Seeking Answers for an Invisible Disease: The GE NFL Head Health Initiative

Unlike other diseases, a concussion or mild traumatic brain injury (mTBI) is an invisible disease. There is currently no gold standard for diagnosis, says Teena Shetty, MD, MPhil, a neurologist and Founder and Director of the Concussion Clinic at the Hospital for Special Surgery (HSS) and also a member of the GE NFL Head Health Medical Advisory Board (MAB). HSS is one of the six sites participating in the GE NFL Phase II study and Dr. Shetty personally evaluates potential candidates to determine if they are appropriate for the study and meet all the criteria.

“What we see clinically is very difficult to establish and many patients return to play, school, or work without adequate diagnosis, treatment, and rehabilitation after injury. Inadvertently, they may be prolonging their own recovery time. Because the injury is invisible, it is difficult for these patients to grasp the severity of it. The possibility of being able to influence recovery earlier and give objective evidence to guide patient management is very compelling,” she adds. “This can have a remarkable effect on patient compliance and return to work or play decisions, and also provides better patient management.”

Mitchel S. Berger, MD, Professor and Chairman, Department of Neurological Surgery, Director of Brain Tumor Surgery Program at
“Our work with the Head Health Initiative is intended to derive clinical tools, including MR biomarkers‡, that will have wide utility in a broad array of clinical settings,” Dr. McCrea says. “Most concussion patients are not seen in an acute trauma setting.”

He also points out that mTBIs don’t just occur in a sports setting... they are often falls, bicycle accidents, car injuries, and soldiers injured in the line of duty.

“It is no surprise that mTBI is a major health issue especially in the military,” says Sidney R. Hinds II, MD, Colonel in the U.S. Army Medical Research and Material Command, and Department of Defense (DoD) Brain Health Research Program Coordinator, Blast Injury Research Program Coordinating Office, and a GE NFL MAB member. “(Because) we have improved our protective equipment and our military medical system to mitigate more severe head injuries, the vast majority of the DoD’s TBIs are diagnosed in the non-deployment setting and occur as a result of training, participation in athletics, falls, and motor vehicle accidents,” he says. When an injury occurs, education, research, and current clinical recommendations are all utilized to protect the soldier and prevent additional injury. “Researchers in the DoD are collaborating with other agencies—the NIH and VA—as well as academia and industry to try and answer the knowledge gaps that exist in understanding mTBI,” he adds.

‡The use of MR data as surrogate biomarkers for mTBI or other diseases remains as technology in development which represents ongoing research and development efforts of GE Healthcare in conjunction with other researchers and healthcare institutions.
Initial impressions from the Head Health studies

The studies being conducted under the Head Health Initiative are intended to help improve the diagnosis of concussion in adolescents and adults. The initial pilot phase had 140 subjects with mTBI, as well as healthy controls. Phase two started in spring 2016 and runs across six sites. The goal is to have 350 mTBI patients and 175 age, gender and education-matched controls. Phase II runs through the end of 2017. Each mTBI participant is enrolled in a longitudinal MR: two done acutely—at 72 hours and at one week—then subsequent MRs at two weeks and again at three months. Part of this effort includes correlating MR imaging findings with the current standard of care for diagnosis—a neurological assessment of cognitive function that includes memory, balance, and executive function. The hope is that correlating the neurological exam with MR imaging will allow for a clear idea of areas in the brain that are truly affected by the injury and what that means in terms of cognitive function.

According to Dr. Shetty, a surprising number of patients had incidental findings on their anatomical MR exams. In particular, white matter changes were seen in young patients—changes that clinicians would typically not see outside of an aging brain in... 

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a patient with risk factors such as hypertension, high cholesterol, and microvascular disease.

“We still don’t have an answer to this and are trying to better understand if these are risk factors for prolonged recovery,” she says.

One preliminary finding using rs-fMRI suggests that it is the connectivity between networks rather than connections with a network that may correlate to symptom severity, Dr. Shetty says. Another initial finding using volumetry and comparing gender found that women who did not recover had smaller volumes in their thalamus compared to women who did recover.

It is almost as if the tools are outrunning the clinical understanding.

