New Developments in Magnetic Resonance Imaging of the Brain

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Summary: Magnetic resonance imaging (MRI) continues to have a large impact on the diagnosis and management of a number of diseases, especially diseases associated with brain injury. The strengths of MRI are the unique contrast that can be obtained, and the fact that it is not harmful and that it can be readily applied to human and animal models. The past decade has seen development of functional MRI techniques that measure aspects of hemodynamics and water diffusion that are playing an important role. Indeed, these techniques are having a major impact on management of brain injury. The development of MRI continues at a rapid pace and a renewed push to increased spatial and temporal resolution will extend the applicability of anatomical and functional MRI. Increased interest in molecular imaging using MRI is increasing the number of processes that can be imaged in the brain. This work reviews some new developments that are being made in anatomical, functional, and molecular MRI of the brain, with comments about usefulness for work in the area of neuroprotection. **Key Words:** Molecular imaging, functional imaging, manganese imaging, perfusion, diffusion MRI.

Magnetic resonance imaging (MRI) continues to have a large impact on diagnosis and management of a number of diseases of the brain.[1] The importance of MRI lies in the excellent soft tissue contrast and the large number of specific biological and physiological parameters that can be measured. In addition, there is growing application of MRI to animal models of human disease, especially the mouse.[2] There continues to be rapid progress in development of MRI of the brain for use as an anatomical, functional, and molecular imaging technique. Specifically, new developments in MRI detectors and acquisition strategies[3] and the availability of higher magnetic fields[4,5] are pushing MRI resolution to near histological levels in humans and animals. The widespread application of functional MRI techniques to monitor hemodynamic changes associated with normal and pathological conditions continue to grow and aid in understanding the function of the normal and diseased brain.[6–8] The wealth of information from molecular biology and new techniques to make specific contrast agents is fueling the development of molecular imaging techniques that enable specific biological processes to be imaged with MRI.[9,10] The rapid development of MRI will ensure that it will continue to impact our ability to define neuronal injury, to monitor the progression of the injury, and to judge the efficacy of new treatments. The goal of this paper is to give an overview of recent work about new developments in anatomical, functional, and molecular MRI, which, although at an early stage, show promise for impacting MRI of brain injury.

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Anatomical MRI of the brain

Two major advantages of MRI are the excellent soft tissue contrast that can be obtained using a variety of flexible MRI parameters and acquisition strategies and the nondestructive nature of MRI, enabling any sample to be imaged, be it the human or mouse brain. FIG. 1 shows examples of anatomical MRI obtained from a human brain and a mouse brain showing the excellent resolution routinely available ($1 \times 1 \times 1$ mm^3 in the human and $100 \times 100 \times 250$ μm^3 in the mouse) and the excellent gray-white matter contrast available from anatomical MRI sequences. In the human brain, so-called T_1 weighting gives bright white matter with respect to gray matter, and in the mouse brain T_2 weighting gives bright gray matter with respect to white matter. This illustrates some of the range of contrast MRI generates. Indeed, with this standard I_1 and I_2 MRI contrast and resolution,

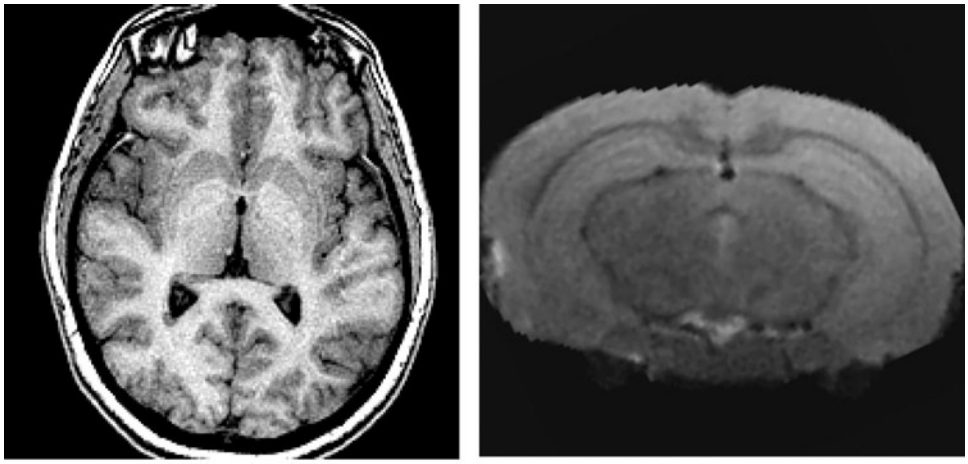

FIG. 1. MRI images of human brain (A) and mouse brain (B). The human image was obtained in a 3 Tesla MRI at approximately 1-mm^3 resolution. White matter appears bright in the T_1 weighted image. The mouse brain image was obtained in an 11.7T MRI at approximately 0.0025-mm^3 resolution. White matter appears dark in the T_2 weighted image. The image was from a live mouse and signal from the skull and muscle were removed from the image. The change in contrast afforded by different MRI contrast is responsible for the wealth of information available from MRI. (Human image courtesy of S. Talagala and mouse image courtesy of A. Silva, NINDS, NIH).

a large amount of information about pathophysiology has been obtained in human and animal brain injury models, especially detailing the evolution of the region injured due to a number of diseases including stroke and traumatic brain injury.[1]

