C. RESEARCH PROJECTS

A wide range of new and ongoing research projects will benefit from the next-generation 3T Vida MRI system. These projects include clinical and translational imaging of the cerebral cortex, brainstem, spinal cord, heart, lungs, liver, prostate and knee; high-resolution structural, functional, anatomical and physiological imaging of the developing and aging brain, as well as disease entities ranging from Alzheimer's disease, movement disorders, multiple sclerosis, migraine, chronic pain, and cancer to diabetes, heart failure and pulmonary fibrosis; and MR technology research. Many of our users are internal Martinos Center investigators, but because of its unique capabilities, the next-generation 3T Vida MRI has attracted great interest from investigators across the Mass General Brigham system including researchers from the MGH main campus (see ***Major User Projects 3, 7, 10, 15, 17 & 22: Simonyan, Montesi, Malhotra, Gerstner, Das & Rosenzweig***, BWH (see ***Major User Projects 2, 13, & 16: Tempany, Maier & Rathi***), other Boston area hospitals (see ***Major User Projects 4, 19, 24 & 26: Napadow, Gholipour, Afacan & Nezafat***), and Boston area universities (see ***Major User Project 8: Lewis***). The requested system has received broad interest from users across multiple research domains and body parts, with approximately 40% of our assembled users projecting utilization for neuroimaging, 35% focused on cardiovascular, body and fetal imaging, and 25% on imaging technology and development.

The research projects listed in this proposal are reflective of the NIH-sponsored research that has been performed for many years at the 3T facility at the Martinos Center and include many impactful, large-scale research efforts, including **two P41 NCBIB Center grants** (***Major User Projects 1 & 2: Rosen & Tempany***), a **P50 NIDCD Clinical Research Center grant** (***Major User Project 3: Simonyan***), a **P01 NICCH Center grant** (***Major User Project 4: Napadow***), **two R35 NHLBI Outstanding Investigator Awards** (***Major User Projects 17 & 22: Das & Rosenzweig***), a **DP5 NIH Director's Early Independence Award** (***Major User Project 18: Lee***), and **at least 30 R01-equivalent projects** led by our Major Users that will directly benefit from the proposed instrument. This illustrious portfolio of users has driven an overwhelming demand from 3T studies utilizing the state-of-the-art 3T Prisma and Skyra scanners, which are currently seeing more requests than they can accommodate due to the outdated hardware and software on the 3T Tim Trio, for which the proposed instrument will serve as an upgrade and replacement. At the current pace of utilization, this volume of NIH-sponsored research will be maintained and increased in the timeframe past the desired upgrade, as the next-generation 3T Vida and other similar high-performance systems are expected to become the prevailing whole-body 3T research platforms used worldwide for large-scale, multi-center research studies. *Conservatively, we estimate that 24 out of 26 of our Major Users, comprising **88% of the estimated usage of the 3T system**, will be active when the new system is turned over to the Martinos Center and available for use.*

Major Project 1 Title:	Center for Mesoscale Mapping
Grant Number:	P41 EB030006
Project Start/End Dates:	07/01/2020–06/30/2025
Principal Investigator:	Bruce Rosen, M.D., Ph.D., Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

The core mission of this research program is to bridge the microscopic and macroscopic scale evaluation of brain structure and function for human translational neuroscience, by developing and applying next-generation imaging tools to study the spatial distribution and temporal orchestration of *mesoscopic* events in the human brain. This mission is embodied in the P41 NCBIB Center for Mesoscale Mapping (CMM), which has set forth a vision of bringing together interdisciplinary teams of engineers, physicists, and basic and clinical scientists to develop multiscale imaging tools that will address complex neuroscientific questions. We focus on developing new technology that is directly responsive to the needs of our collaborators, pushing the boundaries of spatial and temporal resolution, efficiency, and quantitative accuracy in ways that will advance the work of our Collaborative and Service Users, many of whom will become prime users of the next generation 3T Vida MRI scanner. The CMM is organized around four key *Technology Research & Development* (TRD) projects:

TRD1: Cross-scale integration and modeling: TRD1 will improve mesoscopic *ex vivo* MR imaging to enable direct visualization of cortical and white matter features that define architectonic boundaries and influence the signal measured by *in vivo* MRI, such as cortical laminae, vessels, fibers and neurons.

TRD2: Acquisition technology for in vivo functional and structural MR imaging at the mesoscopic scale: TRD2 will create MR technology to achieve human brain imaging at the mesoscopic scale with diffusion, functional, and structural contrasts at 400-600 μm isotropic voxel size with high fidelity and SNR, *utilizing high-performance gradients to boost the speed and efficiency of image encoding*. TRD2 will combine novel encoding and reconstruction strategies such as gSlider-SMS (1) with combined RF and B_0 shim-array hardware (2) to take advantage of newly available instrumentation including the next-generation 3T Vida.

TRD3: Removing the biological limits for *in vivo* human brain MRI: TRD3 will push the spatiotemporal resolution of fMRI down to its biological limits. Since MR encoding is limited primarily by gradient performance, TRD3 will refine the design and development of gradient coils and sequences optimized for avoiding peripheral and cardiac nerve stimulation. At the same time, novel acquisition and reconstruction strategies will be developed to encode and remove biological nuisance modulation of k-space data from respiration and subject motion.
TRD4: Integrating electromagnetic multifocal brain stimulation and recording technologies: TRD4 will develop new techniques for magnetoencephalography source mapping and precise targeting of novel *multichannel* and single-channel transcranial magnetic stimulation. Multi-focal stimulation will be optimized by leveraging in vivo MRI, enabling online analysis of brain responses and development of closed-loop paradigms.
Collaborative and Service Projects. Through dynamic "push-pull" relationships, our Collaborative Projects offer unique biological problems that drive the development of tools by each TRD project and, in return, guide us in the design and optimization of our toolbox for practical use in a real-world setting. Our Service Projects apply these tools to better understand the human brain at the mesoscopic scale in health and disease. Examples of new capabilities enabled by our TRD's include using resting-state fMRI networks to guide the extraction of neuropathological tissue blocks during autopsy to test network-based theories of neurodegeneration *(CP1, PI: MacDonald, NIH RF1 AG056326)*, developing high spatiotemporal resolution structural, functional, and anatomical imaging for assessing tissue properties in aging *(SP1, PI: Kennedy, R01 AG056535)*, epilepsy *(SP2, PI: Ma, R01 NS109439)*, anxiety and depression *(SP4, PI: Balchandani, R01 MH116953)*, and enabling diffusion imaging at the mesoscopic scale to map tumor cell size and density using oscillating gradients *(CP6, PI: Xu, R01 CA109106)*. Our tools will be disseminated through open-source software and industrial partnerships and used to train the next generation of neuroscientists at this next frontier.

NEED FOR THE PROPOSED INSTRUMENT

The next-generation 3T Vida system with high-performance gradients will benefit the research in the CMM and facilitate translation of the developed imaging methods to commercially available 3T systems. It will also help fulfill a central mission of the CMM: to develop new technologies for dissemination to Collaborative and Service users, thereby further amplifying the benefits of the next-generation 3T MRI system to the broader research community. A common theme underpinning the CMM TRDs is the use of 3T MRI for high spatial, temporal and diffusion resolution imaging to probe neural tissue structure and function at the mesoscopic scale. As such, the large number of collaborations falling directly under the CMM will benefit from the enhanced encoding capabilities and accelerated imaging sequences available on the next-generation 3T Vida.

Key technology being developed by TRD2 for the CMM includes high spatiotemporal resolution fMRI and diffusion MRI acquisitions at 3T. Such acquisitions require both parallel imaging and slice-acceleration, which are made possible by high channel count array coils due to the multiplicative interaction between in-plane and slice undersampling. However, even with a 32-channel coil, the current Tim Trio 3T scanner is limited in its ability to achieve such high acceleration factors due to the outdated architecture and slow image reconstruction system, which prohibit the use of cutting-edge acceleration techniques such as SMS. For example, the typical BOLD fMRI sequences on the Tim Trio use up to R=2 in-plane acceleration to achieve 2 to 2.5 mm isotropic voxel size and TR's of 3 seconds or longer without the use of SMS. The availability of SMS on the next-generation 3T Vida in combination with strong and fast gradients will enable much faster acquisitions with SMS factors of at least 6-8 and TR's on the sub-second level, paving the way to adoption of the newer acquisitions developed by TRD2. The Open Recon interface will greatly accelerate the implementation and evaluation of these highly under-sampled acquisitions by providing results in real-time on the scanner console.

The high-performance gradients on the 3T Vida platform with G_{max} of 200 mT/m and slew rate 200 T/m/s will enable translation of the advanced structural and functional imaging paradigms and high spatial resolution readout strategies developed at the CMM to more readily accessible gradient regimes for whole-body imaging. The higher G_{max} will help bridge the gap in gradient performance between one-of-a-kind research scanners like the Connectome MRI scanner and the lower gradient strengths on clinical systems and offer a valuable intermediate testing platform for accessing gradient parameters beyond what is currently attainable on state-of-the-art systems like the 3T Prisma. The knowledge gained from CMM-driven studies on the next-generation Vida will in turn motivate new efforts to explore and characterize the advantages of such high gradient strengths on a commercially available system, thereby facilitating multi-site comparisons and clinical trials.

Major Project 2 Title:	Advanced Technologies – National Center for Image Guided Therapy (AT-NCIGT)
Grant Number:	P41 EB028741
Project Start/End Dates:	01/06/2021-12/31/2025
Principal Investigator:	Clare Tempany, M.B., B.Ch., Department of Radiology, BWH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

The Advanced Technologies-National Center for Image-Guided Therapy (AT-NCIGT) is dedicated to advancing patient care using image-guided therapy. The mission of this National Center for Biomedical Imaging and Bioengineering is to investigate and develop innovative tools for image-guided therapy. The team at AT-NCIGT is developing new technologies to probe human tissue, harness the power of large data sets with computer science, and introduce new intraoperative technologies to see, guide and treat patients better. We aim to help the physician improve the efficacy and reduce the morbidity of minimally invasive procedures by providing intra-operative image based anatomic and physiologic information in real-time. Drawing upon our longstanding expertise in body imaging and minimally invasive image-guided therapy, we are leading efforts to improve image-guided interventions using multi-modal imaging. A major focus of the AT-NICGT is to enable technologies for oncologic interventions in the prostate, including robotics for MR-guided focused ultrasound surgery. Our Center has convened multidisciplinary teams of investigators working in all aspects of image-guided therapy from acquisition and optimization of multi-parametric 3T MRI to image processing, registration, segmentation, navigation and image display, organized in the following *Technology Research & Development* (TRD) projects:

TRD1: Imaging cancer heterogeneity: TRD1 is working to integrate measures of tissue metabolism, MRI and histopathology to improve the assessment of tumor heterogeneity. New diffusion imaging sequences such as b-tensor encoding are being developed to characterize the cellular architecture of prostate cancer (**Figure 1**) (3).

TRD2: Deep learning: TRD2 is developing state-of-the-art algorithmic and data curation approaches based on information theory to enable weakly supervised deep learning for image registration and segmentation. These approaches can generate maps of cancer growth and distribution from sparse biopsy samples and assist in MRI-guided prostate biopsy.

TRD3: Intraoperative devices: TRD3 is developing intraoperative needle guidance systems that model needle deflection to enable precise surgical navigation and tissue sampling. These systems precisely measure the *in vivo* tissue response and derive optimal insertion paths for applications such as in-bore MRI-guided prostate interventions.

Through 10 Collaborative Projects and 10 Service Projects and a T32 training program in image guidance, precision diagnosis and therapy, the technology developed in the AT-NCIGT is being disseminated to sites nationally and internationally, magnifying the developed tools' impact on image-guided therapy.

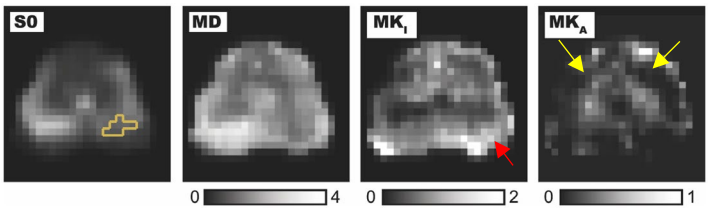

Figure 1. **Tensor-valued diffusion encoding improves the detection of microscopic tissue heterogeneity in prostate cancer.** Tumor region of interest (yellow outline) is similar to background prostate tissue on T2 imaging (S0) and mean diffusivity (MD) maps. A high degree of isotropic heterogeneity corresponding to spherical cells in the tumor stands out as bright signal on the isotropic kurtosis (MK_I) map (red arrow), compared to the high anisotropic kurtosis (MK_A) in the prostate tissue stroma corresponding to normal ellipsoidal cells (yellow arrows).

NEED FOR THE PROPOSED INSTRUMENT

The engineering challenges associated with minimally invasive image-guided intervention in the prostate in particular will benefit significantly from the advanced gradient capabilities and high-channel count body MRI coils of the next-generation 3T Vida. The stronger gradients will enable shortening of the echo time of conventional diffusion-weighted spin-echo MRI as well as novel b-tensor diffusion encoding approaches. Shorter echo times will boost the SNR of diffusion-weighted images and decrease susceptibility-induced artifacts from adjacent bowel and rectal gas. Our current tensor-valued diffusion encoding sequences on the Siemens 3T Skyra (G_{max}=60 mT/m) and Prisma (G_{max}=80 mT/m) scanners feature voxel sizes of 3 x 3 x 4 mm^3 and 2 x 2 x 4 mm^3, respectively, which are insufficient for characterizing small tumors in the prostate. Utilizing the stronger gradients and integrated parallel transmit on the new Vida, we will be able to achieve voxel sizes of 2 mm^3 isotropic with greater transmit homogeneity, which will reduce partial volume effects and reduce parameter bias, thereby increasing statistical power for detection of differences between cancers of different Gleason scores. The shorter TE's accessible on the next-generation 3T Vida will also help increase signal contributions from prostatic tissue stroma, which has short T2 values. Current biophysical models do not model this compartment separately. Multidimensional MRI methods that are being developed by TRD1 to map T2 and diffusion properties of cancer tissue (4) will benefit from the wider range TEs achievable with G_{max}=200 mT/m on the next-generation Vida. Furthermore, the higher b-values accessible using the stronger gradients will increase the sensitivity of conventional and tensor-valued diffusion experiments to cellular restrictions in cancerous tissues. Finally, the Open Recon platform will enable custom multi-dimensional MRI analyses to be outputted directly on the scanner, facilitating the translation of methods for imaging cancer heterogeneity and adoption in MR-guided interventions.

Major Project 3 Title:	Understanding Disorder-Specific Neural Pathophysiology in Laryngeal Dystonia and Voice Tremor
Grant Numbers:	P50 DC019900; R01 DC011805
Project Start/End Dates:	09/15/2021-08/31/2026; 03/19/2012-02/28/2027
Principal Investigator:	Kristina Simonyan, M.D., Ph.D., Department of Otolaryngology/MEEI, Department of Neurology/MGH

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Laryngeal dystonia (LD) and voice tremor (VT) are hyperkinetic neurological disorders that significantly impair voice and speech production. As vocal communication is a vital part of our daily life, LD and VT symptoms have a negative impact on the patient's quality of life, extending beyond speech motor alterations and often causing occupational disability and life-long social isolation. A major contributor to suboptimal clinical care of these patients is the limited understanding of their distinct clinical characteristics and neural pathophysiology. This challenge is not trivial to overcome because research in these phenotypically complex and heterogeneous disorders necessitates a large-scale, cross-disciplinary approach that utilizes advanced multimodal methodologies for the detailed investigation of their clinical phenomenology and neural pathophysiology.

To meet this clinical need, we have formed a multi-institutional, cross-disciplinary Center research program that is focused on the delineation of unique clinical and pathophysiological features of LD and VT in order to establish the fundamental framework for the enhanced clinical management of these disorders, including their accurate diagnosis and disorder-specific therapies. The basis for our approach includes our recent studies that have revealed LD-characteristic brain functional alterations in the speech sensorimotor and inferior parietal cortex, basal ganglia, thalamus, and cerebellum (5-11), proposing that LD, similar to other forms of focal dystonia, may represent a large-scale functional network disorder (12). We have identified extensive overlap between LD and VT functional brain abnormalities, suggesting a similarity of their pathophysiological mechanisms (13). Moreover, common to both LD and LD/VT patients, the severity of voice symptoms correlate with increased brain activity in the putamen and inferior frontal gyrus (7, 10, 11, 13), suggesting that functional abnormalities in these disorders may be similarly targeted by novel therapeutic options.

Our research goals will be accomplished through highly collaborative clinical research studies across the three Center Projects, a Scientific Core that incorporates the Clinical Research and Data Science components, and an Administrative Core that provides an overall organizational infrastructure to the Center activities. The Center sites include MEEI, MGH, UCSF, and the University of Utah. Aim 1 will characterize the clinical and imaging phenotypes of LD and VT, with a focus on accurate differentiation between LD and VT phenotypes. Aim 2 will work toward a comprehensive understanding of disorder-specific neural pathophysiology in LD and VT using multimodal brain imaging. Aim 3 will conduct deep brain stimulation (DBS) in LD and VT. Aim 4 will develop machine-learning platforms for differential diagnosis of LD and VT using the Center's shared repository of speech acoustic, neurophysiological, laryngeal and brain imaging data.

