

## Medicine Plus

Global Opinion

### Current status and future challenges in brain imaging: Insights from leading experts

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The field of brain imaging is rapidly evolving, driven by technological advancements and a deeper understanding of the brain's complexity. To gain insights into the current status and future directions in brain imaging, we interviewed 15 renowned scholars during the 2023 and 2024 Annual Conferences of the Organization for Human Brain Mapping (OHBM). These experts provided valuable perspectives on the remarkable progress and significant challenges facing the field. Here, we offer brief summaries of these discussions in their own words.



**Alan C. Evans**, Montreal Neurological Institute, McGill University, Canada

The current status of brain imaging is one of remarkable progress and significant complexity. Over the past few decades, we have seen the field evolve from rudimentary positron emission tomography (PET) studies to advanced multimodal neuroimaging techniques. Structural and functional brain imaging have now established themselves as distinct disciplines, blending mathematics, statistics, imaging, and neuroscience. We have moved beyond simple activation studies to sophisticated analyses involving structural variability and connectomics, offering a comprehensive view of brain networks and their dynamics.

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However, this progress brings its own set of challenges. One of the main hurdles we face is the integration and analysis of the vast amounts of data we are now able to collect. We need to develop more refined and specific experimental paradigms to discern subtle differences in brain activity and structure. The field is also grappling with the need for global collaboration. Traditionally dominated by Western research teams, we must now combine data from diverse genetic backgrounds across the world to truly understand the variations in brain structure and function. Looking ahead, the future of brain imaging lies in large-scale data integration and the application of machine learning and big data analytics. We are on the brink of a new era where we can study millions of subjects, thanks to the infrastructure and computational power we have developed. This will allow us to answer complex questions about brain diversity and disease with unprecedented statistical power.

Another critical challenge is the translation of our observational data into explanatory, mechanistic models. We are just beginning to understand the spatial-temporal dynamics of brain connectivity influenced by genetic and environmental factors. The next step is to develop models that can explain these patterns and provide insights into the underlying mechanisms.

In conclusion, while brain imaging has made incredible strides, we must continue to innovate and collaborate on a global scale. The integration of diverse data sets, the development of advanced computational models, and the translation of our findings into practical applications will be key to overcoming the challenges ahead and advancing our understanding of the human brain. For further reading, see Ref.<sup>1</sup>



**Arno Villringer**, Max Planck Institute for Human Cognitive and Brain Sciences, Germany

The field of brain imaging is incredibly dynamic and multifaceted. Currently, we see a profound integration of various research directions within our laboratory. My personal focus lies in the interaction between the body and the brain, exploring how this interplay influences both brain and systemic diseases. It is clear that every bodily disease has a reflection in the brain, and conversely, brain disorders have systemic effects. This holistic perspective aligns well with traditional Chinese medicine, which views the body as an interconnected system.

Our ongoing projects include large-scale studies on the interactions between diet and the brain, examining why we often overeat and the changes in the brains of overweight individuals. Another key area is the brain-heart interaction, investigating how brain activity can induce heart diseases and vice versa. Additionally, we have been exploring the somatosensory system for many years, aiming to understand the top-down and bottom-up neural mechanisms involved in diseases.

Despite the progress, we face numerous challenges. Artificial intelligence (AI) holds great promise for breakthroughs but also poses risks of misuse and fabrication. Ensuring reproducibility in our research is another significant challenge. Furthermore, the world is fraught with conflicts that divert resources from research, which should be directed toward improving human well-being.

Looking forward, one of our exciting hypotheses, recently published, suggests that hypertension originates in the brain rather than elsewhere in the body. Confirming this could revolutionize our understanding and treatment of the condition. To enhance originality in technology, methods, tools, and results translation, we need a solid foundational education, encouragement of interdisciplinary research, and long-term funding to allow for sustained research efforts. For further reading, see Ref.<sup>2</sup>



**Bharat B. Biswal**, Department of Biomedical Engineering, New Jersey Institute of Technology, USA

Currently, my research in brain imaging encompasses several diverse directions. One major focus is on big data analysis, similar to the work in patient classification and subtype analysis. Another key area involves investigating signal characteristics to identify unique features that could provide insights into behavioral, physiological, and clinical indicators. Additionally, I am deeply involved in exploring brain white matter.

Looking to the future, someone once said, “The best way to predict the future is to create it.” If we envision a particular future, we should strive to build it. I believe the younger generation has immense potential and creativity. They are the drivers of future innovations. We must support and guide them while also learning from and listening to their perspectives. In this era of opportunities and challenges, we should encourage young people to pursue their dreams and work together to create a better and more progressive future.

