Project Description. This is a revised application for the development of a shared 9.4T human MR system to be sited at the Nathan Kline Institute for Psychiatric Research (NKI). Since the last submission in 2019 we have made the following progress:

1. NKI purchased the 9.4T magnet for the project from the University of Minnesota. The magnet is in temporary storage at J. Supor & Son Trucking & Rigging Co., Inc, in Kearny, NJ. See Figure 1.
2. Magnet integrity was independently certified by Tesla Engineering's magnet division.
3. An architectural design company was contracted (Jack L. Gordon Architects). A draft plan for the magnet site and dedicated laboratory has been completed. New York State is supporting the estimated $5m budget for this custom 9.4T lab.
4. GE Global Research has entered partnership with NKI to co-develop this 9.4T system and to train new engineers. Tom Foo (Chief Scientist in the Biology and Applied Physics group at GE Research Labs) is now a co-PI. GE has received funding to develop a head-only 7T MR system NIH-U01EB026976. We will benefit from that project with a newly developed console and gradients that will be extended to our 9.4T system.
5. 15 current and additional planned NSF projects will directly benefit from the scanner. PIs for these projects have provided letters of support.
6. NKI and Columbia University have signed a resource sharing agreement and plan for this 9.4T system development, use and education project.
7. In addition to his Columbia faculty appointment, contact PI J. T. Vaughan now has a paid NKI appointment as Director of the Ultra High Field MR program.
8. The proposed educational training component has been markedly enhanced, with commitments from 10 local institutions to incorporate the project into their training programs. This essential component is also represented in the Strategic Advisory Committee.
9. Fifty investigators from the Greater New York, Tri-State area have expressed in writing their interest to be major or minor users of this shared instrument, uncovering significant, pent-up demand.

Fig. 1: 9.4T, 65cm bore magnet received at local warehouse. Alexandre Franco (L) and Thomas Vaughan (R) provide scale.

In brief, these efforts have dramatically increased project feasibility and readiness, with the prospect of providing a $12M resource for NSF research in the NY tristate area at the cost to NSF of only $4M.

A. Information about the Proposal.

A.1 Instrument Location and Type. Instrument Location: The Center for Brain Imaging and Neuro-modulation (C-BIN) at NKI, Orangeburg, NY. This location gives shared access to hundreds of scientists from the Greater NY - Tri State area. New Instrument Description: The proposed second generation 9.4T MR instrument is being developed with new head gradient and multi-band radiofrequency (RF) spectrometer technologies. This head-only system will be capable of both *in vivo* and *ex vivo* imaging of humans, non-human primates (NHP) and rodents with unprecedented spatial, temporal and spectral resolution. This combination of magnet field strength and gradient performance will give us the highest resolution in structural, functional, and metabolic imaging achievable to date.

A.2. Justification for Submission as a Development Proposal. Shared-use research instrument. The 9.4T MR instrument will be available for shared use by investigators from NKI, Columbia and New York University and 7 other major research universities in the Tri-State area. New instrument capabilities. This will be the first 9.4T human head-only MR system equipped with a gradient set capable of simultaneously achieving field strength and slew rates of 140 mT/m and 810 T/m/s, respectively. With this system, we will acquire *in vivo* images and spectra from humans, NHPs, and smaller laboratory animals to facilitate comparative and translational studies on a single scanner. Targeted specifications include: 1) in-plane spatial resolution for brain structural imaging of 50 microns, 2) maximal temporal resolution of functional MR imaging (fMRI) measured connectivity events of less than 100ms, 3) maximal spatial resolution of fMRI of 100s of microns, and 4) high resolution spectroscopic measurement of metabolites and neurotransmitters in human brain comparable to values heretofore achievable only in small rodent models in high resolution systems of the same or higher field strengths. Instrument development activities. The proposed instrument will leverage the local talents and resources of the three lead institutions (NKI, Columbia and NYU) and others, to create a 9.4T-based UHF MR Laboratory at NKI. The director of this laboratory will be Dr. J. Thomas Vaughan, a world-leading expert in UHF Magnetic Resonance (UHF-MR), at NKI with a state-funded 0.25 FTE line (in addition to his positions at Columbia). As Engineering Director and PI in previous centers, Dr. Vaughan and his teams have designed, built, and consulted on the building of numerous other UHF systems, including 9.4T and 10.5T human systems, with a range of ongoing UHF collaborations. The proposed system will utilize the same 9.4T, 65cm bore magnet that Dr. Vaughan used to build the first 9.4T

system [1]. Automated multi-channel RF shimming was invented and first used on that system to achieve the first homogeneous 9.4T human brain images; however, the prototype Magnex head gradients coupled with the magnet bore generated problematic eddy currents for EPI sequences that compromised fMRI data acquisition. Combining lessons learned from this first generation effort with known (measured) performance benchmarks, the proposed instrument herein will resolve issues such as bore-gradient eddies and enhance performance with faster, stronger commercial gradients and a custom multi-channel, multi-band, multi-nuclear RF spectrometer and coil set to create a high performance, second generation, 9.4T neuroimager. In-house instrument development: We propose to create a unique MR system that is not commercially available. It will be designed and developed by Dr. Vaughan's team at Columbia together with a team of GE engineers led by co-PI Dr. Thomas Foo (Chief Scientist, GE Research Labs Biology and Applied Physics group) and collaborator Dr. Doug Kelley (GE Global 7T Product Manager). To maximize the time and cost efficiency of this project we will incorporate proven components and subsystems when they are available. For example, the certified existing 9.4T magnet dramatically reduces costs and avoids delays. The gradient system we will use was first developed for GE's head-only 3T research system (ESP) at the Mayo Clinic[2]. This gradient set is being improved and strengthened for use in GE's new 7T system. We will adapt and modify the GE Signa 7T console and gradient subsystems for our 9.4T development (see GE Healthcare quote for 7T console). The RF front end to be built in-house will be interfaced to the GE console with 300 to 400 MHz frequency conversion. The RF front end will also interface a custom 8 channel, class AB broadband linear power amplifier by Communication Power Corporation (CPC) with the GE console (see CPC quote). This custom transmit and receive front end will in turn interface to multi-channel RF coil assemblies. While a modest budget will support the first coils built for human head, NHP, and small animal studies, experiment-dedicated coil development will be a continuing activity for this system and the experiments it supports. Experiment-specific coil development will be typically supported by funded projects. Requirements from the development team: This technology, software, and methods development project requires and benefits from a team of scientists, engineers, and technicians capable of covering many topics. Systems-level engineering and applications experience is required for overall system conception, specification, design, and development oversight. Drs. JT Vaughan, Christoph Juchem and Ray Lee from Columbia, and Tom Foo and Doug Kelley of GE fit this role. The in-house design, development, and building of the RF/analog spectrometer consisting of RF transmitters, RF receivers and RF coils are a specialty of JT Vaughan and will also involve his post-docs and students, with additional support from Dan Sodickson and his team at NYU. Dan Myer of CPC will produce the power amplifier according to JT Vaughan's specifications and design. While GE will supply the gradients, C Juchem and his team working with D Kelley and GE will troubleshoot and solve any gradient and shim coil issues, a critical part of this effort. Dr. Sairam Geethanath, MR imaging physicist, data acquisitions and processing programmer, will work with the applications scientists to make full use of this 9.4T system. We will hire a system service engineer to maintain the system by monitoring and performing cryogen fills, running routine QA, troubleshooting and repair, system operation and training for investigators in need of these services, and for general experiment support. Co-PIs Michael Milham (CBIN Director at NKI) and Alexandre Franco (Director of Computational Neuroimaging Laboratories at NKI) and Colcombe (Director of Design, Acquisition & Neuromodulation Laboratories at NKI) will provide administrative support and coordination with the larger imaging center at NKI, as well as informatics and analytic support. Significant time-consuming development activities. Significant time will be required to conceive, design, develop, integrate, implement, and apply this system. Much of the time will go to implement, test and evaluate, and iterative design correction and optimization of the head gradients for this system. Similarly, a significant amount of time and attention will be dedicated to the design and integration of the custom 400 MHz RF/analog spectrometer and RF coils. Finally, time will be required for protocol design and optimization for experiments on the system. Long instrument development timeframes. The proposed instrument is not "plug-and-play." While we are starting with a magnet, a back-end console, gradients and an RF power amplifier, these components plus significant in-house designed components and interface hardware and software must be integrated into a high performance system in a new comprehensive lab environment. Per the above paragraph, some of the longer term development items will be 400 MHz RF/analog spectrometer and coils, data acquisition and processing programming, and potential troubleshooting required when fitting and optimizing new gradient and shim coils in the magnet. Construction of the UHF lab facility to house and support this system will be another long-lead item. Risks mitigation plan: Fortunately, the first generation 9.4T instrument has already demonstrated feasibility and set the bar for human neuroimaging performance levels. GE's new HG4 gradient coil should prove a significant step toward realizing the inherent benefit of

9.4T brain imaging. The previous generation, HG3 gradient coil has achieved top performance marks in a head-only 3T magnet at Mayo Clinic. The RF/analog section will require time and effort, but JT Vaughan has done all of this successfully before. While these efforts are time consuming and technically challenging, we have assembled a team eminently capable of overcoming these hurdles, particularly given Vaughan's decades of experience in solving precisely these problems in UHF MRI.