NEED FOR THE PROPOSED INSTRUMENT:

Functional neuroimaging of speech production is challenging due to the need to adapt existing and develop new scanning protocols that minimize orofacial movement artifacts during speaking. In addition to these technical challenges, the detailed structural and functional neural organization of the speech production system remains minimally explored, with many aspects of central speech control still being unclear. The next-generation Vida system will provide the most advanced software for neuro-based applications that will facilitate the clinical characterization of LD and VT. The new system also offers an improvement on maximum gradient strength of 200 mT/m and slew rate (200 mT/m/s); the improved hardware alongside a suite of accelerated imaging methods (SMS, compressed sensing and Wave-CAIPI) will allow for higher image quality without sacrificing imaging time. We will utilize the BioMatrix Tuners to stabilize shim and reduce B0 inhomogeneities in the vicinity of the larynx and obtain high-sensitivity imaging using the 64-channel head/neck coil. Finally, we will use the physiological recording equipment offered on the new Vida system to improve our current physiological monitoring set-up, which is cumbersome at best. The combined advancements of the next-generation Vida system will enable us to study speech variations between LD and VT patients and overcome limitations of the Tim Trio, which we use for the majority of our current imaging studies.

Major Project 4 Title:	Boosting Mind-Body Mechanisms and Outcomes for Chronic Pain
Grant Number:	P01 AT009965
Project Start/End Dates:	08/01/2018–07/31/2024
Principal Investigator:	Vitaly Napadow, Ph.D., Department of Radiology, MGH/Spaulding Rehab/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Chronic pain is the most prevalent and disabling medical condition (14). A recent Institute of Medicine report on pain (14) deemed a multimodal approach to be optimal. Many promising mind-body therapies (e.g., mindfulness meditation (MM)) are actually characterized as predominantly "mind" taking advantage of top-down brain-based mechanisms of action, without fully integrating bottom-up "body" based mechanisms. Greater integration of "mind" and "body" elements via multimodal approaches may enhance clinical outcomes.

Multimodal analgesic strategies enhance benefits to patients by targeting multiple pathways that contribute to chronic pain (15). Mind-body therapies can involve "mind" and/or "body" elements. Migraine is characterized by sensitization of the brainstem trigeminal sensory complex (16-19), leading to up-regulation of cortical excitability (20, 21). Neurophysiological and clinical outcomes for migraine headache may be enhanced by a multimodal interventional approach that targets (1) central sensitization; (2) autonomic dysfunction; (3) neuroinflammation. In this project, we evaluate synergistic combinations of top-down and bottom-up therapies for migraine headache (22). To do this, we: **(1)** Investigate brainstem and cortical mechanisms for reducing cortical excitability by respiratory-gated auricular vagal afferent nerve stimulation (RAVANS)-augmented MM, applying cutting-edge fMRI and MR spectroscopy (^{1}H-MRS) techniques; **(2)** Evaluate central and peripheral autonomic outcomes in conjunction with fMRI data to assess MM+RAVANS tVNS improvements in central autonomic network dysfunction; and **(3)** Investigate how the mechanisms assessed in Aims 1-3 are inter-related.

Our prior research suggested that migraine can be ameliorated by MM (23). To augment this top-down mind-body intervention, we propose a targeted bottom-up therapy, RAVANS (24, 25). RAVANS coordinates VNS stimulation to the respiratory cycle and reduces evoked pain intensity and temporal summation of mechanical pain in addition to overall reduction of anxiety in patients with pelvic pain. Such respiratory gating enhances the potential synergy, both conceptually and neuro-physiologically, of combining tVNS with MM, which explicitly focuses attention on one's own breathing with a calm and alert mind, promoting relaxation. In summary, our projects will substantially enhance the understanding of mechanisms supporting mind-body therapies and determine how synergistically combined top-down (i.e., MM, predominantly "mind") and bottom-up (i.e., RAVANS tVNS, predominantly "body") therapies, can work together to augment neurobiological outcomes for migraines.

NEED FOR PROPOSED INSTRUMENT

The next-generation Vida offers BioMatrix technology that includes respiratory and cardiac monitoring and acquisition of real-time physiological data concurrent with neuroimaging — a key component of our ability to deliver effective RAVANS therapy and determine whether our therapy mitigates migraines in conjunction with structural and functional MRI measures. The data recorded by the BioMatrix sensors are particularly relevant to our study as changes in physiologic parameters such as respiratory rate and heart rate can serve as reliable indicators of a reduction in anxiety and/or pain. This monitoring system will demonstrate any improvements that RAVANS provides as a therapeutic approach while eliminating the need for cumbersome external monitors and software interfaces, which are prone to failure and may provoke discomfort in pain-sensitive patients.

The new Vida also features high-performance gradients and the latest sequence advances, including SMS for diffusion MRI and ASL, which we will use to acquire accelerated high-resolution imaging to identify how our therapeutic method may better ameliorate migraines. Furthermore, the ability to push the spatial resolution of diffusion and fMRI will support our efforts to assess structural and functional changes in the cranial nerves (i.e., CN V, trigeminal nerve), as well as axonal integrity in patients suffering migraines, which have thus far been difficult to assess with the other clinical 3T systems at the Martinos Center, the Skyra and Prisma. We will use the enhanced acquisition hardware and software available on the next-generation Vida to detect and highlight the relevant neurobiological changes that may be improved by our therapeutic approach. The product diffusion, functional, and PCASL MRI sequences on the new Vida will enable robust and detailed longitudinal assessment of the episodic migraine patients evaluated in this randomized controlled neuroimaging trial. In sum, the new Vida system will facilitate quantitative measurements of migraine improvement in small structures like the brainstem while demonstrating the qualitative benefits of our therapeutic approach.

Major Project 5 Title:	Mitigation of Peripheral Nerve Stimulation (PNS) in MRI
Grant Number:	R01 EB028250
Project Start/End Dates:	05/01/2020–01/31/2024
Principal Investigator:	Bastien Guerin, Ph.D., Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Peripheral nerve stimulation (PNS) in MRI results from electric fields induced by gradient coil switching, which may stimulate the largest nerves in the body. The current generation of whole-body MRI gradients with G_{max}=80 mT/m and maximum slew rate of 200 T/m/s is largely constrained by PNS rather than amplifier power, mechanical issues or heat removal. Addressing these PNS limitations will allow faster imaging, higher resolution

and reduced distortions in many sequences routinely used for research and in the clinic for head/neck and body imaging, such as EPI, DWI, bSSFP, RARE and PROPELLER.

We have developed a gradient design tool with explicit PNS constraints and are validating the PNS benefits by experimental tests of optimized whole-body gradient designs. The state-of-the-art boundary element (BEM)-stream function (SF) approach for designing the gradient Mcoil winding patterns optimizes the magnetic field subject to electrical, mechanical and thermal constraints but ignores the primary limiting factor: PNS. PNS is only assessed after construction of a coil prototype on volunteers, which is costly and slow. In this project, we model magneto-stimulation in peripheral nerve models that consider: i) the coil wire pattern; ii) detailed shaping of induced electric fields by tissue boundaries; iii) dependence of the stimulation effect on relative orientation of the electric field and nerves; and iv) non-linear nerve dynamics based on nerve type and branching.

We will leverage detailed simulations of PNS in realistic electromagnetic/nerve body models to predict PNS thresholds of gradient coils without the need to build and test prototypes (**Figure 2**) (26-28). We simplified this computationally intensive step using a modified neural activation function (29), which we call the "PNS Oracle" as it provides a computationally quick way to assess nerve response while correlating better to the stimulation threshold (27). Our results indicate that we can increase PNS thresholds by 2x for whole-body gradient designs. The cost is a moderate increase of the linearity error (5%) and inductance (32%). The winding patterns support substantial PNS improvements with the proper tools to uncover them in the design phase. We will incorporate our PNS analysis into an industry-standard BEM-SF design optimization framework and validate our designs in a PNS threshold study of healthy volunteers.

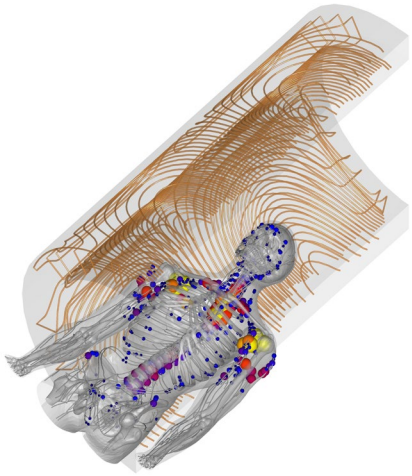

Figure 2. Results of the recently developed PNS Oracle for evaluating gradient windings and PNS mitigation strategies. E-fields are computed in a detailed body model and projected onto the nerve fibers. Nerve response is assessed by solving the neurodynamic model or through a linearized "PNS Oracle." Activation thresholds are displayed facilitating determination of the "when, why and where" of PNS activation.

NEED FOR THE PROPOSED INSTRUMENT

The next-generation 3T Vida system represents the first commercially available, whole-body high gradient strength and slew rate scanner with G_{max} of 200 mT/m and slew rate of 200 T/m/s. As such, it serves as an ideal test-bed for our electromagnetic simulations of PNS. We will leverage our longstanding experience working with Siemens to ensure that the operational limits of this high-performance whole-body gradient are used to best effect, in a safe and reproducible manner. We will validate the predicted PNS thresholds and develop optimized protocols that will ensure the robust and safe use of this and future commercially available high-performance gradients. We will conduct an IRB-approved study to validate the predictions of the PNS Oracle by measuring the coil PNS thresholds in healthy volunteers.

The high gradient strength and slew rate on the next-generation Vida scanner will facilitate the development of self-calibrating techniques such as our proposed PRE-excitation Targeting of the Potassium System (PRE-TAPS) to increase the PNS threshold by applying pre-pulses to the gradient system prior to spin excitation to induce a refractory state in sensitive nerve regions, such that the nerves cannot be excited again during gradient pulses used for contrast- or image-encoding. We will optimize the PRE-TAPS method on the new Vida by testing waveforms that are amplitude and frequency modulated to determine which shapes result in the greatest PNS threshold increase. We will perform an IRB-approved study using the high-performance gradient system on the new Vida to validate PRE-TAPS, in which we will compare PNS thresholds with and without PRE-TAPS applied.

Major Project 6 Title:	Microstructural Response of the Myocardium to Mechanical Load
Grant Number:	R01 HL159010
Project Start/End Dates:	07/01/2021 – 06/30/2025
Principal Investigator:	David Sosnovik, M.D., Department of Cardiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

The goal of this study is to use diffusion tensor MRI (DT-MRI) to evaluate how the microstructure of the heart changes in response to pressure and volume overload in the setting of aortic valve dysfunction. DT-MRI is a technique that enables the physical and structural properties of the myocardium to be imaged and quantified noninvasively (30, 31). DTI has been used to characterize myocardial sheet architecture via ribbon tractography

(32), but most studies to date have been largely limited to *ex vivo* imaging (33-37) or to normal volunteers *in vivo* (38). We will use DTI to develop a new set of phenotypic biomarkers that will independently assess myocardial microstructure in the setting of aortic valve stenosis and regurgitation, advancing an understanding of LV remodeling and the identification of new treatment targets (39-41).

Our group has previously developed diffusion MRI sequences to perform DTI of the heart *in vivo*. We have developed highly accelerated and free-breathing protocols to image the entire heart *in vivo* in less than 10 minutes (42). Recent advances using gSlider-SMS (1) provide higher resolution up to 2 mm isotropic with full heart coverage (**Figure 3**) using real-time slice repositioning to compensate respiration.

NEED FOR THE PROPOSED INSTRUMENT:

The new instrument will provide a state-of-the-art whole-body 3T scanner with the highest performance gradient system to date for us to leverage for our studies. The new Vida will also improve scanner accessibility, which has been a significant bottleneck to accruing more patients for these challenging exams. For cardiac DTI, the next-generation Vida scanner's whole-body gradient with peak strength of 200 mT/m is well-suited to advance cardiac DTI by reducing the amount of time spent on diffusion encoding and thereby reducing TE and improving SNR. Combining motion compensation with diffusion encoding in cardiac DTI necessitates short TEs that can be achieved more efficiently on the new Vida scanner compared to the existing Skyra and Prisma 3T scanners at the Martinos Center. The powerful gradient system will allow us to push the boundaries of cardiac DTI by imaging faster and at higher spatial resolution beyond the 2-mm isotropic resolution proposed in this project.

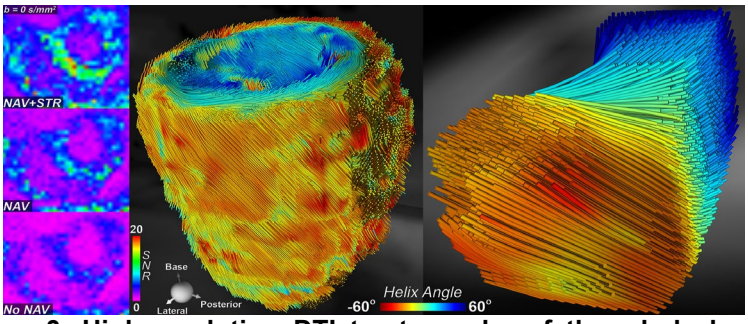

Figure 3. High-resolution DTI tractography of the whole human heart using generalized slice dithered enhanced resolution (gSlider) MRI. Left: Short axis slice showing SNR improvement with slice-following navigation and our spatiotemporal registration algorithm. Center: Fiber tracking of the whole heart of a healthy subject acquired with navigated M2-gSlider. Helix angle is defined with respect to the center axis, base to apex. Right: Section of the same heart showing detail of fiber orientation, epicardial to endocardial.

Our project will use the improved acquisition and advanced image reconstruction capabilities of the next-generation 3T Vida to assess myocardial function. We will utilize bSSFP sequences for high spatiotemporal cine imaging to visualize the motion of the left ventricular wall in patients with and without aortic stenosis/regurgitation. The bSSFP images will benefit from the strong and fast whole-body gradients on the next-generation 3T Vida to reduce TR as well as the improved field homogeneity of the 60-cm bore size magnet to limit banding artifacts. The high peak gradient amplitude will enhance our ability to map structural alterations in myocardial fiber organization and functional impairment from chronic mechanical load. Furthermore, the availability of SMS will enable much faster EPI-based acquisitions with slice acceleration factors ~2-3x, which combined with in-plane acceleration factors of ~2-3x may enable up to 6-9-fold total acceleration, depending on the receive coil used.

The next-generation 3T Vida features 128 receive channels enabling state-of-the-art coil technology such as the 30-channel body coil delivered with the system and higher channel count arrays, including our custom-built 64- and 128-channel cardiac array coils (43, 44). The built-in cardiac and respiratory monitoring through BioMatrix physiological sensors are paramount to identifying viable images of the heart relative to subject respiration. Furthermore, the new system allows for fast image reconstruction, which will be critical for choosing the appropriate image acceleration to apply for optimal image quality and are most effectively addressed by the modern generation of scanners with significantly improved whole-body gradients such as the new Vida. The next phase of this trailblazing cardiac DTI research will ensure immediate and continued need for the instrument.

Major Project 7 Title:	Vascular Leak and Outcomes in Idiopathic Pulmonary Fibrosis (IPF)
Grant Numbers:	R61 HL158540; K23 HL150331
Project Start/End Dates:	04/01/2021–03/31/2026; 04/01/2020-03/31/2025
Principal Investigator:	Sydney Montesi, M.D., Department of Medicine, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

The goal of this project is to determine whether advanced lung magnetic resonance imaging (MRI) techniques and molecular biomarkers of vascular leak can be used as surrogates of ongoing lung injury to identify idiopathic pulmonary fibrosis (IPF) subjects at risk for accelerated disease progression and those most likely to benefit

from adjuvants to anti-fibrotic therapy, including trihydroxyphenolic compounds such as epigallocatechin-3-gallate (EGCG), a principal component of green tea. IPF is a progressive, ultimately fatal disease with a median survival of less than 4 years from the time of diagnosis. Despite an overall poor prognosis, the clinical course of IPF is highly variable, with some patients experiencing rapid disease progression, while others have prolonged periods of stability. There are no current tests by which IPF disease activity, which greatly limits the ability to assess the efficacy of novel anti-fibrotic treatment strategies.

Vascular leak is a cardinal response to lung injury and contributes to pulmonary fibrosis when dysregulated. Alveolar-capillary permeability is increased in the lungs of IPF patients, and the extent of that increase has been shown to associate with disease progression and mortality. Dynamic contrast-enhanced (DCE) imaging is a powerful advanced MRI technique assesses vascular permeability. This technique is well established clinically to assess increased blood-brain barrier and tumor vessel permeability. Our research has shown that DCE-MRI is a sensitive method for quantifying pulmonary vascular permeability in IPF (45, 46). We have recently launched an NIH-funded phase 1 clinical trial to assess the safety and optimal dose of EGCG as an adjuvant to antifibrotic agents such as nintedanib and pirfenidone. The trial will use DCE-MRI to track vascular permeability of patients randomized to EGCG versus placebo. The data generated from this early-stage clinical trial will advance the use of DCE-MRI as a key noninvasive imaging biomarker of IPF treatment response.