In making brain science more accessible to the public and improving everyday life, it is essential to balance the pursuit of theoretical knowledge and practical applications. While understanding how the brain works is a noble quest, we must also find ways to address practical issues, such as helping patients with brain tumors. Though theoretical and practical questions may sometimes overlap, they can also diverge. Both types of inquiries are valuable, and we should not always focus solely on application-oriented questions. For further reading, see Ref.<sup>3</sup>



**Catie Chang**, School of Engineering, Vanderbilt University, USA

Currently, my research interests in brain imaging are broad but have a significant focus on functional magnetic resonance imaging (fMRI) analysis. One key area of our research involves understanding temporal fluctuations in fMRI signals. We analyze the fluctuations in time series or connectivity matrices to identify brain signatures of specific ongoing processes, such as physiological factors (like respiration and heart rate) and states of alertness. While traditionally, these physiological or state-related components might be removed to focus on other effects, our lab explores how these signals can provide new biomarkers and insights into disease and aging.

For example, investigating fMRI patterns linked with alertness could yield valuable clinical information, particularly since disruptions in vigilance-related pathways may occur in a number of diseases. This has led to collaborations with clinical researchers as we investigate what insights these data components can offer. Additionally, multimodal imaging remains a long-standing interest, such as combining electroencephalography (EEG), physiological signals, and fMRI. Integrating these measurements will be immensely powerful and is an exciting direction for our research. Our next big plans include applying multimodal approaches to various clinical populations. Combining fMRI with EEG and physiological signals from the body may help us gain comprehensive insights into specific diseases. We are also exploring how to integrate information from these signals using machine learning and other signal-processing techniques. For further reading, see Ref.<sup>4</sup>



**Christian Beckmann**, Donders Institute for Brain, Cognition and Behavior, Radboud University, The Netherlands

Many clinical conditions, behaviors, and cognitive processes are realized through mechanisms within the brain. Hopefully, we will eventually overcome the limitations of studying only oxygen metabolism and develop new biophysical methods to measure different aspects of brain activity and interactions. Imaging technology will continue to advance our understanding of how brain regions communicate and interact.

Our next major research plan involves extensive work on the concept of normative modeling, which is a fundamental and essential topic. While larger datasets are beneficial, normative modeling can effectively reflect spatial positions even with moderately sized datasets, accounting for uncertainties in sparsely distributed regions. Additionally, we will continue exploring the concept of overlapping gradients. Traditional methods divide the brain into discrete units, assuming constancy within these units, which biologically does not make sense. Instead, we aim to develop models that respect underlying biological features and create probabilistic atlases showing transitions and gradations between different brain regions. This approach will provide a more nuanced understanding of brain organization and function. For further reading, see Ref.<sup>5</sup>



**Daniel Margulies**, Integrative Neuroscience & Cognition Center, University of Paris and Centre National de la Recherche Scientifique, France

One of our contributions to the field of brain imaging is the work on the cortical gradients of functional integration. This research has unexpectedly gained immense popularity and has had a substantial impact on how we understand the brain's organizational principles. However, what I am most proud of is the cultural impact within the neuroimaging community, particularly through initiatives like the Neuro Bureau at the OHBM. This initiative, which we started 15 years ago, fosters an open, social, and supportive environment among researchers, especially students and postdocs. Maintaining this community spirit is crucial for keeping people engaged and active in the field.

Looking to the future, one of the most promising directions is a deeper understanding of the brain's organization and functional specialization. We aim to describe the characteristics of functional specialization along different axes and explore why specific functions localize where they do. This involves examining the factors along these gradient axes and studying the brain's performance across them. While our primary focus is on humans, extending these studies to animals is also essential. Understanding why certain species possess specific cognitive abilities while others do not requires cross-species research, helping us translate principles across different organisms. For further reading, see Ref.<sup>6</sup>



**Francisco Xavier Castellanos**, Department of Child and Adolescent Psychiatry, NYU Grossman School of Medicine, USA

In the field of brain imaging, my most representative and proudest achievement has been fostering a collaborative and supportive environment for young scientists. Another major contribution I have made is advocating for data openness, a concept I brought from the worm research community to neuroimaging. This idea was significantly propelled by Mike Milham, who did most of the work to actualize it. Open data has revolutionized the field by enabling researchers to address complex questions without the constant need to secure new funding for small-scale studies. This shift towards open science and data sharing has greatly accelerated advancements in brain imaging research.

