MRI

UHF MRI techniques break ground in measuring brain physiology and function

Innovation with Integrity

The Center for Neuroscience Imaging Research (CNIR) in the Institute of Basic Science (IBS), Suwon, Korea, is working to develop novel neuroimaging techniques to investigate underlying biophysics, physiology, and biology, and to utilize new tools for animal and human brain research.

In his position as CNIR director, leading the CNIR which has more than 100 employees and 10 principal investigators, Dr. Seong-Gi Kim aspires to surpass mere comprehension of brain processes; his aim is to delve deeper into the underlying causality. He is driven to understand the reasons behind specific neural responses and the factors influencing them. This curiosity about the intricate workings and relationships behind brain function has been the driving force of his career at the forefront of magnetic resonance imaging (MRI) research, with a strong emphasis on its application in clinical settings.

"My background is in human functional MRI (fMRI), and I want to understand the contributing factors to the fMRI signal," Dr. Kim explains. *"I'm looking to find how we can utilize fMRI to solve questions that have never been addressed before. We want to move beyond correlation to determine causality. For example, if you use fMRI and see an active area, what's driving that specific activity? We're developing tools to understand that."*

fMRI is a non-invasive technique that measures changes in blood flow related to neural activity. Ultra-high field (UHF) MRI enhances the sensitivity of fMRI, enabling more accurate and localized mapping of brain activity in response to specific stimuli or tasks. This capability helps researchers study brain function and investigate the neural networks involved in different cognitive processes.

Working with cutting-edge technology from Bruker BioSpin, Dr. Kim and his colleagues are pushing the boundaries of UHF MRI with the ultimate purpose of finding new ways to measure brain physiology and function.

Measuring brain physiology and function

MRI is one of the world's most powerful and versatile neuroimaging tools for the noninvasive measurement of brain structure, physiology, and function with high spatial and temporal resolution. The CNIR's Functional Neurovascular Mapping Team develops high-resolution MRI and optical imaging approaches for detecting neural or hemodynamic responses to external stimuli (including optogenetic and electric), and for mapping functional activities in animals and humans. Two major approaches are used: macro- and meso-scale functional imaging with UHF MRI and wide-field optics, and microscale mapping with multi-photon microscopy in health and disease.

"We want to provide tools for neuroscientists to enhance their research dramatically," Dr. Kim explains. *"Our goal is to provide information they've never seen before. By giving them the big picture, we can help scientists pinpoint the information they are looking for in detail, so they can find what is most likely to be the underlying mechanism or the source of the neuropathology and decide on the next steps."*

The team is made up of the Advanced MR Neuroimaging and Neurovascular Coupling units. With availability of ultrahigh magnetic fields (7 Tesla MRI for humans, and 9.4 Tesla and 15.2 Tesla MRIs for animals), the Advanced MR Neuroimaging team focuses on developing ultrahigh resolution fMRI, layer-specific fMRI, and dynamic blood oxygenation level-dependent (BOLD) MRI with hypoxic/hypercapnia challenge in animals and humans. These fMRI techniques are combined with cell-type-specific optogenetic, chemogenetic, or electric modulations for determining neural circuits in healthy and diseased animals.

For example, Dr. Kim and his team use fMRI with optogenetic neural manipulation as a powerful tool that enables brain-wide mapping of effective functional networks. This work includes mouse optogenetic functional magnetic resonance imaging (opto-fMRI).(1, 2) In complementary work, the Neurovascular Coupling team uses cellular-resolution optical imaging techniques to investigate the relationship among neurons, glial cells, and the vascular system for developing novel treatments of brain disorders, including Alzheimer's disease, epilepsy, and brain cancer. In such brain disease conditions, the interaction between immune cells introduced from the periphery and innate glial cells present in the brain can play a critical role in the pathological development process.

While Dr. Kim started his career in human studies, his more recent work has turned to preclinical animal studies to learn more about the causality of the effects observed in human research. By studying disease progression and treatment effects in animal models, insights can be gained into potential therapeutic targets for translation to human clinical trials. Dr. Kim believes unraveling the causality of diseases is a fundamental aspect of medical research and healthcare. This research has far-reaching implications for the development of effective treatments, preventive strategies, and public health initiatives, ultimately leading to improved patient outcomes and a healthier population.