NEED FOR THE PROPOSED INSTRUMENT

The new 3T Vida system will advance our research projects by enabling us to demonstrate detailed physiological imaging of IPF disease progression and response to therapy through the advanced image acceleration and high spatiotemporal resolution acquisitions available for thoracic MRI. First, the BioMatrix Technology includes a built-in physiological monitoring system that enables respiratory gating while acquiring high-resolution images by accounting for motion-compromised signals. We can mitigate the motion artifacts that we normally see in lung MRI during post-processing through retrospective gating and potentially reacquire motion-degraded data during the scan. We will also take advantage of the 30-channel body coil and new sequences available on the Vida system for body imaging, such as compressed sensing GRASP-VIBE for DCE-MRI of the lung, which will enable free-breathing scans in patients and healthy volunteers at high temporal resolution via accelerated image acquisition. The GRASP-VIBE sequence, available as part of the Turbo Suite Excelerate package, will be particularly helpful in patients who cannot perform breath holds, which is often the case in advanced IPF. Finally, the powerful reconstruction computers delivered with the new Vida system will enable significant improvement in image reconstruction speed for free-breathing DCE scans, in which timing is critical to ensure that the appropriate data points are captured for measuring pulmonary vascular permeability. All of these features available on the next-generation Vida will bolster the clinical translation of experimental protocols for the evaluation of IPF to the next generation of high-end commercial 3T MRI systems.

Major Project 8 Title:	Sleep-Dependent Modulation of Cerebrospinal Fluid Flow in Aging and Across Genetic Risk for Alzheimer's Disease
Grant Numbers:	R01 AG070135; R01 AT011429
Project Start/End Dates:	02/01/2021–01/31/2026; 04/01/2021-03/31/2026
Principal Investigator:	Laura D. Lewis, Ph.D., Department of Biomedical Engineering, Boston University

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Sleep is essential for cognition and healthy brain function. Sleep patterns change substantially in aging, and neurodegenerative disorders such as Alzheimer's disease are associated with disrupted sleep yet are not well understood. Sleep is associated with altered clearance of toxic protein aggregates such as amyloid-β and tau from the brain, through cerebrospinal fluid (CSF) flow that carries waste out of the brain, suggesting that disrupted sleep may contribute to neurodegeneration by reducing CSF-based brain clearance. Understanding sleep-associated CSF dynamics in typical aging and in individuals at genetic risk for Alzheimer's disease is critical to determine whether and how CSF flow could serve as a potential biomarker or target for intervention.

The current gap in knowledge reflects a technical barrier: previously, it was not possible to image CSF flow during sleep at fast time-scales. We recently developed simultaneous measurement of neural activity, hemodynamics, and time-varying CSF flow using fast fMRI and EEG (**Figure 4**). Using this technique, EEG slow waves during non-rapid eye movement sleep were coupled with waves of blood oxygenation and CSF flow (47). Intriguingly, this pattern suggests a possible mechanism driving CSF flow: slow waves in neural activity drive blood volume oscillations, which produce waves of CSF flow. Neural activity during sleep may therefore drive large-scale waves of blood and CSF flow, with downstream impact on brain clearance and neuronal health.

This neural and CSF coupling underlying sleep is expected to have significant impact on brain physiology in aging. We hypothesize that coherent neural activity causes CSF flow through a hemodynamic mechanism, and that this pathway is disrupted in aging and with genetic risk for Alzheimer's disease. To test our hypothesis, we

will use our multimodal fast fMRI/EEG technique to measure slow waves, hemodynamics, and CSF flow, in young and older adults. We will test whether sleep-dependent CSF flow is reduced in older adults, and whether it is associated with genetic risk for Alzheimer's disease. We will then establish the temporal link between neural activity and CSF flow dynamics across these cohorts. Finally, we will test whether hemodynamics mediate the link between neural activity and CSF flow, and whether reduced vascular responses are associated with less CSF flow in aging. In a separate R01 project, we will determine whether synergistic drive of respiration and neural activity enhances CSF flow in the human brain. We will test how spontaneous respiration is associated with CSF flow and test whether slower breathing drives higher flow.

NEED FOR PROPOSED INSTRUMENT

The proposed Vida scanner will be vital for advancing our goal of increasing the temporal sampling rate of fMRI to capture both slow and fast neural activity at 3 Tesla and measure the spatial distribution of time-varying CSF flow in relation to neural activity. Currently, our fMRI data are acquired on the 3T Prisma scanner with a single-shot gradient-echo SMS-EPI sequence at 2.5 mm^3 isotropic voxel size using slice acceleration factors of up to 8 times. These runs are acquired back-to-back while subjects are sleeping. The high gradient strengths and slew rates of the next-generation scanner will facilitate the acquisition of higher SNR fMRI data by shortening the echo times, which we will use to increase the temporal resolution of our measurements to <350 ms and spatial resolution to <2 mm^3 isotropic voxel size. Increasing spatial resolution is critical for our measurements as brain volume declines in aging and neurodegeneration. Higher spatial resolution will improve our ability to map the fMRI signal and CSF flow dynamics while avoiding partial volume artifacts.

This project will also use phase-contrast (PC) MRI to validate CSF flow measurements obtained with fast fMRI. While fast fMRI measures CSF flow and the BOLD signal simultaneously, a major limitation of our current approach is that it has only thus far allowed for CSF flow measurements in a single direction and location. We will use PC-MRI to map CSF flow across the brain and gain a global understanding of how the observed patterns change in different parts of the brain. Performing high-quality PC-MRI depends on achieving a balance between the encoding velocity (v_{enc}), TR and SNR. Sensitizing our images to CSF flow ~5-8 cm/s will require strong bipolar gradients to achieve a relatively low v_{enc}. On the current Prisma with G_{max}=80 mT/m, we are currently able to encode at a v_{enc} ~10 cm/s using TR values of ~25 ms. Our goal is to further decrease the v_{enc} to below 10 cm/s in order to capture the expected reduction in sleep-dependent CSF flow with aging. The higher peak gradient amplitudes on the Vida will broaden the range of encoding velocities and sensitize our PC-MRI measurements to slower velocities below 5 cm/s without compromising on TR.

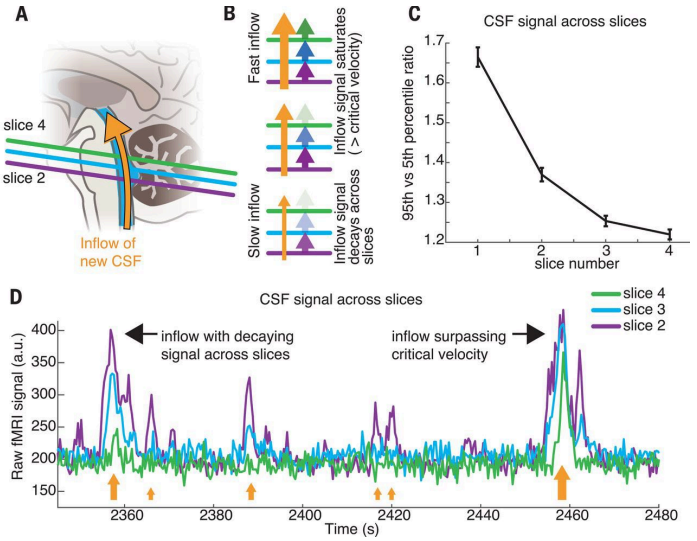

Figure 4. Fast fMRI enables simultaneous CSF and BOLD measurements. (A) New CSF flowing into the imaging volume generates bright signal. (B) Inflow signals are largest on the bottom slice and decrease in amplitude inwards. (C) Mean amplitude across slices decays in ascending slices. (D) Example time series from the bottom slices of the imaging volume in the fourth ventricle demonstrates the largest signal in the lower slices (e.g., slice 2) and smaller signal in higher slices (e.g., slice 4). Orange arrows schematically illustrate flow velocity.

The high-end image reconstruction computer that will be delivered with the Vida system will translate directly into higher data quality. At high acceleration rates, fMRI and phase-contrast EPI data have high computational complexity and are time consuming to reconstruct. Luckily, the computation is readily parallelized, and the high-end compute option makes use of GPUs to accelerate and facilitate real-time image reconstruction, which is currently not attainable on the Prisma and impossible on the old Tim Trio that the Vida will replace. Any delays in image reconstruction make it difficult to assess data quality online and can result in irreplaceable loss of valuable data, depending on the subject's phase of sleep. Thus, the faster image reconstruction computer will improve data quality and enhance the yield and efficiency of these time-consuming measurements.

The physiological recording equipment on the new Vida system offers a dramatic improvement over our current set-up, which is performed through two ECG leads placed on the chest across the heart and a piezoelectric belt placed around the chest. This can be especially uncomfortable and difficult to tolerate for

cognitively impaired individuals. The BioMatrix technology will lead to faster, simpler patient preparation, offering vast improvements to provide real-time physiological monitoring alongside fMRI and PC-MRI acquisitions.

Major Project 9 Title:	Advanced Neuroimaging Through Novel Encoding Strategies and Hardware Design
Grant Number:	R01 EB028797
Project Start/End Dates:	02/01/2020–11/30/2023
Principal Investigators:	Berkin Bilgic, Ph.D., & Jason Stockmann, Ph.D., Dept. of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

The goal of our research program is to develop synergistic hardware, data acquisition and image reconstruction strategies that can drastically reduce the artifacts of fast echo planar imaging (EPI). Diffusion MRI (dMRI) and fMRI are key tools used in large-scale imaging studies to probe functional and structural information about the brain. They are typically acquired using EPI, which provides fast encoding but suffers from severe geometric distortion artifacts. The lengthy readouts incur T_2- and T_2*-related voxel blurring and decrease the SNR by constraining TE to be very long. We aim to "fix EPI" by drastically improving its efficiency and geometric fidelity to provide rapid, high quality neuroimaging data. To this end, we are designing a head-only 64ch *AC/DC* combined receive and B_0 shim array (48, 49) to improve acceleration capability and B_0 field homogeneity. We have developed *Wave-CAIPI* trajectory for EPI acquisition to enable high in-plane acceleration ($R_{inplane}$) and mitigate distortion, blurring and minimize TE in dMRI. We have already successfully combined gSlider with dynamic B_0 shimming to achieve whole-brain 1mm isotropic, 64-direction diffusion acquisitions (see Figure 5) (2). We will disseminate the developed software and hardware designs to enable next-generation brain imaging.

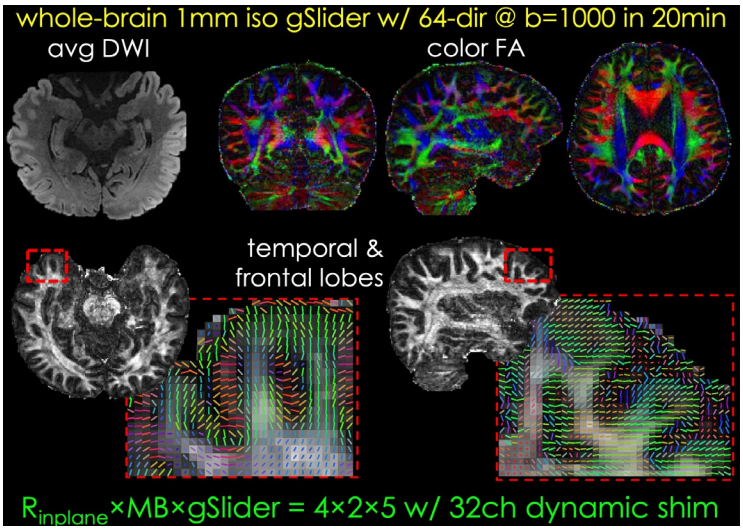

Figure 5. Combination of high in-plane acceleration and 32ch AC/DC dynamic shimming provides high geometric fidelity in diffusion imaging, even in hard-to-image regions of temporal and frontal lobes. Using simultaneous multi-slab acquisition with gSlider radiofrequency encoding boosts the SNR, allowing for 1 mm iso. resolution, 64-direction data to be acquired in 20 min on a clinical 3T scanner.

NEED FOR THE PROPOSED INSTRUMENT

The proposed Vida scanner offers a much-needed and forward-looking alternative to the Martinos Center Prisma and Skyra scanners as the latest commercially available Siemens 3T system equipped with cutting-edge gradient and RF technology and up-to-date software for sequence development. As the Prisma and Skyra scan slots are typically booked back-to-back for weeks on end, it is challenging to reserve imaging slots for the development and implementation of the advanced methodology proposed in this R01. Progress on achieving our technical aims has been delayed by the acute shortage of available scan time.

The high-performance gradient coil with G_{max}=200 mT/m and slew rate of 200 T/m/s will enable us to acquire dMRI images with much shorter echo times and provide a critical boost in SNR for acquiring high *b*-value dMRI data, which will become SNR-limited as we overcome the spatial encoding burden using our new acquisition methods. The decreased echo spacing during the EPI readout will provide additional reductions in geometric distortion and voxel blurring, providing an attractive technology to other major users of the Vida scanner who are eager for any opportunity to improve resolution and reduce distortion in their fMRI and dMRI acquisitions. All neuroscience R01s in addition to the Collaborative and Service Projects encompassed in the CMM (***Major User Project 1***) stand to benefit from reduced EPI distortion by adopting our newly-developed hardware and software on the latest Siemens platform. Moreover, we will take advantage of the new Open Recon framework to implement and disseminate our methods. Our efforts will thus be highly synergistic with the CMM and facilitate translation of high b-value, high spatial resolution dMRI to the latest commercially available 3T system.

The AC/DC coil proposed as part of this project is synergistic with the unique BioMatrix hardware provided on the Vida platform, which is not available on any other scanner at the Martinos Center. The shim control software will take advantage of the BioMatrix CoilShim technology, which is integrated into the head/neck coils on the Vida system, as well as the available BioMatrix respiratory sensors to enable real-time B0 shimming. The

shim array will enable us to apply multi-band, slice-group-optimized dynamic shimming by taking advantage of the dynamic linear shims and high gradient strength and slew rate to minimize geometric distortions, including those arising from physiological variations, ultimately improve the fidelity of submillimeter diffusion tractography.

As a fruitful byproduct of this project, the proposed AC/DC coil will benefit many other major users on the upgraded scanner and further augment the capabilities of the scanner for their use. For example, Dr. Andronesi (***Major User Project 14***) is an "early adopter" of the tools to improve 3T MR spectroscopic imaging for detecting 2-HG, a challenging metabolite to study due to its small spectral peak and vulnerability to line broadening and lipid contamination. The shim array will improve B_0 homogeneity by narrowing the spectral linewidth and reduce lipid contamination through volume-tailored lipid suppression shimming (50). The sensor output from the BioMatrix respiratory sensors will be fed into our shim control software to enable real-time multi-coil shim updating to compensate for the effects of respiration. Nulling the field offsets caused by breathing is expected to benefit Dr. Barry's R01 (***Major User Project 12***) on fMRI of the cervical spine, a region where spatiotemporal B_0 field fluctuations cause severe time-varying distortion in EPI slices. Getting the developed shim array into the hands of Martinos Center users is the ideal way to "test-drive" the tools before we release them to the broader research community. The next-generation Vida with state-of-the-art software and hardware is the ideal platform to test and disseminate the tools we develop for optimal compatibility with other leading research sites.

Major Project 10 Title:	Characterization of Functional Iron Deficiency and Repletion in Heart Failure with Preserved Ejection Fraction
Grant Number:	R01 HL159514
Project Start/End Dates:	07/01/2021-06/30/2025
Principal Investigator:	Rajeev Malhotra, MD, Department of Medicine, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Heart failure (HF) is a major public health problem worldwide, and half of patients presenting with HF have preserved (HFpEF), rather than reduced ejection fraction (HFrEF). However, HFpEF remains a therapeutic challenge, given current limited understanding of causal and contributing factors. Functional iron deficiency (FID) is present in approximately half of all patients with either HFpEF or HFrEF. Correction of FID improves exercise capacity in HFrEF; however, less is known about the functional impact of FID in patients with HFpEF or in the general population. Hepcidin, a hormone synthesized predominantly by the liver, is considered the master regulator of iron homeostasis. We have previously demonstrated that lower hepcidin levels are cardioprotective in animal model studies and that elevated hepcidin levels in symptomatic HFrEF patients precluded normalization of FID with oral iron supplementation in the NIH-sponsored multi-center IRONOUT-HF Trial.

In our preliminary studies of HFpEF patients undergoing comprehensive cardiopulmonary exercise testing (CPET) to track all components of the O_2 pathway, FID with reduced Tsat/hepcidin ratio was associated with exercise cardiac output, peripheral O_2 extraction, pulmonary vascular resistance and peak VO_2, implicating FID as an important determinant of multiple aspects of exercise capacity (51). We now propose to measure iron status and hepcidin levels in a referral cohort with suspected HFpEF (MGH ExS, N=1,100) to understand the role of FID in relation to functional capacity, leveraging existing CPET measures of low-level, intermediate and peak exercise O_2 utilization. We hypothesize that FID arises in the setting of inflammatory states that precede HFpEF, characterized by impaired ability to augment O_2 utilization. In Aim 1, we will determine the relationship between FID and exercise intolerance in a dyspneic referral population at MGH. We will investigate how FID relates to organ-specific dysfunction indicative of HFpEF sub-phenotypes. In Aim 2, we will prospectively investigate how treatment of FID in a randomized trial of iron repletion in 66 HFpEF patients improves exercise capacity and influences distinct mechanisms of exercise intolerance. We will contextualize the FID in vascular structures by measuring in vivo myocardial iron levels using cardiac MR-based T2* mapping.