“We now understand that individual recovery and outcomes after mTBI are influenced by a number of neurobiological and other factors,” explains Dr. McCrea. “MR imaging gives us an objective marker of the injury grade and the acute path of physiology to use in our prediction models to determine how recovery and outcome are influenced by neuro injury.”

This information is then balanced against other patient data, such as history of migraines, prior injury (especially mTBI), and a host of psychological factors including co-morbid depression.

With MR imaging, it is now possible to quantify the extent of neurobiological injury, Dr. McCrea says.

“The Head Health Initiative has really attacked this mTBI issue from both sides hardware and software,” adds Dr. Berger. From GE Healthcare redesigning systems to accommodate different sizes of heads and necks to using the most advanced imaging paradigms available to determine structural, metabolic, and physiological changes, Dr. Berger believes the initiative has been comprehensive. He would, however, like to see efforts to perform more quantitative volume metrics on patients.

“One of the missing pieces of the puzzle in understanding the severity of a concussion is to know more about the total volume of the brain, including the subarachnoid space and ventricles, and the thickness of the skull and the muscles under the scalp,” Dr. Berger says. “So the question is, if we have an individual who has larger subarachnoid spaces, does that individual have a higher susceptibility to an injury that could show up with DTI or rs-fMRI?”

**Neuropsychology of mTBI**

Advances in MR imaging over the last few years have catapulted the study of neurobiology of concussion and natural history of neurobiological recovery, says Dr. McCrea. For years, the clinical focus was on the assessment of symptoms and performance on cognitive testing, as well as other clinical assessment tools. But those tools are not able to provide a direct view into the brain.

“It is truly the advancement in MR imaging that provides the bridge to the next great frontier—brain injury science,” says Dr. McCrea. “With MR, we can visualize effects of injury on structure and function, rather than rely on symptoms reported by a patient or performance on a cognitive test.”

In the acute phase, MR helps visualize the effect of mTBI on blood flow, functional connectivity, and the integrity of fiber tracks, and white matter tissue functional connectivity. All of which, Dr. McCrea says, have to function in harmony for the brain to run at a normal steady state.

“That translational data informs us of the mechanism and pathology of the injury. That’s a much deeper dive than if the patient reports headaches and dizziness,” he adds. “Now, we have the ability to image and visualize changes and correlate those anatomical and biological changes with the manifestation of symptoms. MR has taken us light years ahead in the pathophysiology of mTBI.”
Connections between mTBI and PTSD

In addition to his work on the GE NFL Head Health Initiative, Dr. Hinds is also a co-primary investigator of the Chronic Effects of Neurotrauma Consortium, a large multi-center trial that is a collaboration between the DoD and the VA—one of the first shared research projects between these two institutions. The study incorporates neurocognitive testing, advanced imaging, biomarkers, and visual and vestibular areas of research. The goal of the research is to better understand areas currently lacking in information regarding mTBI: Natural history, neurodegenerative effects and association of other medical conditions such as post-traumatic stress (PTS).

“mTBI is a very heterogeneous disease process with many factors that play a part in why two people exposed to the same type of head injury can have different trajectories of symptoms and recovery,” Dr. Hinds explains. “As a neurologist, we like to figure out disease processes based on lesion location and clinical manifestation. We rely on objective diagnostics like neuroimaging to help us confirm the diagnosis and manage our patients’ clinical condition.”

mTBI can be focal, multi-focal, diffuse or some combination of these. Further, Dr. Hinds explains that there is an association between mTBI and behavioral issues such as PTSD and sleep disorders—and even chronic pain.

“There is an overlap. Depending on the person, some of these issues may already exist before the head injury,” Dr. Hinds says. “That may compound the injury and recovery, as well as our knowledge of what is truly affecting the patient. Sleep disorders, post-traumatic headache, and PTSD are associated with mTBI in the military.”

These behavioral and psychological factors also compound the research, and therefore large, longitudinal studies such as the Defense and Veterans Brain Centers’ 15-year study, TRACK-TBI, the NCAA CARE Consortium, and the Chronic Effects of Neurotrauma Consortium are necessary for this type of subanalysis, Dr. Hinds says.