Maybe the most important contribution of anatomical MRI to the study of brain injury has been the use of T_2 weighting to define lesions. It is well established from careful work in animal models and human studies that the size of ischemic regions is accurately quantitated by enhanced contrast in T_2 weighted images.[11–13] The enhancement is primarily due to changes in water content due to edema and tissue loss.[14] Complicating this is the fact that hemorrhage can lead to decreases in T_2 and thus decreases in image intensity in T_2 weighted images.[4,15] This is very useful for determining if hemorrhage associated with stroke has occurred in the brain. However, the presence of blood can lead to ambiguity if water content changes are offset by blood effects. Hemorrhage is very complex in MRI depending on the age, size, hematocrit, and state of hemoglobin (e.g., oxy-, deoxy, met-), and all of this must be taken into account.[15] There is well-known T_2 enhancement in white matter if there is demyelination. Indeed, detecting lesions in white matter of multiple sclerosis (MS) patients was an early triumph of MRI.[16] While the use of T_2 weighted MRI has been very important for the clinical management of a number of diseases of the brain, there is a need to increase the specific characterization of lesions. For example, staging a stroke or MS and predicting response to specific therapies cannot be done as of yet based solely on anatomical MRI.

While the use of anatomical MRI has been very important for the clinical management of a number of diseases of the brain, there is need to increase the specific characterization of lesions. The frontier for anatomical MRI is to push the resolution to better match brain anatomy and pathophysiology. There are important reasons to try to extend resolution to the 200- to 400-μm range in humans and below 100 μm in animal models within reasonable scan times. Presently MRI divides the brain into gray and white matter, and although useful, this division does not begin to capture the rich anatomy of the brain. For example, myelination in the cortex has been used to parcellate numerous brain areas in the monkey and human brain.[17] MRI is very sensitive to myelin, as demonstrated in FIG. 2A, which shows a proton-density-weighted MRI of fixed human brain at 100-μm resolution.[18] Dark regions due to white matter can be readily separated from light regions due to gray matter. Within the gray matter dark regions related to myelin can be seen. At one point (arrow in FIG. 2A) there is a transition to a sharp line of myelin. This transition represents the beginning of area V1 in the visual cortex. The challenge now is to achieve sufficient resolution and contrast to enable myeloarchitecture to be resolved throughout the brain. FIG. 2B demonstrates that in a 3T MRI resolutions of $350 \times 350 \times 500$ μm^3 can be obtained from the cortex.[18] In this image T_1 weighting was used to distinguish white and gray matter and a bright line was detected in the cortex (arrows in FIG. 2B). This has been assigned to the dense myelin in the cortex in V1. This is a first step in making it possible to divide cortical areas using anatomical MRI contrast. Similar results have been

