

# Combined Positron Emission Tomography and Magnetic Resonance Imaging Scanners—Potential Neurological Applications

a report by

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Recently, there has been great interest in combining positron emission tomography (PET) and magnetic resonance imaging (MRI), and a number of integrated scanners capable of simultaneous acquisition have been developed and successfully tested in small animal<sup>1,2</sup> and human<sup>3</sup> imaging. These efforts are broad enough to deserve their own review, something beyond our scope here. Instead, in this article we will focus on potential applications, especially in the brain.

What can we learn if we use simultaneous PET and MRI to study the brain? To answer, we will break this question into parts: Why combine the information provided by PET and MRI? Why acquire PET and MR data simultaneously? Why focus on neurological applications initially?

Answering the first question is straightforward. The complementary anatomical and functional information obtained from separately performed MRI and PET examinations have long been combined either by performing a parallel analysis or by using software co-registration techniques to merge the two data sets. However, one major assumption that has been made in these cases is that no changes in underlying conditions have occurred between the two studies; increasingly, investigators are recognizing that this is not the case, particularly when assessing a subject's mental state, which may change in a matter of seconds, but also in some diseases such as acute ischemic stroke where changes can occur in a matter of minutes. As we probe illnesses of the mind more thoroughly, the state of the mind and the state of the brain at any given instant become more relevant.

This leads to the second and more challenging question. The simultaneous acquisition of PET and MRI data would allow the temporal correlation of these signals. Assessment of a number of diseases could benefit from simultaneous PET/MRI: quantitative measurements of brain cancer, neurodegenerative diseases, acute and chronic stroke, including stroke recovery, breast cancer, pelvic malignancies, cardiac imaging, etc. Identifying which of these many applications will be the first to have widespread clinical impact is an exercise in predicting the future—always a difficult task. Perhaps more importantly, we might more profitably first discuss the fundamental measurement approaches that simultaneous technology opens up. Once implemented and validated, these technical tools could significantly influence a wide range of applications and contribute to the acceptance and successful clinical impact of PET–MRI.

Finally, answering the third question of—why start with brain—is simple: the enormous global burden from neuropsychiatric illnesses is higher than the burden from any other disease category in the developed world. These tremendous unmet medical needs make the brain a logical place to begin investigation. Furthermore, the brain's favorable imaging characteristics (generally stationary, good size compared with the field of view, multiple intrinsic contrasts of both structure and function/metabolism, etc.) and the wealth of MRI methods that work well in the brain will facilitate these initial efforts. In the following, we first discuss some of the methodological opportunities in a combined scanner and then describe how these could benefit neurological applications, particularly focusing on brain cancer, Alzheimer's disease, and ischemic stroke.



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## Technologies Enabling New Science

Simultaneous acquisition immediately brings to mind the possibility of improving the performance of one instrument by using the information obtained from the other modality. For example, a number of corrections must be applied in PET to obtain a correct quantitative measure of the activity concentration in a specific voxel, and the accuracy of some of these corrections, in principle, could be improved by including the MR information. As we consider the combination of MR and PET data, from a technical perspective PET might initially appear to benefit more from the addition of simultaneous MR data. However, the temporal correspondence of PET signals might help us better understand a number of MR techniques *in vivo*. In the end, combined PET/MRI will likely be a more quantitative tool than the two methods alone, and a number of diseases may yield their secrets best to highly quantitative methods. Here we describe three technical improvements made possible via simultaneous acquisition.

### Magnetic-resonance-assisted Motion Correction

Voluntary and involuntary movements (i.e. cardiac or respiratory motion) are difficult to avoid and lead to degradation (blurring) of PET images and, in more severe cases, to the introduction of artifacts. These effects become particularly relevant when a quantitative voxel-by-voxel analysis is performed, especially considering the recent improvements in the spatial resolution of PET scanners.

Improved motion correction could be very beneficial to PET, and an elegant solution presents itself in a combined PET–MRI instrument, where the MR could be used to provide motion tracking and replace an optical tracking system. With proper pulse sequence programming, MR data can be acquired continuously during the PET data acquisition and can be used to characterize the independent motion of each of the voxels of interest. An MR-based motion correction approach could be used in difficult situations, such as correcting for internal motion associated with respiratory or cardiac activity in whole-body applications. External markers can, at best, approximate the motion of organs assuming a rigid body transformation, while the MR data could be used to more accurately model the movement of the internal organs using non-rigid body transformations. In the case of neurological applications, efforts have been made to minimize these effects by using different techniques to restrain the head of the subject<sup>4–6</sup> or, alternatively, to correct based on the motion detected using external optical markers,<sup>7,8</sup> but these methods have had limited success (e.g. 2–3mm accuracy at best). Solving the rigid body motion case of head/brain imaging is an important and appropriate first step toward the implementation of corrections for the more complex motions seen in the body.