B. Research Activities to be Enabled

B.1. The proposed 9.4T system and lab will be a shared research platform serving a broad spectrum of research and development. The engineering research and development still needed to improve and refine this tool is one band. This will include RF coil development, B0 multi-coil development, Safety and Image sequence and reconstruction methods. Scientific applications of this instrument offer the compelling reasons behind the engineering effort to build it. The many applications might be broadly categorized into structural, metabolic, and physiological or functional MRI. A few examples follow.

A. Technical Development

i) RF coil development: RF coils for an MR machine are like lenses for a camera. In the hands of a photographer, there are lenses for every subject and condition. Similarly, every investigation could benefit from a coil optimized for a given experiment. This is especially important for the short wavelengths at 9.4T where coil design must start with electromagnetic (EM) field simulations, SAR and temperature calculations, and distributed circuit and transmission line (Transverse EM) design[3,4]. Human and NHP sized coils at 9.4T frequencies aren't commercially available. RF coil development must therefore be a continuous pursuit by experienced engineers and physicists. Fortunately we have such expertise in Dan Sodickson's Center for Advanced Imaging Innovation and Research at NYU which includes Chris Collins, Riccardo Latannzi and Ryan Brown, Yi Wang's MRI Research Institute at Cornell which includes Simone Winkler, and Thomas Vaughan's Columbia MR Research Center including Ray Lee.

ii) Multi-coil B0 shimming: Equally important as RF design is for ultrahigh frequencies is static field design for high magnetic fields. Especially in the structure of the head, field susceptibilities make for challenging imaging and spectroscopy. In the face of these challenges, thinner slice and smaller volume selection requiring stronger, more accurate and precise static field gradients are needed to take advantage of the UHF benefits. For these reasons new B0 field localization and shimming technologies and techniques must be developed and applied to different experiment conditions. One such approach, invented and developed by Juchem and his team at Columbia, is the dynamic multi-coil technique (DYNAMITE) for B0 shimming in rodent, NHP and human brain. This approach provides dramatically better B0 homogeneity than standard methods based on conventional spherical harmonic coil technology and in the future should come close to completely eliminating B0 inhomogeneity as a problem. It is therefore ideally suited for the challenging B0 field inhomogeneities encountered at 9.4T. Moreover, MC hardware employs a narrow single-layer design as opposed to multi-layer spherical harmonic coil systems, thereby taking up less valuable bore space especially in a head-only system.

iii) Safety: There are two components to MR safety at 9.4T, both static and radiofrequency field related. RF fields can cause 1st, 2nd and 3rd degree burns at any field strength including 9.4T[5]. These risks can be mitigated by predicting accurate and precise temperature maps for given coils, research subjects and RF protocols, before an experiment. The PI and his former postdoc and research associate, Devashish Shrivastava have done much research in this area including at 9.4T over the years[6]. Accordingly, hundreds of research subjects have been safely scanned at 9.4T without incident. Dr. Shrivastava is now the Senior Expert on Tissue Heating at the FDA, and has an Adjunct Appointment with Dr. Vaughan at Columbia where they continue their safety research together. Chris Collins at NYU and a collaborator with Dr. Vaughan's safety research and on this proposal is also renowned for his RF SAR and temperature numerical modeling and predictions. Static fields also present well known ferromagnetic force hazards that must be guarded against. Acoustic noise from switched gradients can also be more pronounced and must be controlled by protocol design and ear protection. Experiments will be carefully considered and approved by our IRB and IACUC.

iv) Imaging Sequence and Reconstruction. Dan Sodickson (co-PI) leads a group at the Center for Advanced Imaging Innovation and Research (CAI²R; NYU) with extensive experience developing novel MR sequences and RF coils for high- and UHF MRI. With the proposed 9.4T scanner, the group at CAI²R will be able to further advance technological research areas already underway, including: understanding the interactions of ultra-high EM fields with biological tissue[7–10], using artificial intelligence for MRI reconstruction[11–13]; developing rapid image acquisition techniques using compressed sensing[14,15], parallel imaging[16], and rapid radial imaging[17–19]; developing novel transmit and receive coils for high-field MRI[20–27]

and characterizing EM field interaction with tissue[28,29]; attenuation correction of simultaneous MR and PET acquisition[30]; and biophysical modeling of diffusion[31] and MR relaxation in complex tissue geometries[32]. Sodickson's group has developed substantial relevant intellectual property as demonstrated by patents in the fields of RF coil design (US Patent App.15/966,827; 9,874,615; 15/196,305; 14/686,127), pulse sequences (US Patent App.9,921,285; 14/697,099), image reconstruction (US Patent App.15/495,511), and EM field interactions (US Patent App.9,989,422; 9,903,921; 15/522,804; 15/494,384). Work from Sodickson's group will be translatable and informative for the 9.4T platform.

Researchers who will benefit from *Technical Development* research:

Researchers and Project Information
R. Lee (Columbia) (c): Developing dyadic fMRI methodology to quantify and model human brain-to-brain interactions; *NSF #1926789; 01-OCT-19 to 30-SEP-22*
R. Lattanzi (NYU) (c): CAREER: Interactions of Radiofrequency Electromagnetic Fields with Biological Tissue: New Tools to Address Challenges and Exploit Opportunities; *NSF #1453675; 1-FEB-15 to 31-JAN-21;* Novel Software Tools For Rational Design And Assessment of MR Coils; *NIH R01 EB024536; 01-JUL-17 to 30-APR-22*
D. Sodickson (NYU): Center for Advanced Imaging Innovation and Research (CAI²R); *NIH P41 EB017183; 30-SEP-14 to 31-JUL-24*
J. T. Vaughan (NKI, Columbia): Imaging in non-uniform fields: Simultaneous transmit and receive (STAR); *NIH U01 EB025153; SEP-30-17 to JUN-30-22*
Y. Ge (NYU): In vivo Insights of Small Vessel Changes with Age Using USPIO-Enhanced MRI; *NIH R01 NS108491; 15-SEP-18 to 30-JUN-23*
R. Brown (NYU): Neuroenergetic Adaptations In Alzheimer's: Implications on Amyloid Burden and Cognition; *NIH R21 AG061579; 01-MAR-19 to 28-FEB-21;* Multinuclear MRI Assessment Of Diabetic Peripheral Neuropathy; *NIH R01 DK106292; 01-JUL-15 to 30-APR-19 (*Completed Project)*
C. Collins (NYU): Next-generation RF Coils with High-permittivity Material for Improved Performance in MRI ; *NIH R01 EB021277; 21-SEP-16 to 31-JUL-21;* TR&D 2: Unshackling the Scanners of the Future: Flexible, Self-correcting, Multisensor Machines; *NIH P41 EB017183; 30-SEP-14 to 31-JUL-24*
Y. Wang (Cornell): *QSM to Guide Iron Chelating Therapy in Transfusional Iron Overload; NIH R01DK116126; 01-FEB-19 to 31-JAN-24*
S. Winkler (Cornell): Human Connectome Mapping Using Ultra-high-resolution MRI: a Technological Pathway; *NIH R00 EB024341; 6-AUG-19 to 31-MAR-22*

B) Scientific Applications

i) Spectroscopy: At 9.4T, this instrument is a high-resolution NMR spectrometer comparable to instruments in organic chemistry and pharmaceutical labs (see Fig.2). However, the proposed instrument's bore size will allow observation of human brain metabolism *in vivo*. The ability to resolve groups of coupled spins improves with increasing magnetic field - even given the increased individual resonance line-widths with field strength [33,34]. For example, glutamate and glutamine, which are not resolved at 1.5T, are resolved progressively better as B0 increases from 4T[35], to 7T[34,36], and to 9.4T[37]. Indeed, Tkac et al.[38]
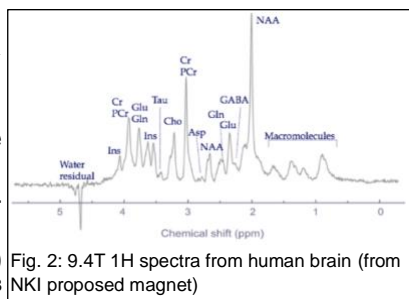

Fig. 2: 9.4T 1H spectra from human brain (from NKI proposed magnet)

showed that single voxel spectroscopy at 7T allows reliable detection of up to 17 metabolites in human brain. More recently, Chadzynski et al.[39] showed the feasibility of *in-vivo* proton MRS imaging (1H MRSI) of the healthy human brain at 9.4T. Using a stimulated echo acquisition mode (STEAM) pulse sequence, they were able to obtain reasonable quality and SNR of the acquired spectra to obtain reliable quantification of 12 metabolites. The benefits of higher field strength, combined with the proposed instrument's gradient system, will yield unprecedented ability to resolve metabolite concentrations *in vivo* in rodents, humans and NHPs on the same system. The gains in spectral resolution and simplification and improved SNR together translate into significantly higher gains in the ability to quantify metabolites. Although we focus on 1H spectra, the benefits of the proposed system will accrue to an equal or greater degree in more signal impoverished 23Na[40,41] and 13C[42,43] MRS. **Researchers who will benefit from *Spectroscopy* research:**

Researchers and Project Information
R. Brown and G. Madelin (NYU): Quadri-nuclear MRI to Study Brain Energy Metabolism; *NIH*