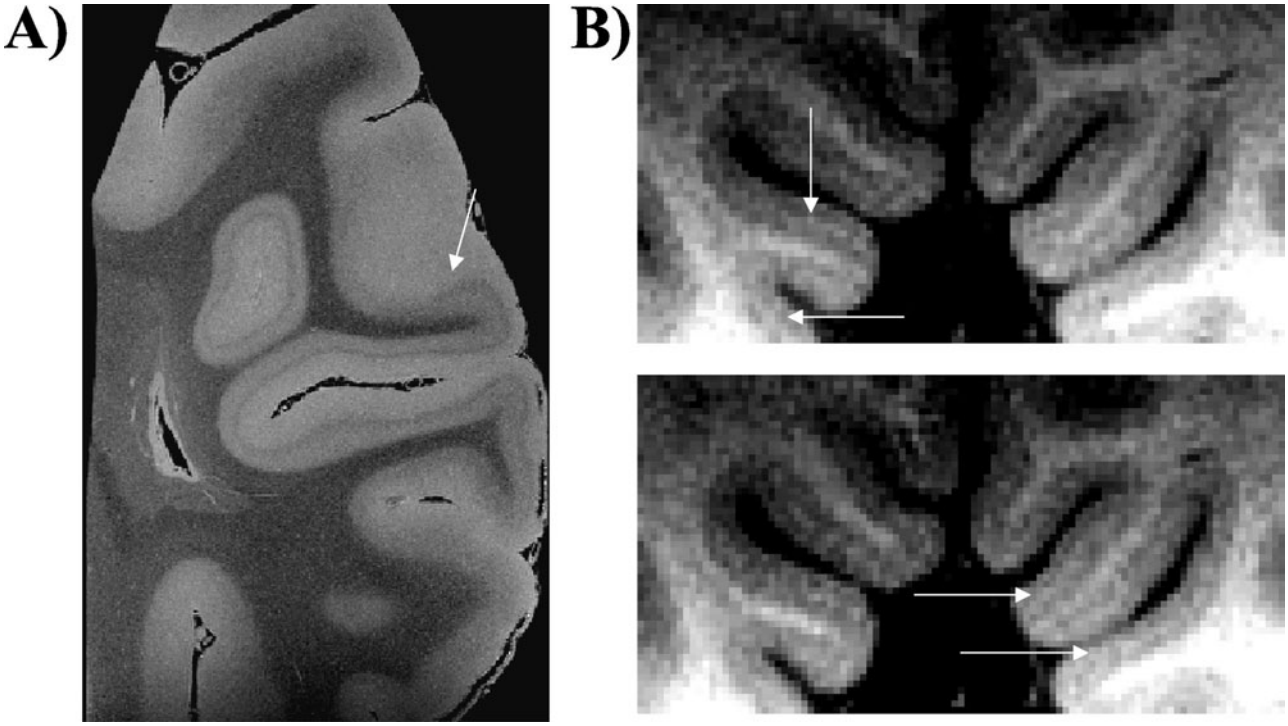

FIG. 2. High-resolution MRI of human visual cortex from fixed tissue *in vitro* (A) and a live person (B). The fixed tissue image (A) is a proton density weighted image obtained on a 4.7T MRI at approximately 100-μm isotropic resolution. White matter is dark compared to gray matter and myelination in the cortex can be readily detected. The arrow indicates the transition zone that marks the beginning of area V1 in visual cortex. Two contiguous slices from a normal volunteer separated by approximately 500 μm are shown in B. These images were obtained on a 3T MRI at resolution of 350 × 350 × 500 μm. White matter is bright in these T_1 weighted images and the arrows indicate regions where the myelin strip in area V1 can be readily detected. (adapted from Barbier et al.).[18]

obtained at 1.5T and areas delineated by myelin have been compared to boundaries detected by functional MRI.[19] It will be interesting to apply these high resolutions to studying brain injury. The recent development of parallel MRI for the brain[3] makes it likely that resolution will improve so that there are at least 10-fold more pixels characterizing the brain than presently used in clinical studies.

Another possible advantage of obtaining very high-resolution MRI may be to better define complex pathology. Recent work using a mouse model of neurological disorders caused by mis-regulation of iron illustrates this point. Iron response protein-2 (IRP-2) is a key translational regulator of the transferrin receptor and ferritin, which are key proteins in iron metabolism. A knockout mouse missing IRP-2 was recently generated and shown to develop a neurological disorder and have focal increases in ferritin and iron in different regions of the brain.[20] MRI has been used to detect increases in brain iron due to shortening of T_2 by many investigators, and therefore MRI study of the IRP-2 knockout mice was undertaken to use MRI to follow the phenotype.[21] FIG. 3A shows T_2 weighted images from individual control and IRP-2 knockout mice. When region of interest analysis was performed it demonstrated no significant changes in T_2 in regions that had been shown to accumulate iron by histology. The MRI was taken at resolutions of 100 × 100 × 250 μm^3 and so every brain area was defined by many pixels. Therefore, it was possible to look at distributions of pixels in different brain regions. FIG. 3B shows examples of histograms of T_2 *vs.* number of pixels obtained from cortex and dorsolateral geniculate nucleus for control (blue) and IRP-2 knockouts (yellow). Cortex showed no significant change in the histogram (blue and yellow overlap so only yellow is visible); however, the histogram from dorsolateral geniculate nucleus had a significant number of pixels shifted to shorter T_2 in the knockouts (yellow and blue do not fully overlap), consistent with an accumulation of iron. Unexpectedly, there were also a significant number of pixels shifted to longer T_2. Indeed the shift to longer and shorter T_2 balanced so that the average T_2 was not different. The most likely cause of a longer T_2 in MRI is accumulation of fluid. Histological analysis of these mice verified the presence of numerous fluid-filled vacuoles in those areas of the brain that also had increased iron.[21] This result illustrates what we believe will be an increasingly common finding as MRI begins to be routinely performed at much higher resolutions; namely, an ability to detect a variety of pathological processes that may be occurring within a region of the brain. In the case of the IRP-2

