



Non-invasive brain mapping: TMS is safe, effective in young children



Shalini Narayana, MS, MBBS, PhD, conducts TMS mapping.

Transcranial magnetic stimulation (TMS) is safe, reliable and effective to map motor, speech and language function in young children with refractory epilepsy or a brain tumor, according to research published in *Frontiers in Neurology* by Le Bonheur Neuroscientist and Director of the TMS Laboratory Shalini Narayana, MS, MBBS, PhD.

In 47 TMS motor mapping sessions, motor cortices were successfully mapped in 90% of children under three years old, and in 13 TMS language mapping sessions, language areas were located in 92% of children ages five to six years old. This is the largest known study reporting TMS mapping of motor

cortices in toddlers and language cortices in preschool children. TMS maps can be used for presurgical planning to preserve language and motor function and provide a baseline for post-surgical changes in these functions.

"Accurate presurgical mapping of motor, speech and language cortices, while crucial for neurosurgical planning and minimizing post-operative functional deficits, is challenging in young children with neurological disease," said Narayana. "Our data show that TMS can be a useful tool in mapping eloquent cortices in children with epilepsy or a brain tumor."

TMS provides several advantages for mapping the language and motor areas of the brain in young children. Mapping is still possible with TMS even when patients are unable to fully cooperate due to disease or developmental delay. TMS is non-invasive, never requires sedation, does not require the patient to remain still and can be guided by previous MRI scans. For all of these reasons, TMS is a promising method for brain mapping for a young child for whom other methods, such as MEG and fMRI, have been unsuccessful. Without a viable functional mapping method, surgical options that could greatly improve cognitive function and quality of life may be delayed.

This study was a retrospective review of TMS motor and language mapping studies at Le Bonheur. Forty-seven motor mapping sessions were performed with 36 children under three years old and were successful in locating the motor cortex in 90% of children. TMS was also used to assess the risks and benefits of surgery in 11 children with lesions near the motor cortex. TMS results were used in the surgical navigation system, and motor function was preserved or improved in nine of the 11 children who underwent surgery. Two children had mild, predicted weakness after surgery.

A separate cohort of 13 children ages five and six underwent TMS language mapping, and language areas in the temporal lobes were localized in 92%. Seven of these children underwent surgery and the TMS results provided a presurgical baseline and were used on the surgical navigation system. Post-operatively, none of the children were found to have speech or language deficits.

Overall, TMS was well-tolerated by most children and described as painless. About 20% of the children undergoing motor mapping experienced seizures during or immediately after TMS. All of the children who experienced seizures had a history of refractory epilepsy with frequent seizures, and seizures during or after TMS were consistent with their typical seizure pattern and deemed not to be directly caused by TMS.

"In our study, TMS was safely applied in young children with serious epilepsy syndromes," said Narayana. "All our data so far indicate that the use of TMS in children is safe and effective."

The Hunt for HAEC

Le Bonheur fellow develops novel scoring system for HAEC diagnosis



Ruth A. Lewit, MD, MPH

In the largest study to date reviewing Hirschsprung-associated enterocolitis (HAEC) diagnostic scoring systems, a novel scoring system for HAEC developed by Le Bonheur Pediatric Surgery Fellow Ruth A. Lewit, MD, MPH, was recently published in the *Journal of Surgical Research*. This new scoring system may help reduce the rate of underdiagnosis of HAEC, allowing for earlier diagnosis and treatment of patients. Of the 369 episodes of HAEC reviewed in the study, 173 (46%) met the diagnostic cutoff for the new score but did not meet cutoffs for previous scoring systems used for HAEC.

"Improved diagnosis of HAEC has the potential to reduce hospital admissions, limit morbidity and improve outcomes," said Lewit. "This novel scoring system for HAEC has several advantages over previous scoring systems, but most importantly may help reduce the rate of underdiagnosis of HAEC."

Two scoring systems exist for diagnosing HAEC – the Pastor score, published in 2008, and the Frykman score, published in 2018. The accuracy of these scores, however, is limited due to their restrictive nature and neither has been widely adopted in clinical practice. Lewit and her team aimed to develop a new diagnostic tool that provided better utility and diagnostic accuracy in a clinical setting.

For the purpose of this study, an HAEC diagnosis was defined as treatment consisting of antibiotics, bowel rest and rectal irrigations. This study evaluated the existing HAEC systems and developed a new scoring system by evaluating 1,450 encounters with 200 patients and 369 HAEC episodes at four centers worldwide. The Pastor and Frykman scores were retrospectively calculated for each episode, and Lewit identified six variables to include in the new scoring system.

The variables that are significantly associated with diagnosis of HAEC – fever, bloody diarrhea, obstipation, distention, dilated loops of bowel on x-ray and leukocytosis – were used to create a new score. When reviewing HAEC episodes through the Pastor and Frykman scores, 46% did not meet their criteria but did meet the cutoff for the new score. This suggests that 46% of patients would have been underdiagnosed with HAEC using the previous scoring systems.

