Exploring the Link Between Neonatal Brain Injury and Sucking

Early detection of injury leveraging emerging technologies

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PROBLEM: Current methods of identifying infants with neonatal brain injury (NBI) may not be sensitive enough to detect in the neonatal period and others are too costly to be used routinely

STUDY DESIGN: Longitudinal cohort

EXPECTED OUTCOMES: Demonstrate clear evidence of the association between early abnormalities in feeding performance and underlying brain injury

Every year in the United States, approximately 500,000 babies are born preterm. Advances in technology and neonatal care have increased survival rates of premature infants up to 90%.[1]

Despite these advances, the incidence of neonatal brain injury remains high.[15] It is estimated that 50% or more of very low birthweight preterm infants will be diagnosed with periventricular leukomalacia (PVL)[2] and the number of preterm infants who will be diagnosed with some form of intraventricular hemorrhage (IVH) is reported to be 12,000 annually.[3]

Because of the documented high incidence of brain injury among preterm infants, the association of prematurity with neurodevelopment and disability remains a significant concern.[4] Premature infants have a documented increased risk for adverse neurodevelopmental outcomes including:

- Cerebral palsy
- Cognitive impairment
- Speech and language delay
- Sensory dysfunction

All of these adverse neurodevelopmental outcomes can affect long-term physical health with a higher risk of disease.[2]

The basis of concern regarding the association of prematurity with neurodevelopment and disability, is the fact that during the third trimester of gestation, the brain goes through rapid expansion and folding.

This cerebral cortical maturation has been shown to be disrupted by preterm birth[5] and underscores the importance of developmentally supportive practice in the NICU during a time of extreme vulnerability.[6] A primary healthcare goal becomes identifying and intervening in those infants at highest risk, as early as possible, in order to take advantage of neuroplasticity; the peak time period when the brain can compensate for injury and disease.[7]

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Detecting Neonatal Brain Injury

A major challenge to early identification of infants with neonatal brain injury (NBI) is the fact that current methods for diagnosing brain injury may not be sensitive enough to detect an injury in the neonatal period (e.g. cranial ultrasound) or may be too costly for routine identification of brain injury (i.e., magnetic resonance imaging).[8] Therefore, identifying a common neonatal behavior that reflects the overall integrity of the central nervous system and correlating that behavior with advanced neuroimaging capabilities, would be a substantial advancement in early identification of NBI. To that end, we have partnered with NFANT Labs LLC to study the challenge of early identification of neonates at risk for brain injury and poor, long term developmental outcomes.

Sucking as a Neurodevelopmental Biomarker

Successful infant feeding is a complex neonatal behavior that requires integration of physiologic function and neurobehavioral ability.[9,10] Sucking is considered the most precocious purposeful motor skill of the newborn[11] and is considered an early window into the overall integrity of the central nervous system.[12]

A number of researchers have demonstrated that early sucking performance is predictive of later neurodevelopmental outcomes.[13-15]

However, previously reported methods have been a limiting factor in the ability to interpret and generalize findings. Limiting methods include sensory degrading modifications to nipples, cumbersome equipment, and subjective measures of sucking performance.

Neuroimaging Techniques Offer Opportunity for Early Diagnosis and Treatment

Research on human brain development has seen an upturn in the past few years due to increasing use of noninvasive neuroimaging tools for studying the anatomy and function of the developing brain. We are witnessing advances not only in the instrumentation optimized for the pediatric population, but also in research focused on the human fetuses in utero, neonates, and older children.[16] MRI methods such as volumetric T1 imaging and Diffusion Tensor Imaging (DTI) are being used more frequently in children to determine the gross anatomy and structural connectivity of the developing brain. On the other hand, to study the brain function, functional neuroimaging techniques, such as magnetoencephalography (MEG), electroencephalography (EEG) and near-infrared spectroscopy (NIRS) can be used to assess electrophysiological functions of the developing human brain. Findings from multiple neuroimaging methods can be combined to answer specific scientific questions regarding pediatric pathology[17-19] or typical human brain development. Neuroimaging can offer critical information about both normal as well as abnormal human brain development. Although most of the currently available tools are designed for adult use, at Boston Children's Hospital we have developed and refined hardware and methods especially tailored for pediatric use. Such technological advancements address specific issues relevant to pediatric populations and will promote wider adoption of neuroimaging for both clinical and research purposes.