NEED FOR THE PROPOSED INSTRUMENT:

This project will leverage cardiac MRI to characterize cardiac structure, function, and T2* mapping in patients with HFpEF. The next-generation 3T MAGNETOM Vida features two key hardware innovations: strong 200/200 gradients and the magnet homogeneity of a 60-cm bore diameter system, similar to the 1.5T MAGNETOM Avanto used for our clinical cardiac MRI studies. These features will be of particular benefit for our planned investigation of myocardial iron content using T2* mapping, which is sensitive to iron overload in the heart. The improved gradient performance and magnetic field homogeneity of the next-generation Vida will enable shorter TE's to be measured by multi-echo GRE sequences while reducing susceptibility artifacts found at 3T and thereby boosting the SNR of T2* mapping in the heart. Furthermore, the system will come equipped with 128 receive channels, which will be of value in leveraging several custom RF coils dedicated for cardiac MRI at the Maritnos Center, including a 64-channel cardiac array coil that was recently reported (44) and may form the

basis for future clinical prototypes. The BioMatrix respiratory sensors will facilitate respiratory triggering without use of a navigator, which will enable imaging of heart failure patients who typically cannot hold their breath for extended exams. The respiratory sensors will be particularly useful to monitor and assess patients' ability to perform the breath-hold maneuvers, such that the duration of sequences can be individually adapted to their respiratory capacity. The improved software (e.g., compressed sensing cardiac cine, MyoMaps) will allow us to obtain complete short axis scans of the whole heart during single breath-holds, thus shortening long acquisition times for LVEF measurements and simultaneously improving subject comfort and workflow.

Major Project 11 Title:	Brainstem-Based Imaging Biomarkers of Premanifest Synucleinopathy
Grant Number:	R01 AG063982
Project Start/End Dates:	05/15/2020–04/30/2025
Principal Investigator:	Marta Bianciardi, Ph.D., Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Brainstem imaging holds great promise in assessing premanifest synucleinopathies in older adults, when neurodegeneration is expected to affect the brainstem and the olfactory bulb, before spreading to other brain areas during symptomatic stages. Brainstem-based biomarkers can fill the currently existing holes in diagnosing synucleinopathies such as Parkinson's disease at an early stage when treatment can be most effective in delaying the development of full-blown neurodegeneration. However, existing imaging methods are incapable of resolving the details of tiny deep brainstem nuclei, especially in older adults affected by movement disorders that often accompany synucleinopathies, limiting the development of brainstem-based biomarkers of premanifest synucleinopathies.

To fill this gap, the central goal of the proposed research is to create a probabilistic atlas of twenty arousal and motor brainstem nuclei in healthy elderly subjects by advanced 3T and 7T MRI. The atlas will be used to evaluate the utility of brainstem-based biomarkers of premanifest synucleinopathy in assessing the integrity of brainstem nuclei microstructure and connectivity pathways. To achieve this goal, we will map the brainstem nuclei atlas to both advanced (e.g., 7T or 3 Tesla 'Connectom') and standard structural and functional brain images of controls and subjects with premanifest and *de novo* manifest synucleinopathy. We will test the hypothesis that brainstem microstructure and/or connectivity pathways are altered in premanifest synucleinopathy compared to controls, and that these changes become stronger and affect more brain regions in *de novo* manifest synucleinopathy. Finally, we plan to verify the translational validity of the developed biomarkers of premanifest synucleinopathy on 3 Tesla clinical MRI. This proposal builds on our recently published ultra-high field MRI work in living humans, reporting a probabilistic atlas of 18 arousal and motor brainstem nuclei in healthy young adults (52-56), as well as on preliminary results demonstrating changes in brainstem nuclei microstructure and connectivity pathways in premanifest synucleinopathy (**Figure 6**). Thus, our project will provide two important new tools: a structural atlas of brainstem nuclei and brainstem-based biomarkers of premanifest synucleinopathy.

NEED FOR PROPOSED INSTRUMENT

A major goal of this project is to reproduce the connectomes depicted in **Figure 6** on more widely available 3T systems, thereby enabling dissemination of brainstem-based biomarkers of premanifest synucleinopathy to clinical settings. Crucially, the new Vida will help us bridge our current 3T findings on the MGH Connectome scanner to the latest commercially available Siemens 3T MRI system equipped with high performance whole-body gradients and facilitate the translation of advanced imaging methods in the brainstem to clinical settings, using more powerful gradients than what are currently available on other 3 Tesla scanners (e.g., Prisma).

Beyond serving as a translational platform, the high performance gradient system on the next-generation Vida including high G_{max} of 200 mT/m and slew rate of 200 T/m/s will improve the image quality for our structural and functional MRI acquisitions at 3T in elderly subjects and those with premanifest and *de novo* manifest synucleinopathy by offering higher spatial resolution and faster encoding, particularly for EPI-based sequences like fMRI and diffusion MRI. The high-performance gradient system will provide better SNR for diffusion MRI studies by enabling more efficient diffusion encoding with shorter and higher amplitude gradient pulses and shorter TE's. Furthermore, the 32-ch head and 64-ch head/neck coils will enable highly accelerated parallel imaging for anatomical, functional and diffusion MRI. In patients with associated movement disorders such as Parkinson's disease, we will take advantage of the cutting-edge fast MR acquisition technology embedded in the latest sequences on the Numaris X software platform such as SMS, compressed sensing and Wave-CAIPI for accelerated anatomical, structural and functional imaging, which will enable us to acquire high-fidelity data in these motion-prone subjects. We will also take advantage of the built-in BioMatrix physiological monitoring

capabilities with faster sampling rates for cardiac and respiratory measurements to remove physiological noise sources from our resting state fMRI measurements in the brainstem.

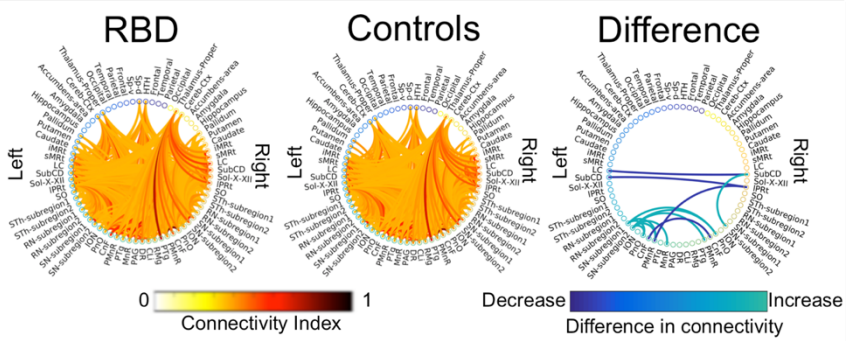

Figure 6. *In vivo* structural connectome of seventeen brainstem nuclei relevant for premanifest synucleinopathy (e.g. REM sleep behavior disorder, RBD) by advanced 3 Tesla Connectome MRI. Left) Connectome in RBD patients; **Middle)** Connectome in age- and gender-matched elderly controls; **Right)** Statistically significant differences in structural connectivity between groups ($p < 0.01$). Note that alterations of connectivity pathways in premanifest synucleinopathy occur specifically within brainstem nuclei, in line with animal and *ex vivo* human studies.

In summary, the next-generation 3T Vida system will greatly facilitate the translation of advanced imaging methods for structural and functional connectome evaluation to 3 Tesla clinical settings, by boosting the gradient capabilities available for cutting-edge clinical translational research studies in the brainstem. Specifically, this technology will increase the sensitivity and speed of diffusion and functional imaging, allow for more accurate connectomics evaluation at 3 Tesla, and increase the reproducibility of 3 Tesla results with those obtained with advanced (e.g., 7 Tesla or 3 Tesla 'Connectom') MRI scanners. Thus, it will promote the use of brainstem-based imaging biomarkers of premanifest synucleinopathy in clinical settings and advance the research objectives of this project to develop a powerful clinical tool for evaluating brain connectivity pathways in living humans and advance the understanding, diagnosis and treatment of premanifest synucleinopathy.

Major Project 12 Title:	Spinal Cord Functional Connectivity as a Biomarker of Spinal Cord Dysfunction
Grant Number:	R01 EB027779
Project Start/End Dates:	06/01/2019–02/28/2023
Principal Investigator:	Robert Barry, Ph.D., Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Nearly all multiple sclerosis patients have focal lesions throughout the spinal cord, yet no established clinical imaging technique can predict disability progression referable to the cord. Given the central role of spinal cord dysfunction in these patients, there is an important but largely unmet clinical need for non-invasive measurements of cord activity and functional organization (57). MRI of the human cervical spinal cord remains challenging due to the size and location of the cord. The spinal cord is a long, irregularly shaped structure only ~1.5 cm in diameter that is surrounded by pulsating cerebrospinal fluid, large vertebral bodies, and several centimeters of muscle and fat, amplifying the challenges of reliable and robust shimming across the cervical spinal cord (58, 59). The additional close proximity of the lungs create time-varying fluctuations in B_0 that correlate with the respiration cycle and need to be monitored for physiological noise correction (60).

The study of spontaneous fluctuations in the blood oxygenation level dependent (BOLD) signal has recently been extended from the brain to the spinal cord (61). These studies hint at the translational potential of using spinal cord resting-state fMRI signals in a range of clinical situations that involve spinal pathology and where a noninvasive metric of disease progression and treatment response is needed, including multiple sclerosis, spinal cord compression, spinal cord injury, and chronic pain. For example, focal lesions in the cervical spinal cord have been shown to disrupt local resting-state functional connectivity in patients with multiple sclerosis (62). *The goal of this project is to develop and evaluate novel spinal cord fMRI technologies to detect and characterize functional networks in the human spinal cord and to probe alterations in the functional organization of spinal cord networks in the presence of pathology.* Specifically, we will (1) develop and evaluate next-generation fMRI methods to non-invasively detect functional networks in the human cervical spinal cord and (2) characterize spinal cord network dysfunction in patients with relapsing remitting multiple sclerosis. While this grant aims to develop new methods for spinal cord fMRI at 7 Tesla, this work is also being conducted at 3 Tesla so that new spinal cord fMRI technologies may be used at a more commercially available and clinically relevant field strength. For resting-state connectivity of the human spinal cord to be used as potential biomarker for disease progression or treatment effects, robust measurements of spinal cord signals at 3T is needed because 7T scanners are currently only available in a limited number of research institutions.

NEED FOR THE PROPOSED INSTRUMENT

The acquisition of a next-generation Siemens 3T Vida MRI scanner will support this project in two key ways. First, the Vida BioMatrix Tuners (e.g., CoilShim and SliceAdjust) contained within the neurovascular coils are designed to provide significant improvements in reliable B_0 shimming across the cervical cord. These tuners detect local B_0 inhomogeneities for each subject and actively compensate for them via the local shim coils. This advanced shimming will adapt to the significant anatomical variations in the size of the neck and muscle/fat content that vary considerably across subjects. The next-generation Vida also features a 64-channel head-neck coil with integrated shims that will help with the inhomogeneity issues that are conventionally seen in spine imaging. With the capability of advanced and improved shimming, imaging quality will significantly increase and will only improve with the integration of multi-coil shimming capabilities being developed by ***Major User Project 9, led by Drs. Bilgic & Stockmann***. This would then remedy the technical difficulties we had experienced in our preliminary results (e.g., overcoming the susceptibility differences between imaging tissue and air). Our resources could then focus on characterizing the spinal cord network itself using these better images. As such, the advances we make on this next-generation scanner are clinically and translationally relevant and comparable. By fine-tuning the shim capacity of this scanner, clearer images of the spine can be acquired with better SNR. *No other commercially available 3T scanner is currently able to make these claims.*

Second, the Vida BioMatrix sensors embedded within the scanner table automatically detect respiration directly via the induced magnetic field shift. This innovative approach to monitoring the subject's respiratory cycle obviates the need to connect additional sensors to the subject, which is time-consuming and can be unreliable or produce problematic data due to physiological differences in how subjects breathe. The elegance of this innovative approach to physiological monitoring ensures that respiratory traces will be recorded for all subjects and thus available for use in post-processing of the fMRI data. The ability to gain real-time information about respiratory and cardiac motion, combined with the advances in multi-coil shimming, will further enable improved data quality. It is only through reliable and robust image quality that we will able to ascertain spinal cord functional connectivity for our project's goals.

The challenges of spinal cord MRI are well-known and predominantly technical in nature. As such, they may be addressed through the careful development of novel hardware and software solutions. The features of the next-generation Siemens Vida reflect a major advance in clinically available and standard hardware that has been designed to address the multifaceted and considerable challenges of local B_0 inhomogeneities in the neck and respiratory-induced physiological noise. The next-generation Siemens Vida scanner is the most advanced of its kind and will significantly impact the development of next-generation methods for spinal cord MRI and fMRI.

Major Project 13 Title:	Development of Methods for a Simplified and Reliable Prostate Cancer MRI Exam
Grant Number:	R01 CA241817
Project Start/End Dates:	06/01/2020-05/31/2025
Principal Investigator:	Stephan Maier, M.D., Ph.D., Department of Radiology, BWH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Over the past decade, multi-parametric MRI has significantly advanced the detection and characterization of prostate cancer, as evidenced by its adoption in the PI-RADSv2 clinical assessment system for prostate MRI. PI-RADSv2 was established by an international team of experts that acquires quantitative multi-parametric MR images but largely relies on qualitative image evaluation (63). Although this grading approach achieves reasonably good separation between normal and abnormal prostate tissue, it does not achieve adequate separation between indolent and aggressive disease. High-value protocols that provide greater diagnostic accuracy while minimizing invasive and costly endorectal radiofrequency coils are being investigated. The use of body coils versus endorectal coils may come at the cost of extended scan time and reduced image quality in terms of spatial resolution, signal-to-noise ratio and signal bias, which negatively impacts sensitivity and specificity of multi-parametric MRI. With the increased adoption of multi-parametric MRI exams for prostate evaluation, there is also the desire to integrate the support by the most recent revolution in diagnostic imaging, i.e., machine learning. However, in order to avoid having to train neural networks for each specific system and protocol, reproducible and thus preferably quantitative imaging protocols are essential.

To overcome these limitations, we propose a multi-faceted project of pulse sequence development, investigation of apparent diffusion coefficient (ADC) validity and reproducibility and novel post-processing strategies in prostate cancer. The objective is to improve lesion characterization with quantitative MRI and to understand and minimize the influence of protocol choices and scan hardware, hence improving overall reproducibility. Aim 1 develops a low distortion MRI sequence for rapid concurrent quantification of T2 and diffusion. Aim 2 examines ADC variations from the range of diffusion times that are typically accessible on state-of-the-art clinical MR systems. Aim 3 introduces advanced handling of low noise diffusion data, which is

indispensable for achieving high accuracy and precision with noninvasive external coils. Aim 4 introduces a novel ADC computation approach that fully captures the complex diffusion signal decays in tissues while being largely protocol and system independent. The resulting images and quantitative maps exhibit considerably less noise, which can be traded for higher spatial resolution and/or shorter scan duration. Taken together, the consistently quantitative nature of the data and its ubiquitous validity and comparability will greatly facilitate new recommendations for diagnostic thresholds that are more sensitive and specific for aggressive disease.

NEED FOR THE PROPOSED INSTRUMENT

This NIH-funded prostate cancer imaging project relies on high gradient performance for prostate diffusion imaging on a whole-body system. In particular, this project investigates the effect that gradient performance has on quantitative estimation of ADC using extended-range b-value diffusion MRI data with high quality and sufficient SNR up to 3500 s/mm^2 for the clinical assessment of prostate cancer (**Figure 7**). For a given diffusion-weighting, the higher G_{max} of 200 mT/m on the next-generation Vida scanner will enable more efficient diffusion encoding, leading to the ability to acquire higher b-value data with shorter diffusion times and echo times. In our current project, we have sought to maximize the gradient performance of currently available whole-body MRI systems with a G_{max} of 80 mT/m by simultaneously turn on gradients along all three principal axes. However, this approach is limited by the peak performance of the gradient amplifiers. The proposed upgrade at the Martinos Center to a next-generation 3T Vida system will permit the exploration of a wider range of diffusion times and echo times. We are also seeking to simplify prostate MRI acquisitions by avoiding the use of an endorectal coil in order to ensure optimal biopsy access. We will take advantage of the high channel-count body and spine matrix coil elements to gain high-sensitivity images with decreased susceptibility effect from insufflation of the endorectal coil bulb. In summary, the collaborative research environment between the Mass General and Brigham and Women's Hospitals will greatly facilitate the use of this novel instrument to broaden our knowledge about the effect of gradient performance in prostate cancer imaging and pave the way to using stronger gradients on whole-body MRI systems for clinical trials and multi-site imaging studies.

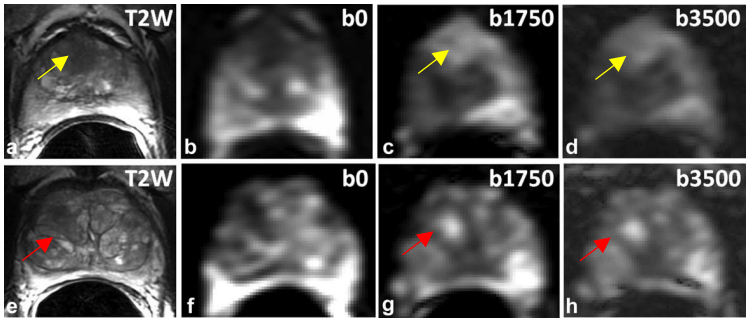

Figure 7. Representative images showing the improved detection of prostate tumors with high b-value diffusion-weighted MRI. (a-d) T2 hypointense tumor in the transitional zone (yellow arrow) is difficult to see on the b=0 image and clearly lights up against the background tissue on the b=1750 and b=3500 s/mm^2 datasets. (e-f) A T2 hypointense tumor in the right transitional zone shows restricted diffusion on the higher b-value data (red arrow) and was shown to have high cellularity corresponding to a Gleason 10 tumor on histopathology.