To continue moving mTBI research forward, better classifications of brain injury beyond mild, moderate, and severe must be developed to apply the diagnostics and therapeutics that work best across the spectrum of TBI.

“We are putting everything we know into practice—building a better airplane as we fly it—to use the best scientific answers we have right now, then implement it into clinical guidelines to use now and not wait for research breakthroughs,” Dr. Hinds says. “As we get more information and scrutinize it with more scientific evidence, we’ll continue to incorporate it into practice.”

As an example, the military uses a progressive approach in return to duty from mTBI. Both physical and cognitive challenges are introduced in a step-wise approach to get the soldier back to normal daily functioning. If that person is not following a typical or expected trajectory, additional tests or specialists are engaged. For all soldiers, a battery of tests based upon the patient’s condition is used to ensure symptoms are resolved before returning to duty.

“This approach has really been a game changer for the military and it builds upon the knowledge and research that we have, and we hope to continue improving it,” Dr. Hinds adds.
Therein lies the conundrum: It is the advanced sequences that in some instances may not yet be commercially available, such as rs-fMRI, (high direction) diffusion, and spectroscopy, that may further help unlock the mystery of mTBI.

However, susceptibility weighted imaging (SWI) is one available sequence that HSS now routinely uses in brain MR sequences for mTBI patients, thanks in some part to Dr. Shetty’s involvement in the Head Health Initiative. “SWI is very interesting; it shows tiny little areas of blood not visible on a routine MR,” Dr. Shetty explains. “It would also be invisible on CT, although CT is a really good tool for larger pools of blood—subdurals, subarachnoids—and to help with midline shift and edema in the emergency patient. However, CT doesn’t help with the diagnosis and prognosis of a mild head injury, which is an epidemic not previously recognized.”

Changing the clinical perspective

“The more interesting part is the discussion that goes beyond the natural history of recovery in symptoms and functional connectivity, but is focused on how long it takes for recovery at the brain level,” Dr. McCrea says. “The implications are that these time frames may not fully overlap and that the time course of neurobiological recovery lags behind clinical recovery.”

This new knowledge regarding recovery timelines will culminate in the release of new international consensus guidelines in May 2017. It is also in this capacity that MR biomarkers, which may be prognostic of brain recovery, could be utilized to determine when a person is no longer at risk and can return to work, play, or active duty.

“We no longer manage concussions on a switch; now, we manage them on a dial,” Dr. McCrea explains. For example, as a patient achieves clinical recovery, they can assume low-grade, non-risk activity with exposure to contact or risk of re-injury; over time, they can “dial up” their activity level as they gradually return to unrestricted activity. This approach allows the brain to achieve a complete neurobiological recovery and protect individuals during that period of vulnerability after injury from re-injury, Dr. McCrea says.

Seeing so many concussed patients has changed Dr. Shetty’s perspective and altered how she views neuroimaging in these patients. While in the ER, CT is the best test for detecting moderate or severe head injury, but it is not valuable in mTBI patients. Although MR is more valuable, the results tend to come back normal.

“I am more likely to order an MR if something is not right with the patient—for example, if they have severe symptoms or are taking a long time to recover,” Dr. Shetty says. “I may employ more advanced sequences in these cases and look forward to the day when these sequences are clearly validated so we can better interpret them to help influence our patient care decisions.”
Dr. Berger agrees that there is a very defined role for MR in the setting of brain injury and trauma. While he doesn’t foresee any change in the use of MR in an acute setting, data from the GE NFL Head Health Initiative as well as other mTBI and TBI studies are demonstrating clinical value for MR in the subacute and chronic stage.

“Where I think we could be using MR (more) is in the chronic phase, using SWI to look for micro hemorrhages that can tell us there have been structural changes to the white matter tracts,” Dr. Berger explains. “We could use that information to advise an individual if they should be in contact sports again.”

There is also a better understanding that diagnosis and treatment of mTBI must be personalized to the patient. To achieve this, however, a more complete understanding of the population is needed, Dr. Norbash says.

