Multimodality Imaging

Introduction

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Noninvasive “multimodal” in vivo imaging is not just becoming standard practice in the clinic, but is rapidly changing the evolving field of experimental imaging of genetic expression (“molecular imaging”). The development of multimodality methodology based on nuclear medicine (NM), positron emission tomography (PET) imaging, magnetic resonance imaging (MRI), and optical imaging is the single biggest focus in many imaging and cancer centers worldwide and is bringing together researchers and engineers from the far-ranging fields of molecular pharmacology to nanotechnology engineering. The rapid growth of in vivo multimodality imaging arises from the convergence of established fields of in vivo imaging technologies with molecular and cell biology. The cross-pollination of these disciplines has been accelerated in part by the establishment of the National Institutes of Health NCI P20 and P50 awards, for example, and by the sheer potential of the technology.

Multimodality imaging is widely considered to involve the incorporation of two or more imaging modalities, usually within the setting of a single examination using, for example, dual- or triple-labeled optical or nuclear medicine “reporter” agents or by performing ultrasound or optical studies within the MR, single-photon emission computed tomography (SPECT), or x-ray computed tomography (CT) environment. Clinically, the best example of multimodality imaging is seen in the rapid evolution of PET-SPECT and PET-CT scanner hybrids. The PET modality has developed into perhaps the most used “multimodal” imaging method. The incorporation of PET into single, hybrid, and multimodality units to provide functional (typically, from injected F-18DG studies) and anatomic information is becoming extremely popular, so much so that, for example, PET/CT hybrids can be found in outpatient screening centers located in shopping malls.

The role of any multimodal imaging approach ideally should provide the exact localization, extent, and metabolic activity of the target tissue, yield the tissue flow and function or functional changes within the surrounding tissues, and in the topic of imaging or screening, highlight any pathognomonic changes leading to eventual disease. Multimodal clinical NM, PET, and MRI techniques have to date fallen into the growing fields of molecular and functional imaging for primary-to-metastatic cancer screening of the body, neuroassessment of gliomas, and functional neuroimaging exams. Newer tools seen in integrated neuroimaging methodologies that possess potential multimodal utility include near-infrared spectroscopy (NIRS) or optical imaging for real-time assessment of wavelength-specific absorption of photons by oxygenated and deoxygenated tissues. NIRS is promising in that the contrast mechanism for the signals is closely related to that of intrinsic optical imaging of exposed cortex using visible light. Because of this, NIRS is an inexpensive means of assessing the newborn or the ischemic brain oxygenation. As such, it is ideal for combination studies in the MR scanner, for example. NIRS has only recently been used to investigate functional activation of the human cerebral cortex, although effort has begun to use imaging systems that allow the generation of images of a larger area of the subject’s head and, thereby, the production of maps of cortical oxygenation changes.

A second new field with multimodal potential is the incorporation of two-dimensional electroencephalography (EEG) and magnetoencephalography (MEG) techniques. The clear utility of EEG/MEG lies in the fact that the observed signals are directly coupled to neuronal electrical activity. That is, EEG and MEG reflect the electric potential and magnetic fields resulting from synaptic transmembrane currents in neurons. Importantly, the EEG and MEG scans can be rapidly and noninvasively acquired as the neuronal activity is being monitored, as in epilepsy, for example. Because of this, many new reports of the unity and biological function of acquiring the EEG signal together with functional MRI (fMRI) examination have appeared to shed new light on the high-speed dynamics of neuronal activation and activation center communication and processing.