"The new scoring system offers several advantages," said Lewit. "The new score includes signs that are frequently seen in HAEC, maximizes sensitivity compared to previous scoring systems and is simple and designed specifically to be used in a clinical setting."

Further study is needed to externally validate the new score before implementing clinically on a wide scale.

Awards and Honors

Guerrier, Kim receive Le Bonheur Junior Faculty grants

Le Bonheur Cardiologist Karine Guerrier, MD, and Le Bonheur Endocrinologist Ahlee Kim, MD, have received Le Bonheur Junior Faculty grants for their proposed research. The Le Bonheur Junior Faculty grants support early-career faculty members as they develop their research programs at Le Bonheur Children's.



Karine Guerrier, MD

electrocardiogram and potentially predict disease development in youth with a family history of HCM.

Guerrier's project, "Machine Learning to Identify Pediatric Cardiomyopathy," will use artificial intelligence to identify hypertrophic cardiomyopathy (HCM), a disease that thickens heart muscle, making it hard for the heart to pump blood. As HCM is associated with sudden cardiac arrest, especially in young athletes, detection is critical.

Guerrier plans to develop a tool that can find changes indicative of HCM in



Ahlee Kim, MD

glycemic control and arterial stiffness, with the goal to better understand the pathogenesis of cardiovascular disease in youth with type 1 diabetes.

Kim received a renewal for the project, "Arterial Stiffness in Pediatric Type 1 Diabetes." In pediatric type 1 diabetes, high blood sugar (poor glycemic control) damages blood vessels, leading to cardiovascular disease and other conditions. Arterial stiffness reflects the elasticity of blood vessels and could serve as a marker of vascular function in diseases like Type 1 diabetes. Kim will look for a potential relationship between

West receives a Le Bonheur Grant



Alina Nico West, MD

Alina Nico West, MD, PhD, has received a Le Bonheur grant for the project, "Achieving Consensus Diagnostic Criteria for Post-Traumatic Hypopituitarism (PTHP) in Children Using Modified Delphi." PTHP is caused by injury to the pituitary gland, usually as a result of traumatic brain injury. While it occurs in both children and adults, it can be particularly damaging in children because the resulting hormone deficiencies can interfere with child development. West's project will attempt to tackle the lack of consistent diagnostic criteria for pediatric PTHP, which has hindered efforts to study this condition. West will survey experts in the field to build consensus-based diagnostic criteria for pediatric PTHP, setting the stage for improved diagnosis and treatment of children with PTHP.

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Beating Hearts, Beating Cancer

Association of persistent tachycardia with early myocardial dysfunction in children undergoing allogeneic hematopoietic cell transplantation

Children undergoing hematopoietic cell transplantation (HCT) have high rates of tachycardia, or fast heart rates, which were associated with the development of systolic and diastolic myocardial dysfunction, according to research published in *Bone Marrow Transplantation* by Le Bonheur Cardiologist Jason Goldberg, MD, MS, and colleagues. University of Tennessee Health Science Center and Le Bonheur Heart Institute cardiologists care for children who receive cancer therapy at St. Jude Children's Research Hospital. This research can help clinicians more closely evaluate and identify issues with heart function among children who receive HCT.

"We have to understand the early risk factors for development of cardiac dysfunction in pediatric HCT as we know that recipients of HCT during childhood are at increased risk of accelerated cardiovascular morbidity and mortality later in life," said Goldberg.

The study reviewed 80 pediatric patients who had allogeneic (non-self) HCT between 2015 and 2019 at St. Jude Children's Research Hospital. All patients had echocardiograms at baseline (within 60 days prior to infusion), early post-HCT (between infusion and 90 days post-infusion) and at 1 year of follow up



Le Bonheur Cardiologist Jason Goldberg, MD, MS, (front left) consults with the cardio-oncology team members. Goldberg published research that could help physicians identify heart function problems in children who receive hematopoietic cell transplantation.

(within 90 days of 1-year after infusion). In the early post-HCT time period, 64% of patients had tachycardia, 25% had systolic (pumping) dysfunction and 48% had diastolic (relaxing) dysfunction. Patients with tachycardia were thirteen times more likely to develop systolic dysfunction and four times more likely to develop diastolic dysfunction.

Other risk factors for cardiac dysfunction included patients who received anthracyclines prior to HCT; those patients were seven times more likely to have early tachycardia. Systolic dysfunction was also more

prevalent in the female gender and in patients who received ace-inhibitor therapy pre-transplant.

"Tachycardia likely exists as a marker of systemic inflammation," said Goldberg. "This, together with other acute post-HCT derangements and previous cardiovascular insults from known cardiotoxic agents, may result in cardiac dysfunction."

These findings can assist in creating a cardiovascular assessment protocol for post-HCT patients to help prevent and treat early myocardial dysfunction. In addition, this research can inform longer-term investigations to determine whether these early cardiovascular abnormalities are related to late cardiovascular morbidity.