### Partial Volume Correction

Partial volume effects are caused by the limited spatial resolution of any imaging modality and lead, in the case of PET, to an under- or overestimation in tissue activity concentrations that depend on the activity distribution and the size of the structures from which the measurement is being made. For example, this makes absolute quantification very difficult in the case of cerebral blood flow, cerebral glucose metabolism measurements, or neuroreceptor studies because some structures of interest in the brain are of a smaller size than the spatial resolution of the current PET scanners.

When PET and MR data are acquired simultaneously, we can use the high-resolution anatomical information in the MR images to determine the size of the structures analyzed and improve retrospective quantitative analysis of the PET images. In general, this becomes an image segmentation problem. For partial volume corrections in the brain, one would need to differentiate between not only white and gray matter and cerebrospinal fluid in the MR images, but also other small structures. The excellent soft-tissue contrast provided by MRI can easily facilitate this, even when the PET and MRI data have been acquired separately.<sup>9,10</sup> However, in addition to the challenges posed by the segmentation task, errors in the registration of PET and MRI data acquired separately have limited the accuracy of partial volume correction methods in the past. The *post hoc* co-registration task is further complicated by at least two other factors. First, the higher spatial resolution achievable with state-of-the-art PET scanners allows one to dissect biological processes in more detail. Second, as PET tracers with higher specificity are developed, the available anatomical information is increasingly limited. These

problems are eliminated in the case of an integrated system, where simultaneity guarantees spatial correlation. Ultimately, the anatomical information provided by the MRI can be used as prior information to regularize the PET images in statistical reconstruction algorithms.<sup>11–13</sup>

### Image-based Arterial Input Function Estimation

The analysis of dynamic PET data using tracer compartment models allows the estimation of parameters of interest related to normal and pathological changes in tissue function or metabolism. However, accurate quantification requires an input function to these models (i.e. plasma–time activity curve of the tracer delivery to the tissue). The ‘gold standard’ method for determining the arterial input function (AIF) is the arterial blood sampling technique, in which samples are drawn from an artery and the activity measured over time. The procedure

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requires catheterization of the radial artery, which limits its usefulness in routine clinical PET studies, and also may not be accurate if there is carotid artery stenosis or a mismatch between arterial flow to the organ of interest and arterial flow in the wrist. Alternatively, less invasive methods such as arterialized venous blood sampling or non-invasive techniques for obtaining the AIF (i.e. image-based, population-based) have been proposed. One image-based approach is to derive the AIF from a region of interest (ROI) placed across major blood vessels (e.g. aorta) after tracer administration.<sup>12,13</sup> Correct definition of the ROI over the vessel and correction for confounding effects such as spill-over from adjacent tissues or partial volume effects in the case of relatively small vessels can be challenging with only the PET images to guide placement.

In a combined scanner, the anatomical and physiological information provided by MRI could be used for this purpose. Using the co-registered MR anatomical images, the position and the size of the vessels of interest can be accurately determined. With the co-administration of both MR and PET tracers, MR could also provide additional information about the curve (i.e. first 30–60 seconds) and any local changes in blood flow, potentially reducing the problems of bolus delay and dispersion inherent in the global AIF estimate. In some cases, the AIF may still not be a suitable predictor of the plasma input function and additional information regarding metabolites may be required.

### Promising Initial Neurological Applications

The excellent soft-tissue contrast makes MRI superior to CT for providing morphological information for neurological applications. As a result of this, the majority of patients who receive a PET examination typically receive a MR scan as well as part of their routine care. In addition to providing the anatomical context for analyzing the PET data, a number of MR methods have been developed for assessing cerebral blood flow (CBF) and cerebral

blood volume (CBV), water diffusion, and metabolite concentrations. All of these advanced MR methods are available in the combined scanner and can be profitably combined with PET methods. In this section we will describe some of the more promising initial brain applications.

## Brain Cancer

The most common primary brain tumor, glioblastoma (GBM), is a uniformly fatal tumor afflicting approximately 13,000 persons each year in the US.<sup>14</sup> Despite aggressive therapy with surgery, radiation, and cytotoxic chemotherapy, the median survival is nine to 12 months and fewer than 5% of patients survive for five or more years. There is a desperate need

We expect that new molecular neuroimaging applications will emerge, providing new and exciting scientific and medical benefits.

for new therapies in GBM patients and there are now emerging data suggesting that one class of therapies—anti-angiogenesis therapies that block vascular endothelial growth factor (VEGF) receptors— may be effective in brain cancer.<sup>15</sup> However, the mechanism of action of anti-angiogenic agents in any cancer remains poorly understood.