R21EB027263; 01-MAY-20 to 28-FEB-22
G. Madelin (NYU): Simultaneous Multinuclear Magnetic Resonance Fingerprinting for Data Fusion of Quantitative Structural and Metabolic Imaging; *NIH R01EB026456; 01-JUL-18 to 31-MAR-22*
I. Kirov and G. Madelin (NYU): Quantitative Sodium MR Imaging and Proton MR Spectroscopy in Traumatic Brain Injury; *NIH R01NS097494; 15-JUL-16 to 30-APR-21*
D.C. Shungu (Cornell) (c): Mechanistic Assessment of N-Acetylcysteine as an Antioxidant Therapy for Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Through Dose Response and Treatment Target Engagement; *NIH R01NS116887; 01-JUL-20 to 30-APR-25*
D. Guilfoyle, J. Hrabe (NKI): An Investigation of resting state NAA and NAAG fluctuations in rat brain at 21.1T; **
C. Juchem (Columbia) (c): In Vivo Metabolomics of Oxidative Stress with 7 Tesla Magnetic Resonance Spectroscopy; *NMSS RG 4319-A-1; 01-APR-15 to 31-MAR-18 (*Completed Project)*

**This project is a currently active protocol (P17721_E003-NMR) at the National High Magnetic Field Laboratory, supported by NSF Cooperative Agreement No. DMR-1644779 and the State of Florida. (c) - Strategic Advisory Committee Member

Other minor users and projects that we identified: Jacqueline Gottlieb (Columbia; NIH - R01EY025965).

ii) Structural Imaging

3D amplified MRI (aMRI). PIs Kurt, Zhang, Weickenmeier and Balchadani (NSF LEAP-HI 1953323) are pursuing next-generation mechanical neuroimaging of the human brain at UHF (7T) by combining diffusion tensor imaging (7T DTI) combined with magnetic resonance elastography (7T MRE), to measure the high-frequency mechanical response of the brain *in vivo*. This work is ongoing at the Biomedical Engineering and Imaging Institute at Mount Sinai. Scaling this work to 9.4T will allow for even higher resolution characterization of brain structure and motion and unprecedented detail for diffusion tractography.

Ex vivo. The advent of MRI has transformed biomedical research due to its ability to characterize the macroscale structure of body organs, including the brain, in high detail - thereby replacing the need for dissection approaches, which are both laborious and destructive. Importantly, the lack of disturbance to the underlying neuroanatomy during *ex vivo* MRI allows a reliable assessment of neuroanatomy, even in cases of advanced putrefaction[44] and maceration[45] – information which may be lost during dissection[46]. Recent postmortem human biobank efforts, e.g., the Allen Institute[47], are defining a new frontier in brain genomics by providing postmortem gene expression data and multimodal structural MRI from the same individuals immediately postmortem[48].
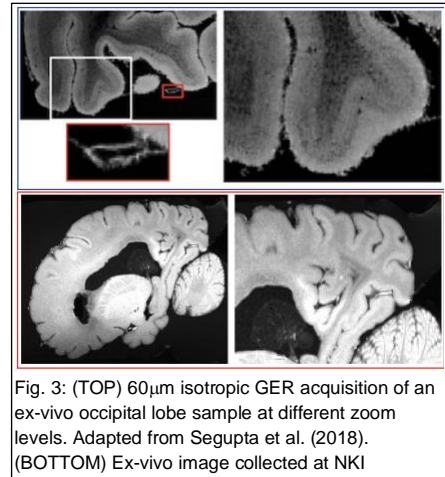

Fig. 3: (TOP) 60μm isotropic GER acquisition of an ex-vivo occipital lobe sample at different zoom levels. Adapted from Segupta et al. (2018). (BOTTOM) Ex-vivo image collected at NKI

Despite their value, limitations in resolution have bounded the utility of postmortem MRI, as the level of detail in the images achieved has not been comparable to those of histologic techniques. While 7T MRI scanners are improving this, even initial efforts at 9.4T are achieving unprecedented levels of image quality (see Fig.3[49]). The proximity of the proposed 9.4T platform to local NIH-funded biobank efforts (i.e., CommonMind and psychENCODE[50]) and commitments of Major Users such as Drs. Haroutunian and Roussos will generate multimodal data with resolutions and quality that will be transformative for brain genomics research. At present, using the current Siemens 3T Tim TRIO at NKI, we have already collected images of 62 newly contributed samples (1-2 samples per week - even during COVID pandemic) from the Mt. Sinai-based Biobank. Structural scans are performed overnight with a voxel size of 0.5x0.5x0.5mm (maximum Tim TRIO resolution - See Fig. 3). We will extend this collaboration with the 9.4T and collect images with a much higher resolution. Consistent with the NKI open sharing research model (e.g., International Neuroimaging Data-sharing Initiative), all data generated will be openly shared, ensuring rapid and broad impact.

High resolution In Vivo Brain Atlas Generation. The validity of interpretation for fMRI results depends greatly on the ability to identify the neuroanatomical structures in which the functional signal of interest occurs. Over the last few years, MRI-based digital atlases have been developed to guide neuroanatomical localization in structural MRI scan volumes in humans [51–54], NHPs (including macaques [55–58] and non-macaque species[59,60]), and rodents[61–63]. While representing an advance, these atlases remain markedly limited by spatial resolution in primates (150μm voxels *ex vivo* and 250μm *in vivo*) and field distortion in

rodents despite higher resolution. The authors of these atlases either leave large regions of the brain unlabeled or must concede to blind triangulation and best guesses to map critical neuroanatomical regions. The increased resolution of the 9.4T platform (10μm structural voxels when MION is used) will reveal incredibly detailed neuroanatomical features for the production refined MRI-based atlases. Using several distinct structural[64] and diffusion imaging sequences[56], together with robust functional localizers[58] and stable RF coil positioning[65], these atlases will help ascertain the neuroanatomical localization of experimental results down to the details of cortical layers and small subcortical subdivisions.

NHP - Surgical targeting / neuromodulation. The rhesus macaque, with a brain volume of 100cc, is the most widely used NHP experimental model in neuroscience. The overall anatomy of the macaque brain is strikingly similar to that of humans. However, much of the fine anatomical and functional detail (sub-nuclei of the thalamus or laminar organization of the cortex) cannot be resolved with 3T MRI. The enhanced resolution of the proposed 9.4T platform will serve to increase the spatial accuracy of surgical planning.

Researchers who will benefit from *Structural Imaging* research:

Researchers Project Information
P.. Balchandani (Mt. Sinai): LEAP-HI: Tackling Brain Diseases with Mechanics: A Data-Driven Approach to Merge Advanced Neuroimaging and Multi-Physics Modeling; *NSF #1953323; 19-MAY-20 to 30-JUN-25;* Cross-correlation of Biomechanical, Connectomic, and Pathologic Markers in Alzheimer's Disease at 7T MR ; *NIH R21AG071179; 15-SEP-20 to 31-AUG-22;* 7T Neurosurgical Mapping Protocol For Endoscopic Resection of Skull Base Tumors; *NIH R01CA202911; 01-AUG-20 to 31-MAR-21;* 7T MRI To Reveal Structural, Connectomic and Metabolic Imaging Markers for the Neurobiology of Depression; *NIH R01MH109544; 23-SEP-16 to 30-JUN-21;* Transdiagnostic Multimodal 7 Tesla MRI of the Locus Coeruleus in Human Pathological Anxiety; *NIH R01MH116953; 15-MAR-19 to 31-DEC-23*
V. Haroutunian (Mt. Sinai) (c): Alzheimer's Disease Research Center- Neuropathology Core; *NIH P30AG066514* ; *01-MAY-20 to 28-FEB-25*
P. Roussos (NKI and Mt. Sinai): Large-scale Transcriptome and Epigenome Association Analysis Across Multiple Traits; *NIH I01 BX004189; 01-OCT-18 to 31-MAR-21;* Large-scale Transcriptome and Epigenome Association Analysis Across Multiple Traits; *NIH I01BX004189 ; 01-OCT-18 to 31-MAR-21*
Roussos and Haroutunian: Understanding the Molecular Mechanisms That Contribute to Neuropsychiatric Symptoms in Alzheimer Disease; *NIH R01 AG067025; 15-SEP-19 to 31-MAY-24;* Understanding the Protective and Neuroinflammatory Role of Human Brain Immune Cells in Alzheimer Disease; *NIH R01 AG065582; 15-FEB-20 to 31-JAN-25;* The 3D Genome in Transcriptional Regulation Across the Postnatal Life Span, with Implications for Schizophrenia And Bipolar Disorder; *NIH U01MH116442 ; 01-SEP-18 to 31-MAY-23*
S. Chang (Yale): Toward a Macaque Model of Social Brain Dysfunction in Real-life Social Interactions; *NIH R01MH110750; 01-JUL-16 to 31-MAR-21;* Behavioral and Neural Bases of Combining Oxytocin and Naloxone For Optimally Enhancing Interactive Social Attention; *NIH R01MH120081; 14-AUG-19 to 31-MAY-24*

(c) - Strategic Advisory Committee Member

Other minor users and projects that we identified: Heidi Schambra (NYU; NIH - R01NS110696); Guillermo Horga (Columbia and NYSPI; NIH - R01MH117323); Hyojung Seo (Yale; NIH - R01NS118463).

iii) fMRI

Cortical Layer fMRI*.* The current high-resolution standard resolution for fMRI-BOLD at 3T is 1mm in-plane for whole brain coverage[66]. At 9.4T, this can be increased to 0.1mm for whole brain imaging. One application of this would be to image activity in individual cortical layers. Similarly, at 9.4T, temporal resolution for whole brain imaging can be increased to 0.1ms, making it possible to explore temporal dynamics in much greater detail, nearing the temporal resolution of optical imaging. The ability to examine BOLD signal at such remarkably improved temporal and spatial resolutions will be profoundly transformational. As reviewed by Finn et al. [67], current state-of-the-art UHF imaging at 7T only allows differentiating cortex into two or three layers. "Layer fMRI" even within such limits is sufficient to confirm models of feedforward and feedback in primary cortical areas. We expect the further jump to 9.4T will enable fully distinguishing 6 cortical layers - an unprecedented achievement *in vivo*. Such layer fMRI at 9.4T will enable the study of cortical micro-circuits with a particular focus on regulation of hemodynamic responses in capillary beds versus macro-vessels, i.e., laminar neurovascular coupling[68].