Reflecting on the field's past and future, brain imaging has seen explosive growth over the past 30 years. Initially, our analyses were quite basic, often limited to measuring large brain regions. Today, we have a wealth of complex data and advanced algorithms to understand the brain's intricate workings. However, we still face significant challenges in fully understanding brain function and using imaging to improve mental health treatments.

One promising area is the application of imaging techniques like transcranial magnetic stimulation (TMS) to target specific brain areas in mental disorders. Tools like TMS, focused ultrasound, and infrared laser techniques are emerging, offering new ways to influence brain activity. Successful translation will depend on our ability to refine these technologies and integrate them into clinical practice effectively. Overall, while significant challenges remain, the future of brain imaging is bright, with numerous opportunities for innovation and discovery. For further reading, see Ref.<sup>7</sup>



**Michael Breakspear**, School of Psychological Sciences, University of Newcastle, Australia

Currently, my main research interest is developing wave theories related to brain function, specifically focusing on the wave-particle theory of the brain. This involves not only theoretical work but also creating a strong connection between theory, models, and data. We need to conduct experiments and use brain imaging data to test our models, ensuring that there is a tight linkage between the models and the brain mapping data. While theoretical work is essential, its true value comes when it is closely integrated with data that everyone is interested in.

The future of brain imaging holds many opportunities, especially in developing better experimental research, new ways to inspect experimental data and new theoretical models. Advances in neuroimaging methods, connectomics, and new technologies present new opportunities. For me, the most exciting aspect is the development of brain wave models and large-scale brain dynamics models that can explain the data we obtain, offering a bridge between statistical models and biophysical neural field models.

My future research plans include applying our wave equations to study dementia. This involves understanding how neural field theories can describe cognitive decline in conditions like Alzheimer's disease, which is a major challenge affecting a large portion of the population. We know about amyloid and tau proteins and tissue loss, but we lack an understanding of cortical function loss. Applying neural field theories to describe early cognitive decline in dementia could be a major breakthrough in the next five years. For further reading, see Ref.<sup>8</sup>



**Michael D. Fox**, Center for Brain Circuit Therapeutics, Harvard University, USA

My current research interest is centered on what I call the causal information sources in human brain functional mapping. Most functional brain mapping has been based on correlative neuroimaging, which is sufficient for predicting disease biomarkers. However, for interventions like TMS or deep brain stimulation (DBS), causal inference becomes crucial. Thus, our research focuses on brain lesions, TMS sites, DBS targets, and other areas that can provide causal links between brain regions and symptom changes. Our work demonstrates that brain lesions causing depression, TMS targets for relieving depression, and DBS electrodes modulating depressive symptoms all converge on a common depression circuit. This convergence of causal mapping is pivotal because it underscores the importance of causal inference for developing therapeutic targets. This foundational work provides a path for identifying therapeutic targets for various disorders.

The future of our field involves developing new treatment methods. Identifying therapeutic targets and developing treatments that can help patients who currently have no effective options would be important. This entails moving from statistical models to biophysical and neural field models that can explain the data we obtain. My next research interest also includes exploring the brain-body connection. This involves understanding how localized brain damage can significantly affect other organ systems, potentially using neuromodulation to treat diseases like cancer by controlling tumor growth through brain circuits connected to the lungs. This exciting frontier in neuroscience holds great potential for new therapeutic strategies.

In terms of translating research into practical applications, brain imaging should be used to guide interventions rather than just for diagnosis. This “neurosurgery model” utilizes imaging to guide procedures like DBS and TMS, offering a faster route to clinical impact than using imaging solely for diagnostic purposes. For further reading, see Ref.<sup>9</sup>



**Michael Milham**, Child Mind Institute, USA

One of my most representative and impactful works is the 1000 Functional Connectomes Project where we demonstrated the feasibility of aggregating resting-state fMRI data collected independently from different sites. This was a significant milestone, as many doubted the meaningfulness of combining data from different scanners. By showing it was possible and sharing the data openly, we set a precedent for open data sharing in the field, fundamentally changing the culture of neuroimaging research.

Looking forward, I believe that resting-state fMRI and functional connectomics will continue to be focal points in my research. I am particularly interested in how patterns of functional interaction change over time and how these changes impact behavior. Another exciting direction is the integration of multimodal approaches, such as combining fMRI with magnetoencephalography (MEG), to capture a more comprehensive picture of natural cognitive processes.