"I wanted to go back to basics, in a way, to understand what was going on," Dr. Kim says. *"The degree of manipulation in human observational studies is low, so I went back to animal studies to answer questions about why we were seeing certain things. That's where fMRI really benefits this work, as you can silence one part of the animal's brain or activate another to see what changes to determine the causality of observations."*

Seong-Gi Kim, Ph.D., joined the human fMRI research team at the Center for Magnetic Resonance Research, University of Minnesota, in 1991, which produced one of the first human fMRI papers. After spending a decade at the University of Minnesota and advancing his academic rank to full Professor, Dr. Kim moved to the University of Pittsburgh to build a state-of-the-art neuroimaging center. Dr. Kim was appointed as the Paul C. Lauterbur Chair in Imaging Research, which was created for the honor of Nobel Laureate, MRI-inventor Paul C. Lauterbur. Dr. Kim moved back to Korea in 2013 to direct the CNIR and to serve on the faculty of Sungkyunkwan University. His research interest focuses on developing MRI techniques for measuring brain physiology and function, to determine relationships between neural activity and hemodynamic responses, and to apply imaging tools for answering questions about systems neuroscience.

Overcoming hurdles in preclinical animal studies

MRI allows researchers to obtain detailed and high-resolution images of the brain's anatomical structures in small animals, such as rodents. This technique enables the precise visualization of brain regions and their connectivity, aiding in understanding neural circuits and brain organization. However, achieving high spatial resolution in rodent imaging can be technically demanding, requiring specialized hardware and pulse sequences. To minimize movement during imaging, rodents are usually anesthetized, which can affect brain function and potentially confound study results. Although rodent models are widely used in neuroscience research, findings from rodents may not always directly translate to humans due to species differences.

Dr. Kim and his team use UHF MRI to address these challenges by enhancing the sensitivity of various imaging techniques, such as fMRI and molecular imaging, enabling researchers to investigate brain activity and specific molecular processes with higher precision. Higher field strengths can result in higher sensitivity, which is crucial for high-resolution imaging. UHF MRI also facilitates chemical exchange-sensitive MRI or spectroscopy investigations, allowing researchers to measure concentrations of specific neurochemicals in the brain, which can provide valuable insights into neurological disorders and brain function.

To achieve flexible manipulation of neural excitation throughout the mouse cortex, Dr. Kim and his collaborators incorporated spatiotemporal programmable optogenetic stimuli generated by a digital micromirror device into an MRI scanner via an optical fiber bundle. Brain-wide effective connectivity of atlas-based cortical regions is generally congruent with anatomically defined axonal tracing data, but is affected by the types of anesthetics that act selectively on specific connections. The use of fMRI combined with flexible optogenetics opens a new path to investigate dynamic changes in functional brain states in the same animal, through high-throughput brain-wide effective connectivity mapping.(3)

"While there are still species differences, using UHF MRI in rodent studies may yield more relevant findings compared to lower field strengths, bridging the gap between preclinical and clinical research," Dr. Kim says. *"UHF MRI studies in animal models can provide valuable insights into basic brain function, which can guide human neuroimaging studies and advance our understanding of human brain networks and cognition."*

Identifying potential therapeutic targets

The insights gained from Dr. Kim's UHF MRI work in neuroscience research also have the potential for clinical translation, particularly in identifying potential therapeutic targets for drug development and personalized treatment strategies. Preclinical studies with UHF MRI can assess the effectiveness of potential therapeutic interventions before advancing to human clinical trials, which can help in optimizing treatment protocols and identifying drugs that are more likely to be effective in humans. The technique can also identify specific biomarkers related to disease progression and treatment response, which may be useful for diagnosing neurological disorders at early stages and monitoring disease progression in clinical settings.

"These tools are useful for basic research, but they also need to be easy enough to be useful for humans in a clinical setting," Dr. Kim explains. *"Identifying the root causes of a disease allows for the development of targeted and more effective treatments. Treating the cause rather than just managing symptoms can lead to better outcomes and potentially even cure the disease."*

Their fMRI work includes the use of BOLD contrast to map brain activation in humans and animals. Non-invasive mapping of cerebral perfusion is also critical for understanding neurovascular and neurodegenerative diseases. However, perfusion MRI methods cannot be easily implemented for whole-brain studies in mice because of their small size. This non-invasive, repeatable, simple hypoxia BOLD-MRI approach is viable for perfusion mapping of rodents. Yet it also has potential clinical applications, including cognitive neuroscience, psychology, and clinical research to better understand brain disorders, cognitive processes, and the underlying neural mechanisms of various functions.(4)