Multiscale Biophysical Modeling. Computational models of neural processing, as well as accurate biophysical modeling of neurovascular coupling at mesoscopic scale, will dramatically benefit the field [71].

Research using invasive recordings suggests that the mesoscopic organizational level of the brain represents an intermediate comprehensive level of analysis, at which information from single neurons (microscopic scale) and large-scale areal function (macroscopic scale) meet [72]. For example, generative models of the neurovascular coupling at the macroscopic scale (e.g., DCM[73]) allow linking non-invasive macroscopic data with neuronal mass models and with non-invasive and invasive electrophysiological data[74,75]. Biophysical modeling is required to bridge computational models at different spatial scales (e.g., neural mass models, canonical microcircuit) with invasive and non-invasive electrophysiological measures[76]. The proposed 9.4T effort will allow us to improve the accuracy of computational models by improving the spatial resolution of each of the modalities commonly used to construct models - structural MRI, diffusion MRI and functional MRI - this is particularly important for fMRI, which at present is limited to measurement of the macroscale. Researchers with biophysical modeling projects that we have identified that will greatly benefit from the 9.4T include, Dr. Bijan Pesaran (NSF-1557886; NSF-1926800; NIH-R01NS104923), Dr. Samuel Neymotin (NIH-R01DC012947 ; DoD-W911NF1910402)[77], Dr. Nikolaus Kriegeskorte (NSF #1948004) and Dr. Stephan Bickel who recently submitted a proposal to NSF[78].

Inclusion of small animals in comparative studies. The ability to image mice, rats, NHP and humans on the same magnet at high spatial and temporal resolution will transform *in-vivo* translational neuroscience.

Researchers who will benefit from *Functional MRI* research:

Researchers and Project Information
B He (NYU) (c): CAREER: Large-scale brain dynamics underlying visual perceptual awareness; *NSF #1753218; 01-FEB-19 to 31-JAN-23;* NCS-FO: Understanding How Prior Knowledge Shapes Visual Perception in the Individual Brain; *NSF #1926780; 10-JAN-19 to 30-SEP-23*
D Shohamy (Columbia) (c): CRCNS Research Proposal: Collaborative Research: Prioritization of memory reactivation for decision-making; *NSF # 1822619; 01-OCT-18; 30-SEP-21;* Differentiating Reward Seeking and Loss Avoidance with reference-dependent learning models Reference-dependent Learning Models ; *NIH R01MH121093 10-SEP-19 to 30-JUN-23*
S Colcombe, M. Milham (c) (NKI): Mapping Interindividual Variation in the Aging Connectome; *NIH R01 AG047596; 01-SEP-15 to 31-MAY-21;* The NKI Rockland Sample II: An Open Resource of Multimodal Brain, Physiology & Behavior Data from a Community Lifespan Sample ; *NIH R01MH124045***; 01-APR-21 to 31-MAR-26*
L Parra (CCNY): Assessing Student Attentional Engagement from Brain Activity during STEM Instruction; *NSF #1660548; 01-SEP-17 to 31-AUG-21;* CRCNS: Targeted Stimulations in Brain Network of Networks; *NSF #1515022; 01-OCT-14 to 30-SEP-19*;* Effects of Direct-Current Stimulation on Synaptic Plasticity; *NIH R01NS095123; 15-MAY-16 to 30-APR-21*
D Sodickson, G Buzaki (NYU): Non-invasive Radio Frequency Stimulation of Neurons and Networks ; *NIH R01NS113782; 30-SEP-20 to30-JUN-25*
S Kastner (Princeton): Attentional Selection from Natural Scenes; *NSF #1328270; 31-AUG-13 to 30-JUN-17*;* Functions of the Thalamus in Attention and Perception; *NIH R01 EY017699*; *01-APR-07 to 31-MAR-22;* Neural Mechanisms of Attention; *NIH R01MH064043; 01-JUL-01 to 31-JAN-21;* Dynamic Thalamocortical Gating of Corticocortical Communication in Visual Active Sensing ; *NIH P50 MH109429; 15-APR-18 to 31-MAR-22*
R Marsh (NYSPI, Columbia): Task-control Circuits as Targets for Obsessive Compulsive Behaviors in Children; *NIH R01MH115024; 01-JUL-18 to 30-JUN-22*
C Schroeder (c); P Lakatos (NKI); Milham (c); Franco: Silvio O. Conte Center: Neurobiology and Dynamics of Active Sensing (Administrative , Control of Thalamo- cortical Dynamics in Auditory Active Sensing, Neuroimaging, and Computational Cores); *NIH P50 MH109429; 15-APR-18 to 31-MAR-22*
L Davachi (NKI and Colombia) (c): NCS-FO: Using computational cognitive neuroscience to predict and optimize memory; *NSF #1631436; 01-SEP-16 to 31-AUG-20*;* Medial temporal lobe contributions to episodic memory; *NIH R01 H074692I; 01-JAN-07 to 31-MAR-22;* Hippocampal memory circuits in delusions; *NIH R01MH112733; 16-July-18 30-April-23*
Schroeder (c); Milham (c): Defining neuronal circuits and cellular processes underlying resting fMRI signals; *NIH R01H111439; 01-APR-18 to 30-JUN-21*
V Ferrera (Columbia) (c): Focused Ultrasound for Noninvasive Brain Stimulation; *NIH R01MH112142; 1-APR-17 to 31-JAN-22*

ZS. Chen (NYU): NCS-FO: Closed-loop neuromodulation for chronic pain; *NSF #1835000; 01-FEB-19 to 31-JAN-22;* CRNS: An Integrative Study of Hippocampal- Neocortical Memory Coding During Sleep; *NIH R01 MH118928; 12-JUL-18 to 30-APR-23;* CRCN: Dissecting Neural Circuits for Acute Pain; *NIH R01NS100065; 15-JUL-16 to 31-MAY-21*

M Aly (Columbia): CAREER: How Memory Contributes to Goal-Directed Attention; *NSF #1844241; 01-MAR-19 to 29-FEB-24*

S Neymotin and P Lakatos (NKI): Cortical and Thalamic Mechanisms of Selective Auditory Attention; *NIH R01DC012947; 10-DEC-12 to 30-JUN-23*

S Neimotim: Training biophysical thalamocortical models to play games through biologically realistic reinforcement learning rules; *DoD W911NF1910402; 15-JUL-19 to 14-JUL-22*

B Pesaran (NYU): Predictive Models of Brain Dynamics During Decision Making and their Validation Using Distributed Optogenetic Stimulation; *NSF #1557886; 15-SEP-16 to 31-AUG-21;* Multimodal State Estimation through Neural Coherence in the Parieto-Frontal Network; *NSF #1926800; 01-SEP-19 to 31-AUG-22;* Predictive Models of Brain Dynamics During Decision Making and Their Validation Using Distributed Optogenetic Stimulation; *NIH R01NS104923; 25-SEP-17 to 31-AUG-22*

N Kriegeskorte (Columbia): Testing the limits of deep neural network models of human vision with optimized stimuli; *NSF #1948004; 01-JUL-20 to 30-JUN-23*

S Bickel (Northwell): Weakly Evanescent Transverse Cortical Waves (WETCOW) Theory: Experimental validation via intracranial electrophysiological recordings in humans; **

* Completed Project; ** Proposal submitted to NSF's Collaborative Research in Computational Neuroscience (CRCNS) program. *** Pending project approval; (c) - Strategic Advisory Committee Member; NYSPI: New York State Psychiatric Institute

Other minor users and projects that we identified: Michael Cole (Rutgers; NIH - R01MH109520, NIH - R01AG055556), Bharat Biswal (New Jersey Institute of Technology; NIH - R01AT009829), Peter Rudebeck (Mount Sinai; NSF - 1926800, NIH - R01MH110822, NIH - RF1MH117040, NIH - R01MH118638), Yoshinao Kajikawa (NKI; NIH - R01DC015780), Joshua Kantrowitz (Columbia and NYSPI; NIH - R01MH123142), Virgina Rauh (Columbia and NYSPI; NIH R01ES030039), Michael Goldberg (Columbia; NIH - R01NS113078, NIH - R21EY028749, NIH - P30EY019007), Mohammed Milad (NYU and NKI; NIH - NIH R33MH111907), Vilma Gabbay (NKI and Mount Sinai, NIH-R21MH121920, NIH - R01MH120601), Roozbeh Kiani (NYU; NIH - R01MH109180).

