Featured Articles

Dealing with Brain Disease

Atsushi Maki, Ph.D.
Hisaaki Ochi, Ph.D.
Masashi Kiguchi, Ph.D.

OVERVIEW: Brain disease has become a subject that can no longer be ignored when considering QoL in the modern context. While improvements in medical technology and living standards have helped tackle many forms of illness, humanity still lacks effective measures for dealing with diseases of the brain, the seat of consciousness. To take on this major societal challenge and contribute to global development, Hitachi is striving to develop solutions for dealing with brain disease. To achieve this, it is important to decode the meaning of complex neural circuits made up of more than 14 billion neurons each with thousands of interconnections to other neurons. In response to this challenge, Hitachi is working on ways of assessing clinical effectiveness by consolidating techniques for observing the function, structure, and behavior of cranial nerves and by understanding and modeling the processes that take place in the brain.

INTRODUCTION

ALONG with advances in medical technology, recent years have seen interest in ways of considering the state of ill health in the world based on use of disability-adjusted life-year (DALY) statistics[(1), (2)] that take account not only of disease incidence and mortality rates, but also the effect on a patient's life after contracting a disease. Fig. 1 shows DALY statistical data compiled from World Health Organization (WHO) statistics. The figure shows 2000 and 2012 data for middle-income countries experiencing rapid growth, and 2012 DALY statistics for high-income countries that are recognized as foreshadowing the future of the entire world.

The DALY statistic is also used in Japan, where it is generally calculated by the formula: (number of deaths × standard life expectancy at age of death in years) + (number of incident cases × disability weight of disease × average duration of case, in years, until remission or death), although certain corrections have also been added in recent years.

This DALY statistic can be thought of as a quality of life (QoL) indicator in the narrow sense of relating to health and gives an indication of how much mental disorders and other forms of brain disease (hereafter "brain disease") affect QoL. Also, from the trend in the DALY statistic, it is also known that the diseases that clearly increase in step with economic development are brain, neoplasm, heart, and musculoskeletal diseases. Based on data obtained by the analysis of direct medical costs, direct non-medical costs, and indirect costs[(3)], the economic cost of brain disease is in the order of 440 trillion yen when estimated in terms of national gross domestic product (GDP). This is approximately 5% of the total GDP.

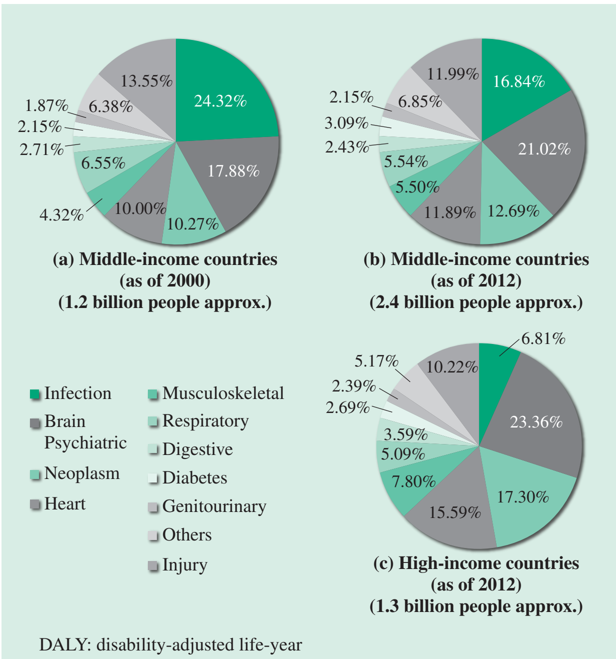


Fig. 1—International DALY Statistics.
The graph shows DALY statistics for different causes of health problems presented by income band (World Bank classification). Note, however, that stroke, which is usually classified as a heart condition, has been reclassified in the "brain psychiatric" category in this graph.

Techniques for the scientific understanding of the brain will be essential if prevention and treatment for this major societal challenge are to be established. This article describes the current progress and future plans for the development of technologies being undertaken by Hitachi to understand the brain in collaboration with clinical institutions.