One of our current major research plans involves developing smartphone applications to gather real-world measurements and capture fluctuations in behavior and mood. These apps will collect subjective reports and use passive methods like changes in voice and physical activity to objectively monitor progress. This approach expands the scope of mental health care and research, offering better ways to understand and address signals related to conditions like depression. For further reading, see Ref.<sup>10</sup>



**Paul M. Thompson**, Keck School of Medicine, University of Southern California, USA

Over the past 30 years, my research has evolved through various stages, focusing on different themes approximately every five years. Initially, my work involved studying brain development in children through repeated MRI scans, using tensor-based morphometry to measure growth patterns. This led to the creation of a time-lapse movie of cortical development from ages 4 to 21 years, which remains one of our most cited works, showcasing the sequence of brain maturation from sensory areas to language and frontal regions during adolescence. A major shift in my research occurred with the introduction of genetics into brain imaging. Collaborating with Margie Wright in Brisbane, we studied brain images of twins to understand the genetic basis of brain structure. This work demonstrated the strong heritability of various brain features, leading to the establishment of the ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) Consortium. ENIGMA focuses on meta-analyses of imaging and genetic data to identify genetic variations that influence brain structure and function. This collaboration has grown to include studies on various neurological and psychiatric disorders, employing standardized methods across multiple sites to generate large datasets for robust analysis.

The future of brain imaging lies in the integration of AI and big data. Public datasets like the UK Biobank and the Human Connectome Project have provided immense resources for developing sophisticated AI models. These models can extract complex patterns from imaging data, offering new insights into brain function and its relationship with genetic and environmental factors. AI's ability to process vast amounts of data and identify subtle patterns will revolutionize our understanding of the brain, leading to more precise diagnostics and personalized treatments. One of my most challenging yet rewarding recent projects involves using AI to predict brain variability based on genetic data. This work, which was recently submitted for publication, demonstrates that genetic markers can account for about 7% of the variance in brain structure across populations. This significant finding supports the potential of genetic research in explaining brain variability and lays the groundwork for future studies linking genetic variations to brain health and disease. For further reading, see Ref.<sup>11</sup>



**Russell Poldrack**, Stanford Data Science and Department of Psychology, Stanford University, USA

One of my most representative and proud projects is the MyConnectome project, where I conducted 104 scans of my own brain and subsequent studies to understand individual variability. The project highlights the importance of detailed, longitudinal data to grasp the nuances of brain function and variability over time.

Looking forward, I believe computational modeling will play a crucial role in understanding the cognitive functions of the brain. With the advancement of AI models, these computational tools will become essential for unraveling the complexities of brain functions. Additionally, there's a need to focus on understanding short-term changes in brain function, spanning days to weeks, rather than just long-term changes over years. This could provide valuable insights into dynamic brain processes.

I have also been involved in discussions about the Research Domain Criteria (RDoC) framework, particularly regarding the ontology of what our experiments measure. This involves understanding the consensus and disagreements within the research community and using neuroimaging to elucidate these questions. My future research will continue to explore these aspects, aiming to clarify our scientific measures and their implications.

We have been working on open neuroimaging databases for a long time and are now planning to use these databases to develop foundational models for fMRI. Similar to how large language models address various problems, we hope to leverage our extensive databases to help researchers better handle smaller datasets. We have already made some progress in this area. For further reading, see Ref.<sup>12</sup>



**Thomas Nichols**, Big Data Institute, University of Oxford, UK

Currently, my research is focused on managing and analyzing large-scale neuroimaging data, particularly from the UK Biobank. This work has two main branches. The first involves extending existing tools, such as linear and mixed linear models, to handle the immense scale of Biobank data. For instance, tools like R, FSL, and SPM, which work well on single data, need to be scaled up to process tens of thousands of scans. The second branch focuses on developing new methods that address challenges unique to large datasets. A pertinent example is the issue of statistical inference with large sample sizes, where traditional hypothesis testing can become less informative due to the near-ubiquity of significant results. In these scenarios, new methods are needed to precisely characterize uncertainty within massive datasets.

The future of our field hinges on data sharing and the availability of large datasets. Some of my most impactful work, like demonstrating issues with cluster-level inference, relied on shared resting-state data. Open science and collaborative projects, like Hackathons and the Brain Imaging Data Structure (BIDS), are reshaping how we conduct research. BIDS, for example, has standardized data formats and fostered widespread collaboration, significantly advancing our field.