"BOLD imaging has revolutionized the study of brain function because it allows researchers to non-invasively investigate brain activity in vivo," Dr. Kim says. *"When a specific brain area becomes active, there is an increase in the demand for oxygen and nutrients to support the increased neural activity. In response, blood flow to that area is increased to meet*

this demand. However, the increase in blood flow occurs at a higher rate than the increase in oxygen consumption. As a result, the ratio of oxygenated to deoxygenated hemoglobin in the blood changes, leading to an increase in the concentration of oxygenated hemoglobin. The MRI scanner detects these changes in blood oxygenation levels by measuring the magnetic properties of hemoglobin. It has been used in a wide range of animal studies and is well established in humans, but the specificity and sensitivity greatly benefit from ultra-high magnetic fields."

World-class MRI technology

Over Dr. Kim's long career in fMRI, he has worked with instruments from several vendors. His more recent interest in the Bruker UHF BioSpec instruments was sparked by the company's reputation and the availability of the highest commercially available preclinical MRI instruments. These instruments offer unparalleled signal-to-noise ratio (SNR) for in vivo imaging and enable groundbreaking research, whether addressing fundamental questions or treatment of diseases. In addition to increased sensitivity, Dr. Kim's reasons for choosing Bruker's UHF instruments include higher magnetic susceptibility and increased spectral dispersion, which enable his team's novel studies.

"When I moved to Korea, I bought the BioSpec 9.4 Tesla instrument as a default, because that's what I'd used for a long time," he remarks. *"But sensitivity is very important in fMRI research, which is why I decided to order the BioSpec 15.2 Tesla. When you go to a higher field, you also need to improve your experimental technique, and it's had a significant impact on our research and what we're planning. Plus, the Bruker instruments work well with multiple lines of our research, so that was part of the decision-making process."*

More than the technical capabilities, however, it was the support from Bruker that freed up Dr. Kim's time and energy to pursue these new fields of study.

"When I became a Bruker user, the support was so good, I didn't need to waste my time changing the set up and fixing issues. Now I can concentrate on science. It's a big plus."

A world-leading center for brain research

The combination of UHF MRI with other cutting-edge neuroscience techniques holds great promise for advancing the understanding of the brain and its disorders, leading to improved clinical diagnostics and treatments in the future. In one upcoming project, Dr. Kim and his team are expanding their research to perform more sensitive molecular imaging to quantify concentrations of specific neurochemicals in the brain. This work has implications for studying neurotransmitter imbalances and metabolic changes in neurological disorders.

Even with his center's record of success, Dr. Kim remains committed to a future that focuses on solving new questions and exploring novel methods for assessing brain physiology and function.

"From an international perspective, my goal is to bring our center to the next level," he says. "I want our center to become a global pioneer in the field. We want to have an impact on scientific research that will pave the way for future generations of discovery."

For more information about Bruker's preclinical imaging solutions, please visit:
https://www.bruker.com/en/products-and-solutions/preclinical-imaging.html

References:

1. Shim, H. J., Im, G. H., Jung, W. B., Moon, H. S., Dinh, T. N. A., Lee, J. Y., & Kim, S. G. (2022). Protocol for mouse optogenetic fMRI at ultrahigh magnetic fields. STAR protocols, 3(4), 101846. https://doi.org/10.1016/j.xpro.2022.101846
2. Jung, W. B., Jiang, H., Lee, S., & Kim, S. G. (2022). Dissection of brain-wide resting-state and functional somatosensory circuits by fMRI with optogenetic silencing, Proc. Natl. Acad. Sci., USA 119 (4), e2113313119. https://www.pnas.org/doi/abs/10.1073/pnas.2113313119
3. Kim, S., Moon, H. S., Vo, T. T., Kim, C. H., Im, G. H., Lee, S., Choi, M., & Kim, S. G. (2023). Whole-brain mapping of effective connectivity by fMRI with cortex-wide patterned optogenetics. Neuron, 111(11), 1732–1747.e6. https://doi.org/10.1016/j.neuron.2023.03.002
4. Lee, D., Le, T. T., Im, G. H., Kim S. G. (2022) Whole-brain perfusion mapping in mice by dynamic BOLD MRI with transient hypoxia. Journal of Cerebral Blood Flow & Metabolism. 42(12), 2270-2286. doi:10.1177/0271678X221117008

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