A number of quantitative MR methods, ranging from MR spectroscopy to dynamic contrast-enhanced (DCE) MRI to dynamic susceptibility contrast (DSC) MRI to diffusion MRI, have been used to improve cancer imaging,<sup>16,17</sup> and have also been applied with varying degrees of success to probing therapeutic mechanisms. However, even with these tools certain findings remain puzzling. For example, the reduction of contrast enhancement observed in patients treated with VEGF inhibitors has been the subject of controversy. Specifically, it may be that the radiographic responses observed with these agents may simply be related to improved blood–brain barrier (BBB) function and not an underlying antitumor effect. More tumor-specific measures of response are urgently needed to address this issue, and combined MR–PET may be able to provide this. More specifically, PET tracers for studying glucose metabolism (e.g. 18F-fluorodeoxyglucose [FDG]), amino acid transport (e.g. 11C-methionine [MET]),<sup>18</sup> or cellular proliferation (e.g. 18F-fluorothymidine [FLT])<sup>19,20</sup> have been proposed, but they too can be influenced by permeability or other delivery factors. A fully quantitative and reproducible method to estimate parameters of interest (e.g. FDG or FLT transport and phosphorylation rates) may well provide greater insights into therapeutic mechanisms. The simultaneous measurement of permeability to MRI tracers such as gadolinium agents and PET tracer uptake could help quantify precisely how tumor proliferation, tumor vascular properties, and antitumor effects occur and interact, thus enabling a more precise understanding of tumor biology and therapeutic response, perhaps even on an individual basis.

## Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia in older adults, affecting 4.5 million people in the US. Neuroimaging techniques

(i.e. PET, single-photon emission computed tomography [SPECT], and MRI) have been investigated for assessing changes in brain morphology and physiology or amyloid deposition in these patients, have proved more useful than neuropsychological tests for the early diagnosis of AD<sup>21</sup> because the pathological manifestations of AD appear years in advance of the cognitive symptoms.

PET and MRI provide complementary information in the assessment of AD patients.<sup>22–25</sup> On the one hand, PET can inform about cerebral glucose metabolism, amyloid deposition (using amyloid binding tracers such as Pittsburgh Compound B [PIB]),<sup>26</sup> or the status of neurotransmitter systems (e.g. cholinergic, serotonergic, dopaminergic). On the other hand, MRI can be used to exclude other causes of dementia and, more importantly, to assess morphological changes and the integrity of neurons, fiber tracts, and neuronal circuits involved in memory processes.<sup>27</sup> These methods have proved useful not only in the early diagnosis of AD, but also in the differential diagnosis of AD from other dementias, and they have been proposed for assessing disease progression and therapy monitoring.<sup>28</sup> Obtaining these data in a single imaging session is a major convenience, an issue particularly important in these often elderly and fragile patients. We note the complete commercial success of PET/CT over PET alone, suggesting that the benefit from ease of patient scheduling is substantial, a benefit previously considered modest.

The quantitative analysis of FDG uptake or PIB binding would also be greatly improved using the methods described in the previous section. For example, it was suggested that changes in FDG uptake do not reflect impaired glucose metabolism but rather brain atrophy. Partial volume correction of the PET data based on the MR information would clarify this issue. Very often, long studies (e.g. 60–90 minutes) are performed and the quality of the data is compromised by motion; this could potentially be addressed in a combined scanner, as described above. Understanding the progression of pathological changes (e.g. amyloid deposition) in AD will require longitudinal studies. Ideally, these studies would be quantitative, reproducible, and minimally invasive, hence the need for an MR-based estimate of the AIF. A more reliable method to evaluate AD patients would in turn reduce the number of subjects required to answer a specific question. This could be particularly important now that treatments for AD are beginning to evolve, and combined measurements could be useful for patient selection (e.g. select mild cognitively impaired subjects that are likely to progress to AD) and monitoring treatment efficiency.