MRI MEASUREMENT TECHNIQUES FOR EARLY DIAGNOSIS OF BRAIN DISEASE

MRI Measurement Techniques

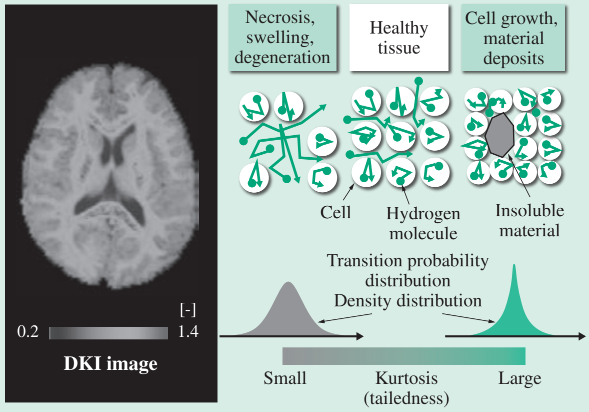
Magnetic resonance imaging (MRI) is a diagnostic imaging technique that utilizes the principle of nuclear magnetic resonance. Compared to X-ray computed tomography (CT), features of MRI include that it does not expose subjects to radiation and that it can obtain information on biological function as well as morphological information. Typically, the signal-to-noise (SN) ratio of an MRI system is proportional to its static magnetic field strength, and the performance of MRI systems has improved rapidly in recent years with systems of 3 T or more having been developed to enable imaging with high resolution and contrast (see Fig. 2).

The aging of the populations in developed nations in particular has made dealing with the rapid increase in neurodegenerative diseases such as Parkinson's and Alzheimer's disease an issue of particular concern. As with other major diseases, the prognosis is significantly improved by early diagnosis and treatment. However, because the early physical symptoms are similar to many other diseases, neurodegenerative disease has to date been diagnosed from the presence of major morphological changes of the brain in MRI scans, meaning that differential diagnosis could not be performed until the disease was well advanced. This has created a need for early differential diagnosis techniques.

This chapter describes diffusion kurtosis imaging (DKI) and quantitative susceptibility mapping (QSM), two diagnostic applications of MRI developed for the early diagnosis of neurodegenerative disease.

MRI: magnetic resonance imaging

Fig. 2—3-T Superconducting MRI System.
The 3-T superconducting MRI system (Hitachi Medical Corporation) shown here combines a 74-cm oval bore with high image quality achieved using four independent transmission channels.



DKI: diffusion kurtosis imaging

Fig. 3—Overview of DKI.
The figure shows an example DKI image. Hitachi is developing a technique for identifying the minute structural changes that occur in the early stages of neurodegenerative disease with the aim of enabling early diagnosis.

DKI

Diffusion weighted imaging (DWI), a diagnostic application of MRI that utilizes the diffusion of hydrogen molecules to image tissue characteristics, has already demonstrated its usefulness in the diagnosis of conditions such as brain infarctions and brain tumors. Whereas DWI uses the diffusion coefficient obtained by assuming that the transition probability distribution of molecular diffusion follows a normal distribution as its main diagnostic indicator, there has been growing interest in recent years in analytical methods that assume a non-normal distribution because of their ability to take full account of how the fine structure of tissue restricts diffusion. The reason for this interest is that these techniques have the potential to provide a sensitive means of identifying the minute changes in microstructure caused by disease.

DKI can image changes in the amount of insoluble material and density of tissue cells by using the kurtosis (tailedness) of the transition probability distribution as an indication of the extent to which the diffusion of hydrogen molecules is restricted by tissue structure (see Fig. 3). It can show the minute changes in white matter and gray matter structure that occur in the early stages of neurodegenerative disease. One of the challenges of DKI is that, while it dramatically increases the amount of diagnostic information that can be obtained, it takes longer to capture an image than DWI. However, this time has been shortened by using error propagation analysis to identify the imaging conditions that minimize measurement error[4]. Hitachi has led its competitors in the commercialization of this technology, making it available for routine clinical testing, with clinical research into the identification of Parkinson's disease symptoms currently underway in collaboration with Iwate Medical University[5].

QSM

The variable magnetic susceptibility of tissue causes localized variations in the magnetic field inside a body that is exposed to the magnetic field of an MRI magnet. QSM measures the MRI signal phase difference due to this spatial variation in magnetic field inside the body and performs a quantitative calculation of the magnetic susceptibility distribution in the tissue to produce an image of the distribution of magnetic susceptibility due to the presence of things like proteins and iron (see Fig. 4). This can observe iron deposits in tissue affected by degenerative disease prior to the appearance of morphological changes.