In contrast to many of the imaging modalities mentioned, fMRI provides good spatial localization (0.5 to 2 mm, limited only by the signal-to-noise ratio) of an increased blood oxygenation activity with a relatively good temporal resolution (0.1 to 10 seconds) by measuring the blood oxygenation level–dependent change in image

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intensity response.\textsuperscript{13} This change in signal depends on a number of physiological features, such as the concentration of deoxygenated hemoglobin, blood flow, regional proton density, and blood volume. Like many modalities, however, inferences about neuronal activity made from the fMRI examination is limited by our real understanding of the coupling between the observed blood flow–dependent signals and the real neuronal electrical activity within the region of the signal change. Nonetheless, fMRI is becoming a potentially exciting area for multimodality imaging. Functional neuroimaging using EEG together with fMRI, with its insight into blood oxygenation level–dependent dynamics and relationship to the evoked neuronal magnetic fields, has become the new event horizon in functional neuroimaging. This is also true for a number of novel approaches using information from the NIRS signals acquired during the fMRI examination.\textsuperscript{14–15} The correlation of the observed electric/magnetic, optical, and MRI signals to biophysical models of neuronal circuitry is state-of-the-art in fMRI research. Notwithstanding, it is noted that in that most tomographic imaging methods have a relatively coarse resolution, the observed effects reflect the averaged activity of thousands or millions of neurons. This will require new modeling approaches, in which local populations of neurons are treated as statistical ensembles, for example.

A great deal of emphasis has been seen in the development of new and novel MR contrast agents, largely because MR has the superior spatial and temporal resolution in the volumetric 2-D and 3-D tomographic imaging technologies. Emerging imaging-based assays of vascular status beyond the conventional knowledge of the microvascular permeability to a blood-borne MR-visible tracer extend to receptor ligands bound to gadolinium taking advantage of binding to blood-borne molecules such as albumin or thrombin. More recently, we have seen transgene expression (B-galactosidase, tyrosinase, engineered transferrin receptor) being visualized using T1-shortening contrast MRI.\textsuperscript{16} In addition, macrophages can be marked with certain iron-containing contrast agents which, through accumulation at the margins of glioblastomas, ameliorate the visual demarcation in MRI. Finally, the field of labeling exogenous “stem” cells with MR-sensitive ion nanoparticles has emerged to a near-clinical reality in which implanted or injected cell trafficking and assimilation can be monitored by MR.\textsuperscript{17}

Beyond the clinics, there is also a growing interest in building and designing dedicated devices for specific applications, such as high-resolution scanners for imaging small animals of use in the many new molecular imaging centers appearing worldwide for reporter gene-expression imaging studies in small animals.\textsuperscript{18–20} The coupling of nuclear and optical reporter genes represents only the beginning of far wider applications of this research. Initially, fluorescence and bioluminescence optical imaging, in providing a cheaper alternative to the more intricate microPET, microSPECT, and microMRI scanners, have gathered the most focus to date. In the end, however, as animal models develop in complexity and size, the volumetric tomographic technologies, which offer deep tissue penetration and high spatial resolution, will be married with noninvasive small animal optical imaging.

The presentations at the 2004 Princeton Conference in Baltimore, Md, that highlighted the development and new topics in multimodality imaging deal with the efforts to bring NM, encephalography, MRI, and optical techniques into a clinical and human neuroimaging reality. Much of the attention within this session deals with the major challenge to all attempts to integrate multimodality approaches arising from the realization that distinct physiological mechanisms underlie the signal generation for different imaging modalities. As was made clear during this multimodality imaging session, much of the work to be done in the near future will focus on several topics. First, we need an understanding of the coupling between the measured signals and the underlying neuronal or metabolic activity of a tissue to relate the observed electric/magnetic, optical, and MRI signals to biophysical models of neuronal circuitry or genetic expression.\textsuperscript{21} Second, we need to move beyond our understanding of the expression of upregulated endogenous genes, coding for simple transporters and hexokinase/thymidine kinase genes. Third, we should explore the molecular behaviors of tissues or tumors that would serve as specific targets for patient-tailored therapies. We feel that the field of multimodal imaging is clearly directed to providing noninvasive analyses of both endogenous and exogenous gene expression in the “molecular imaging” animal models that are effectively translating new treatment and therapy strategies from experimental into clinical applications that are poised to make clear clinical impacts.

References

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