## Ischemic Stroke

Stroke is the third leading cause of death in the US and the leading cause of adult disability. The majority (85%) of the 780,000 stroke cases reported yearly are of the ischemic type in which a major intracranial artery is occluded. Consequently, blood flow and, implicitly, glucose and oxygen delivery to corresponding regions are impaired. The degree to which these regions are affected depends on the actual reduction in blood flow. Based on the pioneering work performed with PET (i.e. measurements of CBF, oxygen consumption, and oxygen extraction fraction), three major tissue compartments have been identified: core (irreversibly damaged tissue), penumbra (at-risk tissue), and oligemia (tissue with preserved neuronal integrity and normal/slightly reduced perfusion). These methods are still considered to be the gold standard

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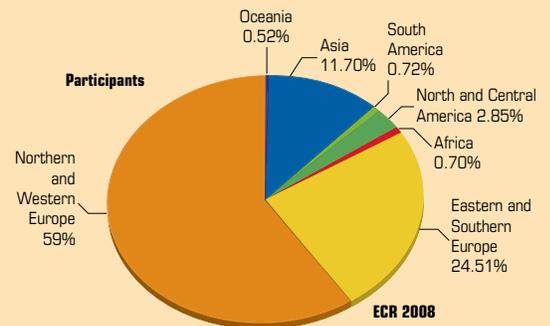
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for non-invasively identifying the tissue compartments,<sup>29,30</sup> but the idea has been adopted and further developed using MRI techniques. Diffusion-weighted imaging (DWI) is arguably the most sensitive method for detecting hyperacute ischemia, and the DWI lesion reflecting cellular injury is thought to accurately predict the ischemic core. Perfusion-weighted imaging (PWI) identifies hypoperfused tissue, and the PWI–DWI mismatch is thought to reflect tissue that is potentially salvageable (similar to the PET penumbra) and is the target of some recanalization therapies.

Obtaining structural and functional information with MRI and PET data at the same time seems desirable in these patients, as ‘time is brain.’ However, the PET studies that would be the most useful in the acute phase of ischemic stroke (i.e. those involving O-15- or C-11-labeled tracers) are also the most challenging logistically, requiring significant resources such as operating cyclotrons and synthesis laboratories that will likely not be routinely available, thus limiting the utility of the technique in the hyperacute phase. Nevertheless, as Heiss stated, “The time has come to calibrate simpler and widely applicable functional imaging procedures—especially diffusion- and perfusion-weighted MRI—on PET in order to make these modalities a reliable tool in the study of acute ischemic stroke.”<sup>31</sup> Specifically, simultaneous measurements might elucidate the ongoing debate concerning the relationship between the PWI–DWI mismatch and the PET penumbra.<sup>31–34</sup> For example, it has been reported that in some instances the DWI lesion is actually reversible and may in fact include penumbral tissue. Similarly, the complete meaning

of MRI PWI lesions could be better elucidated with PET. Cross-validation PET and MRI studies is likely to lead to the adoption of new PWI thresholds<sup>35</sup> that will allow a better selection of those patients who might still benefit from therapeutic interventions beyond the accepted three-hour time window.

## Conclusions

There are of course other neurological applications where PET–MRI could have a significant impact. To give a few more examples, the reduced radiation compared with PET–CT could be particularly useful for assessing medically intractable epilepsy in children using FDG or <sup>11</sup>C-flumazenil (FMZ) PET. In Parkinson’s disease, PET and MR data could be used to interrogate simultaneously different phases of a complex pharmacological response: on one hand, PET ligands have been developed to study the rate of dopamine synthesis, release, transport, and receptor expression; on the other hand, Functional MRI (fMRI) has been used to study neuronal activation after amphetamine stimulation.

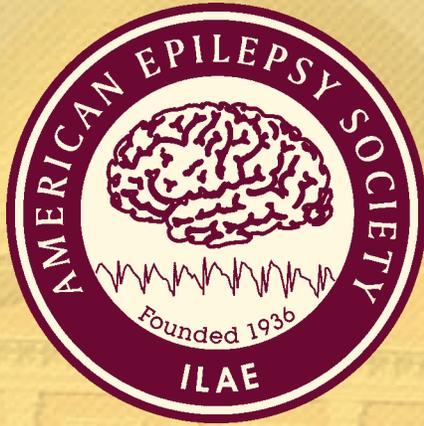
For years, simultaneous PET–MRI was thought of as the ‘Holy Grail’ of molecular imaging in general, and of neuroimaging in particular. Despite the substantial difficulties one has to face in bringing these two imaging modalities together, the opportunities are wide open. Although a range of existing studies where data from both modalities are required might benefit from this new imaging technique, we expect that new molecular neuroimaging applications will emerge, providing new and exciting scientific and medical benefits. ■

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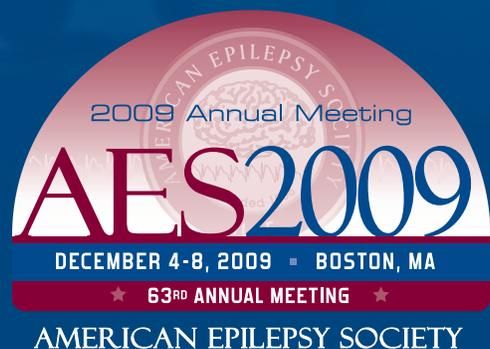
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