 MR spectra from 76 infants with mean (SD) gestation age of 38±2 weeks and birth weight of 3211±666 grams were analyzed. For MR scans performed during TH, rectal temperature (33.4±0.4°C) was maintained within therapeutic range. Mean (range) regional brain temperatures during and after TH were 33.5°C (31.3-35.7) and 37°C (34.3-39.9), respectively. Results are summarized in Table 1. In terms of cellular energy state, there was a

significant negative correlation between temperature and PCr and a significant positive correlation between temperature and Cr, Fig. 2. Additionally, temperature correlated significantly with total choline and the neurotransmitter glutamate, Fig. 3. No correlation was found between temperature and NAA or lactate.

Conclusion(s): At lower brain temperatures, the metabolite concentrations suggest a higher energy status, decreased membrane metabolism, and neurotransmission. On the other hand, markers for neuronal/axonal maturation and aerobic/anaerobic metabolism had no correlation with temperature. Metabolites not affected by temperature may be a candidate biomarker for injury stratification during TH in infants with HIE.

Table 1. Correlation between brain temperature and metabolites

	Cellular Energy State		Membrane Metabolism	Neuronal/Axonal Maturation	Neurotransmission	Anaerobic Metabolism
	PCr	Cr	Choline	Total NAA	Glutamate	Lactate
Basal Ganglia Pearson *r* 95% CI *p*-value	-0.32 -0.47 to -0.16 0.0002*	0.62 0.50 to 0.71 <0.0001*	0.61 0.49 to 0.71 <0.0001*	-0.07 -0.10 to 0.24 0.40	0.50 0.36 to 0.62 <0.0001*	0.07 -0.10 to 0.24 0.44
Thalamus Pearson *r* 95% CI *p*-value	-0.38 -0.45 to -0.3 <0.0001*	0.53 0.40 to 0.64 <0.0001*	0.37 0.21 to 0.50 <0.0001*	-0.01 -0.18 to 0.15 0.87	0.39 0.24 to 0.52 <0.0001*	-0.01 -0.17 to 0.16 0.93
Gray Matter Pearson *r* 95% CI *p*-value	-0.37 -0.50 to -0.21 <0.0001*	0.55 0.42 to 0.66 <0.0001*	0.54 0.41 to 0.65 <0.0001*	0.01 -0.16 to 0.18 0.92	0.55 0.42 to 0.66 <0.0001*	-0.02 -0.19 to 0.15 0.83
White Matter Pearson *r* 95% CI *p*-value	-0.51 -0.62 to -0.37 <0.0001*	0.49 0.35 to 0.61 <0.0001*	0.39 0.23 to 0.52 <0.0001*	0.03 -0.14 to 0.20 0.72	0.25 0.09 to 0.41 0.003*	0.02 -0.15 to 0.19 0.83

*Denotes statistically significant correlation. Phosphocreatine (PCr); Creatine (Cr); N-acetyl-Aspartate (NAA).

Table 1. Relationship between brain temperature and metabolites, by brain regions.

Figure 1. Brain temperature and metabolites were analyzed at the following regions of interest.

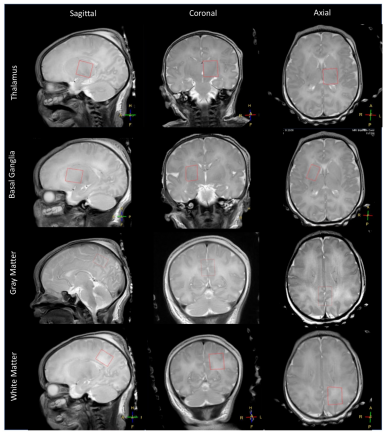

Figure 1. Regions of interest selected for analysis.

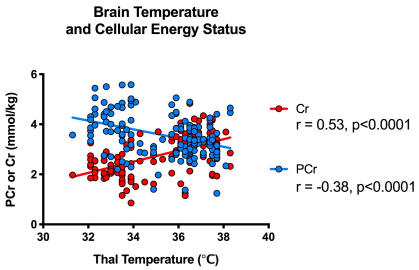

Figure 2. Brain temperature vs. energy metabolism

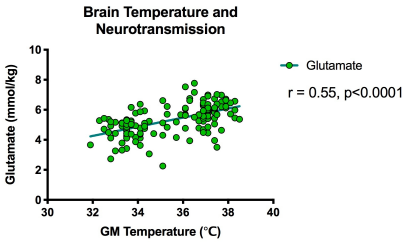

Figure 3. Brain temperature vs. neurotransmitter glutamate

IMAGE CAPTION:

Table 1. Relationship between brain temperature and metabolites, by brain regions.

Figure 1. Regions of interest selected for analysis.

Figure 2. Brain temperature vs. energy metabolism

Figure 3. Brain temperature vs. neurotransmitter glutamate

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