Challenges lie in understanding and interpreting big data. Large datasets provide better statistical power but also bring complexities in modeling and interpretation. The sheer volume of data increases the risk of confounding effects and subtle interactions, necessitating advanced statistical techniques and careful analysis. Looking ahead, I am particularly excited about modern statistical methods for characterizing spatial uncertainty in cluster or thresholded statistical images. These new methods, which did not exist a decade ago, are transforming how we detect and describe signals in neuroimaging data. For further reading, see Ref.<sup>13</sup>



**Thomas Yeo**, Centre for Translational MR Research, National University of Singapore, Singapore

Choosing my most representative and influential work is difficult, but I would say our 2011 brain mapping paper stands out. However, in the clinical realm, if personalized brain network mapping techniques can enhance brain stimulation, that might be our greatest contribution.

My current research interest has progressed beyond merely understanding the brain to exploring personalized treatments for brain disorders. After my PhD, I transitioned to cognitive neuroscience over the past 15 years. In the past few years, I started questioning the impact of my work and whether it was making a real difference to society. This led to my interest in personalized brain stimulation, which aligns well with my lab's work on personalized brain mapping. We are now exploring personalized TMS research and techniques.

The beauty of resting-state fMRI lies in its ability to identify multiple personalized brain networks in a single MRI scan. Therefore, a single MRI scan can be used to identify brain stimulation targets related to different disorders. We

are currently working on depression but are collaborating to extend our research to anxiety disorders. For further reading, see Ref.<sup>14</sup>



**Vince Calhoun**, Tri-Institutional Georgia State University/Georgia Institute of Technology/Emory University Center for Translational Research in Neuroimaging and Data Science (TReNDS), USA

My most representative and influential research is associated with Independent Component Analysis (ICA) and the development of the Group ICA of fMRI Toolbox (GIFT). Reflecting on this, I would emphasize the importance of letting data speak for itself and the critical role of data-driven methods in brain research. While hypothesis-driven research is crucial, especially when specific questions need to be addressed, relying solely on pre-existing assumptions can limit discovery. This is where data-driven approaches like ICA come in, allowing us to uncover patterns and insights we might otherwise miss. Currently, we are applying data-driven multimodal analysis to minimize the biases introduced by preset assumptions.

Looking forward, I remain optimistic about the clinical applications of our work. Despite the slower-than-expected progress and numerous challenges, the intersection of new algorithms, models, and deep learning with our understanding of brain cognition holds promise for significant advancements. It is essential to ask the right questions—those that can be translated into clinical settings to impact individual diagnoses and outcomes rather than merely highlighting differences.

My next major research plan continues to focus on multimodal data fusion, a field that remains underexplored. The complexity of integrating information across modalities presents a significant challenge, but it is not insurmountable. Although many are working with multimodal data, fewer are tackling the integration of this data to extract meaningful cross-modal information. This integration is crucial for advancing our understanding of the brain. For further reading, see Ref.<sup>15</sup>

The future of brain imaging research is poised for significant advancements driven by technological innovations and interdisciplinary collaboration. Integrating diverse data sources, developing personalized approaches, and fostering open science practices will enable researchers to uncover new insights into the brain's complexities. These efforts are crucial for precise brain mapping, improved diagnostic tools, and innovative treatments for neurological and psychiatric disorders.

The contributions of experts like Alan C. Evans, Arno Villringer, Bharat B. Biswal, Catie Chang, Christian Beckmann, Daniel Margulies, Francisco Xavier Castellanos, Michael Breakspear, Michael D. Fox, Michael Milham, Paul M. Thompson, Russell Poldrack, Thomas E. Nichols, Thomas Yeo, and Vince Calhoun highlight the importance of global collaboration, data sharing, and advanced computational models. Emphasizing personalized brain mapping and targeted interventions, alongside the application of machine learning and AI, will enhance our ability to analyze vast data and develop individualized treatments.

In conclusion, the future of brain imaging is bright, with opportunities for transformative discoveries that will deepen our understanding of the human brain. Open science and data transparency will drive collaborative and reproducible research, accelerating discovery and innovation. The collective efforts of the global neuroscience community will lead to groundbreaking insights and improved clinical outcomes, enhancing the quality of life for those affected by brain disorders.

*Of note, the group of experts interviewed was selected through convenience sampling, which lacks national and gender representativeness.*

#### **Informed consent statement**

All participants' informed consent statements have been obtained.

#### **CRedit authorship contribution statement**

**Xiaomeng Hu:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Chao-Gan Yan:**

Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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