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New Horizons for the Next Era of Human Brain Imaging, Cognitive, and Behavioral Research: Pacific Rim Interactivity

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Abstract Beginning in the 1990's, substantial advances have been made in the ability to image the living human brain. Functional MRI, PET, and other modalities have been developed to provide a rich means for assessing brain function and structure across spatial and temporal dimensions. Such methods are now the preferred means to examine the brain *in vivo*, with several thousand articles now appearing in the literature each year. The next era of human brain imaging is upon us now as technological developments reach a level where data can be processed quickly and combined with other biological information to provide fundamentally new applications and insights. This new era will involve and require the collaborative participation of leading research groups from around the world to share information and expertise for understanding observed effects and synthesizing these into new knowledge. One particular community that is gaining in its prominence in the field is that of the Pacific Rim, whose collective research efforts present an important corpus of research effort into brain structure and function. The Pacific Rim represents an important community of researchers interested in the greater sharing of ideas. In this special issue of Brain Imaging and Behavior, we focus on emerging areas of research that utilize brain imaging methodology, and discuss how current developments are driving the expansion of functional imaging research. Moreover, we focus on the robust interaction of researchers from around the Pacific Rim whose collaborations are significantly shaping the future of brain imaging.

Keywords Neuroscience · Neuroimaging · Computational biology · Cognition · Behavior · International collaboration · Grid · Pacific rim

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Introduction

In the early 1990's, several significant developments occurred that revolutionized the study of the human brain. Firstly, the discovery of the blood oxygenation level dependent (BOLD) magnetic susceptibility effect of hemoglobin (Ogawa et al.

1992) enabled the non-invasive, high resolution, and moment-by-moment measurement of hemodynamic changes using MRI. Secondly, the ability to rapidly manipulate the BOLD signal over time using sensory, cognitive, and behavioral stimulation enabled localization of fundamental brain functions (Bandettini et al. 1992). Thirdly, the proliferation of magnetic resonance imaging (MRI) scanners in medical centers and academic departments in the North America and Europe made it possible to obtain exquisitely high resolution images of the brain. Finally, the growth in the ability to perform a high speed imaging technique known as echo planar imaging (EPI) on clinical scanners further expanded the accessibility of functional MRI to a much wider research community for the routine study of *in vivo* brain function.

In the decade or more that has elapsed since then, the number of neuroimaging studies of brain anatomy and cognitive function, in healthy subjects and patients, has increased dramatically. Indeed, nearly 2,500 peer-reviewed articles currently appear in the literature each year using functional MR brain imaging to examine the human brain in health and disease (Bandettini 2007). Many advancements have been made in this time, ranging from those involving improvements in technology (Bellgowan et al. 2006), development of novel data processing methods (Yamashita et al. 2005), better understanding and interpretation of hemodynamic MR signals (Buxton 2001), and the integration of multiple modalities to address specific neuroscience questions (Dale et al. 2000). Other techniques have also emerged in recent years, such as diffusion tensor imaging (DTI), that permit the assessment and mapping of white matter fiber tractography (Golay et al. 2002, Bammer et al. 2003) and magnetoencephalography (Halgren et al. 2000) for measuring fine timescale changes in neural magnetic fields. These approaches have been widely applied to the study of high temporal-resolution neurophysiology (Ogawa et al. 2000), normal cognitive processes such as working memory (D'Esposito 2000), abnormalities of brain anatomy in psychiatric disease such as in schizophrenia and other psychoses (Narr et al. 2005, Pantelis et al. 2007), as well as in brain development in children (Casey et al. 2000). Studies in neuropsychiatric samples, such as schizophrenia, have been a particularly important driving force, increasingly with regard to neuroimaging genomics studies (Hariri and Weinberger 2003). Multimodal studies of brain structure and function over the lifespan are being conducted to map the course of brain maturation and structural change due to aging (Madden et al. 2007). Real time feedback of brain function and "brain reading" (Cox and Savoy 2003, Norman et al. 2006) are becoming much more popular. In addition, the number, range, and depth of the scientific questions that functional and structural imaging is addressing continue to grow.

Over the same time period of rapid growth in neuroimaging have occurred impressive developments in data acquisition sequences (Basser and Jones 2002), sophisticated statistical analysis tools (Friston and Price 2001, Smith et al. 2004), as well as large-scale grid computing (Van Horn et al. 2006). The increasing size of collected neuroimaging data has necessitated greater digital storage requirements, encouraged the use of high-volume database technology, as well as thorough description of that information through the developments of meta-data frameworks (Van Horn and Gazzaniga 2005). As researchers seek to combine neuroimaging data with genomic and other biological measurements, technological issues take on an importance central to multimodal data integration and neuroimaging's broader role in the neuroscience enterprise.

