

## Advanced neuroimaging in traumatic brain injury: an overview

Luke G. F. Smith, MD,<sup>1</sup> Eric Milliron, BS,<sup>2</sup> Mai-Lan Ho, MD,<sup>3</sup> Houchun H. Hu, PhD,<sup>3</sup> Jerome Rusin, MD,<sup>3</sup> Jeffrey Leonard, MD,<sup>1,4</sup> and Eric A. Sribnick, MD, PhD<sup>1,4</sup>

<sup>1</sup>Department of Neurological Surgery and <sup>2</sup>The Ohio State University College of Medicine, The Ohio State University Wexner Medical Center, Columbus; and <sup>3</sup>Department of Radiology and <sup>4</sup>Division of Neurological Surgery, Nationwide Children's Hospital, Columbus, Ohio

Traumatic brain injury (TBI) is a common condition with many potential acute and chronic neurological consequences. Standard initial radiographic evaluation includes noncontrast head CT scanning to rapidly evaluate for pathology that might require intervention. The availability of fast, relatively inexpensive CT imaging has fundamentally changed the clinician's ability to noninvasively visualize neuroanatomy. However, in the context of TBI, limitations of head CT without contrast include poor prognostic ability, inability to analyze cerebral perfusion status, and poor visualization of underlying posttraumatic changes to brain parenchyma. Here, the authors review emerging advanced imaging for evaluation of both acute and chronic TBI and include QuickBrain MRI as an initial imaging modality. Dynamic susceptibility-weighted contrast-enhanced perfusion MRI, MR arterial spin labeling, and perfusion CT are reviewed as methods for examining cerebral blood flow following TBI. The authors evaluate MR-based diffusion tensor imaging and functional MRI for prognostication of recovery post-TBI. Finally, MR elastography, MR spectroscopy, and convolutional neural networks are examined as future tools in TBI management. Many imaging technologies are being developed and studied in TBI, and some of these may hold promise in improving the understanding and management of TBI.

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In the United States, traumatic brain injury (TBI) accounts for more than 280,000 hospitalizations and 50,000 deaths annually.<sup>52</sup> The most common causes of TBI include falls, impact against an object or with an object, and motor vehicle collisions.<sup>67</sup> It is estimated that more than 3 million people in the United States are living with a long-term disability from a TBI.<sup>82</sup> Despite advances in our understanding regarding the pathophysiology of TBI, there has not been a significant improvement in patient outcomes over the past 2 decades.<sup>64</sup>

A recent study showed that TBI patients may have a 7-fold increased mortality rate even 13 years after the initial injury.<sup>40</sup> Additionally, the cognitive decline following TBI can be progressive over time, suggesting that TBI may be better viewed as a chronic illness.<sup>46</sup> Even after mild TBI (mTBI), studies have shown that up to 20% of patients are unable to return to work within the 1st year.<sup>51</sup>

Current, commonly used neuroradiological imaging modalities lack the ability to accurately diagnose and predict future cognitive decline following a TBI; however, there are promising advances in neuroimaging that may address these shortcomings.

### TBI: Definition and Initial Evaluation

The definition and diagnosis of TBI has changed over time.<sup>21</sup> The Glasgow Coma Scale (GCS) is one of the most commonly used methods of stratifying TBI. Using the GCS alone, TBI is classified as mild (scores  $\geq 13$ ), moderate (scores 9–12), or severe (scores 3–8).<sup>38</sup> The GCS alone has limitations in long-term prognostication, given that multiple pathologies with different clinical outcomes can result in a low GCS score on initial presentation.<sup>28,37</sup> Newer classifications have added loss of consciousness

**ABBREVIATIONS** ASL = arterial spin labeling; CNN = convolutional neural network; CTP = perfusion CT; DAI = diffuse axonal injury; DMN = default mode network; DOC = disorders of consciousness; DTI = diffusion tensor imaging; FA = fractional anisotropy; fMRI = functional MRI; GCS = Glasgow Coma Scale; MD = mean diffusivity; MRE = MR elastography; MRS = MR spectroscopy; mTBI = mild TBI; NAA = N-acetylaspartate; SWI = susceptibility-weighted imaging; TBI = traumatic brain injury; UHF = ultra-high field.

