POINT/COUNTERPOINT

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Correction for image degrading factors is essential for accurate quantification of brain function using PET

Habib Zaidi
Geneva University Hospital, Division of Nuclear Medicine, CH-1211 Geneva, Switzerland
(Tel: +41 22 372 7258, E-mail: habib.zaidi@hcuge.ch)

Vesna Sossi
University of British Columbia/TRIUMF, Vancouver, BG V6T 2A3 Canada
(Tel: +1 604 822 7710, E-mail: vesna@physics.ubc.ca)

William R. Hendee, Moderator

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OVERVIEW

Quantification of brain function using positron emission tomography (PET) is an emerging research field. For many years, interest in the regional distribution of brain perfusion and metabolism has steadily increased, primarily because many neurological disorders are associated with a decrease of regional cerebral blood flow (rCBF). PET offers the possibility of quantitative measurements of tracer concentration *in vivo*. However, there are several issues that must be considered in order to fully realize this potential. In practice, the measured line integrals must be corrected for a number of background and physical effects, the three most significant being the limited spatial resolution and associated partial volume effect, photon attenuation, and the contribution of events arising from photons scattered in the object and gantry. Many investigators believe that accurate patient-specific correction for these image-degrading factors is essential for quantification of relevant parameters when imaging brain function using PET. Others often neglect them or believe that approximate correction methods can be used with confidence. This difference of opinion is explored in this month's Point/Counterpoint.

Arguing for the Proposition is Habib Zaidi, Ph.D. Dr Zaidi is senior physicist and head of the PET Instrumentation & Neuroscience Laboratory at Geneva University Hospital. His research centers on modeling nuclear medical imaging systems using the Monte Carlo method, dosimetry, image correction, reconstruction and quantification techniques in emission tomography and functional brain imaging, and more recently on novel design of dedicated high-resolution PET scanners in collaboration with CERN. He is Associate Editor for *Medical Physics*, a member of the editorial board of *Computer Methods and Programs in Biomedicine* and the *International Journal of Nuclear Medicine*, and scientific reviewer for several medical physics, nuclear medicine and computing journals. He is affiliated to several medical physics and nuclear medicine organizations and member of the professional relations committee of the IOMP.

Arguing against the proposition is Vesna Sossi, Ph.D. Dr. Sossi is Assistant Professor of Physics and Astronomy at the University of British Columbia (UBC), and head of the physics program of the UBC/TRIUMF PET group. She received her Ph.D. in Nuclear Physics from UBC and changed research fields to PET imaging immediately after her degree. She is actively involved in PET instrumentation and data quantification and reconstruction research, with particular emphasis on quantitative 3-dimensional high resolution brain imaging. She was involved in the early characterization of hybrid PET/SPECT imaging, and was part of the review committee for the 2001 NEMA PET standards. She is a scientific reviewer for several medical physics journals.

FOR THE PROPOSITION: Habib Zaidi, Ph.D.

Opening Statement

During the last decade, neuroimaging has advanced elegantly in the medical and research arenas. PET, with its

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superior sensitivity and spatial resolution, appears uniquely suited to take the lead in this promising field of imaging. Convincing clinical evaluations and research investigations of PET are providing clinicians and neuroscientists with relevant functional information in various pathologies including cerebrovascular disorders, brain trauma, epilepsy, dementia, Parkinson's disease and brain tumors, and in mental disorders such as depression, schizophrenia and obsessive-compulsive disorders. Within the context of functional brain imaging, the aim of quantification is to provide a reliable numerical measure of brain function. For quantitative analysis of PET images, several image-degrading effects must be accounted for, including poor signal-to-noise ratio, limited spatial resolution, and spatially-varying loss or corruption of signal due to photon interactions with matter. Photon attenuation and contributions from scattered photons reduce the accuracy of measured activities and activity concentrations.[1,2] In addition, limited spatial resolution causes an object to appear enlarged if its true size is less than 2–3 times the system resolution. While the total reconstructed counts within the object are conserved, the count density is decreased from the true value because the data are ''smeared'' over a larger area. This characteristic is known as the partial volume effect.

Advances in quantification of brain function (blood flow, metabolism and receptor characteristics) with PET, especially for small structures such as the putamen and hippocampus, rely on two improvements: (1) hardware improvements to enhance spatial resolution and sensitivity, and addition of components to correct for degrading factors (e.g., electronically-delayed coincidence windows for subtraction of random coincidences, and transmission scanning for patient-specific attenuation correction); and (2) software improvements to attain better image quality and achieve more accurate quantification of relevant parameters. Significant progress has been made in the design of high-resolution 3D PET units with the capacity to acquire more accurate depth-of-interaction information.[3] Also, improved reconstruction algorithms have been proposed, and some have been incorporated into software supplied by manufacturers to end-users. In spite of improved algorithms for accurate smoothing of random coincidences, attenuation correction and scatter compensation, and partial-volume effect-correction, however, many PET users still do not correct for these factors, either because they lack confidence in the algorithms, or they do not appreciate the importance of the corrections owing to the absence of physics support in their institutions.