In light of these rapid advances and variety of applications in brain research, the field of neuroimaging is now at a juncture where a new vision is required to chart the course over the next decade of imaging research. In large part, we believe, these new directions can be greatly informed through examination of research efforts occurring on an international scale.

The emerging role of the Pacific Rim

While the early mutual interactions in human brain imaging were driven by scientists based in North America and Europe, such as the highly successful *International Consortium for Brain Mapping* (Mazziotta et al. 2001), the field of brain imaging has experienced increasingly important participation from researchers residing in Asia and in Australia. For instance, the field recently enjoyed the 2008 Organization for Human Brain Mapping (OHBM) annual meeting held in Melbourne, Australia, while a previous and highly successful OHBM meeting took place in Sendai, Japan in 2002. The tenth (2003), eleventh (2004), and twelfth (2005) annual meetings of the *International Society for Magnetic Resonance in Medicine* (ISMRM) have been located in Hawaii, Toronto, and Kyoto, respectively, representing the ISMRM's awareness of the importance of countries around the Pacific Rim as being a focus for scholarly effort in the field. In addition, BIOMAG (www.biomag.org), an annual international conference focusing on magnetoencephalography, was recently held in Japan (August 2008). Being centrally located in the Pacific, Hawaii is increasingly being viewed as an important focal point for Pacific Rim meetings concerning international collaboration and has been the source for important brain imaging research on aging and dementia (Jorm et al. 2005, Saczynski et al. 2006, Stewart et al. 2007). This recent recognition of the Pacific Rim as an intellectual nucleus for the future of human brain imaging is an exciting development and positions researchers in those countries to seek out means for the sharing of data, resources, and ideas.

Domestic large-scale collaborations

Combining data, resources, and intellectual talent has been an important element in many national neuroimaging efforts. The Japan Node of the International Neuroinformatics Coordinating Facility (http://www.neuroinf.jp/) has worked to foster an integrative approach to data and resources sharing between neuroimaging centers throughout Japan (http://platform.nimg.neuroinf.jp/). In the US, the Biomedical Informatics Resource Network (BIRN; http://www.nbirn.net/), National Alliance for Medical Image Computing (NA-MIC; http://www.na-mic.org/), and Cancer Biomedical Informatics Grid (CaBIG; http://cabig.nci.nih.gov/) have each sought to link collaborating neuroscience research centers via high-speed internet, standardized hardware, analysis tools, and database access. The Australian National Neuroscience Facility (NNF) provides access to state-of-the-art neuroimaging facilities as part of their Neuroimaging Platform (http://www.nnf.com.au/platforms/imaging/) and seeks to coordinate ongoing brain imaging activities at several leading Australian research centers. Such examples of national coordination are important developments to reduce duplication of effort across centers and to harmonize large-scale collaborations. One challenge for the next era of human brain imaging is how to further develop and link these efforts on an international level.

Ongoing international activities

International interactivity around the Pacific Rim already forms the basis of several collaborative neuroscience programs. For example, RIKEN Brain Science Institute (BSI) was established in 1997 to serve as a core center for brain science research in Japan, and in 1998, BSI established RIKEN-MIT Neuroscience Research Center (RMNRC) at the Massachusetts Institute of Technology (MIT) in the United States. The aim of this joint center has been to develop a leading, world-class research system, and to promote collaboration with domestic and international research institutes. Partnering with China and Finland, Canada has participated in a very successful neuroscience collaboration program (http://www.cihr-irsc.gc.ca/e/27899.html). Yale University (http://www.yale.edu/opa/outreach/) has promoted several successful international scholar programs focused on greater interactivity with China featuring neuroscientific research opportunities. And yet, while other specific examples certainly exist, continuing international collaborations and consortia between researchers from these countries concerning human neuroimaging have remained relatively infrequent.

Greater pacific rim interactivity?