Our group is uniquely positioned to perform pediatric multimodal neuroimaging studies. To date, there are only 5 MEG systems available worldwide for use on children. Our unique MEG system is tailored specifically for young children birth-3 years old, and to employ pioneering neuroimaging methods to integrate anatomical and functional neuroimaging findings.

> This research program will provide clear evidence of the association between early abnormalities in feeding performance and underlying brain injury.

MEG and MRI/DTI

Foundation: More than 95% of children with CP have sensory deficits that limit their tactile abilities. The development of fine motor skills depends heavily on the somatosensory system. Tactile feedback from mechanoreceptors in the skin is critical to the online modulation of fine motor skills, such as feeding. Previous work by Dr. Papadelis et al. examined sensory processing in typically developing (TD) children and children with cerebral palsy (CP) using MEG and DTI.[16] This was the first study combining findings from multiple neuroimaging techniques to examine the functional (Figure 1) and anatomical (Figure 2) integrity of the somatosensory systems in children with spastic CP.

Functional: Somatosensory fields evoked by the tactile stimulation of the right thumb through a pneumatic stimuli for a TD child vs. a child with CP with left hemisphere more affected (Figure 1). The left panels show the somatosensory-evoked fields recorded with MEG, while the right panels show the underlying generators localized using minimum norm estimates (MNE) overlaid on the child's cortical surfaces at the peak of the most prominent early deflection evoked by the tactile stimulation at around 40–50 ms (M50).

Anatomy: Brain fibers that control the sensation of touch projecting from the thalamus to the post-central gyrus of a TD child (left) vs. a child with CP is reconstructed from DTI data (Figure 2).

Combination: We now can present results from an advanced multimodal neuroimaging method developed by our group to reconstruct functionally-defined sensory tracks by integrating findings from MEG and DTI. Using MEG, we mapped the functionally active regions in the primary somatosensory cortex during tactile stimulation of the thumb (D1), middle (D3), and little fingers (D5) of both hands of children with CP due to periventricual white matter injury (Figure 3). The functionally active regions then were used as anatomical regions of interest for the deterministic DTI analysis. The figure shows the results for a child with unilateral periventricular white matter injury. We can observe that the affected right hemisphere where the brain lesion is visible on the MRI, presents less sensory fibers than the less affected left one.

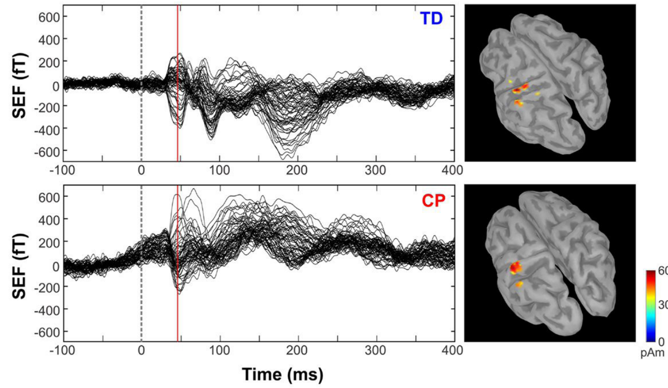

Figure 1. ***Study of the functional integrity of the somatosensory system.*** *Somatosensory-evoked fields evoked by the tactile stimulation of the right D1 (left panels) for a TD and a child with CP (left hemisphere more affected) child from 100 to 400 ms after the onset of the tactile stimulus. Source localization with Minimum Norm Estimates (in pico ampere meter) overlaid on participant cortical surfaces at the peak of the M50.*

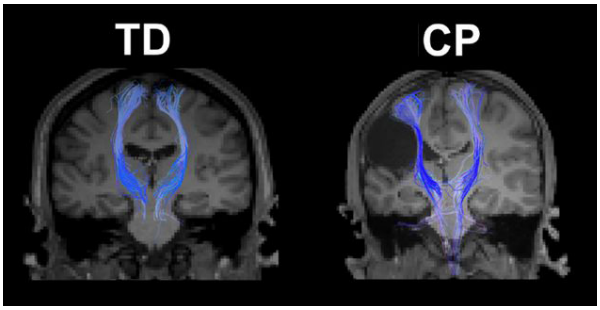

Figure 2. ***Study of the structural integrity of the somatosensory system.*** *Thalamocortical fibers projecting from thalamus to the post-central gyrus for both sides of the brain for a TD and a child with CP (left hemisphere more affected) child.*