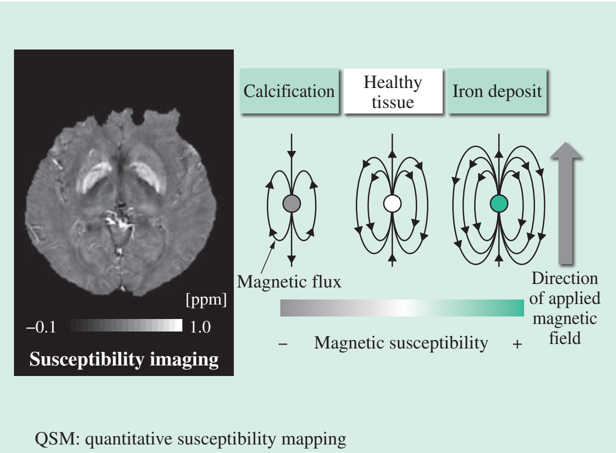


Fig. 4—Overview of QSM.
The figure shows an example magnetic susceptibility image. Hitachi is developing a technique for identifying abnormal iron deposits in neurodegenerative disease tissue.

While past measurement techniques have had problems with deterioration in estimation accuracy for microstructure, a technique has been developed that can detect minute changes by also performing estimation based on spatial frequency[6]. The effectiveness of this technique is currently being assessed through joint research with a university. In joint research with Iwate Medical University, research is underway on its use in conjunction with DKI for the early differential diagnosis of neurodegenerative disease[7], with the hope that achieving early identification will assist with the development of early-stage treatments.

APPLYING OPTICAL TOPOGRAPHY TO BRAIN DISEASE

Optical Topography

Optical topography is a technique developed for imaging brain function under everyday conditions[8]. It enables the topographic observation of brain activity by using two wavelengths of near-infrared light at which tissue is highly transparent to measure and image changes in blood flow due to neural activity on the surface of the brain (see Fig. 5). Research is being conducted into a variety of brain diseases, with optical topography systems developed based on this principle ranging from wearable units that target the frontal lobe to units that perform measurements of the entire head[9], [10], [11]. The technique is being used for an increasing range of clinical applications, with its use in assisting the differential diagnosis of depression symptoms approved for health insurance coverage in 2014. As a non-invasive technique that can perform measurements under everyday conditions, it is also being adopted for use in developmental neuroscience[12], [13], [14] and social neuroscience[15] (see Fig. 6).

Drug Efficacy Prediction Using Optical Topography

Chemical reactions underpin the functions of the brain. This makes drugs an important option for the treatment of brain disease. The safety and efficacy of drugs are determined by conducting large clinical trials, but just as everyone has a different personality, the neural circuits that are established during brain development differ from person to person. This means that the efficacy of drugs for brain disease varies from person to person. On the other hand, whereas the increasing prevalence of brain disease is leading to the increasing prescription of drugs, deciding whether to continue or halt the treatment involves observing the

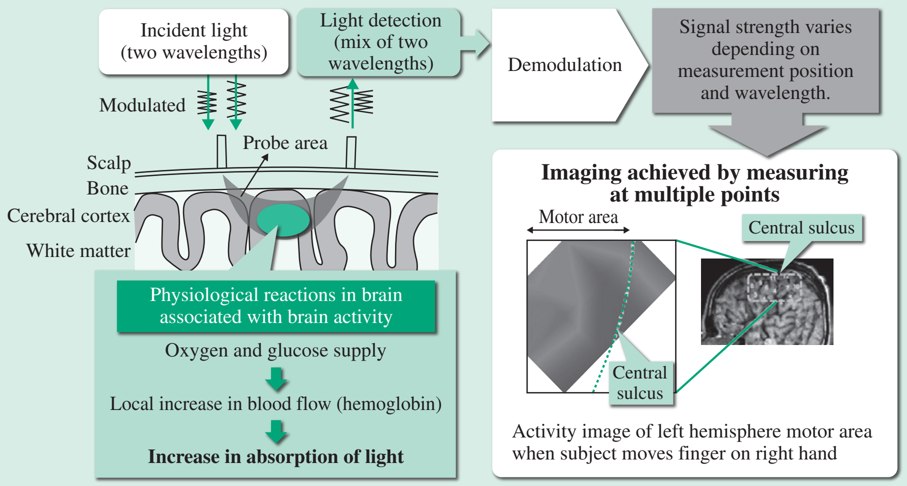


Fig. 5—Principles of Optical Topography.
Near-infrared light modulated at each wavelength and direction of incidence is shone through the scalp to measure changes in blood flow associated with brain activity.

patient for several months after the start of treatment to determine whether there is any sign of an alleviation of symptoms. If a technique were available for confirming the efficacy of drugs used to treat the brain, it would be possible to determine efficacy for each individual in more quantitative ways and to monitor the progress of the treatment.