Earlier PET studies inconsistently reported aging-induced reductions in CBF, oxygen metabolism, and glucose metabolism. Metzler *et al.*[4] have shown that this observation may reflect the absence of correction for the dilution effect of age-related cerebral volume loss. The traditional approach to accounting for the partial volume effect in the quantification of brain PET images uses anatomical information derived from magnetic resonance imaging (MRI) and the spatial resolution characteristics of the PET unit. Although considered as a limiting factor, MR images are generally available for patients undergoing cerebral PET scanning through hospitals' picture archiving and communications systems. Moreover, it has been shown recently that MRI data can be used for attenuation and scatter correction purposes in 3D brain PET imaging using a transmission less scanning protocol.[2] Reconstruction of PET images without attenuation correction can cause excessive count densities and reduced image contrast in regions of low attenuation. Scatter qualitatively decreases contrast by misplacing events during reconstruction, and quantitatively causes errors in the reconstructed radioactivity concentrations by overestimating the actual activity. All of these effects can introduce artifacts into radionuclide images that complicate visual interpretation and cause profound errors in quantification. For these reasons, it is essential to understand both the physical processes that underlie the data acquisition process, and the methods that can be used to correct images for inaccuracies. These correction methods are now widely accepted by the nuclear medicine community as essential for achieving artifact-free, quantitatively accurate data.

In general, there is no rational motivation why sophisticated correction methods for all of the physical degrading effects should not be applied to brain PET images prior to extraction of relevant quantitative data in a clinical and research environment.

Rebuttal

I agree with Dr. Sossi that accurate quantification requires extensive technical and organizational efforts that may be unaffordable for a clinical department with limited scientific support. The first question to be answered is ''What is expected from such studies?'' Investments should be comparable to expectations. The second interesting question is ''Would one expect similar results between images obtained with and without correction for the physical degrading effects?'' The answer would provide a true comparison of the effect of different correction techniques on relevant quantitative parameters when studying brain function using PET. Such an experiment would be difficult to perform with clinical data but should be easily performed using either experimental phantom measurements or Monte Carlo simulation studies, which have the advantage of being able to generate data sets in a controllable manner and switching on and off the effect of the physical degrading factors. Most studies concluded that correction methods improved the quantitative accuracy compared to the case where no corrections were applied.[1] No one would dispute the statement that significant progress in quantitative PET imaging has been made over the last few years as a result of improved correction methods for attenuation, scatter and partial-volume effect. The specific benefits of transmission-based attenuation correction, in contrast with calculated attenuation correction, are the subject of heated debate.[2] Contribution of scatter from outside the FOV remains a challenging issue that needs to be addressed carefully in whole-body imaging especially with large axial FOV 3D PET units. However, this is a less challenging issue in brain scanning. In PET activation studies characterized by low count statistics, subtraction-based scatter correction

methods add considerable noise, which jeopardizes the significance of statistical analysis. This problem has been tackled with iterative reconstruction-based scatter compensation techniques, where the scatter component is modeled within the projector/backprojector pair. This approach results in better noise properties than direct subtraction. Accurate scatter modeling has recently been achieved using computationally efficient fully 3D Monte Carlo simulation-based reconstructions.[5] In addition, correction for partial volume effect might influence the results of statistical analysis in group comparisons. Using Statistical Parametric Mapping analysis performed on subjects with probable Alzheimer's disease and age-matched healthy volunteers, Matsuda *et al.*[6] have shown that the significance of the rCBF decrease in the bilateral amygdala and hippocampi disappeared after correction of partial volume effect, while the significant decrease in the bilateral parahippocampal gyri remained.

Reconstruction methods are continuously being improved, and scanner manufacturers are optimizing the performance of dedicated software by integrating latest algorithmic developments. Maximum *a posteriori* reconstructions using a Bayesian model in combination with a Poisson likelihood function and a Gibbs prior on the image provide images of higher resolution. The value of improved models to correct for attenuation, scatter, and partial-volume effects, performed on raw projection data, preliminary reconstructions, or integrated with the transition matrix of an iterative reconstruction algorithm, is still an open question and remains a good academic problem in functional brain imaging. This question requires further research and development.

AGAINST THE PROPOSITION: Vesna Sossi, Ph.D.

Opening Statement

From an idealistic point of view, absolute quantification is certainly desirable to obtain a truthful representation of the biological process or metabolic function being imaged with PET. In the real world, however, we are faced with a variety of limitations, starting with the observation that PET radioactive decay is statistical in nature and therefore cannot be precisely determined. In addition, photons interact with all forms of matter, instrumentation is capable of only limited spatial, energy and temporal resolution and requires careful calibration, and patient motion during a scanning procedure produces blurred images. Correction algorithms exist for most of these effects. There are, however, three questions that must be addressed: What is the overall cost of applying the corrections, are the available corrections sufficiently accurate to increase the quantitative accuracy of the results, and, most importantly, are the corrections really necessary for every study in order to obtain clinically meaningful results? To answer these questions, four main sources of accuracy loss will be examined: attenuation, scatter, presence of random events and the partial volume effect.