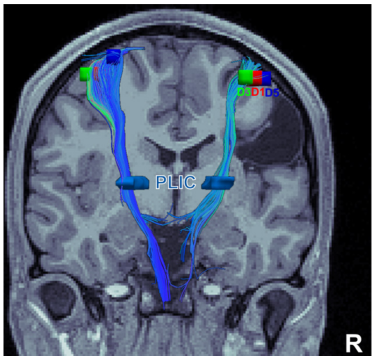

Figure 3. ***Functionally-defined Sensory Tracks of a child with unilateral periventricular white matter injury during tactile stimulation of the thumb (D1), middle (D3), and little fingers (D5).*** *The functionally active regions in the primary somatosensory cortex during tactile stimulation of D1, D2, and D3 are displayed with red, green, and blue color respectively. Such functionally active regions were then used as anatomical regions of interest for the deterministic DTI analysis to reconstruct the sensory tracks shown in the figure. The right hemisphere, where the brain lesion is visible on the MRI, shows less sensory fibers compared to the left hemisphere.*

nfant®Feeding Solution is a noninvasive FDA cleared medical device that objectively measures nipple dynamics during feeding.

nfant Feeding Solution overcomes the limitations of previously reported methods as it is scalable and easily integrated into routine care. nfant Feeding Solution uses standard bottle nipples and so supports the individualized nature of neonatal feeding and respects the importance of sensory feedback in the development of feeding skill. It is an objective tool for the quantitative assessment of nutritive sucking in infants.[20]

Nipple movement is captured in real time and displayed visually on a tablet via the nfant®Mobile App. Feeding data is stored in the nfant®Patient Database for later analysis. Early studies from NFANT Labs[20,21] supports the work of others[14,22] who have suggested that sucking patterns are an early marker for neurodevelopment.

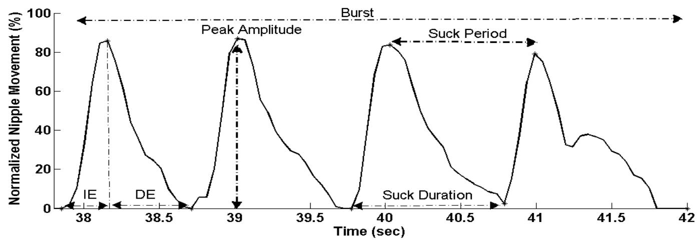

Figure 4. ***Algorithms objectively identify key features and metrics to describe the suck pattern*.**

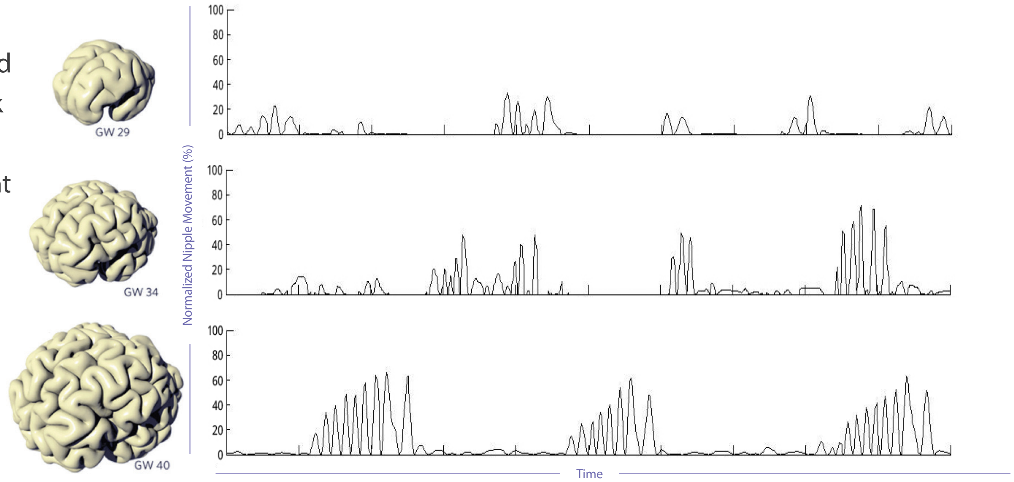

Figure 5. ***Sucking performance is evaluated throughout NICU stay and maturation using nfant Feeding Solution. Metrics are generated from the sucking patterns for each feeding and correlated to maturation.[28]***