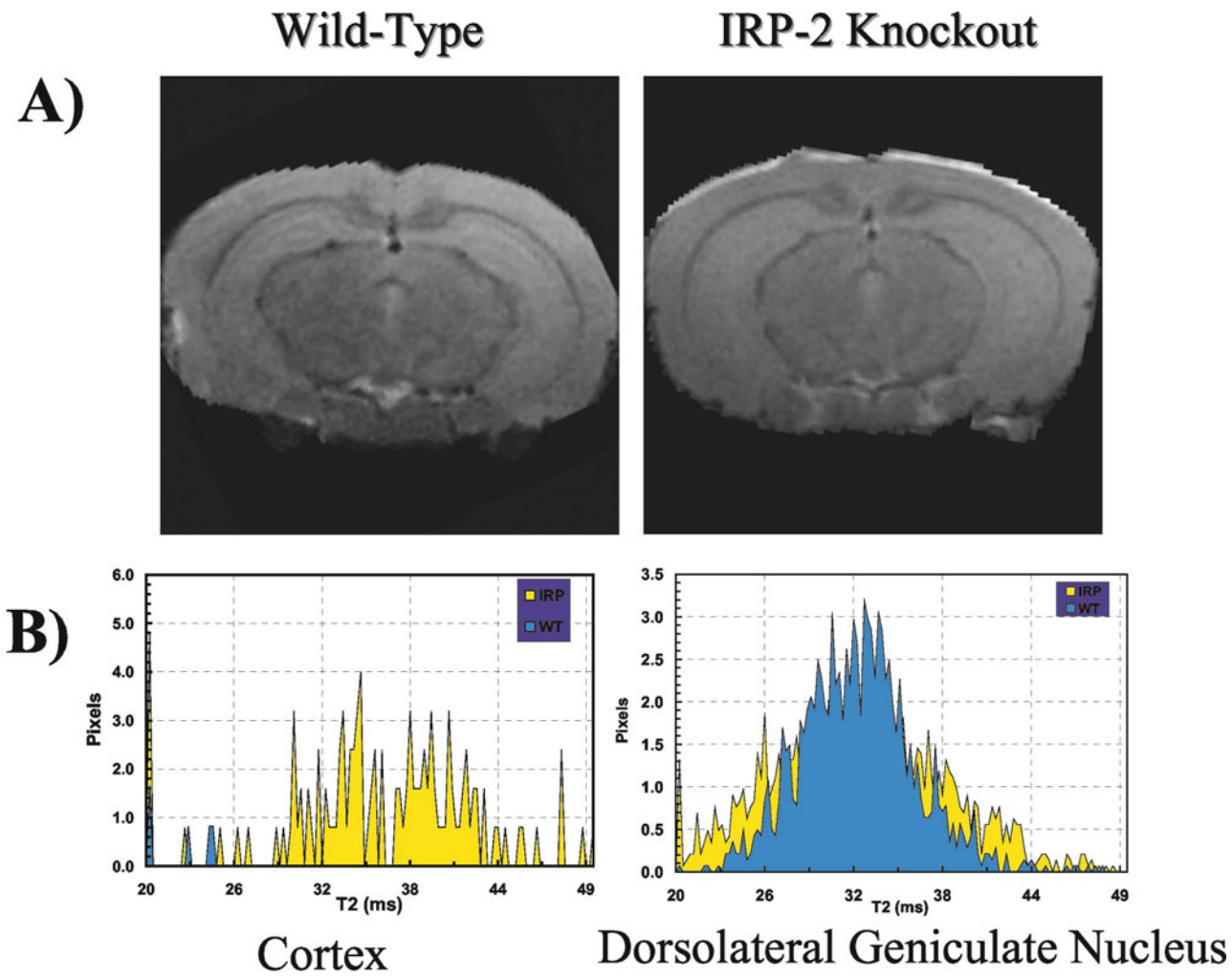

FIG. 3. MRI of normal and iron regulatory-2 knockout mice. A: T_2 weighted images form control and knockout mice. Increased iron is expected to decrease T_2; however, no average decrease can be discerned even in areas shown to have increased iron in the knockout mice. B: Histogram analysis showing number of pixels *vs.* T_2 from cortex and dorsolateral geniculate nucleus. Data from control mice is in blue and iron response protein knockout mice in yellow. In cortex there was complete overlap of the distributions of T_2 from the two groups of mice; however, in dorsolateral geniculate nucleus there was a shift to both lower and higher T_2 values in knockout mice compared to controls. This indicates that there was both an increase in iron and an increase in fluid. Pathology confirmed the presence of vacuoles as predicted by the MRI (adapted from Grabill et al.).[21]

knockout mice, the MRI data indicates that it may be possible to separate the time course of iron accumulation and vacuolization that is occurring and contributing to the neurological disorder that develops.

Functional MRI

The development of MRI techniques that are sensitive to regional blood volume and regional blood flow,[22,23] regional diffusion of water,[24] and most importantly, regional blood oxygenation[25] ushered in the age of functional MRI. The impact of functional MRI has grown rapidly. Due to the fact that changes in neural activity are accompanied by changes in blood volume, blood flow, and blood oxygenation, functional MRI techniques have found widespread use in mapping areas of the brain that are active during performance of a wide range of simple and complex tasks.[6] The ability to map functional areas of the brain has been applied to studying plasticity in the brain as function recovers after brain injury.[26,27]

The other major impact of brain functional MRI techniques may be on the management of stroke. It is clear that for some stroke patients treating with agents that dissolve blood clots can salvage brain tissue; however, there is a significant risk to many stroke victims. A major goal of MRI is to help make the decision of whether to treat a stroke. Changes in regional blood flow and the diffusion of water in brain detected by MRI have been useful for defining tissue damage due to stroke and traumatic brain injury.[7,8,11,13,35] A large number of animal studies have demonstrated that early after the onset of ischemia there is a decrease in the MRI-measured diffusion of water, which leads to enhanced signal on diffusion-weighted MRI.[30] While the exact mechanism un-

derlying this effect is not fully established,[31] the diffusion changes correlate well with loss of high-energy phosphate, loss of ionic balance, and increase in cell volume.[32] Thus, the diffusion changes show early damage and define areas that may evolve to chronic infarcts.[33] Regional blood flow can be inferred from rapid MRI acquisition of the wash-in and wash-out of a bolus of MRI contrast agent which is restricted to the blood.[34] This bolus-tracking experiment allows a number of parameters related to blood volume and regional blood flow to be calculated from MRI. If, after a stroke, there is larger area of perfusion deficit as compared to the area of diffusion abnormality, then it may be possible to restore blood flow and salvage the area that has low perfusion but normal diffusion. The presence of this so-called "perfusion-diffusion" mismatch is beginning to find widespread use in influencing the clinical decisions after a stroke.[8,33,35]