Photon attenuation has been repeatedly identified as the single most important factor in the loss of quantification ability. However, attenuation corrections have also been identified as a significant source of errors because measured attenuation corrections can introduce additional noise in the images, thus reducing the image contrast, which is especially relevant in tumor imaging. Also, a mismatch between the spatial location of the subject during the emission and the transmission scans can introduce significant artifacts into attenuation-corrected images. Finally, the presence of metallic dental implants can introduce artifacts into brain images, not only when CT is used to determine the attenuation correction coefficient, as in new PET/CT scans, but also when a standard positron source is employed for attenuation correction.[7]

Another aspect to be considered is that addition of a transmission scan generally lengthens the scanning procedure and increases the dose of radioactivity that must be administered to the patient. For example, in ^{18}F-flurodeoxyglucose (FDG) PET imaging, a tracer uptake period is generally required after tracer injection and before initiation of scanning. If a post-injection transmission scan is not feasible, the patient must undergo a transmission scan first, and then either lie on the scanning bed for a considerable time before the emission scan is started, or leave the bed and then be carefully repositioned for the emission scan. In addition to reducing the useable scanner time, both options increase the risk of a position mismatch between the emission and transmission scan.

The clinical utility of this correction must also be addressed. Certainly there are PET studies where attenuation correction is essential such as determination of process rate constants with methods that use plasma-derived input functions. There are other applications, however, where attenuation correction is not only unnecessary, but even reported as detrimental. Bengel *et al.*[8] argue, for example, that nonattenuation corrected FDG images yield improved contrast between tumor and background. For head and neck tumors, for example, the contrast in nonattenuation corrected images is approximately twice that in attenuation corrected images.

Detection of scatter events is another major contributor to quantification loss. In 3D brain imaging, the fraction of scatter to total detected events can be as high as 40%. No fully accurate scatter correction methods are currently available. Available methods are based on scatter modeling using physics principles, and often fail to account for scatter originating from radioactivity outside of the field of view. The scatter fraction depends only on the thickness of material traversed by the photons; it does not depend on the injected dose or radiotracer distribution. Therefore, scatter only minimally affects the comparison of images obtained with the same radiotracer in the same patient.

The detection of random events adds a fairly uniform background across the field of view, and thereby reduces image contrast. In contrast to scatter, however, the number of random events is count-rate dependent. If the objective of the study is to compare between two conditions, the effect of random events can be minimized by maintaining similar count rates among scans.

The limited spatial resolution of the scanner causes the partial volume effect, which affects the estimate of radioactivity concentration for all objects that are smaller than the tomographic resolution element. This is often the case in

brain imaging. Several partial-volume correction algorithms exist, but they involve many processing steps and generally require acquisition of an MRI scan to define the anatomical size of the structures involved in the function being investigated with PET. These additional steps are costly in expense and time, and may introduce further errors. For instance, co-registration between PET and MRI images has an accuracy limit of approximately 2 mm, which is fairly large considering that structures of only a few mm are often of interest.

Frequently, PET studies focus on identification of functional differences between subjects scanned under different conditions. In these cases the partial volume effect is approximately constant between the two conditions, since intersubject comparisons are used, and the distribution of radiotracer may not change greatly. In such studies differences of 10–20% in the kinetic parameters derived from the study are often found to be significant.[9] The magnitude of the partial-volume correction may cause some parameter values to increase several fold, with an associated increase in noise.[10] Application of such a correction, if not exact, would jeopardize the ability to detect subtle biological effects. Finally, the effect of image blurring caused by patient motion on the accuracy of the partial-volume correction remains to be investigated.

Rebuttal

Dr. Zaidi is absolutely correct when stating that better image quantification has dramatically improved the investigative power of PET and has contributed to more accurate biological discoveries. He correctly argues that significant advances have been made both in software and hardware associated with PET scanners that yield far more accurate results. As he points out, many of the correction methods require sophisticated measurements and software techniques. This enhanced sophistication requires a high degree of precision and expertise that may not always be available. If imprecise, the correction methods might introduce additional sources of artifact and noise. Correction methods can be implemented only if all sources of potential errors have been thoroughly investigated in the context of the particular scanning protocol. This includes factors often neglected, such as the effects of patient motion on the accuracy of the corrections.

Another aspect to consider is the practicality of obtaining particular correction factors. For example, most of the partial-volume correction methods require MR imaging, which significantly increases the cost of the scanning procedure and the burden to subjects undergoing a clinical examination. It is important to question how much additional information will be acquired by implementing the correction methods. The answer is likely to be different for different types of studies or clinical examinations and for different scanning environments.

In summary, pursuit of absolute quantification should undoubtedly continue, because it provides a more truthful representation of the processes being imaged. It is also important, however, to evaluate on an individual case basis if the additional accuracy potentially provided by the quantification procedures will significantly benefit the outcome of a PET study.

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