For these common issues associated with brain disease, a technique has been devised that uses optical topography to provide information on the efficacy of drugs for the brain (joint research with Jichi Medical University and Chuo University) (see Fig. 7)[(16), (17)].

The technique for assessing the efficacy of drugs for brain disease enables the efficacy of a drug to be predicted early in the treatment, and shortens the several months it subsequently takes to confirm efficacy. In cases where it is difficult for the patient to recognize the efficacy of a drug, it also helps prevent patients from abandoning treatment because it helps them see the benefits of the treatment for themselves. Based on the same idea, the technique can also be applied to new therapies such as neurofeedback and cognitive-behavioral therapy, which seek to (re) construct nerves. By making a biological record of the

	Clinical and research use	Wearable unit for research	
Series	ETG series (clinical use) OTR series (research use)	WOT series	HOT121B
Photograph	FDA-approved model: ETG-4000 		
Application	Clinical applications (insurance-approved) •Assistance with differential diagnosis of symptom of depression •Pre-surgical diagnosis of language dominant hemisphere •Testing for epileptic focus	Frontal lobe research	Research into 46 regions of frontal lobe
Features	Two wavelengths, 24 to 120 sites, standalone	Two wavelengths, 10 to 22 sites, wearable (wireless), simultaneous measurement of four subjects	One wavelength, two sites, reduced skin blood flow, wearable
Sold by	Hitachi Medical Corporation	Hitachi High-Technologies Corporation	Hitachi High-Technologies Corporation
Manufactured by	Hitachi Medical Corporation	Hitachi Kokusai Yagi Solutions Inc.	Hitachi High-Technologies Corporation

FDA: U.S. Food and Drug Administration

Fig. 6—Optical Topography System for Use in Research and Clinical Testing.
The figure shows the range of systems available, including a model for measuring the entire head and wearable units that target the frontal lobe. The systems can be used both to perform detailed measurements of a subject's brain and to study the brain activity associated with communication through the simultaneous measurement of multiple subjects.

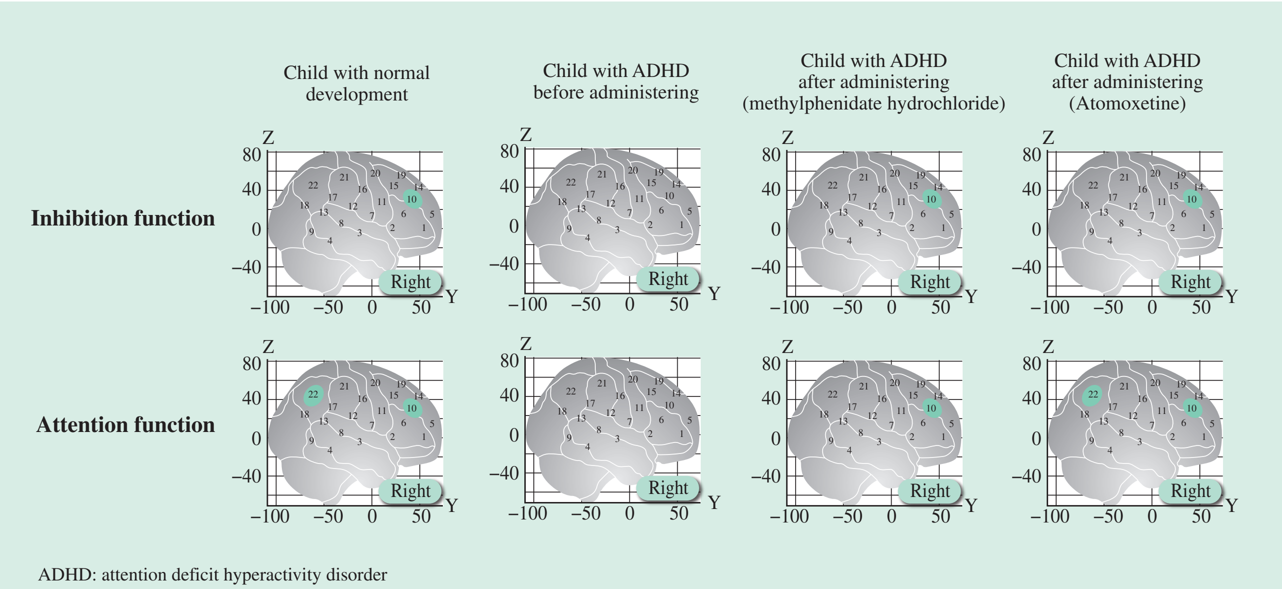


Fig. 7—Drug Efficacy Assessment for Children with ADHD.
Children who were administered methylphenidate hydrochloride sustained-release tablets and Atomoxetine showed the same response as a child with normal development when exercising the inhibition function and attention function (courtesy of Yukifumi Monden of Jichi Medical University).

condition of the brain, this enhances the patient's QoL by facilitating a shift from standardized to precision (personalized) medicine.