While broadly used, there remain a large number of questions about the exact mechanism of the contrast generated by functional MRI techniques and how the MRI measurements relate quantitatively to the processes they are measuring. For example, many studies have verified that blood oxygenation level-dependent (BOLD)-based functional MRI and arterial spin labeling perfusion-based functional MRI report on regions of the brain that are active.[6] Whether functional MRI techniques accurately detect boundaries and the quantitative relation between activity and functional MRI responses[36] remain active areas of work. Recent work has demonstrated that under the right acquisition conditions functional MRI techniques may detect boundaries in subareas of the visual cortex,[37] as well as resolve dominance columns in the visual cortex,[38] indicating that definition of active areas can be quite specific. Furthermore, recent work correlating EEG and functional MRI[39] and work exploring the basis of non-linear effects in functional MRI[40] both demonstrate that a high degree of neuronal specificity is present in the hemodynamic responses that functional MRI detects.

We have been interested in whether functional MRI can report on neuronal signaling across layers of the rodent cortex.[41] Very high-resolution BOLD-based functional MRI from the somatosensory region of the rat brain was obtained during electrical stimulation of the forepaw. FIG. 4A shows an example of a functional MRI activation map overlayed on an image used to generate this data. The activation map was made at $50 \times 50 \times 2000\ \mu m^3$. It is clear that the functional MRI response is heterogeneous across the cortex, with a maximum at the surface, a second peak that corresponds to layer 4 and then a fall-off in intensity in the deeper layers. Indeed, when grouped into three regions corresponding to layers 1 to 3, 4 to 5, and 6 there was a factor of three difference in average BOLD MRI response, indicating a high degree of heterogeneity across the cortex.[41] When the temporal evolution of the BOLD response was examined at 50 ms temporal resolution and $200 \times 200 \times 2000\ \mu m^3$ spatial resolution, there was a characteristic ordering of BOLD onset times across the cortex, as illustrated in FIG. 4B. In this case pixels that activated during different time periods after stimulation are shown. Two interesting results were obtained. First, at these high resolutions the onset of BOLD functional MRI was significantly faster than has been measured previously. A criticism of functional MRI techniques is that they are slow to onset; however, it may be that the slow onsets measured have been due to partial volume effects of larger draining vessels and that onset times measured at high resolution will be faster then presently accepted. Another interesting finding is that regions corresponding to layer 4-5 consistently activated before layers 1-3 or deeper layers. The center of the somatosensory region activated before the periphery as illustrated in FIG. 4B. The ordering of the BOLD onset follows the ordering of the electrical activity measured by a number of workers.[41] This leads to the intriguing possibility that functional MRI techniques may be able to inform about laminar signaling across the cortex.

Detailed characterization of hemodynamics, tissue integrity, and neuronal activity by functional MRI techniques are beginning to find widespread use to study brain injury in animal models and in humans.[26,27] Developments in functional MRI are indicating that this information will be obtained at higher and higher temporal and spatial resolution with an increasing degree of specificity. The impact should be in better defining brain regions affected by injury and for monitoring recovery due to treatment and changes in brain function due to plasticity.

Molecular imaging with MRI

There is rapidly growing interest in making radiological imaging techniques sensitive to specific molecules or biological processes. The marriage of the wealth of information being generated from molecular genetics, the large number of mouse models of human diseases, and imaging is the engine driving the development of molecular imaging.[2,9,10] Nuclear imaging techniques, optical imaging techniques, and MRI have all had aspects of molecular imaging as part of their makeup for a number of years; however, there is renewed vitality as more and more is learned about the pathophysiology of disease and more and more targets for therapeutic intervention become available. Major goals of molecular imaging by MRI are to image the presence of specific molecules with targeted contrast,[42] to be able to monitor cell migration,[43] to be able to follow changes in gene expression,[44] and to develop strategies that enable MRI to monitor other specific biological process. It is an exciting time in

