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EDITORIAL

What Are the Sources of Error in Measuring and Calculating Cerebral Metabolic Rates with Fluorine-18-Fluorodeoxyglucose and PET?

In this issue of the *Journal of Nuclear Medicine*, Wang et al. describe significant intersubject variability of cerebral metabolic rates for glucose (CMRgluc) in young normal males as measured with PET and ^{18}FDG (*1*). This is an issue of major concern for both research and clinical applications of this important imaging methodology. Sensitivity and specificity of a test is heavily dependent on the degree of variability and the amount of overlap in the measured values between healthy control subjects and patients.

The first method to measure cerebral metabolic rate was introduced by Kety and Schmidt in 1948 and was used to investigate various neuropsychiatric disorders (*2,3*). However, it was soon realized that in subjects with diseases outside the central nervous

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system but no evidence of neuro-psychiatric disorders, significant alterations in cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) could be detected with this technique (Kety and Schmidt, unpublished data, 1956). This was particularly apparent when the effects of aging on CBF and metabolism were investigated: significant drops in CBF and $CMRO_2$ were noted. Lack of screening for disorders that might affect brain function was a factor in these unexpected findings. In fact, when a similar, but carefully designed study was carried out with the same technique, the results were quite different; no significant change in CBF or $CMRO_2$ was noted to occur with normal aging (*4*). However, it was noted that minor health conditions did not have a deleterious effect on brain function as measured by this technique.

Since the introduction of ^{14}C and ^{18}FDG techniques, the concerns of variability of measurement of regional and global metabolic rates and related issues have intensified (*5,6*). Quantitative data reported in the literature in both normal subjects and patients with various disorders appear somewhat inconsistent and at times contradictory as discussed by Wang et al. Some investigators have seriously questioned the validity of quantitative measurements in the analysis of data generated from these studies (*7*). The critical question is whether absolute quantitation of various biochemical, pharmacological and physiological functions is achievable with PET and does it play a role in research and clinical applications. The answer is probably yes, but one must be aware of serious issues that need to be addressed for successful utilization of this approach. Wang et al. carefully analyze these critical issues:

1. Normal biological variations resulting in a wide range of measured values that overlap with those noted in subjects with disease.
2. Variations related to instrument performance with regard to measurement of activity concentration in the organ and regions of interest (ROIs) and in arterial blood samples.
3. Variations related to reconstruction and processing of the acquired images, assigning ROIs and finally calculating metabolic rates or other physiologic parameters utilizing kinetic models.

In order to minimize errors caused by biological variations, one must standardize subject selection criteria and screening procedures as well as the condition of the subject before and during the study. Unfortunately, despite vigorous attempts to minimize such sources of variability, subject-related errors should be accepted as unavoidable. We are not aware of any clear cut criteria proven to be optimal for this purpose. In our own center, we have encountered subjects with normal neuropsychological, psychiatric and laboratory examinations who later have been found to have major psychiatric disorders. Some of these subjects were noted to have abnormal PET FDG studies. Obviously, we have categorized these subjects as abnormal and the data generated from these individuals are considered unusable for further analysis.

We believe that a great deal of effort should be spent on the nonbiological sources of error where the investigator may have substantial control. Therefore, this aspect is discussed in more detail than issues related to biological variations.

For quantitative analysis of cerebral metabolic rate, accurate (low systematic errors) and precise (low random errors) measurement of tissue and blood activity concentrations used in the model parameters for calculating CMRgluc are required.

In measuring tissue activity concentrations with a camera, significant corrections are required for scatter, gamma ray attenuation, randoms and deadtime. The possible sources of error in tissue activity concentration measurements may be divided into those due to physical limitations and those due to reconstruction and analysis.

Physical and Camera Limitations

Head motion during imaging is a serious source of error if the scan time is long or the subject is not comfortable during the study. This is a rather trivial problem for studies of short duration where no stimulation or patient response is required.

Camera calibration (in μCi/ml/cpm/voxel) should be performed with phantoms of similar size to the brain so that scatter fraction is comparable between the two. This reduces systematic errors due to inaccuracies in scatter subtraction. Undersubtraction of scatter background reduces image contrast among structures. The measurement of tissue activity concentration should also take into account the attenuation effects of the headholder and skull (*8*). With careful camera calibration, the variabilities related to this source should be limited to 2%–3%.