Correlating Sucking and NBI

MEG data will be used to identify any functional abnormality in the infant's brain network. MRI/DTI data will allow us to reconstruct the brain neural tracts that control feeding process and to estimate any possible structural abnormality. Using the nfant®Feeding Solution and our in-house software for sucking assessment,[27] we will assess the infant's sucking pattern (Figure 4) and identify the infants showing early oral-motor abnormalities while feeding. The sucking assessment will be conducted during the infant's stay in the NICU whereas the neuroimaging scans will be conducted prior to discharge. This will allow us to correlate the sucking performance evaluated early during the NICU stay using the nfant Feeding Solution (Figure 5) with the brain functional and structural abnormalities evaluated later at the time of discharge using our advanced multimodal neuroimaging technique.

Hypotheses and Potential Outcomes

We plan to run neuroimaging studies with MEG and MRI/DTI using advanced tools available at Boston Children's Hospital, in order to assess the complex brain network that controls feeding and sucking in neonates. We will then correlate any deficits in the feeding brain network with early abnormalities identified in patterns of sucking performance during bottle feeding, via nfant Feeding Solution. This research program will provide clear evidence of the association between early abnormalities in feeding performance and underlying brain injury. Similarly, this work will give clinicians robust insights into the brain deficits that possibly underlie the feeding problems they encounter in practice. Furthermore, using an objective tool to assess infant oral feeding in practice, we will insure that feeding problems reflecting early symptoms of brain injury will not be missed. We will combine NFANT Labs experience in the technology-aided clinical assessment of feeding, with the cutting-edge pediatric neuroimaging techniques we use at Boston Children's Hospital to study brain injury in infants.[17,23]

About the Authors

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Dr. Papadelis is Assistant Professor at Boston Children's Hospital / Harvard Medical School. He leads the Children's Brain Dynamics research group that is dedicated to pediatric brain research using advanced multimodal neuroimaging. He has a broad background in neuroimaging, clinical neurophysiology, and biomedical engineering. He received first-rate training in MEG, EEG and DTI from three laboratories in Japan, Italy, and USA. He has more than ten years of experience with neuroimaging experiments for multiple human studies using MEG and EEG technology with both adults and children. He has a demonstrated record of accomplished and productive research projects leading to >40 peer-reviewed articles (on 18 of them he is either first or senior author) and numerous articles in conference proceedings. His work has so far been cited >1200 times. He is Academic Editor in PLoS One, guest editor in special issues of his field, and ad-hoc reviewer in 38 scientific journals, as well as guest editor in special issues of his field.

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Dr. Tamilia is a Postdoctoral Research Fellow at Boston Children's Hospital / Harvard Medical School. She received her M.Sc. (2010) and PhD (2015) in Biomedical Engineering, respectively, from University of Tor Vergata and University Campus Bio-medico of Rome (Italy). Her main research interest is the development of innovative tools and methods to investigate children's development and disorders starting from the neonatal age. In 2015, she received an international award at the 37th annual conference of the IEEE Engineering in Medicine and Biology Society for her study on the development of an innovative feeding bottle that is able to assess the infant nutritive sucking for early diagnosis of neurological disorders in preterm infants. In September 2016, she also received a national award from the Italian National Bioengineering Group for her PhD thesis entitled "New Tools for a Technology-aided Assessment of Newborns' Oral-Motor Behavior".