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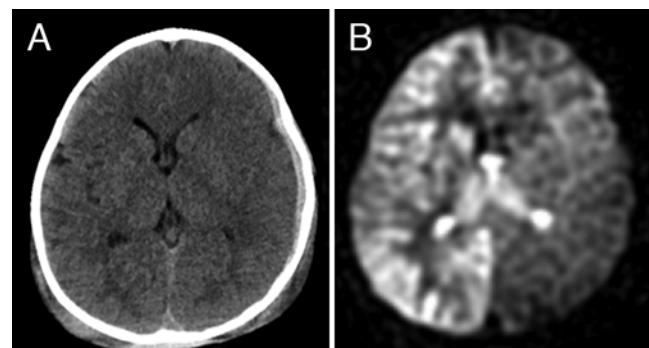
and other clinical factors in the stratification of TBI.<sup>38</sup> The American College of Radiology Appropriateness Criteria endorses that, in the setting of a moderate to severe closed head injury (i.e., GCS scores < 13), a noncontrast CT scan is the most appropriate initial imaging study,<sup>59</sup> and initial imaging in this group should focus on identifying pathologies that could require prompt surgical intervention, such as subdural or epidural hematomas. While useful in this regard, noncontrast head CT scanning has several shortcomings in the evaluation of TBI: underestimation of parenchymal contusions, difficulty in detection of diffuse axonal injury (DAI), and limitations in detecting signs of intracranial hypertension.<sup>8,57</sup> Because of these multiple deficiencies, there is still opportunity to improve postinjury imaging. For example, QuickBrain MRI is a rapid T2 fast spin echo sequence that requires 1–3 minutes for image acquisition; this imaging protocol has been trialed for the initial imaging of pediatric patients with TBI with promising results but is not yet the standard of care.<sup>58</sup>

In mTBI (GCS scores ≥ 13) the New Orleans Criteria, National Emergency X-Radiography Utilization Study II clinical criteria, or the Canadian CT Head Rule can be used to decide if neuroimaging is required.<sup>22,47,66</sup> The diagnosis of mTBI does not mean that symptoms are inconsequential; at 1 year postinjury, many patients with mTBI still report impairment in daily activities and higher rates of psychiatric disorders.<sup>63</sup> The role of advanced imaging is perhaps even more promising in the mTBI subgroup; although traditional imaging findings might be negative, newer modalities may show more subtle changes that have occurred, may assist with prognostication, and may eventually impact treatment.

After the initial standard evaluation with CT, MRI susceptibility-weighted imaging (SWI) is often used in the evaluation of TBI. SWI is a 3D gradient-echo sequence that utilizes filtered-phase data and magnitude data, separately and together.<sup>44</sup> This compilation of information allows for a comparison of magnetic susceptibility differences between tissues, which is particularly sensitive for acute and early subacute microhemorrhages seen in DAI that is often not evident even on conventional T2\*-weighted gradient echo (T2\*GE) sequences.<sup>69</sup> The burden and location of DAI lesions has been used as a prognostication tool.<sup>45</sup> One experimental imaging technique in the evaluation of DAI burden post-TBI is ultra-high-field (UHF) SWI MRI, in contrast to the 1.5T or 3.0T MRI commonly used clinically. Work done by Moenninghoff et al. has demonstrated that UHF SWI MRI reveals an average of 41% more traumatic microbleeds caused by DAI than does 3T SWI, and these lesions appear larger on UHF SWI MRI.<sup>83</sup>