Camera deadtime correction is necessary to account for variable activity in the field of view (FOV) for objects of differing size and configuration. Deadtime correction should be achievable to within 4% for all studies.

In PET cameras with septa, reduced spatial sampling may have a deleterious effect on measured activity concentration; especially where axial sampling is 6–8 mm. This degrades axial spatial resolution so that measured activity concentration depends on the position of the structure with respect to imaging planes (*9,10*) and the underestimation may be as high as 10%–15%. Similarly, spatial resolution is degraded as radial distance increases from the camera axis which results in radial elongation when gamma rays strike the camera crystals in an oblique direction. These effects are minimized by careful PET camera design. In a volume imaging PET camera, spatial sampling problems are reduced by having uniform (2 mm) sampling in all directions and combining this with three-dimensional rebinning of the data (*14*).

Statistical noise in small ROIs may significantly influence measurement

precision where the counts per pixel are low. For FDG brain metabolic studies in which 4–6 Mcts/slice (6 mm thick) are typically generated, this error only becomes an issue for regions of less than 0.5 cm^2 when statistical errors may reach 5%–6%.

Reconstruction and Analysis Errors

Whole-brain boundary definition may be affected by the degree of image smoothing since the perimeter of the region is often defined as 50% of peak activity in the structure (cortex). Oversmoothing may result in overestimation of brain size so that the average counts per pixel is underestimated by up to 2%–3%.

Small regions may have low recovery coefficients: for example a 1 cm^3 structure may have a recovery coefficient (RC) of 0.5 when image resolution using a clinical filter is 8 mm (as in most PET cameras). This may cause a systematic underestimation of tissue activity concentration in small regions (*10–13*). In CBF activation studies, this problem is partly offset by performing baseline and activations in the same subject in the same session. If the same region is studied under both conditions, the RC will be approximately the same for a given region and the fractional change in activity concentration remains reliable. In single measurements, the problem is somewhat complicated. Determination of structural volume from anatomic images may be of value when scaling measured activity concentrations by 1/RC; this however assumes a good correlation between structural size distribution and physiological activity.

The registration between MRI/CT defined templates and PET images may be achieved by two-dimensional or three-dimensional boundary matching and appropriate image resizing and reorientation. Misregistration in the transaxial and/or axial direction may compromise quantitation in small structures. This error is generally in the range of 1–4 mm and is minimized when high quality functional images are acquired and when the anatomical landmarks are well visualized. Errors are significantly reduced when large structures are chosen for analysis.

The assignment of ROIs should be based on individualized anatomic structures rather than on a standard atlas to ensure that the appropriate structures are identified and sampled on functional images. This would require utilizing a complex PET-MRI registration technique known to be reproducible and accurate. This is an area of intensive investigation at this time.

There are several sources of error in arterial blood activity concentration measurements:

1. Venous rather than arterial blood sampling can result in significant variability in measurement of metabolic rates. Even with careful insertion techniques, one may encounter some difficulties in placing the catheter in the distal veins of the hand and withdrawing adequate blood samples in a timely fashion.
2. Whether a dynamic blood sampler with BGO or scintillator detectors or a NaI(Tl) well counter are utilized to count the blood, calibration for ^{18}F activity should be reliable to within 2%–3%. Obviously, cross-calibration between the PET camera and the blood sample counter is needed.
3. Errors related to timing and variability in blood sample volume may add up to 1%–3% uncertainty to the measurement. We generally take 18–22 blood samples of 0.25 ml to define the input function (blood) curve. Mistiming of drawing or counting times and/or using incorrect sample volume adds to errors, as would mixing of pre-existing blood in the arterial line with radioactive blood. Most investigators allow at least five, or preferably ten times the volume of the tubing to drain before blood samples are drawn.
4. Fitting the blood curve for the purpose of deconvolution to calculate the cerebral metabolic rate may result in errors of 2%–3%. We employ a four component exponential fit to describe the blood curve.
5. Measurement of glucose concentration is required for calculating metabolic rates during the course of the FDG experiment and may be variable. Acquiring four to five blood samples to define this over the period of the study is necessary to minimize errors related to this source.
6. Tissue and arterial activity concentration values are used in an operational model where errors may also be introduced.
7. The lumped constant used in calculating metabolic rate varies from 0.42 to 0.52 and could account for the variability among different centers. We must emphasize that 0.52 is the measured value rather than a calculated number as is the case with 0.42 (*14*).
8. The duration and timing of the scans may have an effect on calculated metabolic rates due to dephosphorylation of deoxyglucose-G-phosphate (k4). Thus, timing of scans should be consistent within the scan and among centers if comparable data need to be acquired: e.g., 30–60 min postinjection. Later scanning times (e.g., 60–90 min postinjection) may result in low metabolic rates by 2%–5% without adequate correction for K4.
9. Contamination with fluorodeoxymannose (FDM) while synthesizing FDG may also cause underestimation of metabolic rates by up to 10% due to the difference in kinetics between FDM and FDG. Therefore, the degree of impurity should be known and kept to a minimum.
10. Finally, the operational equation for the calculation of the CMRgluc results in nonlinear propagation of errors so that, for example, a 10% error in activity concentrations may prop-