B.2. Results from Prior NSF Support. The PI and co-PI's have not received any NSF support for the last 5 years. They aim to change this record with this proposal.

C. Description of the Research Instrument and Needs

Introduction and Background: Seventeen years of experience imaging humans at 9.4T and above has convincingly demonstrated the need, the efficacy, and the safety of translational research at these highest of fields. The signal-to-noise ratio, spatial resolution, temporal resolution, and other physical benefits have consistently been documented as being well above the benchmarks set by commercially supported, whole-body 7T systems. Yet currently there is only one such system operational in the US - a 10.5T whole-body system at the University of Minnesota which was purchased to replace the head-only 9.4T system from which the 9.4T, 65 cm bore magnet has been extracted for the goals of the present proposal. The PI of this proposal was the Engineering Director and Engineering Core PI for 17 years at the Center for Magnetic Resonance Research at the University of Minnesota where the world's first 7T, 9.4T, and 10.5T human MR systems were built, tested, and applied[79]. The proposed project will deliver a vastly improved second generation system that leverages lessons learned from the initial 9.4T system and several generations of successful UHF human MR systems, as well as well-tested technical advances in instrumentation by GE. In particular, the latest generation GE head-only gradients coils, which when combined with the 9.4T magnet, have the potential to deliver performance that rivals and possibly exceeds higher field strength scanners - at a notably lower cost.

Objective: The overall objective of this proposal is to develop and build a second generation 9.4T neuroimager by integrating a GE 7T console modified for 9.4T and head gradients with a CPC power amplifier, custom RF coils, and a 9.4T head-only magnet. The experienced engineering team chosen for this task is from the New York City Area and from GE. Academic participants are from NKI, Columbia, NYU, Cornell, Mt. Sinai, Yale, Rutgers, and Princeton. Industry collaborators and suppliers are from GE Global Research, GE Healthcare, Communications Power Corp (CPC), and Flywheel, LLC. The 9.4T magnet is already in our possession and a custom laboratory for siting it is already underway by NY State. NKI has committed to the staffing and maintenance of this facility and 50+ funded investigators have declared their

interest to use this instrument. GE Healthcare, GE Global Research, Columbia, NYU and NKI have committed to lead roles in developing the systems electronics and systems software. In this joint project, GE Healthcare will provide the console electronics used for the 7.0 T MR console, and GE Research will provide a HG4 head-only gradient coil. GE Healthcare and GE Research Center will further provide senior scientists and engineers as consultants who will help guide graduate students and post-doctoral fellows from Columbia, NYU, Cornell, and NKI. In addition to the proposed 9.4T console, this project will provide a tremendous educational opportunity to train students and post-doctoral fellows to build and integrate an MRI system. Such an opportunity is rarely available at academic institutions. The academic partnership with GE is unique as the collaborators have the necessary systems knowledge and expertise to train and guide personnel and students from participating institutions. For a more detailed description of our proposed system, refer to the functional block diagram in Fig 4.

<u>Magnet System</u> The magnet system includes the 9.4T with cryostat and fringe-field shielding, the B0 gradient subsystem, and the B0 shim system with superconductor, passive and active, dynamic shims.

a.) Magnet. The magnet at the core of our MR system is a Magnex Model MRBR 9.4T/650. Having a bore diameter of 65cm, it is designed for imaging human heads, NHP, and other medium and small sized lab animal models. While this bore size is ample for human neuroimaging, it conserves cost, size, weight, shielding, and cryogens over larger, whole-body bore magnets. It is a standard helium cooled (4.2K), persistent superconducting solenoid design wound with 354 kilometers of multi-filament, niobium titanium conductor carrying 218 amps with 78MJ of stored energy. Field drift is less than 0.05 ppm/hr. Field homogeneity over a 30-cm sphere with superconducting shims is ±2.5 ppm, and with passive shims added it is ±1.5 ppm. The 5-gauss fringe field of this magnet extends to 20.2 m axially and 16 m radially from the magnet center. This is reduced by the passive steel shielding that will be built into the room walls measuring 11.9 m by 4.7 m. The magnet coils are protected from quench damage by a resistor and diode network in the helium reservoir. Third order shim coils are each rated to carry a maximum current of 25 amps. The cryostat of the magnet and shims is of conventional design with welded stainless steel helium vessel that is surrounded by two aluminum gas-cooled radiation shields. The cryostat measures 3.15 m long and 3.48 m high, with a 0.65-m clear bore. The complete assembly is contained in a stainless-steel outer vacuum vessel with a vertical service turret located centrally on top of the cryostat. The turret provides access to the helium reservoir for the demountable magnet leads, helium level probe, and helium transfer siphon. The system is equipped with two Leybold model 5100 two-stage cryocoolers with CP6000 compressor units. The helium reservoir contains 2500 L of liquid helium with 1600 L volume above the refill level. The liquid helium evaporation rate is 0.2 L/ hr, and the refill interval is 6 months.
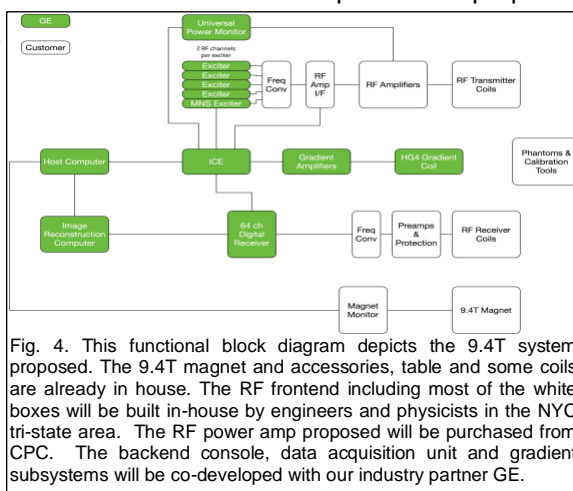

Fig. 4. This functional block diagram depicts the 9.4T system proposed. The 9.4T magnet and accessories, table and some coils are already in house. The RF frontend including most of the white boxes will be built in-house by engineers and physicists in the NYC tri-state area. The RF power amp proposed will be purchased from CPC. The backend console, data acquisition unit and gradient subsystems will be co-developed with our industry partner GE.

Whereas the company who built the magnet is no longer in business, a number of the engineers who designed and built it are now employed at another magnet company, Tesla Engineering Limited of Storrington, West Sussex, England. Tesla recently certified the integrity of this magnet before they ramped it down in Minnesota. They have agreed in contract to install, ramp up, and maintain this magnet once our new building site is ready in about 1.5 years. A full-time, system dedicated engineer will also be hired by NKI for daily monitoring and maintenance of the magnet and system; they will also provide technical support to the system users. The magnet is currently in climate-controlled storage nearby warehouse. Additional specifications for the magnet, cryostat, shims and shielding may be found in [1].

b.) Gradients . Head gradients, GE Model# HG4 will be specified, designed and built to fit our magnet in collaboration with our industry partner at GE Global Research. With a nominal coil efficiency of 0.156 mT/m/A, the head gradient coil will provide 140 mT/m at 810 T/m/s when paired with the SIGNA 7.0 T gradient driver. Such gradient strengths and slew rates are important to realizing the inherent SNR potential of 9.4T and could not be used in a whole body configuration due to coil size and peripheral nerve stimulation limitations. This makes these strong and fast head-only gradient coils ideal for use in our head-only 9.4T magnet. Gradient specifications are listed in the table below. The HG4 gradient coil (Fig. 5) has been designed as the primary head-gradient coil for a new low-cryogen, compact 7.0 T MRI scanner that is being

developed by GE Research under NIH grant U01EB026976. That system has as its core, the SIGNA 7.0 T electronics. GE scientists and engineers will provide assistance to personnel and graduate students from Columbia/NYU/NKI in the design of the gradient mounting to the 9.4T magnet. It is expected that the work will include assistance in the design of the cable connections to the gradient coil, and also the gradient coolant manifold to control coolant to the gradient coil. The HG4 gradient coil has the following parameters: Inner diameter = 42cm; Outer diameter = 58.6cm; Efficiency = 0.155mT/m/A; G_{max} at 900 A = 0.155; SR_{max} at 2100 V = 810; Linearity @ 26 cm FOV < 50.4%; Uniformity @ 26 cm FOV < 42.8%; DC Resistance <0.16 W; DC Inductance < 355mH; Post-compensated eddy current < 0.027%; Net force @ I_{max} < 0.06kN; Net torque @ I_{max} < 0.031kNm; Max. radial leakage field < 3.49mT.

c.) Shims. Limited B_0 homogeneity remains a longstanding problem for MRI as it results in spatial deformation and signal loss[80,81]. Artifacts can be reduced by post-processing corrections[82–84]. However, true signal loss can never be recovered by any post-processing method[85], and experimental B_0 field homogenization is a necessity. B_0 inhomogeneity encountered in the brain is due to (1) magnetic susceptibility variations in and around the head and (2) B_0 imperfections inherent to the scanner. We will overcome B_0-induced MRI artifacts with superconducting, resistive and passive shims included in the magnet description above, and by state-of-the-art B_0 shimming with the Dynamic Multi-Coil Technique (DYNAMITE) tailored to the scanner at hand and specific applications (e.g., NHP prefrontal cortex) to reduce B_0 imperfections to avoid signal cancellation and minimize image distortions.