## CT and MRI Perfusion

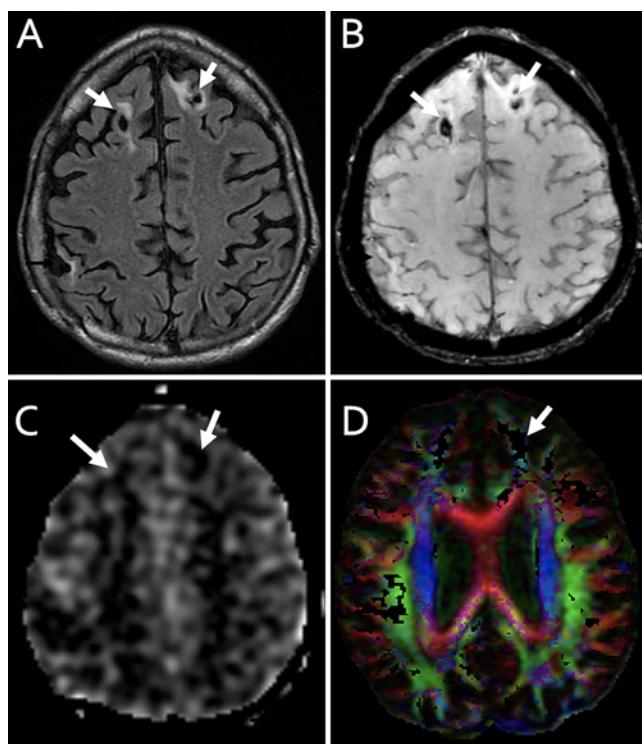
Perfusion imaging is based on the relationship between a defined tissue volume, the mean transit time through that tissue, and flow of blood through that tissue.<sup>14</sup> These relationships identify areas of hypo- and hyperperfusion, and this is clinically most useful for the evaluation of acute cerebral ischemia from cerebral vessel occlusion.<sup>34</sup> Multiple modalities are able to assess cerebral perfusion, including perfusion CT (CTP), dynamic susceptibility-weighted



**FIG. 1.** Images obtained in a patient with an acute head injury from nonaccidental trauma. **A:** CT scan without contrast demonstrating a left-sided acute subdural hematoma and subtle hemispheric edema with loss of gray-white differentiation. **B:** MRI ASL study with left-sided hemispheric hypoperfusion, correlating with the injury seen on the CT scan.

contrast-enhanced perfusion MRI (DSC-MRI), and MRI arterial spin labeling (ASL).<sup>11,75,77,78</sup> Both CTP and DSC-MRI require injection of a nondiffusible intravenous contrast bolus. ASL is performed without a contrast agent and is based on labeling endogenous water in the blood and using it as a tracer.<sup>14</sup> CTP is often advantageous in the setting of acute TBI when intraparenchymal intracranial pressure monitors are used, as they are often not MRI compatible.

In patients who die after TBI, cerebral ischemia is the most commonly noted type of secondary injury on postmortem analysis.<sup>19</sup> While the primary injury is important in outcome after TBI, the incidence of secondary injury and cerebral ischemia is known to cause clinical deterioration and worse outcomes.<sup>43</sup> The theoretical utility of perfusion imaging for TBI would be to identify injured areas of brain at risk for hypoperfusion or global cerebral hypoperfusion, a function that noncontrast head CT is not able to do. Multiple studies have shown alterations in perfusion in both acute and chronic stages of TBI (Figs. 1B and 2C).<sup>13,30</sup> In a study by Soustiel et al., CTP performed within 48 hours of TBI was able to delineate cerebral contusions that required at least 7 days to become apparent on noncontrast CT.<sup>62</sup> A study by Metting et al. demonstrated that, in patients with mild TBI and negative findings on head CT, CTP was able to predict functional outcome at 6 months, based on the presence of frontal lobe perfusion abnormalities.<sup>42</sup> This same group also showed that post-TBI amnesia was associated with frontal lobe abnormalities during the amnesic event.<sup>41</sup> In moderate and severe TBI, several groups have demonstrated that early CTP showing normal or hyperperfusion correlates with a favorable outcome while hypoperfusion correlates with a worsened outcome.<sup>6,79</sup> There are also data to suggest that intermittent CTP can help guide interpretation of cerebral perfusion pressure values and possibly improve functional outcome.<sup>76</sup> Mean transit time from CTP may be useful in determining where an oxygen tensor monitor should be placed by targeting areas most at risk for hypoxia.<sup>23</sup> Although there has been much promising data supporting the use of CTP in TBI, there is still no rigorous clinical investigation to support its routine use or to incorporate this imaging modality as a standard of care.