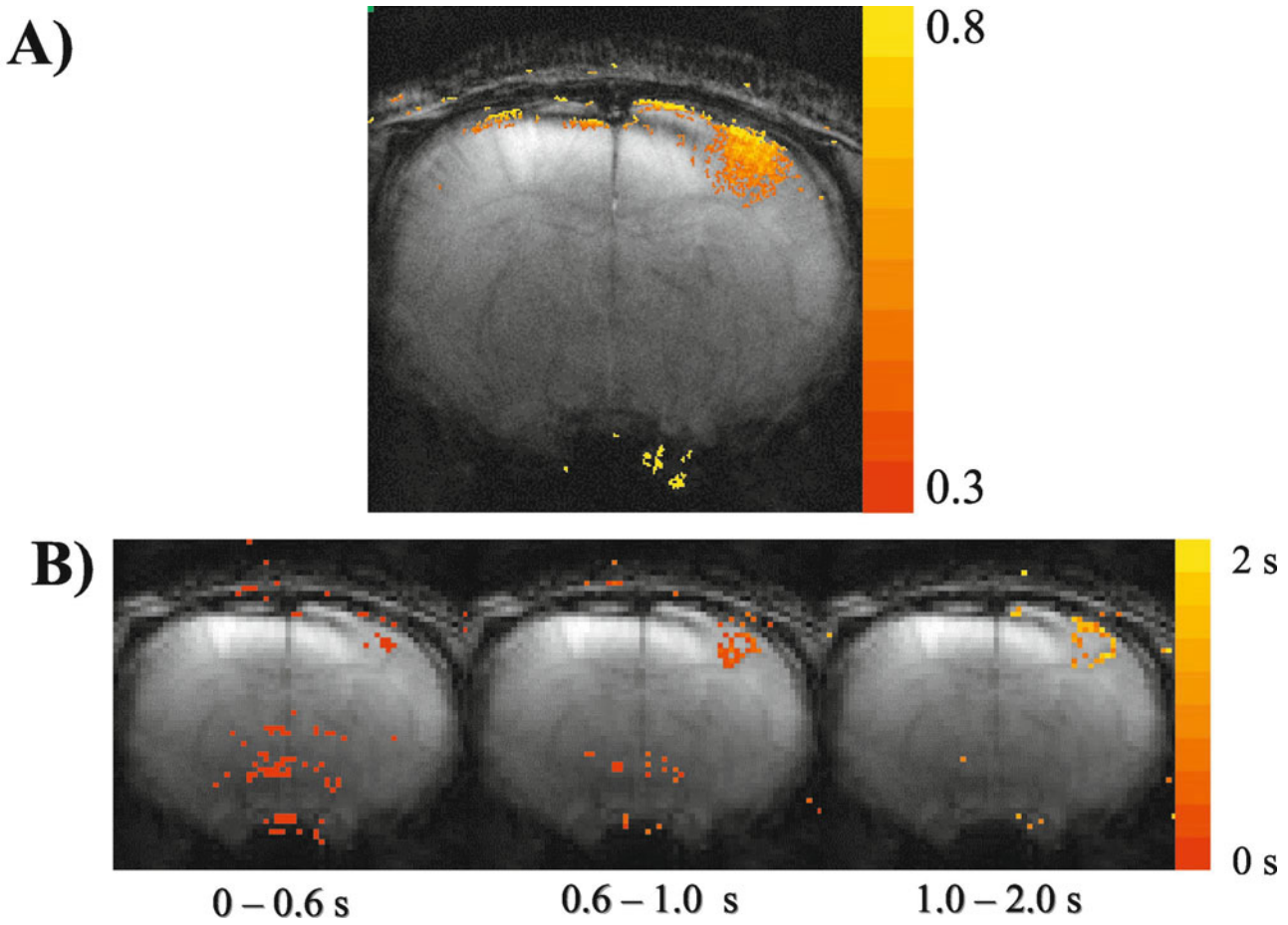

FIG. 4. Blood oxygenation-based functional MRI from the rat somatosensory cortex. A: 50 × 50 × 2000 μm^3 functional MRI map obtained from stimulation of the forepaw overlapped on the image used to acquire the data. A clear heterogeneity in functional MRI intensity was detected across the cortex. B: Pixels that activated in different time-windows during functional MRI after initiating a stimulus to the forepaw. Data were acquired at an effective temporal resolution of 50 ms and a spatial resolution of 200 × 200 × 2000 μm^3. The early onset in the deeper layers spread to upper and lower layers and then to fill in the outer parts of the somatosensory cortex. This shows the high degree of temporal heterogeneity across the cortex (adapted from Silva et al.).[41]

molecular imaging because there are a number of creative ideas being tested on animal models with clear implications for increasing specificity and sensitivity for monitoring and understanding human disease.

Molecular imaging of the brain offers significant challenges, primarily due to the problem of delivering agents through the blood-brain barrier. Nonetheless, several recent studies demonstrate the potential. For example, amyloid plaque can be imaged in mice with targeted MRI contrast after disrupting the blood-brain barrier.[45] This study relied on coupling MRI contrast agents to an amyloid peptide which adheres to plaques present in the brain. In transgenic mice engineered to produce a large number of amyloid plaques specific accumulation of the MRI agent enabled detection of plaques. This strategy of coupling MRI contrast agents to peptides or antibodies that recognize specific targets is rapidly growing area in molecular imaging. Creative ways to get large molecules through the blood-brain barrier will be crucial to the general success of this strategy.

Another very promising area for molecular imaging is to monitor cell migration *in vivo*. Here the idea is to label a specific cell population, either *in vitro* or *in vivo*, with MRI contrast agents and then to follow the movement of these cells in the animal. Typically nanometer-sized iron-oxide-based contrast agents are used and some form of endocytosis is used to get these particles into cells.[46] The advantage of these iron oxide particles is that it has been shown that single cells can cause sufficient contrast change to be detected by MRI.[47] There have been recent examples of MRI-based cell tracking to study diseases of the brain. Oligodendrocyte precursor cells were labeled and injected into the brain in an animal model of demyelinating disease.[48] The migration of the labeled cells were followed and production of myelin was detected using changes in contrast on conventional anatomical MRI. In a similar manner, the migration of embryonic stem cells into an ischemic region of the rodent brain was monitored by MRI after the cells were labeled with contrast and injected into the brain.[49] Rather than label cells