RE-WORK SUPPORT

When a mental illness such as depression causes a person to take a long-term leave of absence from work, it is not easy for them to resume employment soon after the illness goes into remission. Returning to work too soon frequently leads to taking more time off or being re-admitted to the hospital. Consequently, there is an emphasis on rehabilitative training prior to returning to work, with Hitachi providing a "re-work" (return to work) support program that is provided in the form of group training for employees who have taken time off. The objective is for such employees to establish patterns of daily activity, to recover the strength to resume normal work routines, and to avoid taking further time off by equipping them with resilience and the ability to deal effectively with stress in the workplace and elsewhere. This requires that individual employees develop the ability to control themselves by assessing their own state of mental and physical health.

The re-work support program uses factors such as depressive mood[18], stress, patterns of daily activity, quality of sleep, physical fitness, and ability to work (work capability assessment) as indicators of mental health. Typically, mental and physical health assessments involve things like self-evaluation questionnaires or interviews and observation by a clinical psychologist. However, subjective assessments often suffer from poor accuracy, such as an assessment that indicates the patient's condition is very good because the judgment is made in comparison with their experience of severe early-stage symptoms, or a patient pretending to be well in order to hasten a return to work, or, alternatively, deliberately claiming to be in poor health. In response, Hitachi has been developing measurement techniques for the objective assessment of mental and physical health.

Changes in brain function or physiology due to depressive mood, stress, or other factors are measured using brain function measurement systems (optical topography) and autonomic nerve measurement systems (fatigue and stress assessment systems) respectively. Factors like patterns of daily activity and quality of sleep are measured using accelerometers (life logs), and ability to work is measured by monitoring personal computer (PC) use (BM1). The aim is to augment the patient's self-assessment and advice from a clinical psychologist by collecting this data over time and presenting the state of recovery in a variety of visual forms (see Fig. 8), making the re-work support program more effective. This use of measurement-based mental healthcare is currently being trialed through use in the re-work support program described above.

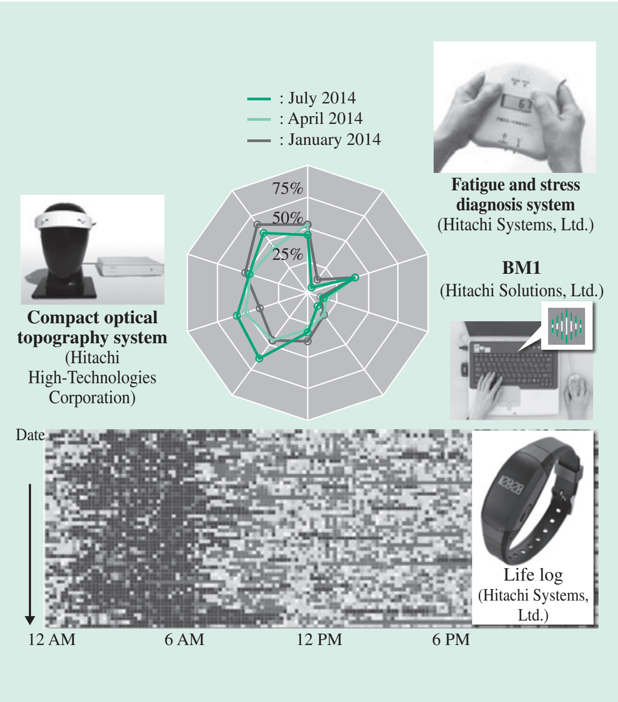


Fig. 8—Visualization of Mental Health.
The figure shows a radar chart that shows how measurements change over time (top) and a "life tapestry" that indicates the pattern of daily activity (bottom).

In the future, it is anticipated that this technology will be combined with information technology (IT) to reduce its cost, and that it will be deployed in comprehensive mental healthcare services that include patient self-assessment after returning to work and help prevent mental illness.