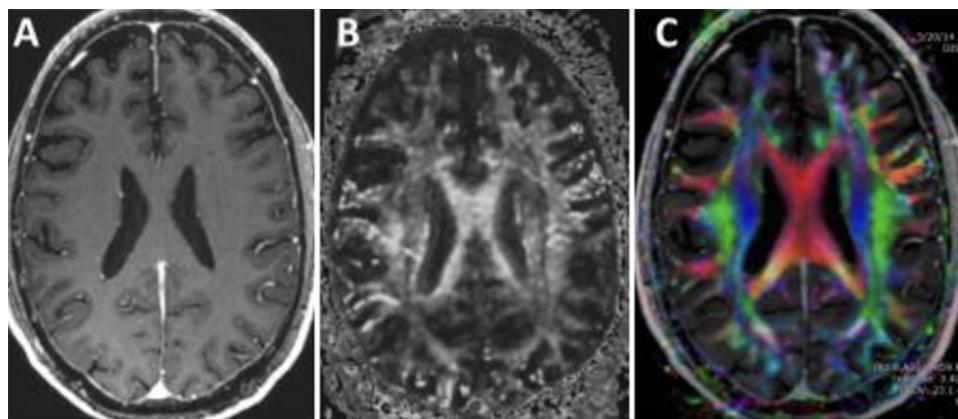
**FIG. 2.** MR images obtained in a patient with chronic TBI. **A:** FLAIR image demonstrating multiple areas of encephalomalacia (white arrows) at the gray-white junction. **B:** Susceptibility-weighted image demonstrating multiple areas of hemosiderosis (white arrows). **C:** ASL image demonstrating areas of chronic hypoperfusion (white arrows). **D:** Diffusion tensor image revealing multiple areas of microstructural injury (white arrow) involving the subcortical U fibers and major white matter tracts, greater than anticipated from macroscopic imaging.

## Diffusion Tensor Imaging

The heterogeneity of TBI has made the development of a classification system difficult.<sup>55</sup> Advanced imaging modalities may provide the key for an improved classification system, allowing for the clustering of TBI patients with similar pathologies, better assessments of new therapies in clinical trials, and improved prognostication. Diffusion tensor imaging (DTI) is an advanced MRI sequence which provides information regarding axonal tracts and may represent a step toward better identification of the many types of TBI. DTI is a spin echo, diffusion-weighted pulse sequence that weighs water diffusion in multiple spatial directions (Fig. 3).<sup>48,49</sup> From this sequence, a variety of different parameters can be measured, with fractional anisotropy (FA) and mean diffusivity (MD) being the commonly reported measures of diffusivity in the literature.<sup>10</sup>

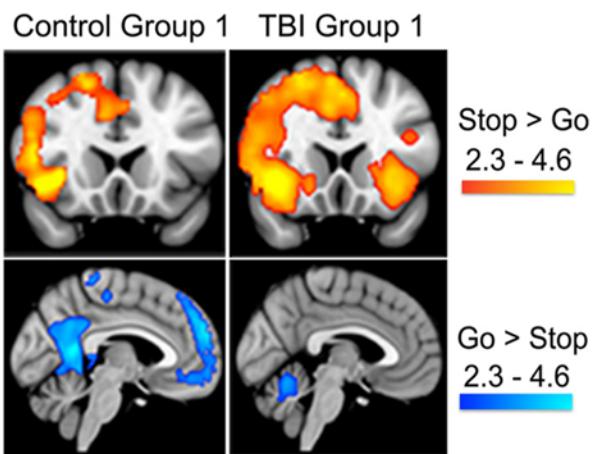
A number of studies have evaluated DTI studies after TBI, with widely variable results reported dependent on the severity of the TBI and the timing of the imaging postinjury. In mTBI, DTI performed in the acute period has shown an increase in FA and an overall decrease in diffusivity, postulated to be due to cytotoxic edema after the injury.<sup>5,74</sup> One study showed that after mTBI the FA and diffusivity normalizes over time.<sup>3</sup> Other work has shown that, after CT-/MRI-negative findings for mTBI, significant decreases in FA can be seen, although these findings have not been replicated in some larger studies.<sup>31,35</sup> In moderate to severe TBI, DTI changes have shown to increase up to 18 months postinjury and to correlate with functional outcomes (Fig. 2D).<sup>73</sup> A meta-analysis of 44 studies confirmed differences in FA and MD between mild and moderate-severe TBI but did not find any time-dependent changes.<sup>71</sup>