agate a 13%–15% effect in CMR.

Taken together, the errors added in quadrature for a 0.5-cm^3 region is limited by careful calibration and correction and may result in quantitative values precise to ±6-±13%. This should be remembered when examining inter- and intrapopulation variances in measured CMRgluc values.

As Wang et al. correctly indicate, variability is significantly reduced when relative rather than absolute values are used in characterizing regional metabolic activity. This has been clearly demonstrated by many centers including our own. For example, regional glucose metabolic rates in certain structures of the brain in patients with Alzheimer's disease overlap with those of age-matched controls. However, by normalizing the measured value in an ROI by that of a structure not affected by the disease, a significant difference between patients and controls can be demonstrated. It is essential to normalize regional values to those that are known not to be affected by the disorder. For example, in normal aging and Alzheimer's disease, it is well established that the cerebellum, the basal ganglia and the somatosensory and visual cortices are not affected unless the disease is well advanced (*15*). However, because of its size and location, the cerebellum is most commonly used for this purpose with excellent results. In fact, certain areas that may appear unaffected based on absolute values, may show significant alterations on relative quantitative measurements.

Unfortunately, unaffected areas of the brain are not well characterized in many neuropsychiatric disorders and may not be known in an individual subject. Therefore, some investigators have opted for whole-brain normalization as a means of minimizing measured variability. Although this has been used successfully in several centers, one must be aware of a potential source of error inherent in this approach. If the percent change in whole brain values is similar to that in the ROI, one might erroneously assume that no significant change has occurred in that location. Therefore, with the whole brain as a reference point, the ratios generated should be checked against another independent measurement to determine their validity.

The success of normalizing a regional value to that of a reference point in elucidating subtle physiological and pathological alterations in the brain has given credibility to SPECT as a respectable quantitative imaging modality. The introduction of high-resolution SPECT imaging instruments and ^{99m}Tc-labeled compounds has resulted in generating high-quality studies with exquisite detail. Considering the cost and the limited availability of PET, SPECT imaging with careful analysis techniques may be successfully employed as a powerful research and clinical tool. Obviously, prospective studies comparing PET and SPECT are necessary to further define the optimal role of each imaging technique in the investigation of various neuropsychiatric disorders.

Finally, correction for atrophy is essential to determine whether measured values on either PET or SPECT images are truly functional and unrelated to structural alterations (*16*). The value of atrophy correction has been clearly demonstrated in several reports (*17*). We have shown that after correction for atrophy (commonly seen in Alzheimer's disease) measured metabolic rates in the whole brain and several anatomic sites known to be affected by Alzheimer's disease appear within normal limits (*17*). In contrast, metabolic changes in frontal lobes demonstrated in normal aging are not accompanied by a significant degree of atrophy and therefore may represent truly functional effect (*18*). This type of analysis is necessary when the effects of pharmacological and other interventions are investigated. The concept of measuring metabolic rates for the entire brain or a structure as a whole may prove to be more useful in measuring brain function than that for a unit of weight (such as 100 g of tissue) (*19*). This type of calculation would require measurement of both the anatomic volumes as revealed by MRI and the metabolic rates determined by PET. We have found this approach quite helpful in separating patients with Alzheimer's disease and other dementing illnesses from age-matched controls by either employing whole-brain or regional values (*20*). The validity and role of this type of analysis must be determined by future studies.

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