References

1. Blencowe H, Cousens S, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013;10 Suppl 1:S2.
2. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol. 2009;8(1):110-124.
3. Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. Pediatr Res. 2010;67(1):1-8.
4. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008;371(9608):261-269.
5. Engelhardt E, Inder TE, Alexopoulos D, et al. Regional impairments of cortical folding in premature infants. Ann Neurol. 2015;77(1):154-162.
6. Als H. Developmental care in the newborn intensive care unit. Curr Opin Pediatr. 1998;10:138-142.
7. Kolb B, Mychasiuk R, Williams P, Gibb R. Brain plasticity and recovery from early cortical injury. Dev Med Child Neurol. 2011;53 Suppl 4:4-8.
8. van Wezel-Meijler G, Steggerda SJ, Leijser LM. Cranial ultrasonography in neonates: role and limitations. Semin Perinatol. 2010;34(1):28-38.
9. Holloway EM. The dynamic process of assessing infant feeding readiness. Newborn Infant Nurs Rev. 2014;14(3):119-123.
10. Browne JV, Ross ES. Eating as a neurodevelopmental process for high-risk newborns. Clin Perinatol. 2011;38(4):731-743.
11. Craig CM, Lee DN. Neonatal control of nutritive sucking pressure: evidence for an intrinsic tau-guide. Exp Brain Res. 1999;124(3):371-382.
12. Mizuno K, Ueda A. Neonatal feeding performance as a predictor of neurodevelopmental outcome at 18 months. Dev Med Child Neurol. 2005;47(5):299-304.
13. Wolthuis-Stigter MI, Luinge MR, da Costa SP, Krijnen WP, van der Schans CP, Bos AF. The association between sucking behavior in preterm infants and neurodevelopmental outcomes at 2 years of age. J Pediatr. 2015;166(1):26-30.
14. Hiramoto A, Takagai S, Tsuchiya K, Suzuki K, Tsujii M, Mori N. Abnormal sucking behavior in infants as a predictor of developmental delay in 18-month or 3-year of age. Journal of Brain Science. 2014;43:5-23.
15. Slattery J, Morgan A, Douglas J. Early sucking and swallowing problems as predictors of neurodevelopmental outcome in children with neonatal brain injury: a systematic review. Dev Med Child Neurol. 2012;54(9):796-806.
16. Papadelis C, Grant PE, Okada Y, Preissl H. Editorial on emerging neuroimaging tools for studying normal and abnormal human brain development. Front Hum Neurosci. 2015;9:127.
17. Papadelis C, Ahtam B, Nazarova M, et al. Cortical somatosensory reorganization in children with spastic cerebral palsy: a multimodal neuroimaging study. Front Hum Neurosci. 2014;8:725.
18. Brown TT, Erhart M, Avesar D, Dale AM, Halgren E, Evans JL. Atypical right hemisphere specialization for object representations in an adolescent with specific language impairment. Front Hum Neurosci. 2014;8:82.
19. Hunold A, Haueisen J, Ahtam B, et al. Localization of the epileptogenic foci in tuberous sclerosis complex: a pediatric case report. Front Hum Neurosci. 2014;8:175.
20. Capilouto GJ, Cunningham TJ. Objective assessment of a preterm infant's nutritive sucking from initiation of feeding through hospitalization and discharge. Neo Inten Care. 2016;29(1):36 - 41.
21. Capilouto GJ, Cunningham TC, Frederick E, Dupont-Versteegden E, Desai N, Butterfield TA. Comparison of tongue muscle characteristics of preterm and full term infants during nutritive and nonnutritive sucking. Infant Behav Dev. 2014;37(3):435-445.
22. Pollitt E, Consolazio B, Goodkin F. Changes in nutritive sucking during a feed in two-day-and thirty-day-old infants. Early Hum Dev. 1981;5(2):201-210.
23. Papadelis C, Harini C, Ahtam B, Doshi C, Grant E, Okada Y. Current and emerging potential for magnetoencephalography in pediatric epilepsy. Journal of Pediatric Epilepsy. 2014;2(2):73-85.
26. Hunold, A., Haueisen, J., Ahtam, B., Doshi, C., Harini, C., Camposano, S., et al. (2014). Localization of the epileptogenic foci in tuberous sclerosis complex: a pediatric case report. Front. Hum. Neurosci. 8:175. doi: 10.3389/fnhum.2014.00175
27. Tamilia E, Delafield J, Fiore S, Taffoni F. An automatized system for the assessment of nutritive sucking behavior in infants: a preliminary analysis on term neonates. Conf Proc IEEE Eng Med Biol Soc. 2014; 2015:5752-5755
28. Figure 5 cortical folding image credit: https://www.physics.harvard.edu/node/618
29. MEG photo page 1: Photo courtesy of the Institute for Learning & Brain Sciences, University of Washington