In patients with mTBI, severely reduced FA has been correlated with worse 3- and 6-month Glasgow Outcome Scale-Extended outcomes.<sup>81</sup> In severe TBI, an increase

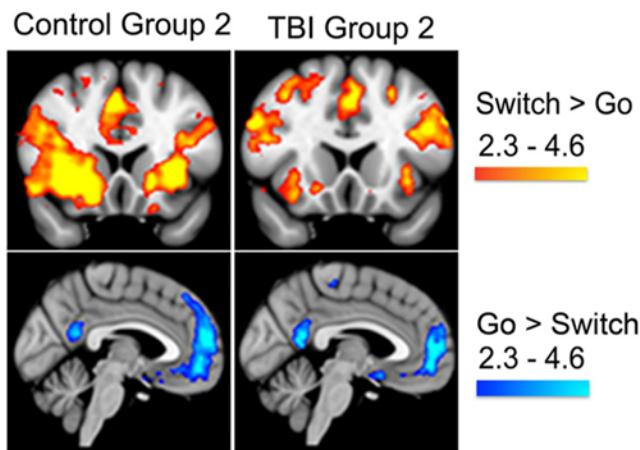


**FIG. 3.** MR T1-weighted and MR diffusion tensor images. **A:** On a T1-weighted sequence with contrast, white matter tracts are not discernable. **B:** A grayscale DTI anisotropy map is shown, with varying grayscale within the white matter, corresponding to the amount of signal for a particular directional-diffusion-sensitizing gradient. **C:** A color DTI anisotropy map is overlaid on the T1-weighted postcontrast image. The multiple colors are noted, with a specific color indicating directionality. Reproduced with permission from Douglas DB, Ro T, Toffoli T, Krawchuk B, Muldermans J, Gullo J, et al: Neuroimaging of traumatic brain injury. *Med Sci (Basel)* 7:E2, 2018. CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

## A Stopping



## B Switching



**FIG. 4.** Functional MRI performed during different mental tasks, comparing brain activation patterns via FA in a control group versus a group with TBI. **A:** Overlay of brain activation associated with correct Stop versus Go trials for controls and patients. **B:** Overlay of FA demonstrating brain activation associated with correct Switch versus Go trials. Reproduced with permission from Jilka SR, Scott G, Ham T, Pickering A, Bonnelle V, Braga RM, et al: Damage to the Salience Network and interactions with the Default Mode Network. *J Neurosci* 34:10798–10807, 2014. CC BY 3.0 (<https://creativecommons.org/licenses/by/3.0/>).

in FA on the initial postinjury DTI was associated with a favorable outcome, and these results are hypothesized to be secondary to axonal regrowth during later recovery.<sup>60</sup> A variety of other cognitive and functional outcomes in mild to severe TBI have been correlated to DTI. A study by Hart et al. utilizing DTI and perfusion ASL performed on retired football players showed a correlation between regional blood flow alterations and cognitive deficits and depression.<sup>20</sup> A recent meta-analysis of 20 studies in adult TBI patients reported that a high FA in most areas of the brain correlated with better cognitive outcomes, particularly memory and attention.<sup>72</sup>