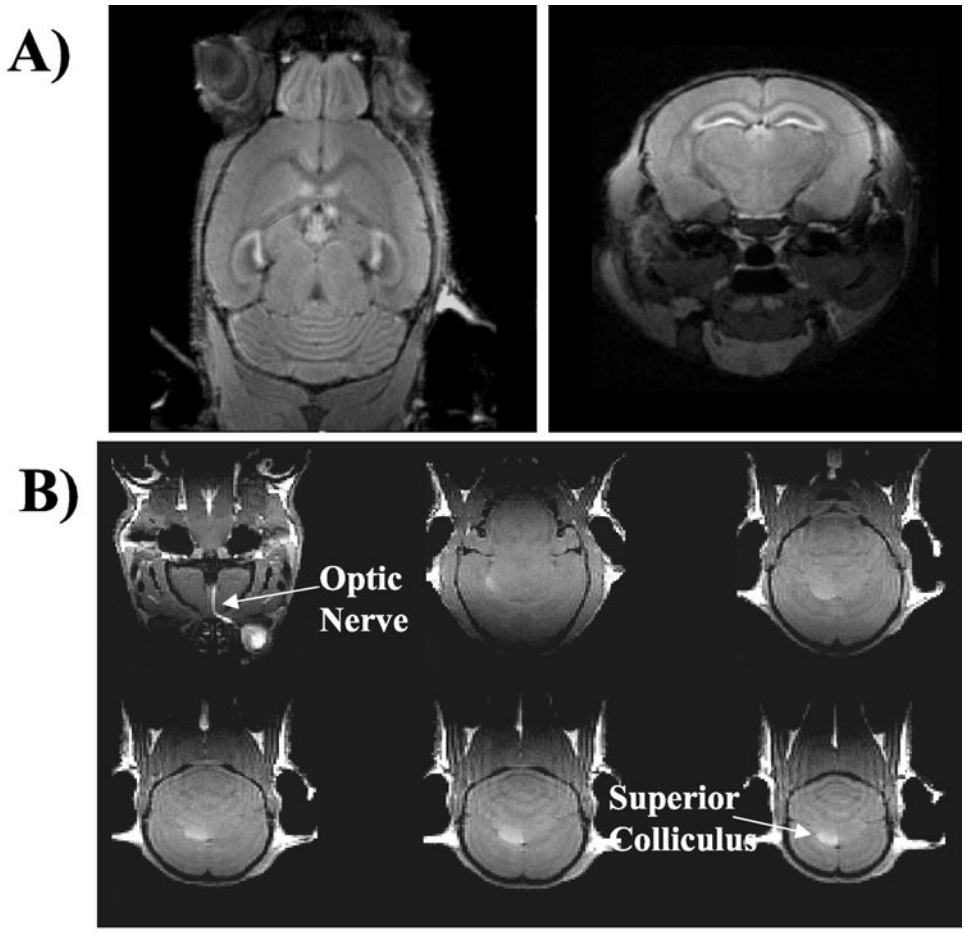

FIG. 5. MEMRI of the rodent brain. A: T_1 weighted images from a mouse brain, 24 h after systemic administration of $MnCl_2$. Images were obtained at 100-μm isotropic resolution. The contrast detected in olfactory bulbs, hippocampus, and cerebellum delineates these structures better than other MRI contrast mechanisms (image courtesy of Jung Hee Lee, NINDS, NIH). B: Example of neural tracing with MEMRI. In this case $MnCl_2$ was injected into the eye of a mouse. 36 h after the injection contrast could be clearly detected in the optic nerve and delineated the projections to the superior colliculus. T_1 weighted MRI was obtained at approximately 90-μm isotropic resolution (adapted from Pautler et al.).[56]

in vitro and follow them after transplantation, it is possible to label endogenous macrophages after injecting iron oxide particles directly into the blood.[50] This strategy has been used to study the time course of macrophage accumulation into an ischemic region of the rodent brain,[51] clearly demonstrating the power of MRI to monitor cell migration.

Our approach to developing molecular MRI techniques that aid in imaging the brain has been to rely on the rich biology of the manganese ion (Mn^{2+}). Mn^{2+} is a very potent T_1 MRI relaxation agent that is known to rapidly enter cells and has a number of interesting biological properties useful for developing it as a molecular imaging agent for the brain. We have capitalized on three properties of Mn^{2+} in particular. First, a simple systemic administration of $MnCl_2$ to a rodent leads to MRI contrast that allows imaging of brain architecture.[52] FIG. 5A shows a control mouse and mouse given an IV infusion of $MnCl_2$ 24 h before MRI. After Mn^{2+}, there is MRI enhancement throughout the brain with particularly large contrast enhancement in the olfactory bulbs, hippocampus, and cerebellum. Studying the time course of enhancement shows that the majority of Mn^{2+} enters the brain through the choroid plexus into the cerebral spinal fluid. Over the course of 24 h the Mn^{2+} moves throughout the brain. Preliminary analysis of high-resolution images of the rat and mouse indicate that a number of features of neuroarchitecture can be detected, including cortical and olfactory bulb layers, the granule cells of the dentate gyrus and CA formation of the hippocampus, and the three cell layers of the cerebellum.[52,53] The molecular mechanism for why Mn^{2+} accumulates specifically in a manner that gives such useful contrast is not clear; however, it may be reporting on cell density. If so, Mn^{2+} will be useful for characterizing a number of pathological conditions that are known to cause changes in cell numbers in specific areas of the brain.