“When we image patients with a brain injury, whether mild or severe, there are a range of findings we can see,” he adds. He cites a recent paper that found a thinning of the cortex in professional soccer players in the area where they head the ball.1 In TBI patients, there may be small bright dots in the deep white matter that could be the result of injured tiny blood vessels not healing properly and generating scar tissue. Or, imaging may detect tiny freckles of a metallic deposit of hemosiderin, which is derived from red blood cells disintegrating in the brain tissue.

“‘In looking at the population, we need to (better) understand in what instances are these findings normal, say for a 60-year-old person, and in what specific distributions are they abnormal and related to brain injury,’ Dr. Norbash says.

**Big data**

It is in this effort to stratify mTBI in population health that Dr. Norbash believes GE Healthcare’s focus on big data and analytics will be rapidly shown as valuable.

“Every scan should become a learning opportunity and be incorporated into a database to become part of our understanding of discriminating and differentiating normal from abnormal,” he adds. “We know our brains are not identical, but they are similarly wired. To thoughtfully address this space, we need to understand the normal population variance and also what cognitive tools and exercises can be developed to help mTBI patients return to (normal) function more quickly.

As Chair of the ACR’s HII, Dr. Norbash is also helping to spearhead the development of TBI-RADS, a standardized reporting and data collection of imaging in patients with TBI. Similar to BI-RADS for breast imaging and PI-RADS for prostate imaging, TBI-RADS will enable radiologists to apply consistent terminology, reduce imaging interpretation variability and errors, and effectively and consistently communicate with referring physicians.

While TBI-RADS is looking at measurable events and identifiable findings that lead to a care pathway, Dr. Norbash believes the need to aggregate data should go even further.

“In the future, we will recognize there are other things we could be measuring,” he says. “Today’s tools may be incomplete, but there are novel post-processing techniques for MR information being continuously refined and developed. So, preserving that data and having it available for future analysis is important.”

This capability extends beyond mTBI to neurodegenerative diseases, as one specific example. When looking at the longitudinal care of patients, Dr. Norbash says radiologists cannot just be diagnosticians. “We need to be conservators of imaging data for future applications. What will help us are the analytic tools continuously being developed that can give us a better understanding of normal and the range of abnormality, including individual variations. There’s no telling what we will be able to figure out in the future with as-yet undeveloped tools and techniques that we can apply to archived datasets.”

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**Advancing mTBI knowledge**

Yet, even with the growing knowledge surrounding mTBI thanks in part to the effort under the GE NFL Head Health Initiative, a number of questions remain unanswered. Dr. McCrea says that in the context of sports, areas that require further investigation are the effects of repetitive concussion or even repetitive hits in the absence of concussion.

An important foundational concept resulting from mTBI research and the GE NFL Head Health Initiative is the need for multimodal imaging to study biomarkers, says Dr. McCrea.

“The pathophysiology of concussion is highly heterogeneous across injuries but also across time,” he adds. The pathophysiological mechanisms of brain injury at 2 hours post-injury are different than at 10 days post-injury.

“Any approach that is confined to a single biomarker solution is likely destined for failure,” says Dr. McCrea. “A single modality is not likely to be the best performer across time and all pathophysiologic mechanisms.”

Bringing together different modalities and biomarkers, based on a patient’s acuity and time point from injury, may be the most powerful and reliable markers for diagnosis and prognosis.

“There is a growing interest in diffusion techniques to study the early acute detection stage, along with perfusion, cerebral blood flow, and other MR metrics,” Dr. McCrea adds.

**What’s next**

Dr. McCrea believes that the findings across various areas of neuroscience research often have implications and relevance in other areas, such as stroke, neurodegenerative diseases (Alzheimer’s, ALS, Parkinson’s), epilepsy and brain injury. The Head Health Initiative’s work on refining MR imaging techniques and the platforms developed for post-processing and analytics could also be applied to these other brain diseases and injuries, he adds.

“There is no question we have to rely on imaging to help define the extent of the disease we are dealing with—whether that be mTBI, epilepsy, or neurodegenerative,” Dr. Berger says. “Imaging will play a huge role physiologically and metabolically, as well as enable explorations of connectivity and volumetry, to help define the foci in the brain that contribute to learning, memory, or degenerative disease, and to help see if we can replete those areas in some therapeutic way.”

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**References**


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**Figure 3. Quantitative perfusion with ASL.**