## Functional MRI

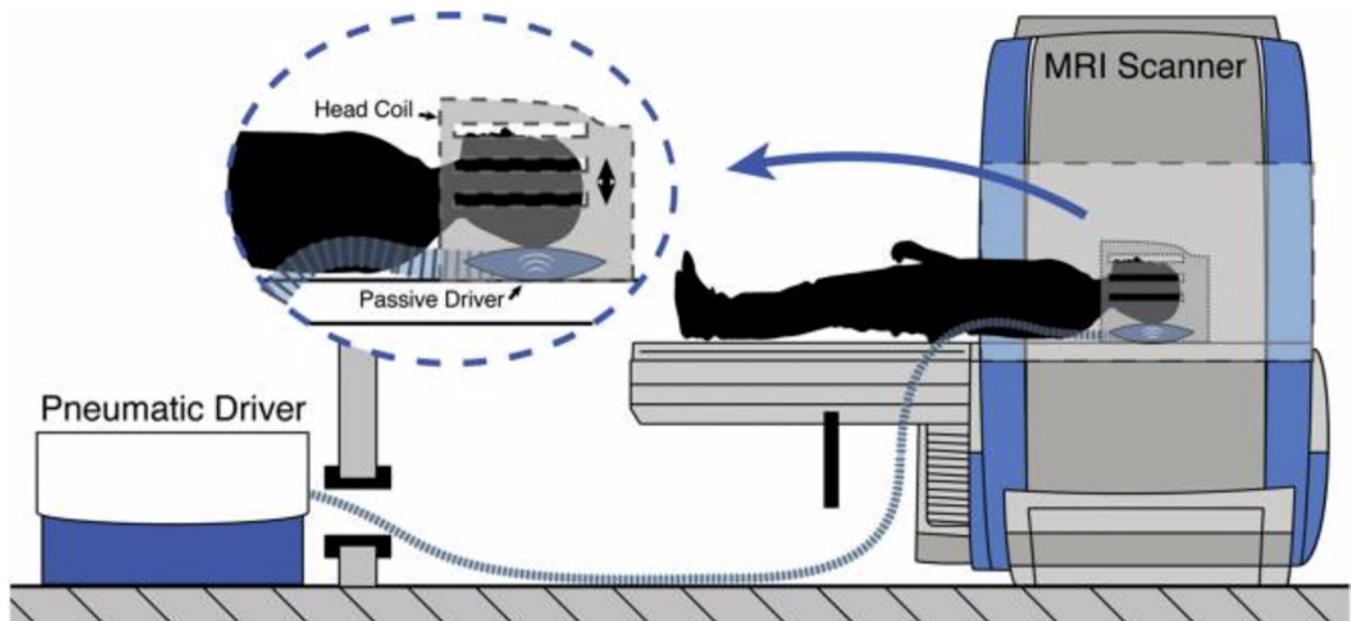
Functional MRI (fMRI) is a technique based on the detection of oxygen extraction of specific brain tissues, providing a surrogate for local brain activity as more oxygen is extracted from the blood.<sup>53</sup> This allows for detection of specific areas of brain activation during different tasks (Figs. 3 and 4).<sup>29</sup> Functional MRI has been used to evaluate the spontaneous activity of the resting, consciousness brain, and from these data, it has been determined that human consciousness involves interconnected circuits, one of the more important is termed the default mode network (DMN).<sup>39</sup>

Patients with severe TBI and subsequent coma are at risk for developing disorders of consciousness (DOC) and even persistent coma. DOC can be divided into unresponsive wakefulness syndrome, also known as vegetative state, or intermittent periods of increased awareness, termed minimally conscious state.<sup>33</sup> The precise number of patients with post-TBI DOC is unknown, and misdiagnoses between DOC states may be almost 50%.<sup>56</sup> Current diagnostic technologies that can predict return of consciousness from coma or from minimally conscious state/unresponsive wakefulness syndrome are lacking.<sup>18</sup> Additionally, there is a lack of preclinical models to test future therapies.

In states of altered consciousness, fMRI has shown that these connections are altered in comparison with the conscious, resting brain.<sup>12,27,70</sup> Threlkeld et al. prospectively studied patients with acute DOC following TBI in comparison with healthy individuals, and they found patterns of recovery in the connections of the DMN.<sup>68</sup> Early recovery of consciousness has been assessed with fMRI after severe TBI, and a small number of patients have demonstrated covert consciousness and higher cortical function, despite appearing to be unresponsive.<sup>16</sup> A randomized clinical trial is currently recruiting severely brain-injured patients to assess for “covert consciousness” with fMRI.<sup>61</sup> Other studies have been performed in patients with chronic DOC, characterizing the changes seen between connections in the DMN in patients with DOC.<sup>12,65</sup> Currently, fMRI represents a very promising technology for prognosticating cognitive recovery after TBI, but further rigorous testing is still required before such results can be used clinically.