Fig. 5: GE HG-4 Gradient Coil

d.) Shielding. Surrounding the magnet, a rectangular box shield comprised of 350 tons of welded plate steel that is 8" thick at the magnet center and tapers to 1" thick at the end plates will be constructed. The end plates contain a window and a door on the system user end, balancing a brass plate bulkhead (patch panel) access on the opposite end. A shield of these specifications has already been deployed and proven effective with this magnet for the past 17 years at the University of Minnesota. Also enclosing the magnet and incorporating the steel magnet shield is an RF enclosure (Lindgren RF Enclosures, Inc., Glendale Heights, IL, USA) to isolate the magnet environment from outside signals by 110 dB at 400 MHz. This shielding installation is included in the building plan by NY State.

e.) Table. The console controlled, shielded motor driven, custom cantilevered table used in Minnesota will be reused. This fiberglass table moves in and out of the magnet and up and down on scissor levers. Slight modifications will be made to the tongue of the table to fit our new head gradients.

RF/Analog Spectrometer. The Spectrometer subsystem is composed of the RF transmitter and receiver sections and RF coils. The transmitter in turn includes programmable signal generators and waveform generators, digital to analog signal converters (DAC), the RF power amplifier, power monitors and fail-safes, transmit/receive (TR) switches, coil element detune switches, and the transceiver or transmit RF coil. All digital control lines, RF signal and power lines, cables and filters are also included. The RF receiver includes the analog to digital signal converters (ADC), preamplifiers, TR switches and coil element detuner diodes, and the receive coils which are typically arrays.
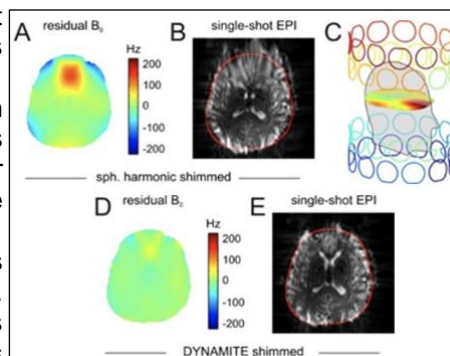

Fig 6: Dynamic-multi-coil shimming results. Major B_0 imperfections remain with conventional B_0 correction (**A**, blue/red), leading to artifacts in gradient-echo EPI (**B**). B_0 shimming with the dynamic multi-coil technique (DYNAMITE, **C**) achieves substantially more homogeneous B_0 conditions throughout the brain (**D**, green) and artifact-free EPI (**E**) as desired for fMRI. Adapted from [86].

a.) Transmitter. The console will provide eight broadband transmit channels mixed upward from 7T to 9.4T Larmor frequencies including 400 MHz for protons. The transmitter designed in-house will include eight parallel, 2kW, broad band class AB linear amplifier channels from CPC. See Fig.7 These channels can be matrix switched into combinations for 1 x 16kW, 2 x 8 kW, 4 x 4 kW or 8 x 2 kW channels. The driver stage can also be tapped as shown for low power CW transmit for experimental simultaneous transmit and receiver (STAR) applications [87]. All channels operate over the specified 30 to 400 MHz band. Multichannel transmit is necessary for RF shimming, necessary for optimizing phase, gain, signal, homogeneity and SAR over a region of interest (ROI), and for multi-band transmit applications. Transmit safety will be addressed by sampling the forward and reflected signal from each power amplifier output channel and assuming the difference is all absorbed in the human or animal test subject. SAR will be monitored this way, per channel,

and equated to thermal dose predictions via an accurate and precise bioheat transfer equation[88]. When SAR is exceeded on any or a combination of channels, the power amplifier is switched off.

b.) Receiver. The receiver will consist of up to 128 proton channels interfacing a receiver coil with up to 128 GaAsFET decoupling preamplifiers, depending on the number of receive coil array elements. Each of the array elements is also detuned during transmit. The 400 MHz pre-amplified receiver channel signals must all be mixed to the 300 MHz receiver inputs of the GE console. 128 multinuclear receiver channels will also be configured for spectroscopy and spectroscopic imaging. While transmit and receive signals will typically be isolated by using a dedicated, sensitive receiver coil nested within a dedicated transmit coil as shown in Fig.8, transceiver coils will also be built and used. For these coils, transmit and receive signals are temporally isolated by means of a transmit-receive (TR) switch per channel. Additional to the transmitters and the receivers, the third component of the RF front end are the coils. Ideally each experiment run on this system will benefit from purpose-built, experiment dedicated coils. While a modest budget is included in this proposal to get started with a human head coil, an NHP head coil, and a coil for mice, coils will be continuously designed and developed for this 9.4T system. We have RF coil experts at NYU (Chris Collins),

Fig. 7. Eight channel, broadband power amplifier with signal, power and control lines. This matix amplifier can be switched between 1, 2, 4, and 8 channels, and hi and low power. 4-port couplers on the output channels will monitor and provide failsafe switching for RF safety assurance.

Cornell (Simone Winkler) and at Columbia (Thomas Vaughan) together with their engineering students dedicated to this task. From a separate equipment budget (see budget - Auxiliary Components) and from investigators' grants, the system will be fully outfitted with physiological monitoring, gating and stimulus equipment for neuroimaging experiments.

c.) RF coils. A standard RF head coil design that has been built and proven for human head imaging at 9.4T is shown in Fig 8. The advantages of a TEM coil are multifold, including multiple, short, independent transmit or transceive elements for low inductance, high frequency operation. This coil is a distributed, cavity shielded design minimizing radiative loss and coupling to the magnet bore for best efficiency and tune and match stability. The independent elements will be driven separately for phase

Fig 8. Exploded diagram showing TEM head coil with nested array receiver and packaging.

and gain control per element for RF shimming required for homogenous, whole head imaging at these ultra-high frequencies. The elements can also be alternately frequency tuned for multi-nuclear spectroscopy and imaging. An element can be removed to provide for an open face and mirror for visual fMRI studies. Diode detuning and switching, and GaAsFET preamps will be incorporated into these coils. Finally, an inner receive array can be nested within a TEM transmit or transceiver coil for high sensitivity and accelerated imaging. We have one such coil already built.

Comparison with Other Systems. No commercially available MR systems match the performance specifications of this proposed 9.4T system. One of the considerations which led to this NSF-MRI proposal is the extraordinary opportunity to obtain an uniquely powerful instrument, a 9.4T scanner with next-generation gradients, for a markedly reduced total cost compared to an off-the-shelf 7T scanner, which costs more than $8 million for the system alone. The purchase of 85, 7T systems and counting underscores the research value of these highest field, commercially available systems; however the specs of the proposed 9.4T will significantly exceed those. For example, the current 7T GE 950 whole body model is installed with whole-body gradients rated at 50 mT/m strength and 200 T/m/s slew rate. Siemens gradient strengths are rated to 80 mT/m with similarly "slow" slew rates. Finally, as empirically measured, SNR in the human brain increases 45% from 7T to 9.4T[89]. In the NYC region, there are currently two, first generation commercial 7T scanners with "weak" whole-body gradients, one at Mount Sinai and another at NYU. Scanners with a magnetic strength greater than 7T, with the gradient strength proposed in this instrument, capable of performing highest resolution human neuroimaging do not exist. There are three 9.4T whole body scanners currently operational in Europe, two in Germany (Tübingen: head-only gradient insert - 60 mT/m amplitude and 400 T/m/s max. slew rate; Jülich: whole body gradient system - 40 mT/m amplitude and 200 T/m/s max. slew rate) and one in the Netherlands (Maastricht - head-only gradient coil - 80 mT/m
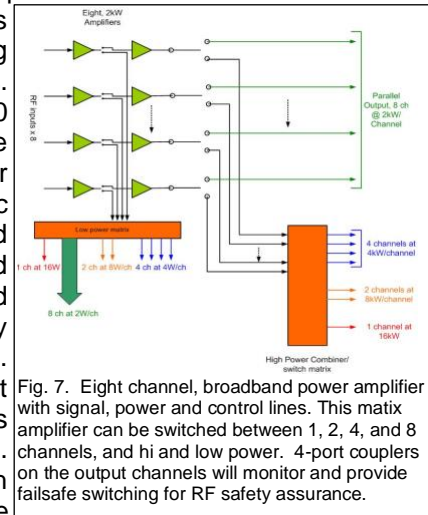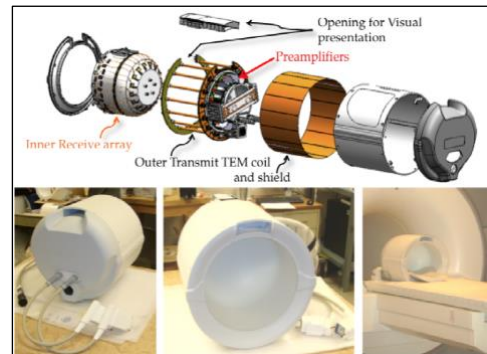
amplitude and 400 mT/m/s max. slew rate). All of these centers have safely performed in-vivo human scans, with vertigo and claustrophobia as the only side effects[89–91]. The University of Minnesota has an operating whole body 10.5T (gradient: 70 mT/m amplitude, 200 mT/m/s max. slew rate)[92]. Currently there are three 11.7T scanners in development, a head-only unit at the National Institutes of Health, and two whole-body scanners, one at Neurospin (France)[93] and another at Gachon University (South Korea). Technical development for scanners with a magnetic strength of 14T or higher are currently underway[94].