Major Project 14 Title:	Development of Next Generation 2HG and Metabolic MR Imaging for Precision Oncology of Mutant IDH and Wildtype Glioma Patients
Grant Number:	R01 CA255479
Project Start/End Dates:	02/01/2021–01/31/2026
Principal Investigator:	Ovidiu Andronesi, M.D., Ph.D., Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Intracranial malignant diffuse gliomas are a leading cause of cancer death in people under age 45. Mutations of isocitrate dehydrogenase (IDH) are frequent, resulting in a particular glioma subtype with a distinct molecular profile, clinical phenotype, prognostic and treatment response (64-67). Current therapy targets pathway by mutant IDH inhibitors (68), synthetic lethality (69), surgical resection (67), radiochemotherapy (70, 71) and targeted mutant IDH inhibitors (72). Mutant IDH tumors produce very high levels of 2-hydroxyglutarate (2HG), which is a unique molecular biomarker present only at trace levels in wild-type patients and increasing by 2-3 orders of magnitude in IDH mutations (73). 2HG in mutant IDH glioma patients is detectable by in vivo magnetic resonance spectroscopy (MRS) and can be used for non-invasive diagnosis IDH mutations (6-8). We have shown in vivo 3D imaging of 2HG is possible by MR spectroscopic imaging (MRSI) and can be employed for treatment monitoring of mutant IDH glioma patients (70, 71). While this work demonstrated the feasibility and clinical utility of 2HG imaging, several limitations restrict its wide clinical potential due to technical problems including: 1) reduced field of view that excludes large parts of the brain; 2) susceptibility to B0 inhomogeneity; 3) ambiguities in quantification of 2HG levels. To overcome these difficulties, we will (1) develop whole-brain 3D MRSI for 2HG imaging of mutant IDH glioma; (2) develop absolute quantification of 2HG levels from whole-brain

3D MRSI; and (3) validate whole-brain 2HG imaging and absolute quantification in mutant IDH glioma patients. We will validate in vivo 2HG imaging against gold standard pathology in a cross-sectional diagnostic study, and we will further assess its performance in a longitudinal study of mutant IDH glioma patients.

NEED FOR PROPOSED INSTRUMENT

The next-generation Vida system will be necessary to continue our development of improved methods for quantitative imaging of tumor metabolism. The new system offers BioMatrix Tuners with shim currents that are incorporated into the global shim algorithm and coils. These allow for significant reduction in localized B_0 inhomogeneities, which is pivotal to the accurate determination of tumor volume for 2HG level mapping. In addition to the real-time field correction that is being developed in this project, we will also take advantage of the Frequalizer function on the Vida, which is a temperature sensor-enabled feature for ensuring long-term frequency stability, as a means of validating our field correction approaches.

The new system also offers the latest advances in gradient strength and slew rate, thereby enabling faster acquisition of the relevant anatomical and physiological parameters in glioma patients. The higher efficiency of image encoding enabled by the high-performance gradients will enhance image quality by increasing SNR and decreasing distortions through enabling reduced echo spacing. The latest software for neuro-based projects including sequences that make use of SMS and Wave-CAIPI for diffusion, perfusion, and 3D anatomical imaging will complement the advances provided by the improved shim and gradient capabilities. The synergistic combination of these capabilities available on the next-generation Vida will help us to achieve our project goal; that is, to continue developing and optimizing a precise method of detecting 2HG mutations as a non-invasive diagnostic tool. Improving our ability to map 2HG may ultimately influence clinical treatment plans, patient management, and lead to earlier and more effective treatment.

Overall, the next-generation 3T Vida will provide better B_0 homogeneity, gradient performance and sequence capabilities that will ensure higher data quality, increased spatial resolution and faster acquisition times. These advanced capabilities will be leveraged to lower the detection limit to smaller tumor size for earlier diagnosis and enable the detection of subtle changes over time indicating tumor progression and response to therapy. In addition to brain tumors, our methods should be readily translatable to other neurological and psychiatric diseases by imaging neurotransmitters such as glutamate and GABA or the antioxidant glutathione.

Major Project 15 Title:	Using MRI and Circulating Tumor DNA to Improve the Interpretation of Response to Immunotherapy and Targeted Therapy in CNS Metastases
Grant Number:	R01 CA244975
Project Start/End Dates:	12/15/2019–11/30/2024
Principal Investigator:	Elizabeth Gerstner, M.D., Department of Neurology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

50% of patients with brain metastases (BM) die each year, and this number is likely to rise as systemic chemotherapies improve. Recent excitement surrounding targeted therapies and immunotherapy has been dampened by the limited durable response to immunotherapy confined to a subset of BM patients. The backbone of BM response assessment criteria, radiographic change in contrast enhancement, can be misleading since treatment-related changes can mimic true progression. Contrast-enhanced MRI provides insight into anatomical features of tumors but provides limited information about biological response. There is a critical need to identify biologically informative, noninvasive markers of BM response since serial BM tissue is challenging to obtain.

To address this challenge, a major goal of this project is to identify noninvasive advanced imaging tools to monitor BM response to therapy, including immunotherapy, and define markers of response or resistance. MRI provides vital anatomical information such as tumor location, size, and shape, and is increasingly providing physiological information about vascular and tumor microenvironment changes. Our previous work has shown that decreases in perfusion as measured by 3T MRI can help predict BM response to immunotherapy. We will apply and validate improved acquisition and analysis methods for perfusion and diffusion MRI to monitor microvascular and cellularity changes in BM. Specifically, we seek to improve the performance of dynamic susceptibility contrast MRI (DSC-MRI) in the assessment of BM through appropriate leakage correction techniques, parametric modeling, vessel size imaging, and estimation of oxygenation. We are also exploring novel diffusion-weighted MRI techniques to quantify changes in cellularity and edema through modelling of the different water compartments (i.e., intra- vs. extracellular water, restricted vs. hindered diffusion).

MRI plays an important role in assessing BM/LMD response to treatment but has limitations. When combined with our unique tissue samples, this proposal represents an **unprecedented opportunity to monitor clonal evolution during treatment** and will provide critical insights into how these complementary approaches can

improve our understanding of BM response or resistance as we develop new therapies for these difficult diseases.

NEED FOR PROPOSED INSTRUMENT

BM are well known to be heterogeneous in their imaging characteristics and response to therapy. Quantifying this heterogeneity across the whole brain and at high spatial resolution is believed to be useful in characterizing the overall genetic evolution and aggressiveness of BM. The high-performance gradients and advanced sequences developed for anatomical and physiological imaging on the next-generation 3T Vida system will enable us to image brain metastases faster and at higher spatial resolution using novel-encoding paradigms, which are vital for boosting image quality and longitudinal data consistency in this patient population, particularly those with advanced disease.

The proposed Vida platform offers several advantages for improving the speed and quality of imaging for these patients, many of whom are seriously ill and unable to tolerate long and involved exams. The availability of Wave-CAIPI 3D sequences for anatomical imaging and SMS technology for slice acceleration of diffusion and perfusion MRI on the Vida will enable higher-resolution imaging than our current clinical protocols with whole brain imaging. In fact, current dynamic susceptibility perfusion protocol used for these studies only offers slab and not whole brain coverage, which is a serious limitation in BM that are multifocal and can be located anywhere in the brain. Using the gradient echo-spin echo DSC sequence developed initially on the Prisma (74), we anticipate being able to achieve high spatial and temporal resolution whole brain DSC with shorter echo times and higher SNR, offering a significant advance for monitoring BM using perfusion imaging and enabling us to characterize the different vascular contributions to BM physiology (i.e., sensitivity to both micro and macrovascular contributions using the concurrent gradient echo-spin echo measurements). If successfully applied and validated in a few pilot patients, we plan to use these sequences in all patients undergoing longitudinal imaging at the Martinos Center. The preliminary data that we have acquired with Dr. Bilgic (***Major User Project 9***) and other experts in MRI acquisition and reconstruction at the Martinos Center suggest that brain metastases and leptomeningeal disease can be visualized with comparable diagnostic quality using post-contrast Wave T1 MPRAGE imaging (**Figure 8**), indicating the promise of this approach. Furthermore, the fast image reconstruction computers on the new Vida system will ensure that the images will be generated in real-time, obviating the need to keep patients on the scanner table for longer than needed and ensuring that all sequences requiring repeat scanning can be performed in the same session, which currently remains a barrier to adoption of these advanced sequences on the other 3T systems that we are using at the Martinos Center.

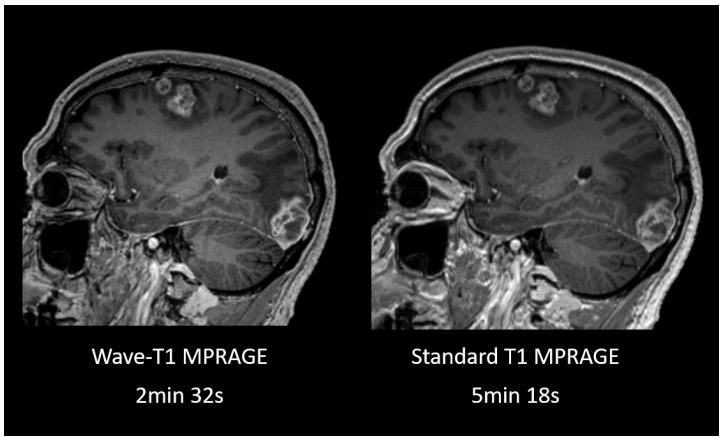

Figure 8. High-resolution post-contrast imaging performed with (left) Wave T1 MPRAGE and (right) standard T1 MPRAGE in a patient with metastatic squamous cell carcinoma demonstrating comparable visualization of the brain metastases using Wave versus standard imaging, with more than 2x reduction in acquisition time.

Major Project 16 Title:	Harmonizing Data Acquisition, Reconstruction, and Analysis for Reproducible, Cross-Vendor, Open-Source MRI
Grant Numbers:	R01 EB032378; R01 MH125860; R01 MH119222; R01 MH116173
Project Start/End Dates:	07/01/2022 – 06/30/2027; 07/01/2021-04/30/2026; 04/01/2019-01/31/2024; 05/01/2018-03/31/2023
Principal Investigator:	Yogesh Rathi, Ph.D., Departments of Psychiatry & Radiology, BWH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

This 5-year R01 project addresses the significant barriers to scientific progress due to the large inter-scanner variability (often greater than 10-20%) present in multi-site MRI data, which substantially diminishes the power of neuroimaging studies to detect subtle pathologies in neuropsychiatric disorders. Inter-scanner biases are a result of differences in implementation of closed-source product sequences (e.g., gradient and radiofrequency pulse shapes and timing), the choice of reconstruction algorithms, as well as variations inherent to the scanner hardware (e.g., gradient strength). Another major challenge is the significant barrier to develop new sequences for each vendor separately. This inhibits the translation of new MRI technologies to research laboratories, as

vendor-specific sequence development environments are closed-source, proprietary, and suffer from a steep learning curve.

In this project, we address these challenges by proposing an "end-to-end" harmonization framework. We propose to develop and disseminate a single open-source *vendor-neutral* MRI pulse sequence development environment containing both standard MRI protocols (e.g., T_1-weighted, T_2-weighted, and diffusion MRI) and cutting-edge quantitative acquisitions (T_1, T_2, T_2*, and quantitative susceptibility maps (QSM)), a unified image reconstruction framework, and novel algorithms for post-acquisition data harmonization to enable multi-site reproducible research and mitigate inter-scanner variability and bias. Our quantitative MRI acquisitions will be efficient (5 min as opposed to more than 15 min) and also comprise of fast, distortion-free diffusion MRI sequences. The performance of standard contrast-weighted protocols and the accuracy of novel quantitative imaging sequences will be rigorously validated on phantoms and in-vivo data acquired from all major vendors (Siemens, Philips, GE) across different 3 Tesla scanner platforms. Further, we will develop and validate novel data harmonization algorithms that will remove any remaining scanner-induced discrepancies in the data due to hardware differences. One of the goals of this project is to reduce inter-scanner variability to the level of those observed within-scanner. The technical developments proposed in this grant will dramatically increase reproducibility across sites and allow for seamless execution of multi-site neuroimaging studies. Thus, the increased statistical power of multi-site studies will facilitate detection of subtle changes in neuropsychiatric disorders. Our open-source first-of-its-kind platform will also accelerate cross-vendor sequence development and enable immediate translation of new sequences into research studies, which currently takes several years.

NEED FOR PROPOSED INSTRUMENT

The next-generation 3T Vida is the first commercially available whole-body 3T MRI system equipped with strong gradients up to 200 mT/m and 200 T/m/s slew rate. Designed to be the next-generation state-of-the-art clinical and research 3T scanner, the proposed Vida at the Martinos Center will serve as a valuable testbed for the harmonized pulse sequences and reconstruction algorithms developed in this project. The proposed Vida will be delivered with the new Open Recon interface of Siemens, which will enable our harmonized image reconstruction and post-processing solutions to be directly integrated in the reconstruction pipeline. By pushing the limits of both the gradient strength and slew rate and leveraging accelerated acquisition methods such as SMS, compressed sensing, and Wave-CAIPI available in the Turbo Excelerate Suite delivered with the Numaris X software, the spatial and temporal resolution of our quantitative and diffusion MRI measurements will be improved while maintaining consistently high SNR to reduce scanner variability within and between exams. The strong gradients and slew rate will also have synergistic benefits with other ongoing NIH-funded projects in our lab focused on mapping the superficial white matter connectome of the human brain using ultra-high resolution multi-contrast diffusion MRI (R01 MH125860) and harmonizing multi-site diffusion MRI acquisitions for studies across the lifespan and in various brain disorders (R01 MH119222). The new Vida will significantly advance our overall goal of reducing inter-scanner variability to the level of that observed within-scanner. Progress stemming from work on the proposed instrument will enable us to advance cross-vendor sequence development and image reconstruction methods on the newest Siemens research platform using the latest commercially available software and hardware.

Major Project 17 Title:	Functional Role and Therapeutic Targeting of Exosomes and Extracellular RNA Biomarkers in Heart Failure
Grant Number:	R35 HL150807
Project Start/End Dates:	06/01/2020-05/31/2027
Principal Investigator:	Saumya Das, M.D., Ph.D., Department of Medicine, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Despite important advances in the treatment of heart failure (HF), >50% of patients die within 5 years of diagnosis at their first hospital admission, and HF remains a leading cause of morbidity, mortality and healthcare expenditure in the United States. With the prevalence of HF expected to increase to 46% by 2030, novel mechanistic insights into HF pathogenesis and strategies to interrupt this progression are a large unmet clinical need. A major research direction in our lab has focused on the role of exosomes or extracellular vesicles (EVs) and their cargo RNAs (EV-RNAs) as novel functional biomarkers. We have discovered and validated plasma RNA signatures that correlate with human HF phenotypes such as adverse structural remodeling after myocardial infarction, fibrosis and sudden arrhythmic death. We found a signature of micro-RNAs that was associated with LV remodeling as measured by cardiac MRI, which is a very sensitive signature of cardiac remodeling. Other small non-coding RNAs are also differentially expressed between patients with beneficial or

adverse remodeling. We are now exploring the possible functional role for these circulating micro-RNAs and other non-coding RNAs, in cardiac remodeling in the post MI heart using cardiac MRI as a primary readout.

We are characterizing the EV RNA content of post-MI patients and correlating with different phenotypes defined by cardiac MRI – specifically, T1 and T2 mapping and diffusion tensor MRI (DT-MRI). This R35 project affords a unique opportunity to develop i) novel clinically useful biomarkers for improved risk stratification of HF patients; and ii) novel therapeutic targets to interrupt the adverse remodeling process. The flexibility and latitude afforded by the R35 mechanism enables the pursuit of these high-risk high-reward experiments that seek to address critical gaps in this field and will also provide time for devoting to mentoring of the next generation of cardiovascular disease investigators.

NEED FOR THE PROPOSED INSTRUMENT:

The current project depends on cardiac MRI for phenotyping of post-MI patients using T1 and T2 mapping and DT-MRI and correlating myocardial remodeling with EV regulation. This project will take advantage of the HeartFreeze motion correction technique and MyoMaps application delivered on the Vida to enable inline T1 and T2 mapping during free breathing, thereby increasing the efficiency of these otherwise lengthy myocardial quantification techniques in our patients, who are often not able to hold their breath for long periods of time. The next-generation 3T Vida features the latest 200/200 high-performance gradients, which will improve the accuracy of cardiac DT-MRI measurements through improved SNR and motion compensation. The proposed instrument combines the static magnetic field homogeneity of the 60-cm bore diameter MAGNETOM Avanto 1.5T compared to wider bore systems and exceeds the gradient performance of a MAGNETOM Prisma, which will improve the SNR of cardiac DT-MRI by enabling more efficient diffusion encoding with shorter echo times for a given b-value.

The new Vida will be delivered with 128 receive channels and a state-of-the-art 30-channel body coil. The high number of RF channels will enable us to make use custom-built higher channel count arrays for cardiac imaging such as the 64- and 128-channel cardiac array coils (43, 44) available at the Martinos Center, which will be particularly useful for the measurement of myocardial fibrosis with higher parallel imaging acceleration factors, and significantly shorten acquisition times while maintaining adequate SNR. The combination of high channel count array coils and a high-performance host computer with advanced image reconstruction capabilities will deliver up to 30% increase in SNR and reconstructed images nearly in real-time, which will be particularly needed at the high parallel imaging factors utilized in this study. The improved SNR, imaging speed, and spatial resolution provided by the proposed instrument would enable us to conduct non-invasive studies of the human cardiovascular system at higher spatial and temporal resolution than previously achieved.