## MR Spectroscopy

Magnetic resonance spectroscopy (MRS) relies on detecting magnetic field interactions between protons, with a key principle being that chemicals in a given tissue can be quantified, allowing for detection of changes in the cellular environment, such as neuron loss or demyelination.<sup>4</sup> In the setting of moderate to severe TBI, early reduction in the levels of *N*-acetylaspartate (NAA) has been postulated to be an early indicator of brain injury, and measurements from specific subcortical regions of the brain have been used to predict long-term cognitive outcomes in this population.<sup>26</sup> In infants with abusive head trauma, MRS performed in the acute period after the injury detected decreased NAA/choline ratios and decreased NAA/creatinine ratios, which correlated with functional outcome 6



**FIG. 5.** Schematic representation of a compressed air pneumatic driver that produces head motion required for MRE. The driver transmits compressed air to a pillow underneath the patient's head, creating motion. Reproduced with permission from Klatt D, Johnson CL, Magin RL: Simultaneous, multidirectional acquisition of displacement fields in magnetic resonance elastography of the *in vivo* human brain. *J Magn Reson Imaging* 42:297–304, 2015. © 2014 Wiley Periodicals, Inc.

months or more postinjury.<sup>1</sup> A meta-analysis by Gardner et al. found that in 9 of 11 studies evaluating MRS studies in athletes with mTBI, there were significant differences in MR spectra following mTBI, leading to the conclusion that metabolic derangements continue after concussion symptoms resolve.<sup>17</sup> MRS could be a useful tool for determining the classification and severity of TBI and also as a prognostication tool; however, more investigation is needed to determine how to best apply this technology.

## MR Elastography

Magnetic resonance elastography (MRE) is performed with an MRI pulse sequence that creates a propagated acoustic wave and a measurable tissue displacement.<sup>50</sup> The pulse required for MRE has been made in experimental models with a driver that converts pressurized air into movement transmitted into a pillow underneath the patient's head (Fig. 5).<sup>32</sup> The displacement information is then converted into an elastogram, giving information about the inherent viscoelasticity of the material being tested. Wuerfel et al. reported that brain stiffness (as measured by MRE) decreases in patients with multiple sclerosis, compared with age-matched healthy controls.<sup>80</sup> A review by Hiscox et al. found 41 studies that have used MRE clinically for a variety of purposes, including studying changes in the aging brain (Fig. 6) and pathological brain stiffness.<sup>24</sup>

Using MRE, preclinical models have produced data that suggest its potential usefulness in TBI. Direct cortical impact injury in mice and rats was found to change the mechanical properties of the posttraumatic brain, as measured by MRE.<sup>2,7</sup> The promise of this technology would be *in vivo* measurement of a mechanical property of the

brain with a noninvasive scan, potentially improving prognostication although much preclinical and clinical validation is required for this emerging modality.