A fundamental motivation for sharing a vision for the future of brain imaging research among Pacific Rim investigators has to do with the current funding climate for the biosciences and what we might be learned from each other in maximizing research support. The current outlook for biomedical research funding in the US has been bleak (Mitka 2007), with some commentators warning of a reduction of overall scientific productivity and the potential loss of a generation of young scientists fleeing research in favor of a more stable domain in which to make their living. Though occasional signs have been seen in some sectors of Canadian research (Kondro 2007), recent concern has been raised about the commitment of the government to Canada's scientific enterprise (Nature Editorial 2008). Similar worries have historically plagued Australian biomedicine (Rouse 2000). Yet, in many ways, Asia is leading the way to examine how to make progress while avoiding the pitfalls of its US counterparts. For example, Japan has kept a close eye on US research spending (http://www.nistep.go.jp/IC/ic040913/pdf/1a_02ftx.pdf) and has been examining ways to advance their biomedical research among other targeted programs. In an attempt to recruit top talent, the Singaporean Agency of Science, Technology, and Research (A*STAR) have recently announced a program to attract talented international biomedical researchers to Singapore (http://www.a-star.edu.sg/biomedical_sciences/323-A-STAR-Investigatorships) offering generous research support, lab space, and staff support for selected investigators. In China, government support for the biosciences is at an all-time high (Wells 2007). Chinese young investigators currently spending time in US labs, are being heavily recruited to return to China to set up and lead large-scale biomedical science initiatives, most notably in neuroimaging (Spinney 2004). According to a 2005 UNESCO report, recent initiatives are positioning China to move ahead of North America, European, and China's Asian neighbors in terms of scientific leadership in many areas—especially the neurosciences (http://portal.unesco.org/en/ev.php-URL_ID = 31407&URL_DO = DO_PRINTPAGE&URL_SECTION = 201.html). While the solutions to how best to fund neuroscience research are beyond the scope of this brief article, they underlie many national activities concerning neuroimaging research. It is important for researchers in all of these nations to be aware of each other's successes in securing government support for brain research and how we have respectively put those research funds to best use. With sufficient government support, international initiatives involving sharing of data and tools can play a pivotal role in human brain research and lead to innovations in neuroscience, informatics, and treatment of brain disorders. The Organization for Economic Co-operation and Development (OECD) has elegantly detailed many of the challenges, lessons, and advantages to be had for governments supporting international collaborative neuroscience (Amari et al. 2002, Boesz and Lloyd 2008).

Taking the pulse of neuroimaging around the pacific rim

As we began developing this special issue, a few constraints needed to be contended with. In a geographical and political sense, the Pacific Rim covers a vast area and encompasses 30 countries that lie along the Pacific Ocean (http://en.wikipedia.org/wiki/Pacific_Rim). However, of those, only a few possess active neuroimaging research programs and, thus, researchers working in the field. While having representation from each of these nations would have been wonderful, there were limits to the number of articles we could include. Thus, we sought to achieve a balance of articles from researchers whose brain imaging research activities best represent that region of the Pacific Rim. We certainly do not wish to neglect any particular country or its research program and hope that investigators in all countries of the Pacific Rim will feel confident that their contributions to the field are valued and worthwhile and we regret not being able to accommodate their efforts here.

In this special issue of *Brain Imaging and Behavior*, articles have been contributed by leading researchers from regions around the Pacific Rim. We invited them to provide visionary pieces concerning the future of their own work, the future of the field of neuroimaging in general, and the role of international collaboration. These articles provide context for the field's current status. They describe the acute versus long-term challenges and pitfalls, where the field is headed, novel neuroscience research applications and increasing clinical utility, emerging imaging acquisition methods, multi-modal approaches, and analysis techniques. Most importantly, the authors showcase recent examples of collaborative efforts, publications, and discuss goals for future endeavors. We have asked them to speculate on what the future might hold and if problems today could be solved, what that might mean for the potential of their brain research.

The articles in this special issue cover exciting and provocative topics pertinent to the future of human brain imaging and the role of Pacific Rim interactivity: The challenges and potential of neuroimaging genetics (de Zubicaray et al.); the role of collaboration for translating neuroimaging techniques to clinical application (Chen et al.); the case for greater effort towards the building of kinetic models of brain activity (Breakspear and Aquino); new methods for high-field *in vivo* MRS for studying brain bioenergetics (Xiao-Hong Zhu et al.); collaborative approach to understand mental operations (Rae and Henry); interesting developments in multimodal neuroimaging (Jiang et al.); the multiplicity of functionally activated brain regions with fMRI across multiple stimulus types (Sung et al.); the linking of neural activity to mental processes (Han and Fang); recent advances in high-field MRS (Chen et al.); the role of hemispheric effects in visual processing (Jiang, Powell, and Ding); how neuroimaging is contributing to social developmental psychology (Sadato et al.); the integration of neuroimaging and behavioral data (Michie et al.); the interpretation of neuroimaging data based on concepts from a network perspective (Korostil and McIntosh); new thinking about the BOLD MR signal and its role underlying cognition (Klassen, et al.); the consideration of individual differences in brain activity (Van Horn, Grafton, and Miller); the current and future state of topological perception (Zhuo et al.); human cortical anatomical networks assessed by structural MRI (Evans et al.); and a Canadian perspective on Pacific Rim interactivity (Grady and Strother). This sample of provocative thought and interesting research from around the Pacific Rim reflects the movement toward enhanced understanding of brain function, cognition, and behavior via *in vivo* imaging that may be built upon through greater international interaction.

Conclusion

The future of brain imaging science is on the horizon and can be expected to grow still further as an international endeavor. The collective work over previous years has been extremely useful in laying the groundwork what will transpire next in brain imaging and for reaching newer goals. This special issue of *Brain Imaging and Behavior* encapsulates these emerging developments and provides a collaboration-based vision for Pacific Rim involvement for the next era of experimental and clinical neuroimaging research.

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