Structural Racism and Childhood Obesity: A call to action

In "Addressing Structural Racism is Critical for Ameliorating the Childhood Obesity Epidemic in Black Youth," Le Bonheur Clinical Psychologist Thomaseo Burton, PhD, and colleagues at other institutions outline the contributions of structural racism, which the authors define as "systems-level practices, norms, rules, and laws that maintain inequity based on race," to childhood obesity in Black youth. Black youth are disproportionately affected by obesity, and Burton and colleagues illustrate how the following aspects of structural racism can account for the prevalence of obesity among Black youth:



Thomaseo Burton, PhD

- Economic factors
- Food and beverage environment
- Physical environment
- Maternal/developmental factors
- Psychological factors
- Biological/medical factors
- Racial discrimination in obesity treatment

The authors suggest that continued research to identify specific feedback loops that maintain the obesity epidemic in Black youth can help inform meaningful changes in policies and treatment approaches.

Closing the Global Mortality Gap

Le Bonheur surgeon publishes research on improving global neonatal surgical outcomes

Children born with gastrointestinal congenital anomalies are eight times more likely to die in low-income countries and four times more likely to die in middle-income countries than children with the same conditions in high-income countries, says research published in the *Lancet* by the Global PaedSurg Research Collaboration.

Le Bonheur Researcher and Director of Surgical Research at the University of Tennessee Health Science Center Ankush Gosain, MD, PhD, contributed to the study as a member of the collaboration. In order to reach the United Nations Sustainable Development Goal to end preventable deaths of children and neonates under five years by 2030, access to quality neonatal surgical care must improve in low- and middle-income countries (LMICs).

"In order to meet this goal, the study showed that dramatic improvements in access to care, guidelines and policies need to be made in LMICs to care for children with gastrointestinal congenital anomalies and allow them a chance at life," said Gosain.

The study focused on outcomes of the seven most common congenital anomalies – esophageal atresia, congenital diaphragmatic hernia, intestinal atresia, gastroschisis, exomphalos, anorectal malformation and Hirschsprung's disease. Three thousand, eight hundred and forty-nine patients with 3,975 study conditions from 264 hospitals in 74 countries were examined. Total mortality rates were 38.9% in low-income countries, 20.4% in middle-income countries and 5.6% in high-income countries. Country income status was associated with the highest risk of mortality. Several other barriers showed a wide discrepancy among high-, middle- and low-income countries including age at presentation, distance patients traveled from home to study hospital and access to parenteral nutrition.

Other results included:

- Chance of dying from a gastrointestinal congenital anomaly is two in five in a low-income country, one in five in a middle-income country and one in 20 in a high-income country
- Leading causes of death were sepsis and respiratory failure



Ankush Gosain, MD, PhD

- Higher mortality in LMICs was associated with sepsis at presentation, higher ASA score at primary intervention and need for blood transfusion and ventilation
- Many patients in LMICs do not have routine components of care including antenatal diagnosis, birth at a pediatric surgery center, effective resuscitation, timely ambulance transfer, use of surgical safety checklist, physician anesthetist at primary intervention and basic neonatal intensive care unit resources.

"Studying gastrointestinal congenital anomalies outcomes in these LMICs brings further attention to the wide disparities showing the neglect of surgery in the global health field. A focus on neonatal surgery has been almost non-existent and is needed to push the mortality rate down in LMICs," said Gosain.

Researchers hope that the results of this study can provide the information necessary to create policies and guidelines needed to advocate for neonatal surgical care within national surgical obstetric plans developed in LMICs.

Research from Le Bonheur, UTHSC highlighted in *Experimental Biology and Medicine*

Experimental Biology and Medicine has highlighted a research article written by Le Bonheur and UTHSC researchers. Tamekia Jones, PhD, Jonathan McCullers, MD, and Sandra Arnold, MD, along with colleagues at UTHSC and Louisiana State University, wrote the article titled "Particulate matter exposure predicts residence in high-risk areas for community acquired pneumonia among hospitalized children."

The authors performed a retrospective analysis to identify factors associated with residence in zip codes in the Memphis Metropolitan area with high- or low-risk of pediatric community-acquired pneumonia hospitalizations. These factors included insurance type, race and particulate matter exposure, specifically PM2.5, a type of air pollution that has been linked to respiratory conditions. The study population included 220 children hospitalized with pneumonia who resided in high- or low-risk areas.

The authors reported:

- Children who resided in high-risk areas were exposed to higher levels of PM2.5 than those who resided in low-risk areas.
- Race was associated with residence in high-risk areas; 86.5% of children who resided in high-risk areas were Black.
- Children who resided in high-risk areas were more likely to have public insurance than those who resided in low-risk areas.

These findings support the link between environmental exposures and childhood pneumonia. The authors also suggest socioeconomic disparity could contribute to the risk of childhood pneumonia.