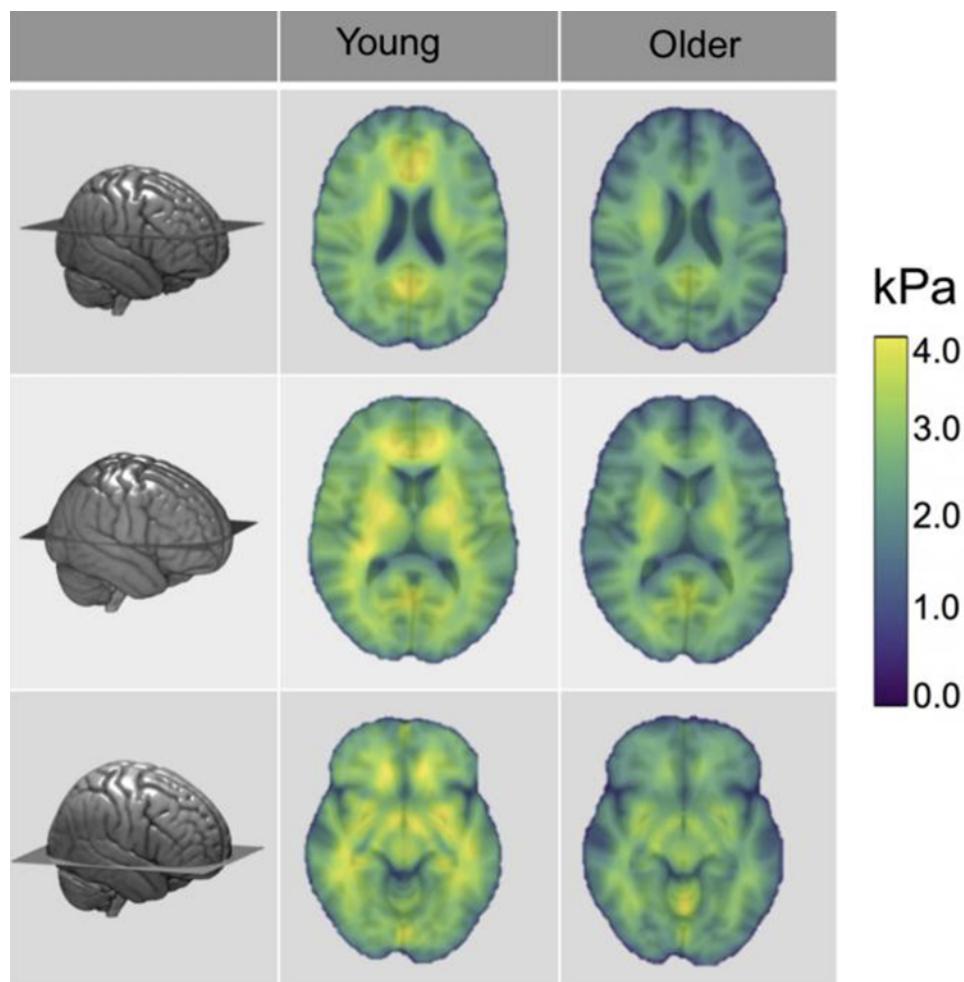
## Convolutional Neural Networks

Convolutional neural networks (CNNs) are a class of machine learning methods, based on biological neural systems, that have recently been applied to imaging interpretation, as reviewed by Chartrand et al. in 2017.<sup>9</sup> CNNs are based on breaking down complex images into simpler connected layers of hierarchical structures. The use of CNNs on large image data sets allows for further fine tuning of these deep learning networks, improving pattern recognition. The recent explosion of collected imaging data, available computing processing power, and improvements in CNN system design has allowed for CNNs to be used in medical image analysis.<sup>36</sup>

Liu et al. described using CNNs to detect cerebral microbleeds, a finding known to occur in TBI, at an accuracy similar to that of an experienced radiologist.<sup>36</sup> This technology has great promise, especially in the field of neuroimaging of TBI with fMRI, such as the analysis of complex, interconnected networks of consciousness and mental processing. This technology could someday be used to decode these networks in patients with TBI to predict recovery and also to tailor specific treatments based on specific damaged interconnections.

## Conclusions

Over the past 50 years, we have witnessed amazing innovation and improvements in the field of neuroimaging. The first CT imaging sessions took 5 minutes per slice



**FIG. 6.** Mean shear stiffness maps produced using MRE. Representative MRE images in younger (middle column) versus older (right column) subjects, demonstrating increasing softness in older brains. Anatomical representations (left column) are shown for illustrative purposes. Reproduced with permission from Hiscox LV, Johnson CL, McGarry MDJ, Perrins M, Littlejohn A, van Beek EJR, et al: High-resolution magnetic resonance elastography reveals differences in subcortical gray matter viscoelasticity between young and healthy older adults. *Neurobiol Aging* 65:158–167, 2018. CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

for acquisition, while current machines acquire an entire study in seconds.<sup>54</sup> In that same timeframe, MRI and other modalities have been invented and changed how we view and treat TBI. The next 50 years of neuroimaging of TBI promise further massive shifts in technological advancement, including better prognostic modalities and the application of deep machine learning.

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### Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

### Author Contributions

Conception and design: Smith, Sribnick. Acquisition of data: Smith, Milliron, Ho, Sribnick. Analysis and interpretation of data: Smith, Milliron, Ho, Rusin, Sribnick. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Smith. Administrative/technical/material support: Smith, Sribnick. Study supervision: Sribnick.

### Correspondence

Luke G. F. Smith: The Ohio State University Wexner Medical Center, Columbus, OH. luke.smith@osumc.edu.