FUTURE OUTLOOK

The workings of the brain are extremely complex and develop over time as information is absorbed from the environment. This dynamic and complex circuitry makes it difficult to achieve a quantitative understanding of the cause and effect relationships that lead to brain disease. Techniques for obtaining a diagnosis have been developed by correlating symptoms with the signals observed using different measurement modalities. However, given the severe social effects of brain disease noted above, there is an urgent need to develop solutions that can genuinely deal with brain disease. While many techniques have been developed for the sake of prevention and treatment that provide results in isolation, as of this time they have yet to reverse the worsening in DALY statistics.

One of the key challenges in all this is to create "precision medicine" that can deal with the highly individual nature of brain disease. By providing consistent measurement indicators that cover everything from prevention to diagnosis and treatment, even if for only a single disease, it will be possible to adapt to individual diversity. To achieve this, it will be necessary to build systems and establish a foundation of knowledge for providing a quantitative understanding of gene expression and variation, and cranial nerve function, structure, and behavior in cranial nerve circuits that are built up over the course of a lifetime. This is because acquiring an understanding of ever-changing cranial nerve circuits will require the collation of systematized knowledge by first classifying brain states based on genes and behavior, and then determining the brain structure and function associated with each classification. In the future, it will be important to build a "development compass" by undertaking research and development of information theory and sensor technology that can integrate the three factors for understanding the brain in an informational sense and interpret them (see Fig. 9).

This integration of new technology platforms and the reconstruction of a foundation of knowledge will accelerate the development of nerve (re)construction techniques that utilize technologies, such as robotics

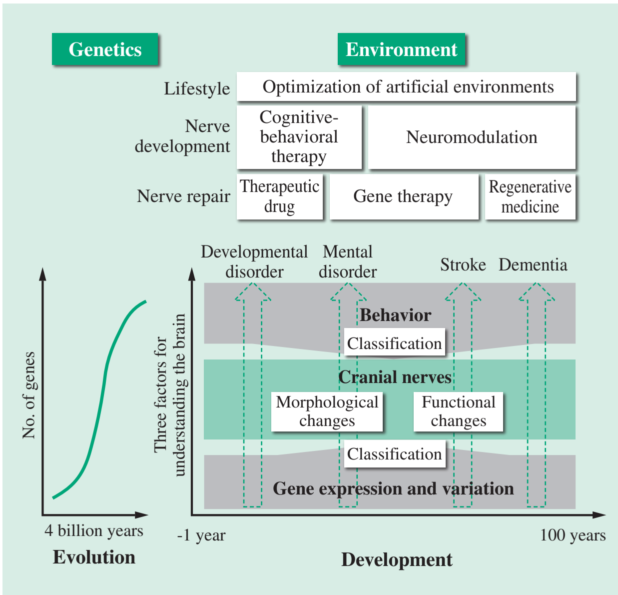


Fig. 9—"Development Compass" for Development of Brain Disease Solutions.
Brain disease can be understood by establishing a foundation of knowledge of the progress of brain development by conducting longitudinal measurements over each age range of the three factors for understanding the brain (indicated by the green dotted arrows). This makes it possible to diagnose and treat individuals and accelerates the development of new therapies.

and information and communication technology (ICT), and the development of techniques for nerve repair based on more biological indicators. Furthermore, the quantitative understanding of brain development will likely extend beyond the healthcare sector and encompass the construction of artificial environments that encourage healthy development. Hitachi intends to pioneer a new future through the pursuit of an understanding of the brain, which is the core of people and society.

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ABOUT THE AUTHORS

Atsushi Maki, Ph.D.

Center for Exploratory Research, Research & Development Group, Hitachi, Ltd. He is currently engaged in work on applied brain science, developmental science, neuro-informatics, and the development of neuro-imaging methods. Dr. Maki is a member of The Japanese Society of Baby Science (JSBS), The Japan Society of Applied Physics (JSAP), The Japanese Society for Medical and Biological Engineering (JSMBE), and The Society of Instrument and Control Engineers (SICE).

Masashi Kiguchi, Ph.D.

Center for Exploratory Research, Research & Development Group, Hitachi, Ltd. He is currently engaged in work on applied brain science, research on a new technique for observing brain activities, and the development of a new model of optical topography. Dr. Kiguchi is a member of the JSAP and the Optical Society of Japan (OSJ).

Hisaaki Ochi, Ph.D.

Center for Technology Innovation – Healthcare, Research & Development Group, Hitachi, Ltd. He is currently engaged in work on medical physics. Dr. Ochi is a member of the Japanese Society for Magnetic Resonance in Medicine and The Institute of Electronics, Information and Communication Engineers (IEICE).