The BioMatrix respiratory sensors enable respiratory triggering even for sequences without a navigator. The sensor will be particularly useful for identifying when a patient incorrectly performs breath-hold maneuvers for certain sequences, such that the duration of the sequences can be tailored to the patients' respiratory capacity, which is frequently compromised in heart failure. In addition, the compressed sensing cardiac cine suite delivered on the Vida will enable us to scan the whole heart in the short-axis view during a single breath-hold, thus shortening the considerable acquisition times for LV ejection fraction measurements. This feature is particularly important for our patients, who are often unable to breath-hold reliably for more than a few seconds, thereby necessitating repeated scans. The advanced software available on the Vida will facilitate the acquisition of higher quality images while streamlining the workflow and shortening overall scan times for this patient population.

Major Project 18 Title:	Revealing Tissue Microstructure in the Brain Gray Matter in Alzheimer's Disease using In Vivo High-Gradient Diffusion MRI
Grant Number:	DP5 OD031854
Project Start/End Dates:	09/14/2021-08/31/2026
Principal Investigator:	Hong-Hsi Lee, M.D., Ph.D., Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

The pathological hallmarks of Alzheimer's disease (AD) in the brain begin to form many years before overt symptoms, offering potential targets for early detection of disease onset with subsequent interventions. While volumetric MRI changes are useful to assess the presence of neurodegeneration, regional cortical volume loss is a relatively late structural marker of neurodegeneration in AD. On the other hand, diffusion MRI (dMRI) is sensitive to pathological changes on the cellular level, at least three orders of magnitude below the resolution of conventional MRI. Most diffusion MRI studies in AD to date have largely focused on white matter changes. However, on histopathology, AD is primarily a cortical disease, particularly in the early stages, and lacking in sensitive imaging biomarkers for structural degeneration at the microscopic level. The ability to probe early microstructural changes in gray matter (GM) in vivo would open the door to assessing disease onset and progression and aid in the development of disease-modifying therapy. This project will bridge the gap in

understanding changes in GM tissue microstructure in AD and mild cognitive impairment (MCI) using a combination of biophysical modeling, ex vivo and in vivo dMRI, and histological validation. We hypothesize that time-dependent dMRI measurements can evaluate the density of axonal varicosities, whose reduction has been histologically observed in the cortex of mild to moderate AD. We will test the hypothesis that in vivo dMRI enables the evaluation of tissue microstructure in the GM of AD and MCI, and that the probed tissue microstructure correlates with clinical progression. **Aim 1** will develop biophysical models for estimating varicosity density and soma size by dMRI in healthy subjects, AD and MCI patients. We hypothesize that axonal varicosity density will be reduced, and neuronal soma size will be increased in early AD. **Aim 2** will validate dMRI measures of neurite and soma structure via Monte Carlo simulations of diffusion and histological analysis in 3-dimensional realistic microstructure based on light and electron microscopy, and micro-CT data. **Aim 3** will assess the correlation of GM microstructural parameters with cognitive dysfunction, PET scans, and blood and CSF protein biomarkers.

By translating our success in assessing white matter microstructure using dMRI to GM, our study promises to provide reliable noninvasive imaging markers of neurodegeneration that are essential for understanding the mechanisms underlying progression of AD. Ultimately, the quantification of GM microstructure could provide prognostic and confirmatory biomarkers for neurodegenerative diseases, facilitating the assessment of treatment efficacy with the emergence of new drugs for AD and related dementias.

NEED FOR THE PROPOSED INSTRUMENT

The next-generation 3T Vida system equipped with 200 mT/m maximum gradient strength and slew rate up to 200 T/m/s will facilitate the broader dissemination of our techniques to probe time-dependent diffusion in GM in aging and Alzheimer's disease. In particular, the strong 200 mT/m gradients will increase the range of diffusion times that can be accessed compared to the current Siemens 3T Prisma MRI scanner equipped with 80 mT/m gradients, the current workhorse for such large-scale longitudinal studies as the Human Connectome Project in Aging. Our preliminary data suggest that the diffusion time dependence in certain cortices such as the frontal and temporal lobes decreases in aging and Alzheimer's disease and may serve as a useful marker to probe the redistribution of transmembrane proteins responsible for water transport, e.g., aquaporin-4, in the aging human brain. The availability of stronger gradients up to 200 mT/m on the next-generation Vida system will offer the possibility of performing multi-site validation studies of this observation in larger groups of aging and Alzheimer's disease patients. The new system will greatly facilitate the dissemination of our methods across a broader range of research scanners. The long-term goal of this project to develop GM microstructural markers that are altered early in aging before the onset of overt dementia. This goal will be facilitated by greater access and cross-scanner harmonization of protocols to usher in the routine use of gray matter exchange signatures in clinical trials of neuroprotective therapies for AD.

Major Project 19 Title:	Enhanced Imaging of the Fetal Brain Microstructure
Grant Number:	R01 EB032366; R01 NS106030; R01 EB031849
Project Start/End Dates:	03/01/2022-12/31/2025; 02/15/2019-12/31/2024; 06/15/2021-02/28/2025
Principal Investigator:	Ali Gholipour, Ph.D., Department of Radiology, Boston Children's Hospital/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

The fetal period of brain development is critical as it involves complex processes of cell proliferation, neuronal migration, and myelination that are particularly vulnerable to disturbances from adverse events in utero and conditions that develop during gestation. Specifically, hypoxia caused by abnormal circulation, is hypothesized to disrupt neuronal migration, thereby causing altered brain connectivity and adverse neurological outcomes. Abnormal brain connectivity has been depicted in newborns and adolescents with critical congenital heart disease (CHD) using diffusion-weighted imaging (DWI). Gross brain abnormalities have also been identified and quantified prenatally in CHD using in utero T2-weighted magnetic resonance imaging (MRI), but the precise location and timing of disrupted neuronal migration that leads to these abnormalities, has remained unclear due to technological limitations of in utero DWI.

The goal of this project is to develop new DWI technologies that remove these barriers to improve our understanding of the maturation of fetal brain microstructure as well as the origins and patterns of its alterations in utero, including CHD and perinatal stroke. In particular, we aim to develop new techniques to address the limitations of current fetal DWI technology by effectively mitigating and compensating for motion and geometric distortion artifacts during acquisitions. This project therefore seeks to create a paradigm shift in the way fetal DWI is acquired and analyzed. The three specific aims of the project are to 1) create a motion-corrected slice acquisition strategy for fetal brain DWI, 2) enhance fetal DWI acquisitions with artifact reduction and compensation by developing new imaging and image reconstruction techniques, and 3) evaluate brain maturation in fetuses diagnosed with congenital heart disease. We will assess the utility and impact of the

technologies developed in this project by analyzing and comparing a large pre-existing cohort of fetal DWI scans with the scans prospectively acquired from both typically-developing and CHD fetuses with these new techniques. Moreover, we expect to gain important knowledge about early disruptions to neuronal migration pathways and formation of brain connections due to compromised circulation and hypoxia in fetuses with CHD. By making fetal DWI more reliable and robust, this study will mitigate a critical barrier to making progress in the fields of developmental neurology and neuroscience. Improved understanding of the impact of adverse events in utero on fetal brain growth and the trajectories of altered brain development can help guide neuroprotective and therapeutic interventions, and enable early, more effective treatments for neurological diseases and mental disorders.

NEED FOR PROPOSED INSTRUMENT

We will take advantage of the high-performance whole-body gradient on the next-generation 3T Vida to improve the reliability and robustness of fetal DWI. As part of ongoing collaborations between investigators at Boston Children's Hospital and the Martinos Center, we will leverage the high gradient strengths up to G_{max}=200 mT/m to achieve shorter echo times and high-sensitivity diffusion MRI measurements of fetal brain microstructure in utero across multiple R01's. The availability of 128 RF receive channels will enable us to use the Body 30 and Spine 32 coils together to gain increased sensitivity to the fetal brain, which is deeply embedded within the mother's body. The TrueShape two-channel parallel transmit system on the next-generation Vida will be utilized to improve inhomogeneity artifacts, which remain a major obstacle preventing the consistent acquisition of high-quality, fetal DTI data. Finally, we will make use of the Open Recon platform to implement multiple strategies for the faster, motion-robust acquisition of fetal brain DTI data, including our in-house developed slice-to-volume registration (75) and more recently introduced deep learning-based parameter estimation methods (76).

Major Project 20 Title:	Toward a Validated In Vivo Imaging Marker of Axonal Damage Predictive of Progressive Disability in Multiple Sclerosis
Grant Number:	R01 NS118187
Project Start/End Dates:	07/01/2021-06/30/2025
Principal Investigator:	Susie Y. Huang, M.D., Ph.D., Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Axonal damage occurs early in multiple sclerosis and is considered the pathologic substrate of progressive disability. The spatiotemporal dynamics of axonal loss in relation to acute and chronic demyelination are not well characterized and likely vary between patients, lesion types, and within the normal-appearing white matter (NAWM). With the emergence of promising therapies targeting remyelination, noninvasive imaging markers with greater specificity to axonal pathology are needed to improve our understanding of disease progression in MS. Histopathological analyses of MS tissue have confirmed significant reductions in axon density within lesions and NAWM accompanied by a range of morphological alterations in axonal structure, including the appearance of ovoids, swelling, thinning, and transection. We have demonstrated the imaging correlates of axonal swelling and loss in the corpus callosum of MS patients using high-gradient diffusion MRI, leveraging the high gradient strengths on the Prisma and Connectome scanners for the *in vivo* microscopic assessment of axonal structure.

Our goal is to validate these cross-sectional imaging findings through longitudinal investigation and systematic comparison against histopathology to gain a better understanding of the spatial and temporal evolution of axonal degeneration in MS and the pathogenic factors influencing disease progression. We hypothesize that chronic demyelination leads to axonal swelling and eventual dropout that can be detected as increased axonal size and decreased density by high-gradient diffusion MRI, and that the degree of axonal morphologic change throughout the brain reflects progressive axonal dysfunction and manifests as progressive clinical disability. We will pursue a longitudinal imaging study to determine the relationship between demyelination and progressive axonal structural pathology in MS lesions and NAWM throughout the whole brain. We will evaluate the relative influence of demyelination and axonal damage on the development of progressive physical disability and cognitive dysfunction in MS.The data generated from this study will advance our understanding of the role of axonal damage in the pathogenesis of MS and facilitate the development of clinically usable *in vivo* imaging markers of axonal structural pathology to aid in patient selection and assessment of treatment response in trials of neuroprotective therapies in MS.

NEED FOR PROPOSED INSTRUMENT

The availability of high gradient strengths up to 200 mT/m on a commercially available, whole-body 3T platform will enable reductions in echo times and diffusion times, resulting in SNR gains of up to 1.8x for b-values ~ 2,500 s/mm^2 compared to the current Tim Trio and 1.6x for b-values ~10,000 s/mm^2 compared to the Prisma (assuming a T2 of 60 ms in white matter) (see **Section A, Figure 3**), allowing us to probe axonal microstructure with greater

diffusion sensitivity. The high-performance gradient package upgrade on the 3T Vida platform will enable the translation of high-gradient diffusion MRI measures of axonal damage to a commercially available system, to apply sensitive diffusion MRI measures of axonal pathology to MS patients in a clinically ready system. While the sensitivity of the ultra-high gradient strengths of the Connectome MRI scanner to restricted water pools and fine crossing structures has been beyond the reach of conventional gradient systems due to SNR limitations, we anticipate that the higher G_{max} and slew rate on the next-generation 3T Vida will pave the way for multi-site clinical studies of axonal pathology in MS and offer a translational pathway for the use of such advanced diffusion MRI measures as outcome measures in clinical trials of neuroprotective therapies in MS. Furthermore, the availability of the latest software platform on the next-generation Vida system will enable the measurement of complementary tissue characteristics in addition to axonal pathology in MS patients, including myelin water imaging and susceptibility-weighted imaging – sequences that are not been readily available on the Connectome MRI scanner due to limitations in hardware and outdated software. The advanced capabilities of the 3T Vida taken as a whole promise to bridge the gap between the known scientific advantages of higher gradient strengths for diffusion MRI studies to commercially available, state-of-the-art systems with greater accessibility to measuring a broad set of pathological alterations in white matter and neuroinflammation, thereby augmenting the value of the axonal measurements that are anticipated using high-gradient diffusion MRI.

Major Project 21 Title:	Atypical Formation of Fiber Pathways and Cortical Folding in the Brain
Grant Number:	R01 NS109475
Project Start/End Dates:	07/01/2019–05/31/2024
Principal Investigator:	Emi Takahashi, Ph.D., Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Emerging brain pathways and morphology are linked in typical and atypical brain development, and such changes can be three-dimensionally imaged by MRI with our technique. The development of cortical convolutions, gyri and sulci is a complex process that typically takes place during prenatal development. Despite numerous theories, neurogenic processes that cause the appearance of gyri/sulci and its relationships to underlying fiber pathways remain unknown.

Lissencephaly (LIS), a rare neurological condition characterized by the lack of cortical convolutions, offers an excellent model to examine the biological processes underlying the development of gyri and sulci. On the other hand, agenesis of the corpus callosum (AgCC) is another neurological disorder that is characterized by a partial or complete absence (agenesis) of the corpus callosum which connects the two cerebral hemispheres. These two developmental neurological disorders are exemplary models to study spatiotemporal links between atypical formation of fibers and gyri/sulci, because LIS has obvious gyral malformations but their relationships to underlying fiber pathways are still elusive, while AgCC has obvious abnormal fiber pathways but their relationships to gyral structures are still elusive. Through our recent investigations using diffusion tensor imaging (DTI) tractography (77-79), we have observed that both LIS patients and AgCC patients had significantly smaller gyrification index (GI) compared to age/sex-matched controls. In addition, in patients with LIS, the spatiotemporal distribution of projection pathways was preserved, but short- to medium-length cortico-cortical association pathways were absent or few in number (**Figure 9**), while patients with AgCC had significantly smaller cortical surface area compared to controls. These observations are in line with suggested relationships between fiber pathways and cortical folding/surface morphology. However, more details of fiber/gyral development in these and other developmental disorders are still elusive. In this project, we will utilize DTI tractography to study detailed links of fiber pathways and gyral formation in LIS and AgCC ranging from the newborn to young adult stages.

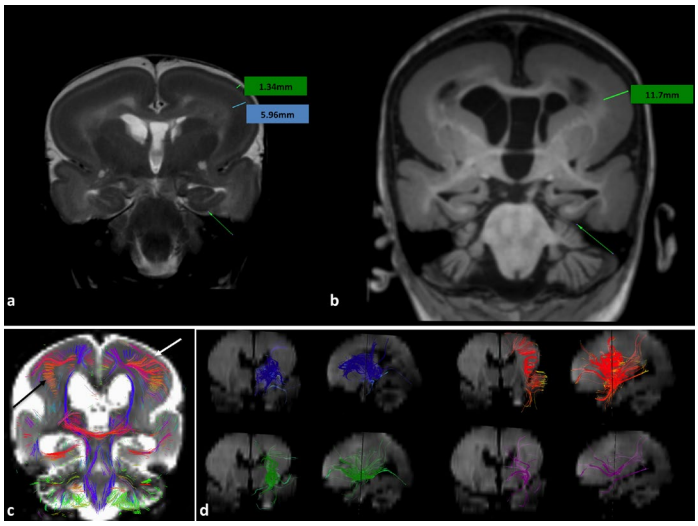

Figure 9. Longitudinal *in vivo* DTI analysis of a patient with lissencephaly revealing altered fiber architecture at two different time points. (a) Newborn and (b) 5 year old brain of the same patient with lissencephaly shows (c) fibers in the upper cortical layers with tangential orientation while (d) fibers in the lower cortical layers have radial orientation. At both time points, short- to medium-length cortico-cortical association pathways were not readily reconstructed.

NEED FOR THE PROPOSED INSTRUMENT

The availability of G_{max}=200 mT/m and slew rate of 200 T/m/s on a commercially available whole-body 3T platform is particularly important for our studies of children and young adults with developmental disorders, for whom comfort and familiarity with a clinical scanner environment are paramount. The enhanced gradient capabilities of the next-generation 3T Vida over the Prisma and current Tim Trio system have encouraged us to migrate our studies from Boston Children's Hospital over to the Martinos Center, which will enable higher sensitivity and high spatial resolution measurements without sacrificing imaging time. The high gradient strengths are particularly beneficial for DTI tractography of developing fiber architectures and will enable reductions in echo times and diffusion times, resulting in more than doubling of SNR for the b-value ranges we will explore. The gain in SNR can then be translated into pushing the spatial resolution of diffusion MRI scans beyond the conventional 2 mm^3 iso. voxel size to minimize partial volume effects with adjacent tissues, which is particularly important in newborn and pediatric brains. The high-performance gradient upgrade will enable the translation of our techniques, which were originally developed to study fiber pathways in postmortem brain specimens on small-bore scanners, to a commercially available system, offering for the first time the opportunity to apply sensitive diffusion MRI measures of developing fiber pathways to LIS and AgCC patients. We anticipate that the higher G_{max} and slew rate on the new Vida will pave the way for multi-site clinical studies of atypical brain development, which rely on cross-site collaborations to amass enough patients and draw robust conclusions in these relatively rare neurological conditions. The new Vida will offer for the first time a translational pathway for the use of higher b-value diffusion tractography to sensitively measure cortico-cortical association pathways in LIS, AgCC and other disorders of white matter development.

We will also take advantage of accelerated MRI acquisition techniques delivered in the latest sequences on the Numaris X software platform such as SMS, compressed sensing and Wave-CAIPI for accelerated anatomical and diffusion imaging, which align with trends in pediatric imaging to decrease scan times and minimize the need for sedation (80). Fast anatomical imaging using Wave- and compressed-sensing T1-MPRAGE sequences in particular will be critical for relating our findings of altered white matter development with abnormalities in gyrification and represents a new opportunity for us to acquire such high-fidelity data in children. The advanced capabilities of the 3T Vida taken as a whole promise to bridge the gap between the known scientific advantages of higher gradient strengths for DTI tractography of the developing human brain to commercially available, state-of-the-art systems with greater accessibility for measuring a broad set of morphological alterations in gray and white matter development.