D. Broader Impacts.

Establish a Model for New Generation of UHF Scanners. The proposed award will re-equip an existing UHF magnet with cutting edge technology, leveraging knowledge gained from prior 9.4T efforts to create the most powerful head-only MRI scanner in the world. The proposed scanner platform will not only improve the resolution and quality of a range of MRI modalities employed in ongoing grants, but will also extend the capabilities of future grants to include highly innovative methods. Novel
Platform for Collaborative, Cutting Edge Integrative and Translational Research. The integrative nature and breadth of ongoing grants included among the "Research Activities to be Enabled" makes the added value of the proposed 9.4T platform particularly promising. For example, the combination of 9.4T scanning with currently ongoing 3T *ex vivo* brain banking efforts led by major users Haroutunian and Russos at Mt. Sinai will take the model of postmortem brain genomics examination to an unprecedented level of spatial resolution and provide a direct translational bridge from *ex vivo* to *in vivo* human imaging studies. It is worth noting that in line with the open data sharing philosophies pioneered in the human and NHP imaging communities by NKI C-BIN Director Milham and colleagues, users will be actively encouraged to openly share data whenever possible - directly benefiting a much broader range of multidisciplinary researchers around the world. Ongoing grant awards such as those led by Drs. Colcombe and Milham (NIH-R01AG047596), Russos (NIH-U01MH116442), Schroeder and Milham (NIH-R01MH111439), and Schroeder, Milham, Franco and colleagues (NIH-P50MH109429) already include explicit data-sharing components, which will be further extended to other participants in this joint effort. Further, the proposed platform will undoubtedly provide unprecedented opportunities for the creation of synergies between engineering and neuroscience programs. This synergy will be promoted and maintained through annual in-person users' meetings held on the NKI campus, during and after the development of the instrument. We will also hold monthly videoconference updates for all major users/substantial collaborators. *A UHF Collaboration Hub.* We intend this regional flagship facility to serve as a prototype for the next-generation head-only UHF scanners as well as a hub for true transdisciplinary collaboration (between technical and biological expertise), technical development, and training. The platform combines lessons learned and knowledge gained by Vaughan and colleagues at the University of Minnesota with cutting-edge technology developed by GE for use in UHF scanners. In particular, we propose to use the latest generation of gradient coils, which are capable of achieving a peak strength of 140 mT/m and slew rates up to 810 T/m/s. Now, by combining the components that worked in the past with current technologies, we are able to combine the UHF of 9.4T, excellent shimming capabilities, and next-generation gradient strength and slew rates to create a brain-dedicated MRI scanner that will be unmatched in regard to performance for *in vivo* human and NHP neuroimaging. *Regional Training and Educational Opportunities.* The 9.4T MR system will generate tremendous training and educational opportunities. NKI's location positions it as a neuroscientific and training resource for the greater NYC area. Located 15 miles from Manhattan, it is near 9 renowned research universities and institutions (Columbia University, Weill Cornell Medical College, NYU main campus, NYU Grossman School of Medicine, Stony Brook University, Rockefeller University, Icahn School of Medicine at Mount Sinai, Memorial Sloan Kettering Cancer Center, Yeshiva University) in NYS, 4 in New Jersey (Rutgers, New Jersey Institute of Technology, Stevens Institute, Princeton University), and two in Connecticut (Yale and UConn). The facilities at NKI have ample space for guest researchers and students for short- or long-term training opportunities. Students from neighboring institutions currently benefit from NKI facilities and use the free daily shuttle service that connects two points of Manhattan to the NKI campus.
Training opportunity with industry: The development of this instrument will be a partnership of academic (NKI, Columbia, NYU) and industrial (GE) researchers. The graduate students from the academic institutions will have a unique opportunity to directly collaborate with industrial leaders that develop high-end medical instruments. GE Global Research in Niskayuna, NY regards this shared venture as a rare opportunity to develop an educational and training internship program to provide a much needed resource for new engineers and scientists for industry growth.
9.4T-dedicated Graduate Course and Workshop. We will partner with the Columbia Medical Physics program to create a graduate course focused on the 9.4T platform; students will learn about the promises

and technical challenges associated with UHF imaging and spectroscopy, and will have opportunities to participate in and to develop 9.4T focused projects of their own. Additionally, senior personnel Juchem from Columbia teaches courses on Principles of Magnetic Resonance Imaging (BMEN E4430) and Principles and Practices of Magnetic Resonance Spectroscopy (BMEN E6410), leads an MRS mentoring program comprising joint mentees ranging from student to junior faculty level from both Columbia as well as extramural institutions in the NYC metropolitan area (i.e., Stony Brook University, part of the State University of NY), and holds an Annual MR Spectroscopy Workshop at Columbia (INSPECTOR Workshop). Vaughan teaches a graduate level MR Instrumentation course and trains graduate students and postdocs in this field as well. All of these activities will greatly benefit from access to this experimental 9.4T platform. A one-day UHF summer workshop organized by the new UHF Laboratory at NKI will also be held at NKI and be tailored to graduate students and postdoctoral fellows (e.g., lectures, tours). The NIH Conte Center directed by Schroeder (P50MH109429) already has funded educational outreach programs in place that will provide access to the 9.4T system during its development: 1) a summer undergraduate research experience (SURE) program and 2) an under-represented minority graduate student research support program in collaboration with City College of CUNY. *Support from Department Chairs.* We have received support for this project from the chairs of the Departments of Biomedical Engineering (X. Edward Guo), Physics (Dmitri N. Basov), Psychology (Kevin N. Ochsner) at Columbia University, the Department of Neuroscience at Mount Sinai (Paul Kenny) and Department of Biomedical Engineering at NYU (Andreas Hielscher). The chairs of these departments are enthusiastic about having their graduate students utilize the 9.4T for their PhD theses and coursework (see details about open door policy). More specifically, we have received enthusiastic commitments from the chair of the Department of Biomedical Engineering at City College of CUNY (Mitchell B. Schaffler), a school system renowned for its ethnic diversity (including many underrepresented minorities, 25.2% Black and 30.2% Hispanic students across its campuses). *Open Door Policy.* The development of this scanner will provide an enormous training opportunity for engineering and MR physics students in the Tri-State area. We will have an open door policy for professors to bring their undergraduate and graduate students to visit the 9.4T scanner while it is being assembled. Priority will be given to local universities that do not have substantial extramurally funded research with the objective of increasing the scientific curiosity of their students. This will be a unique opportunity for students since MRI assembly typically occurs in restricted access settings. We will also publicly document the development phases of the scanner, by creating a wiki page dedicated to the progress of the instrument development and post videos of the building phases of the instrument. Students will be invited to participate in this development project though Vaughan's Instrumentation course and graduate thesis projects. *No Cost Scan Hours for Training.* The scanner will be available, at no cost, to trainees (graduate students, postdoctoral fellows) for 4-hours per week during regular business hours (8AM-6PM, Monday-Friday). Additional free-time off-business hours will be made available when feasible. Such access will be predicated on approval of a short proposal by the trainee to the strategic advisory committee (SAC; with members from the collaborating institutions). Applications will be evaluated monthly by the SAC and awarded on a competitive basis. Success will be based on the impact, innovation, methodological rigor and feasibility of the applications; women, underrepresented minorities, and persons with disabilities will be encouraged to apply to increase diversity in the STEM field and will be given priority when other factors are equal. The availability of the scanner to trainees will be advertised by email to department chairs and researchers/mentors in the Tri-State area. *Establish a Model for Development Open to the Community:* Finally, NKI currently holds an annual Brain Day, during which NKI welcomes the community and provides tours of the imaging facilities. All ages are welcome, and activities include several hands-on activities and conversations with research scientists about careers in brain science and technology and how they can contribute to research; this will now be enhanced by including the 9.4T and the greatly enriched collaborative environment it will create. Scientific discoveries made with the 9.4T will be featured in presentations to the community.

E. Management plan

E.1 Instrument Placement: The proposed 9.4T scanner will be installed in a new facility which will be strategically located close to the current human 3T and small animal 7T MRI systems (see Fig. 9 and budget attachments), as well as the animal facility. This will ease the use of shared personnel with the other imaging equipment and also facilitate the transportation of NHP to the scanner. Since the 9.4T magnet does not have any active shielding, at least 350 tons of steel will be needed to shield the DC magnetic field.

NHP researchers from other local institutions will be able to access the facility for acute sessions through the loading dock located approximately 100ft from the entrance to the 9.4T facility. Animals will be brought from other institutions to the loading dock and then moved directly to the 9.4T animal prep area. The animal

prep area is completely separate from human patient areas, allowing distinct, non-overlapping, access for each of the groups. Following completion of the scanning protocols, animals will be transferred back to the loading docks and transported back to their home facilities. We note that we have been performing research with animal models for +30 years at NKI without a single problem with animal rights advocacy groups. NKI is also in the process of expanding its animal facilities and will include space to allow guest investigators to house NHPs up to multiple months for multi-session imaging protocols or those that require interventions. Guest NHPs will be segregated from the NKI NHP population to obviate the need for quarantine.