The second useful property of Mn^{2+} ion is that it is known to accumulate in excitable cells by being transported on voltage-gated calcium channels. We have dem-

onstrated both in brain and heart that Mn^{2+} can be used to image active regions due to faster accumulation of Mn2+ in active areas.[54,55] In the rodent brain, activation-induced manganese-enhanced MRI (AIM MRI) contrast has been used to map somatosensory regions and localize activity due to pharmacological treatment. This strategy potentially offers an alternative approach to performing functional MRI with the advantage that rather than monitor hemodynamic changes due to activity one can monitor the function of calcium channels. Recently, the idea to monitor calcium influx indirectly with AIM MRI has been applied to imaging excitotoxicity in a stroke model.[56] This work illustrates a potentially important application of AIM MRI, which is to monitor regions where calcium influx is elevated for comparison to regions with low perfusion and altered water diffusion. A major drawback of the use of AIM MRI is that in order for there to be sufficient accumulation of Mn^{2+} over the few-minute time course of activation studies, the blood-brain barrier had to be disrupted to enable increased availability of Mn^{2+}.

The third useful property of Mn^{2+} for MRI of the brain is that it will follow appropriate neuronal pathways leading to a simple, non-invasive way of neuronal track tracing. The first experiments demonstrating this use of Mn^{2+} were performed by simple administration of $MnCl_2$ to the nose and injection into the eye of mice.[57] These results indicated that Mn^{2+} enhancement in MRI delineated the proper connections and could cross synapses to map a neural network. FIG. 5B shows examples of manganese-enhanced MRI (MEMRI) tracing of the path from the eye through the optic nerve to the superior colliculus in a mouse 36 h after initial injection of $MnCl_2$ in the eye. This strategy has now been applied to tracing the connections of a number of brain regions in rodent,[58] bird,[59] and monkey.[60] The two key features of MEMRI tracing of brain connections are that the Mn^{2+} moves anterograde and that it will cross synapses, allowing tracing of neural circuits. The fact that whole anatomical regions can be enhanced means that this is an approach to enhancing specific regions of the brain where normal MRI contrast might not define the specific borders. The ease of use and the ability to study the live animal with repeat administration of Mn^{2+} so changes in connections can be followed make it likely that MEMRI will find widespread application. In particular, it will be interesting to study changes in brain connectivity during plasticity after brain injury.

The ability of MEMRI to enhance the brain to reveal neuroarchitecture, to mark active regions of the brain, and to trace brain connections can impact MRI of the brain in a variety of ways. Indeed, it is possible to combine the different properties of Mn^{2+}. Recently, it was demonstrated that exposure of mice to specific odors along with $MnCl_2$ in the nose allowed mapping of the odor representation in the olfactory bulb.[61] The idea was that the odor caused increased influx of Mn^{2+} into olfactory neurons specifically activated by the odor in the turbinates of the nose. Then the Mn^{2+} tracked to the specific regions of the bulb, enabling the odor representation to be mapped on the bulb. It should be possible to further trace the Mn^{2+} and map the odor onto the primary olfactory cortex and further into the brain. The ability to map specifically activated neural networks with a neuronal tracer is a unique property of MEMRI.

The major hurdle that needs to be overcome to extend MEMRI to the human brain is the well-known toxicity of Mn^{2+}. Chronic exposure to elevated manganese is known to lead to neurological effects that resemble Parkinson's disease.[62] Mn^{2+} ion is also an essential nutrient since it is a necessary component of a number of enzymes including superoxide dismutase and glutamine synthetase. In the studies presented on rodents, doses of Mn^{2+} were used that caused no long-term toxic effects and are beginning to approach dietary levels. New technical developments that can increase the sensitivity of MRI to detecting Mn^{2+} will be important to enable safe applications to humans. The wide range of information available from use of MEMRI makes it worthwhile to pursue strategies that will enable implementation in humans.

Conclusions

MRI is having a large impact in the diagnosis and clinical management of brain injury. More and more often, MRI is used for determining the efficacy of neuroprotective strategies. The day is rapidly approaching where MRI will be accepted as a surrogate marker for clinical evaluation of new treatments. The impact of MRI is based on the great contrast to different tissues and the sensitivity to disease processes. This anatomical information can be combined with the rapidly developing tool-kit of functional MRI techniques that are sensitive to hemodynamics and water diffusion. The combination of anatomical and functional MRI now gives a large range of information that is having an impact on staging a number of diseases of the brain. There is a new generation of progress in MRI that will have applications to many diseases of the brain. The examples given here represent a small sample of the large number of interesting ideas that are being pursued by a growing number of laboratories interested in extending the state-of-the-art in MRI of the brain.

The work illustrated here gives us hope that there is progress in anatomical, functional, and molecular imaging with MRI. A new-generation MRI scanner, optimized for parallel imaging, should make it possible to achieve resolutions ranging from 300 to 500 μm throughout the human brain and 50 to 100 μm throughout the rodent brain in reasonable scan times. This will lead to a quantitative reassessment of the ability of MRI

to characterize the complex pathogenesis associated with many diseases. The increased sensitivity will push functional MRI techniques to enable clear definition of functional activity to the level of columns and potentially order the sequence of activity as it occurs throughout the brain. Finally, molecular imaging is a rapidly growing area that should enable many more processes that occur in the normal and diseased human brain to be detected. This new range of information for MRI should increase our ability to assess injury and predict the efficacy of treatment.

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