Major Project 22 Title:	Understanding the Cardiac Benefits of Exercise at the Cellular and Molecular Level
Grant Numbers:	R35 HL155318; R01 AG061034
Project Start/End Dates:	01/01/2021–12/31/2027
Principal Investigator:	Anthony Rosenzweig, M.D., Department of Medicine, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Heart failure is a growing cause of morbidity and mortality. Despite the best available treatments, prognosis remains poor for many HF patients underscoring the unmet clinical need for new heart failure therapies. This Outstanding Investigator Award application is inspired by the observation that exercise protects the heart, promoting cardiomyocyte (CM) survival and proliferation while reducing fibrosis and inflammation. Yet we understand little of the responsible mechanisms and whether they can be exploited therapeutically. Here, I plan to leverage the longer-term support and scientific flexibility afforded by the NHLBI R35 Outstanding Investigator Award to illuminate the cellular and molecular basis of the cardiac benefits of exercise and to validate potential new therapeutic targets in preclinical models. We discovered that although exercise and pathological stress both induce cardiac hypertrophy, the mechanisms underlying exercise-induced hypertrophy are largely distinct and, rather than leading to adverse sequelae, paradoxically protect the heart (*Cell*, 2010). We also found that exercise dramatically enhances endogenous cardiomyogenesis in the adult mammalian heart (*Nature Comm*., 2018). In some cases, mimicking the changes seen in exercise not only prevents but can *reverse* established heart failure (*Science Transl. Med.*, 2019). *Here we propose a broad program to delineate the cellular and molecular effects of exercise, define the mechanistic pathways mediating cardiomyogenesis and other benefits of exercise, and explore the translational potential of these pathways in preclinical models*.

To describe the heart's adaptive response to exercise in cardiomyocytes and non-cardiomyocytes, a range of unbiased discovery tools will be employed, including single nucleus RNA-sequencing toprovide insight into cell lineage-specific changes in gene expression in response to exercise over time. This approach will be combined with lineage-specific gain- and loss-of-function models to help define crosstalk between cell types. The most promising candidates will be studied in preclinical murine and porcine models to uncover new biological pathways and develop new therapeutic approaches. Specific to porcine models, phenotyping with cardiac MRI

will be paramount as we develop models of heart failure and aging in large animals as well as characterize the cardioprotective effects of exercise downstream from aforementioned molecular mechanisms, using cardiac MRI as the gold standard tool to measure cardiac structure, function, fibrosis, and inflammation.

The R35 mechanism uniquely provides the flexibility and timeframe required to support the proposed unbiased discovery and bioinformatic analyses and the generation of unique animal models. Successful completion of this program will advance our understanding of cardiomyogenesis and the beneficial effects of exercise in the heart, while delineating pathways to mitigate heart failure, thus meeting a pressing clinical need.

NEED FOR THE PROPOSED INSTRUMENT:

All current and planned projects depend heavily on cardiac MRI for noninvasive evaluation of myocardial status in porcine models. Most importantly, cardiac MRI is a key clinical end-point that we can use to translate our phenotyping methods to patients and characterize the efficacy of exercise in the heart. The next-generation MAGNETOM 3T Vida features a 60 cm bore, which is ideal for imaging mini-pigs used in the proposed program. The MAGNETOM Vida also features strong 200/200 gradients, thereby combining the magnetic field homogeneity of a 1.5T MAGNETOM Avanto and exceeding the performance of a 3T MAGNETOM Prisma. Furthermore, it will have a 128 channel receive system, allowing us to use the 30-channel body coil that will be delivered with the system and potentially make use of higher channel count arrays, including the Martinos Center's 60-channel body coil and custom-built 64-ch and 128-ch cardiac array coils for eventual translation to heart failure patients (43, 44). The high number of RF channels is particularly useful for measurement of myocardial fibrosis and achieving higher parallel imaging acceleration factors, significantly shortening acquisition time while maintaining adequate SNR. This combination delivers up to 30% increase in SNR, particularly at high PAT-factors. Together, these features are ideal for cardiac MRI to measure cardiac structure, function, fibrosis, and inflammation since they can significantly reduce TR and reduce B0 inhomogeneity to improve the performance of bSSFP sequences. Other new cardiac MRI technologies used in this proposal include quantitative T1 and T2 mapping and cardiac diffusion MRI, which will benefit from the strong gradients for shorter TE, thereby improving SNR and reducing motion-induced signal loss.

Major Project 23 Title:	Near Real-Time System for High-Resolution Computational TMS Navigation
Grant Number:	R01 MH128421
Project Start/End Dates:	02/01/2022–11/30/2026
Principal Investigator:	Aapo Nummenmaa, Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

The overall goal of this project is to develop a computational system for fast high-resolution modeling of Transcranial Magnetic Stimulation (TMS). TMS is currently approved by the FDA for treatment of major depressive disorder (MDD), obsessive-compulsive disorder (OCD), short-term smoking cessation as well as pre-surgical mapping of eloquent cortex. It is well known that the intracranial electric field (E-field) is the key physical quantity that determines which cortical regions are stimulated. Therefore, computational modeling of the TMS-induced E-fields offer proof of target engagement and may be used to improve targeting and dosing of the stimulation and to improve therapeutic efficacy. The main critical barrier is that none of the currently available computational methods allow both fast and accurate fully individualized modeling of the TMS "hot spots" for interactive neuronavigation. Here, we propose to employ our recently developed high-performance computational approach based on a Boundary Element Model (BEM) accelerated with fast multipole method (FMM) as the backbone (81). To remove the high computational barrier, we propose to utilize the BEM-FMM to pre-compute a fundamental dipole basis set solution that can approximate the E-fields at temporal rates of ~100 ms. The fundamental dipole basis set solution provides a full characterization of the TMS-induced E-fields for ANY coil type and is hence called the 'Magnetic Stimulation Profile' (MSP) of the subject (82).

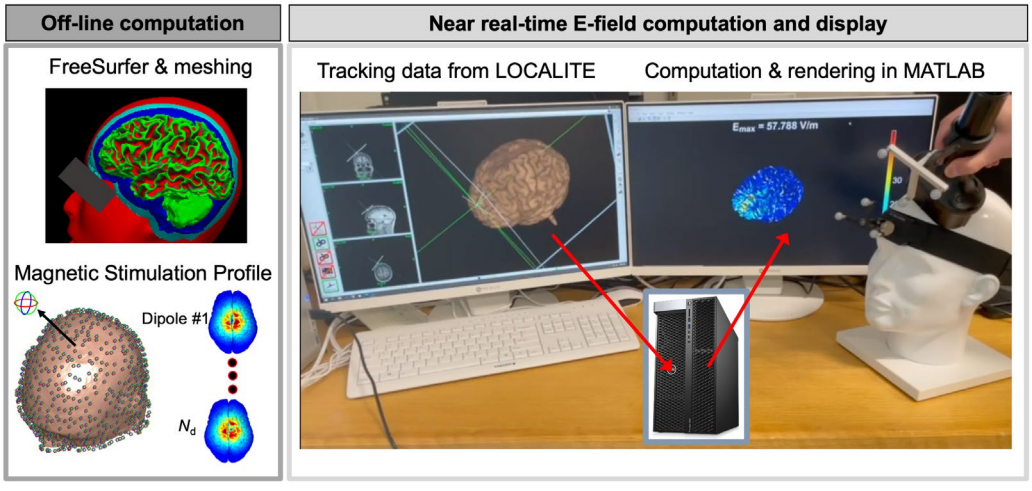

Figure 10: **Computational pipeline for the proposed near real-time E-field engine.**

Specifically, we first develop a fully automatic pipeline for creating geometrically and topologically accurate head models from individual MRIs and to optimize the BEM-FMM solver for maximal computational efficiency to calculate the MSPs 'offline'. We will subsequently interface the MSP-based fast computation approach with both MATLAB-based in-house built neuronavigation system as well as with a commercially available navigator (LOCALITE TMS, Bonn, Germany) to enable interactive and quantitative TMS targeting/dosing. The system will be initially validated using anthropomorphic phantoms with embedded E-field probes. Subsequently, the system will be validated in healthy humans with functional MRI as a reference and finally in neurosurgical patients with intraoperative direct cortical stimulation (DCS) as a gold standard. The system will be commercialized through licensing agreements with neuronavigation system vendors (*e.g.*, LOCALITE, BrainSight) as well as disseminated free of charge for academic users as a stand-alone MATLAB package that can be interfaced with any tracking system as shown in **Figure 10.** Our specific aims to develop a fully general near-real time TMS E-field modeling engine are as follows. Aim 1: Develop a pre-processing pipeline for high-resolution TMS modeling. We will develop and validate a geometrically and topologically rigorous pipeline for creating high-resolution BEM head models from MRI data, using CT as ground truth for skull. The pipeline will be tested using MRIs from 3T MRI scanners with stock sequences and total acquisition time of less than 15 minutes. Aim 2: Develop BEM-FMM for high-resolution computational TMS neuronavigation. Aim 3: Experimental verification of the developed neuronavigator. We will evaluate the developed system in healthy human volunteers using TMS and fMRI motor mapping.

NEED FOR THE PROPOSED INSTRUMENT:

The first critical step towards precise E-field modeling is to create an accurate head model (boundary surfaces of the tissue compartments between skin/scalp, skull, CSF, gray, and white matter) from individual-level MRIs. Since the accuracy of these surfaces is critically important for the precision of E-field estimates, we will develop and validate a fully automated pipeline to generate geometrically and topologically accurate surfaces, suitable for both academic and commercial applications. For best possible data especially for the dura segmentation, the project will benefit from the high G_{max}=200 mT/m of the new Vida that enables maximizing spatial resolution and readout bandwidth to minimize the chemical shift from lipids in the tissue that can hamper the segmentation while maintaining sufficient SNR. Both the subcutaneous fat of skin as well as the lipids in the spongy bone and in the dura mater can confound the segmentation and therefore result in less accurate modeling performance. Moreover, for the planned evaluation of the TMS mapping for pre-surgical localization of motor cortex, we expect that the stronger diffusion-encoding gradients will allow us to map the microstructure of the tumors/lesions for better delineation of the abnormal tissue that will be incorporated in the E-field model with electrical conductivities estimated *in vivo*. The capability of performing all of these MRI acquisitions on a standard FDA-approved clinical next-generation 3T Vida scanner will significantly boost the impact of the project and facilitate deploying the method to other sites in the future.

Major Project 24 Title:	Motion and Distortion Robust Diffusion Weighted Imaging Sequences for Pediatric Patients
Grant Number:	R01 NS121657
Project Start/End Dates:	01/01/2022-12/31/2026
Principal Investigator:	Onur Afacan, Ph.D., Department of Radiology, Boston Children's Hospital/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

The goal of this project is to improve the quality of diffusion-weighted magnetic resonance imaging (DW-MRI) in pediatric patients. DW-MRI has become an important tool in surgical planning for refractory epilepsy, especially with respect to predicting postoperative neurological outcome. DW-MRI not only localizes critical cortical areas governing essential brain functions, but also depicts the underlying fibers connecting these areas. However, current DW-MRI has certain limitations. Diffusion-weighted images are distorted compared to those derived from anatomical MR. Thus, the use of DW-MRI during surgery ideally requires correction for brain shift using intraoperative MRI. Furthermore, the acquisition of highly reliable DW-MR images in infants and very young children in particular is extremely challenging because they are unable to remain still in the scanner. It has been shown that even small differences in the amount of head motion are enough to yield artificial fiber connections in the brain. Although there have been attempts, both prospectively and retrospectively, to make DW-MR imaging more robust to motion and geometric distortions, our ability to generate high quality images in the presence of large, frequent, and uncontrolled motion remains elusive.

Currently the DW-MRI acquisition in this population relies on 1) oversampling the diffusion space; 2) detecting and removing motion-corrupted slices; and 3) using slice-to-volume registration techniques to create motion-free diffusion volumes. However, when the motion is frequent and large, these methods fail because 1) different head positions result in different geometric distortions generating misalignment due to non-rigid deformation between

different volumes, and; 2) motion that occurs during a slice acquisition affects successive acquisitions due to irreversible spin history artifacts arising from other tissues being excited than the one initially targeted. In this project we propose to overcome these challenges by developing a novel sequence that prospectively corrects for position changes due to motion during acquisition in real-time while also correcting for geometric distortions. We will also develop software that will enable real-time correction of these artifacts during acquisition and thereby, will reduce the number of patients who need a repeat MRI scan. To this end, we propose the following specific aims. Aim 1 will develop, optimize and evaluate a dual echo sequence for slice-level geometric distortion correction. Aim 2 will develop and evaluate a novel prospective motion correction technique that estimates and corrects geometric distortions at each position. Aim 3 will develop and evaluate tools for on-scanner motion and distortion correction, reacquisition and diffusion parameter estimation. Aim 4 will apply and evaluate motion and distortion compensation techniques in DW-MRI of pediatric candidates for epilepsy surgery.

NEED FOR PROPOSED INSTRUMENT

The next-generation 3T Vida will advance our efforts to develop a novel, dual echo EPI sequence with reversed phase encoding that can be used to generate slice-level, distortion-free images that allow for more accurate retrospective motion correction, effectively eliminating the effects of distortion. We will take advantage of the Open Recon platform available on the new 3T Vida to implement online scanner image reconstructions that enable SMS, dual polarity GRAPPA and improved distortion correction from dual-echo images by contrast matching and masking. The strong G_{max}=200 mT/m will provide a boost in SNR for our DW-MRI experiments over current state-of-the-art commercial 3T systems with Gmax ~ 80 mT/m by enabling more efficient diffusion encoding and shorter echo times. The SNR gain achieved with the latest gradient technology and high channel-count RF coils, e.g., the 64-channel head/neck coil, available on the Vida 3T can be flexibly traded-off for spatial resolution, which is a key clinical need especially in pediatric patients undergoing epilepsy surgery and will pave the way for clinical translation of motion-robust DW-MRI protocols using such state-of-the-art systems. Upon successful completion of the aims, we will be equipped with motion-robust diffusion MRI acquisitions, whose SNR benefit will combine multiplicatively with the Vida's signal boost to enable better delineation of key white matter tracts in pediatric epilepsy patients.

Major Project 25 Title:	Non-invasive Microstructural Assessment of Neuroinflammation in Chronic Pain
Grant Numbers:	DOD CDMRP CP210203; R01 DA053316
Project Start/End Dates:	04/01/2022-03/31/2025; 06/01/2021-03/31/2026
Principal Investigator:	Marco Loggia, Ph.D., Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Substantial animal research has demonstrated that neuroinflammation (NI) mediated by the activation of glial cells plays a key role in the establishment and maintenance of persistent pain. Nonetheless, our ability to "visualize" NI in living patients is currently limited. Diffusion MRI (dMRI) can provide a highly innovative, non-invasive framework to characterize pain-related NI in vivo. We have contributed to the development a novel, reproducible dMRI-based multi-compartment microstructural model (MCM) for selectively imaging glial activation, which was validated in an experimental rat model of gray matter inflammation induced by intracerebral lipopolysaccharide administration (83). In addition, dMRI is also sensitive to demyelination and axonal loss, and can therefore provide insights into the neurobiological underpinnings of NI.

Our overall goal is to develop noninvasive, mechanistic markers for NI using advanced dMRI and apply these markers to study of the pathophysiological mechanisms of chronic pain and its treatment with alternative therapies such as cannabidiol. We hypothesize that dMRI-derived NI markers will resolve NI-related histopathological mechanisms and distinguish patients who are most likely to benefit from cannabidiol therapy. Through this multimodal research program funded by the DOD and NIH, we will use advanced dMRI and PET markers of NI to stratify patients most likely to benefit from therapeutic intervention. Aim 1 will assess our MCM-based markers of pain-related NI as an objective indicator of pain. Aim 2 will asssess our MCM-based markers as predictors of long-term (6-months) pain response to cannabidiol. We hypothesize that higher pre-treatment MCM markers of neuroinflammation in the thalamus, middle/anterior cingulate and medial prefrontal cortices predict lower pain relief in response to cannabidiol. Aim 3 will develop a multimodal predictor of persistent pain. Because pain is a multidimensional experience, we hypothesize that a composite index, including features from both imaging and behavioral/psychological assessments (quantitative sensory testing, pain catastrophizing, etc.), will yield a higher predictive power than one based on imaging measures alone.

NEED FOR PROPOSED INSTRUMENT

The next-generation 3T Vida equipped with high-performance gradients (G_{max}=200 mT/m/slew rate=200 T/m/s) will enable us to develop, optimize and refine our MCM model to detect with high sensitivity the microscopic

signatures of glial activation noninvasively in chronic pain patients. We will utilize the strong gradients to obtain high spatial resolution, high b-value imaging in the whole brain gray matter of study participants across a wider range of diffusion times than is currently accessible on the other clinical 3T research scanners at the Martinos Center. The advent of high G_{max} on a commercially available whole-body 3T scanner is potentially transformative for our research program, as it will greatly facilitate multi-site studies of neuroinflammation and glial activation in the gray matter of individuals suffering from chronic pain, and offer a noninvasive marker of neuroinflammation that will complement our prior studies, which largely focused on PET-MRI as the modality of choice. Moving away from PET-MRI is advantageous given the limited availability of this technology along with the requisite custom radiotracers, not to mention the adverse effects of excess radiation dose in otherwise healthy individuals. We will take advantage of the Turbo Suite Excelerate options on the new Vida to accelerate our high-resolution structural and functional MRI sequences in these individuals, taking advantage of the compressed sensing and Wave-CAIPI options for 3D imaging, SMS for dMRI and fMRI, and deep learning reconstruction to improve image quality of anatomical imaging. In summary, the next-generation Vida will support our newly funded research program noninvasive microstructural imaging of glial activation to advance an understanding of the pathophysiology and treatment options for chronic pain.