E.2. Instrument Administration: <u>Administrative Oversight: Daily Operations</u>: Drs. Vaughan and Franco will oversee implementation and daily operations as well as long-term planning and strategic development for the newly established UHF MRI laboratory. They will be advised by Dr. Colcombe, who currently oversees daily operations of the C-BIN scanner facilities at NKI, including a 3.0T Siemens Trio (used for human and NHP studies) and a 7T Varian small animal scanner, as well as by Dr. Milham (C-BIN Director). As a full-time NKI employee, Dr. Franco will have primary responsibility for daily operational decisions, in alignment with Dr. Vaughn's leadership (a 25% NKI employee). Drs. Vaughan and Franco will be responsible for preparing annual reports and publications, as well as monthly usage reports for the Strategic Advisory Committee (SAC) to facilitate review of development progress and scan usage allocations (for appropriateness and sufficiency of scan access). They will also be responsible for reconciling scheduling conflicts or difficulties that may rarely arise. The SAC will also be consulted for resolution of conflicts, with majority of votes being the deciding factor. If there is a tie,
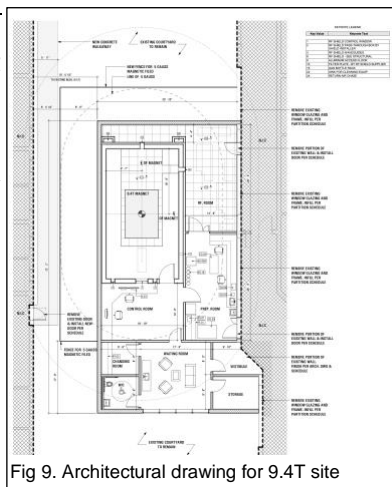

Fig 9. Architectural drawing for 9.4T site

Dr. Convit (SAC Chair) will cast the deciding vote. If he is absent, Dr Davachi (SAC co-Chair) will have the deciding vote. <u>Technical Expertise:</u> Drs. Vaughan, Foo, Franco, and Sodickson will orchestrate the facility design, magnet and console installation, system integration and acceptance testing with the aid of their technical staff, building architects, and the Tesla Engineering LTD contractors. Focusing on the console development and delivery, GE will deliver and install their 9.4T broadband console together with their head gradients and 128 channel, multi-nuclear RF receiver. Dr. Vaughan and his engineering team, working with GE (Foo and Kelley), will install and integrate the CPC broadband RF power amps, specified in a separate equipment quote attached. Pulse sequence programming and RF coils will be developed by the Vaughan and Sodickson labs. Equivalent developments have been accomplished with this 9.4T magnet before; the main difference is that this time we will integrate 2nd generation gradient equipment co-developed with GE, compared to the 'home-built' equipment previously developed in Minnesota. GE will provide training on their console. Safety training will be provided by our experienced team of high field experts. <u>Human Resources:</u> Senior personnel supporting the 9.4T scanner organized per specialization (Note: Other non-senior personnel are not listed due to lack of space in the application). *Principal Investigators:* **J. Thomas Vaughan, PhD (**NKI/Columbia; Administration, Engineering, MRI Technical Support): Lead, hardware configuration specification, design, build, integration, safety, and testing of 9.4T MRI. **Alexandre R. Franco, PhD** (NKI; Administration, Engineering, Human Imaging, Informatics, MRI Technical Support): Co-Lead, Software configuration specification, implementation, testing of 9.4T MRI, lead cloud based informatics efforts, and support for human imaging. **Michael Milham, PhD, MD** (NKI; Administration, Human Imaging): Administrative support and management/supervision on human imaging. **Daniel Sodickson, PhD** (NYU; Engineering): Parallel imaging, transmit and receive. **Thomas Foo, PhD** (GE Research; Engineering): Gradient design and build. *Senior Personnel:* **Stanley J. Colcombe, PhD** (NKI; Administration, Human Imaging): administrative support and management/supervision on human imaging. **Dough Kelley, PhD** (GE Healthcare; Engineering): Console design and build. **Christopher Collins, PhD** (NYU; Engineering): RF, gradient and magnet field modeling. **Ray Lee, PhD** (Columbia; Engineering): fMRI, physiological monitoring and other peripheral instrumentation interface. **Sairam Geethanath, PhD** (Columbia; Engineering): GE EPIC programming. **Christoph Juchem, PhD** (Columbia; Engineering): Multi-coil dynamic shim design and build. **David Guilfoyle, PhD** (NKI; Engineering): X-nuclei spectroscopy and imaging development. **Dikoma Shungu, PhD** (Cornell; Engineering): X-nuclei spectroscopy and imaging development. **Yi Wang, PhD** (Cornell; Engineering): Quantitative susceptibility mapping for high field protocol development and acquisition. **Simone Winkler, PhD** (Cornell; Engineering): RF coil modeling, design and build. **Priti Balchandani, PhD** (Mt. Sinai; Engineering): High field imaging protocol development

and signal processing. **Ricardo Latanzi, PhD** (NYU; Engineering): Physical optimization of MR signal acquisition parameters. **Jia Guo, PhD** (Columbia; Engineering) **Develop and support small animal imaging protocols, Service Engineer, To be Hired** (NKI; Engineering, MRI Technical Support): Operation, maintenance and applications support. **Charles Schroeder, PhD** (NKI, Columbia; Non-Human Primate): Support NHP users. **Vincent Ferrera, PhD** (Columbia): Support for external NHP users. **Brian Russ, PhD (NKI):** Support in awake NHP imaging. **Ranjen Sangoi (NKI):** MRI technician. Strategic Advisory Committee (SAC). We selected 13 members of our SAC to represent the broad interests of different users while attending to diversity and inclusion. The SAC plans to meet quarterly. The committee will include administrators and also representatives of investigators conducting technical development, and both human and NHP imaging. Chair: Antonio Convit, MD, Deputy, Director, NKI (Senior Institutional Official). He is in charge of strategic hiring decisions at NKI and will help implement recommendations of this committee; he has the appropriate experience and standing at NKI and NYU to chair this committee. *Co-Chair:* Lila Davachi, PhD* (Research Scientist at NKI and Dept of Psychology at Columbia); *Administration:* Michael Milham, MD, PhD (*Director of the Center for Biomedical Imaging and Neuromodulation, NKI*); *Engineering and MR Physics:* Riccardo Lattanzi, PhD* (*Radiology Department, NYU*); Ray Lee, PhD * (Columbia ZMBBI); Dikoma Shungu, PhD (Physics in Radiology at Cornell). *Neuroscience and Translational Applications:* Charlie Schroeder, PhD (*NKI, representing NHP users*); Randy Nixon, PhD, MD, (NKI, representing small animal researchers); Vincent Ferrera, PhD (*Columbia, representing external NHP users*); Daphna Shohamy*, PhD, (Psychology Columbia); Vahram Haroutunian, PhD (*Director of the NeuroBioBank at JJ Peters VA Medical Center and professor of Psychiatry and Mount Sinai, major ex vivo researcher*). *Border Impacts / Training:* Christoph Juchem, PhD (Biomedical Engineering and Radiology (Physics) at Columbia University); Biyu He*, PhD (Departments of Neurology, Neuroscience and Physiology, and Radiology at NYU). Notes: * Currently is /or recently was a PI on an NSF grant; Vaughan and Franco and Colcombe will be non-voting members. Maintenance: A service agreement will be signed with GEHC and Tesla Ltd. for the maintenance of the 9.4.

E.3. Procedures for Allocating Instrument Time. Eligible Users. Consistent with established policies of C-BIN, all accredited investigators at NKI and the New York State Psychiatric Institute (NYSPI), sister institutions under the joint administration of the NY State Office of Mental Health, will have ready access to the proposed 9.4T MRI scanner. External, non-NKI users will also be able to request access to C-BIN scanners, either indirectly through collaboration with NKI investigators, or directly following completion of a service contract and business associate agreement. Scheduling priority is given to federally-funded major and minor users to ensure that project goals can be efficiently achieved. Usage Cost. Current Siemens 3.0T MRI scanner usages rates for C-BIN are $675/hour; this cost covers the MRI scanner usage, certified MRI tech and a read of anatomical scans by a licensed neuroradiologist. The same rate and supports will be applied to the proposed 9.4T MRI scanner for use during business hours. A reduced rate of $200 per hour will be applied for usage outside of regular business hours; no MRI technician is provided during such times. Accessible User Time (AUT): AUT for the first year following the award is calculated based on institutional operation of 46 weeks / year (6 weeks/year off), with 40 hours / week of available technician time (minus 5 hours/week for routine cleaning, maintenance and phantom data collection for quality assurance) and 16 hours per week for imaging without a technician present (at night). This will permit 9.4T experiments to be conducted for 51 hours per week. We expect the scanner will be operational to conduct neuroimaging experiments by the end of 2024. Hence, for year #1 of operation (2025) we project 918 hours (18 weeks x 51 hours/week) of accessible user time (AUT) of instrument usage. For years 2+, we expect a minimum of 2346 annual AUT (46 weeks x 51 hours/week). Given the network of MRI-focused investigators in the NYC area already identified in this proposal, and expected growth, we anticipate that the AUT will increase and eventually require an additional radiological tech, which will be supported by user fee revenues. **E.4 Instrument Development:** The proposed timeline for the development of the 9.4T scanner is shown in the Gannt chart.