Major Project 26 Title:	Cardiac MR-based Risk Stratification for Heart Failure and Atrial Fibrillation
Grant Number:	R01 HL158098; R01 HL158077; R01 HL129185; R01 HL154744
Project Start/End Dates:	04/15/2021-03/31/2025; 09/01/2021-08/30/2026; 09/01/2021-08/30/2025; 07/01/2020-06/30/2024
Principal Investigator:	Reza Nezafat, Ph.D. Department of Medicine, Beth Israel Deaconess/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Rigorous research over the past two decades has enabled us to identify patients with hypertrophic cardiomyopathy (HCM) and heart failure (HF) at the greatest risk of sudden cardiac death (SCD) who could benefit from a prophylactic implantable cardioverter defibrillator (ICD). With advances in SCD prevention, the management of HF and HCM has now shifted its focus preventing adverse cardiac remodeling leading to atrial fibrillation (AF). AF is the most common sustained arrhythmia, occurring in nearly 25% of HCM and HF patients, and responsible for a decreased quality of life and increased stroke risk. Currently, we are not able to predict which patients are more likely to progress toward end-stage HF or develop AF. Cardiac MR has played a central role in our evolving understanding of HF and AF. With its high spatial resolution and remarkable tissue characterization capabilities, cardiac MR has emerged as an imaging modality well suited to characterize the HF phenotype at both a macroscopic and microscopic level. Cardiac diffusion tensor magnetic resonance imaging (DT-MRI) is a non-invasive imaging technique capable of characterizing myocardial structure at the micro-tissue level by mapping cardiomyocyte architecture. Cardiac DT-MRI directly yields insight into subtle changes in myocardial structural remodeling. Despite advances in motion robustness, this novel technology has not yet been translated for routine clinical use and requires reduction of acquisition complexity and scan time.

The goal of this research program is to develop novel risk stratification paradigms by leveraging recent advances in cardiac MRI and artificial intelligence (AI) to improve HF and AF management. We will investigate a deep learning (DL) risk model for prediction of adverse cardiovascular outcomes that incorporates (a) standard clinical and imaging parameters and (b) novel cardiac MR signatures that may serve as early *non-invasive* prognostic marker of structural remodeling. We will perform serial cardiac DT-MRI measurements in HCM and HF patients and volunteers to monitor for evidence of myocardial structural remodeling in individuals stratified by degree of relative myocardial hypertrophy. We will leverage a recently developed free-breathing second-order motion compensated *in vivo* cardiac DT-MRI acquisition at the Martinos Center (42). With our deep learning residual noise reduction method (DLD), we can reduce scan time by 4x fold bringing down 32-minute conventional DT-MRI scan to 8 minutes. SMS is being implemented into the sequence and will result in a further reduction in scan time to below 5 minutes.

NEED FOR THE PROPOSED INSTRUMENT

Our current cardiac DT-MRI experiments employ diffusion-encoding gradients with the up to 80 mT/m maximum gradient amplitude available on commercially available whole-body scanners and durations on the order of 5-10 ms. During this time, even subtle cardiac bulk motion can significantly corrupt diffusion-weighted measurements unless steps are taken to mitigate bulk motion artifacts. Recent work has shown that motion compensated diffusion gradient waveforms with nulled first (M1) and second (M2) moments that are unaffected by bulk linear velocities and accelerations can encode diffusion in the presence of cardiac motion (84, 85). This project proposes to use third-order motion compensated diffusion encoding (M3), which necessarily increases the total diffusion encoding duration as compared to monopolar waveforms. Consequently, conferring bulk motion

insensitivity requires longer echo times and reduces SNR using the currently accessible gradient strengths on the Prisma. This is further exacerbated in the high-resolution imaging that we seek to perform using long EPI readout intervals, which introduces lengthy dead times within the sequence before the refocusing pulse and has traditionally limit cardiac diffusion imaging to ~2.5 mm in-plane resolution, which is insufficient for evaluation of myocardial infarcts per cardiac MRI guidelines (86). The newest generation 3T Vida scanner with its higher G_{max} = 200 mT/m will provide higher SNR and improved motion compensation for cardiac DT-MRI, which will translate into acquiring images at higher spatial resolution. We will also leverage the stronger gradients to apply stronger diffusion-weighting and increase our resolution of diffusive motion in cardiac myocardium, thereby enabling us to probe features of cardiac tissue microstructure at the micron level, e.g., myocardial cell size, shape and fiber orientation, as well as extracellular diffusivity, which can be significantly altered in the presence of fibrosis.

Our long-term goal is to develop *in vivo* cardiac DT-MRI markers of myocardial microstructure in an ECG-free exam in which the patient can simply lay down on the scanner without any intervention by staff and be scanned. Beyond the improved gradient capabilities of the new Vida scanner, the high-end image reconstruction system and Open Recon platform that will be delivered with the proposed instrument will be critical for real-time image reconstruction using our accelerated deep-learning based methods. Furthermore, the Vida's advanced physiological monitoring system will be used for better respiratory and cardiac monitoring and correction, especially for our proposed ECG-free, motion-resolved exams. We anticipate with the new Vida system, we can leverage the BioMatrix system to further improve image quality while reducing scan times by decreasing the amount of rejected data and following the patient's specific physiological rhythms. Our future goal is to expand this research to achieve a comprehensive and systematic understanding of the heart beyond the left ventricle and to investigate smaller chamber structures such as the left atrium, which is affected by adverse remodeling in atrial fibrillation. The Vida system will be an ideal platform to develop and propel cardiac DT-MRI into this exciting and technically demanding new area of research.

Minor Project 1 Title:	Deep Learning Reconstruction for Rapid Multi-Component Relaxometry
Grant Number:	R21 EB031185
Project Start/End Dates:	04/01/2022–12/31/2024
Principal Investigator:	Fang Liu, Ph.D., Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

Relaxometry is the most used MRI technique for quantifying tissue properties by measuring the relaxation process of water protons. Multi-component relaxometry measures the relaxation characteristics of multiple water components in human tissues; thus, it can provide useful MR biomarkers to help evaluate tissue composition and microstructure. Different studies have shown various preclinical applications in which multi-component relaxation mapping is applied for assessing diseases such as osteoarthritis and demyelination. However, due to the need to fit a complicated noise-sensitive signal model, multi-component relaxometry typically requires a substantially prolonged scan to acquire many repeated images at different imaging contrasts and with sufficient SNR, limiting its widespread clinical use. While many rapid imaging techniques and reconstruction methods can increase scanning efficiency, they are faced with serious limitations, including estimation bias, image blurring, and insufficient volumetric coverage. The overall goal of this proposal is to develop a novel deep learning-based image reconstruction methods to achieve efficient, robust, and accurate multi-component relaxation mapping at a rapid clinical feasible acquisition for large imaging volume coverage.

In this project, we aim to address the technical challenges of building a deep learning framework that can accurately characterize relaxation-related image features at high acceleration rates. Aim 1 will develop, optimize, and evaluate a new deep learning framework that will enable multi-component relaxation mapping of tissue. This will be built on a deep learning framework called Model-Augmented Neural neTwork with Incoherence Sampling (MANTIS) (87), which has been developed by our team for rapid and accurate single-component relaxometry at high acceleration rates. Aim 2 will explore a new data augmentation approach by using synthetic image datasets to train deep learning models. This will be built on a multi-component Bloch-simulation system that has been pioneered by our group. While this proposal primarily focuses on T2 mapping of the knee, the proposed deep learning framework will be highly generalizable and can be easily adapted for other relaxation parameters, such as T1 and T1ρ with synthetic data training.

NEED FOR THE PROPOSED INSTRUMENT

The next-generation 3T Vida scanner will be vital for advancing our research goals by enabling faster and more robust sampling of multi-component relaxometry MRI data on the latest commercially-available whole-body platform. A major challenge in applying deep learning to MR relaxometry is the large image dimension size. MR relaxometry datasets are usually comprised of many dynamic frames, which demand higher-performance

computing hardware with more GPU memory and longer training times compared with applications using static images. The high-end image reconstruction computer that will be delivered with the new Vida with the latest GPU's will greatly facilitate the development and testing of our methods for rapid relaxometry in the knee. We will also take advantage of the Open Recon interface to implement and evaluate our new deep learning algorithms on the scanner, making use of the container technology to apply our custom reconstruction methods to raw data streamed directly from the scanner console. Finally, we will make use of the Flex coils delivered with the new Vida for high-sensitive T2-mapping of the cartilage and other structures in the knee. Developing our algorithms using the latest hardware and software available on the next-generation Vida will facilitate the dissemination of our techniques to other research and clinical sites that seek to utilize rapid multi-component relaxometry for tissue evaluation in the knee and other organs.

Minor Project 2 Title:	Advancing Methods for Mapping Short-Range Association Fibers in the Aging Brain
Grant Number:	K99 AG073506
Project Start/End Dates:	09/05/2021–08/31/2023
Principal Investigator:	Qiyuan Tian, Ph.D., Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

White matter (WM) demyelination and degeneration are increasingly recognized as important indicators of early pathology in Alzheimer's disease (AD), presenting years before the onset of clinical dementia. WM tissue properties and networks are substantially altered in preclinical AD (88, 89) and variably disrupted in sub-types of mild cognitive impairment (MCI) (90, 91). Long-range fiber tracts connecting distant brain regions in deep WM have been the dominant focus of existing studies in AD, while short-range association fibers (SAFs) connecting adjacent cortical regions are rarely investigated and their alterations with aging remain largely unknown, despite their abundance (90% of all WM connections), vulnerability to neurodegeneration, and importance in mediating cortico-cortical connectivity. Diffusion magnetic resonance imaging (dMRI) is unsurpassed in its ability to infer WM tissue properties at the micron level and, coupled with tractography, is the only method capable of noninvasively mapping WM fibers throughout the whole human brain. Unfortunately, at the spatial resolution that dMRI data are typically acquired in clinical and research studies of AD (2 to 3 mm isotropic), SAFs in the thin layer of superficial WM (~1.5 mm) are virtually missing, resulting in underestimation of short-range cortico-cortical connections and inaccurate structural connectome mapping. To map SAFs accurately, both high spatial resolution (1 mm isotropic or higher) (**Figure 11**) and high diffusion-encoding sensitivity (>2000 s/mm^2) are needed to reduce partial volume effects, incurring lengthy scans.

The goal of this K99/R00 grant is ***to advance dMRI tractography and microstructural imaging at sub-millimeter isotropic resolution for accurately mapping SAFs and the structural connectome in the aging brain***, and ***to determine when, where and how aberrant properties and connections of SAFs occur during aging and how they relate to cognitive and molecular biomarkers in AD***. This proposal builds on our expertise in developing and integrating cutting-edge hardware systems, acquisition strategies and diffusion tractography for mapping the human connectome (1, 92-95).

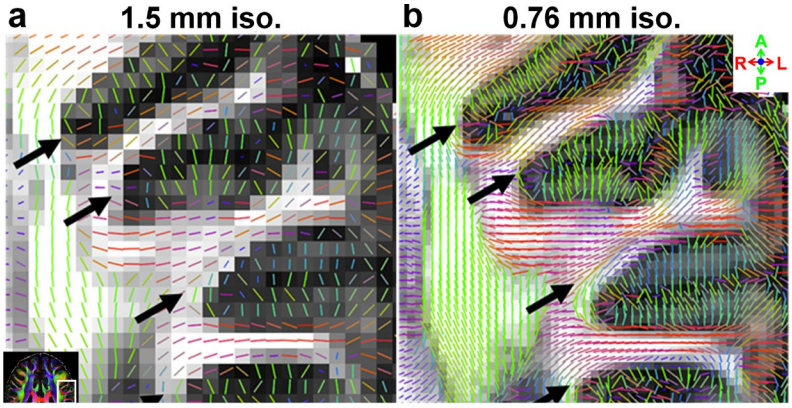

Figure 11. Fiber orientations estimated using diffusion tensor imaging at different resolutions. Sub-mm resolution shows clear advantages in delineating SAFs (arrows). Low-res. data were down-sampled from high-res data.

Aim 1: Determine fundamental trade-offs of dMRI for mapping SAFs; **Aim 2:** Characterize SAF degeneration and its role in aging and AD; **Aim 3:** Investigate the role of SAFs in the spread of tau tangles in AD.

NEED FOR THE PROPOSED INSTRUMENT

We will utilize the high-performance gradients on the next-generation 3T Vida to push the limits of spatial resolution and diffusion-weighting for comprehensive mapping of the superficial white matter of aging and Alzheimer's disease patients. We are currently performing retrospective analysis of dMRI data in the aging human brain acquired high spatial resolution (1.5 mm^3 iso) with b=1,000 s/mm^2 and 3,000 s/mm^2 as part of the Human Connectome Project-Aging study. Using the stronger gradients on the new Vida, we anticipate being able to push the spatial resolution of dMRI to sub-millimeter voxel size ~600-800 um using the gSlider-BUDA

technique being developed by ***Major User Project 9, led by Drs. Bilgic & Stockmann*** and will compare the benefits of these higher SNR acquisitions to those acquired as part of the HCP-A study as a first step toward characterizing the impact of spatial resolution on SAF mapping. The higher spatial resolution will be crucial for ensuring the recovery of accurate microstructural measures in the cortex, which naturally thins in aging and may be quite atrophic in certain cortical regions in AD. The systematic optimization of high spatial resolution, high b-value dMRI protocols on the next-generation 3T Vida will facilitate my transition to independence in the R00 phase of this award, as the new Vida is expected to be adopted as the next-generation commercially available 3T imaging platform that many research and clinical sites will use for multi-center imaging studies of aging and Alzheimer's disease.

Minor Project 3 Title:	Sequence-Universal High-Frequency Prospective MRI Motion Correction with Navigators
Grant Number:	R21 EB029641
Project Start/End Dates:	02/1/2021–11/30/2023
Principal Investigator:	Stephen Robert Frost, Ph.D., Department of Radiology, MGH/HMS

PROJECT DESCRIPTION AND RESEARCH OBJECTIVES

There is an urgent need to address the problem of artifacts caused by motion during MRI acquisitions. The diagnostic value of the soft tissue contrasts accessible with MRI is drastically reduced when a patient moves by even 3 mm during scans that can last for several minutes. The ideal motion tracking and correction system would require no external devices, operate at high temporal frequency to enable tracking of rapid motion, leave the contrast of the MRI sequence unchanged, and function properly in a broad array of MRI acquisition types. Unfortunately, state-of-the-art motion correction requires an external device, so the impact of high-quality motion correction is limited. Here, we pursue an array of innovative technical solutions for MR navigators that will result in a flexible high-frequency prospective motion correction that radically reduces MRI motion artifacts.

In order to achieve this, we will use "cloverleaf" navigators, which have been shown to provide high-frequency motion information but unfortunately only in a limited set of "3D steady-state" sequences. To solve this problem, we will develop fat-cloverleaf navigators, adapting short lipid insensitive binomial off resonant excitation (LIBRE) pulses to selectively excite signal from subcutaneous fat so that motion can be measured in non-steady-state and multi-slice sequences without affecting the water signal of interest. Furthermore, advances in motion tracking with array-coil information, by modelling coil-specific signal changes to predict head motion, will also be used. Several approaches for navigator-based prospective motion correction have been developed, but there is no sequence-universal solution (with high-frequency, low-latency) to rival external camera prospective motion correction. Prospective solutions are essential because they avoid k-space under-sampling and multislice spin history artifacts, and they enable real-time decisions on data reacquisition.

This project will enable the universal clinical use of high-frequency fat-CLN prospective motion correction with several innovative ideas that will provide high-quality motion information in non-steady state sequences such as 2D multi-slice sequences such as Fast Spin-Echo (FSE) T2, which are widely-used clinically and in research. These are representative exemplars; our techniques can be applied to steady-state, non-steady-state and multi-slice acquisitions. During development, an external camera will be used to evaluate motion measurement and prospective motion correction performance. The four prospective motion correction sequences will be validated in clinical brain and body MRI using existing methodology.

NEED FOR THE PROPOSED INSTRUMENT

The next-generation 3T Vida scanner equipped with high performance gradients will be vital for advancing our goals by enabling faster and more robust sampling of navigator data for prospective motion-corrected MRI. The strong G_{max}=200 mT/m and slew rates up to 200 T/m/s on the next-generation scanner will facilitate the acquisition of shorter cloverleaf navigators, which will greatly increase the applicability and accuracy of our prospective motion correction strategies. Furthermore, the new Vida will provide much-needed software updates to facilitate our sequence development efforts, as the current software version on the Martinos Center Prisma and Skyra scanners has reached the end of its support by Siemens. The new scanner will enable us to migrate our development efforts to the Numaris X platform and provide us with a way to future-proof our development efforts for the latest generation of 3T scanners incorporating the latest advanced reconstruction methods. The Open Recon interface and GPU capabilities that will be delivered with the high-end reconstruction computer will also greatly accelerate the reconstruction of retrospectively motion-corrected data acquired using our techniques, thereby offering an efficient way for us and pilot users to view the results online and provide immediate feedback on the efficacy of our cloverleaf navigators. The Siemens 64-channel head-neck array delivered with this system will also enable us to increase the SNR of our navigators, which will improve our ability to accurately measure head motion.