PET data opens novel scientific and clinical lines of research on the neurometabolic processes associated with functional integration and its pathologic disruptions by brain disorders.

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REPLY: We appreciate the comment by Trotta and colleagues (*1*) on our recent study (*2*). Their results contribute to the developing field of metabolic connectivity imaging (*3*). Specifically, Trotta et al. applied a seed-based functional connectivity (sbFC) analysis of ^{18}F-FDG PET data with seeds placed in key regions of the known functional MRI (fMRI)–derived resting-state networks (RSNs). Undoubtedly, along with independent component analysis (ICA) the sbFC analysis is a useful way of exploring RSNs in PET data. Of note, in ICA tested results use standard statistical inference approaches, so they are not really arbitrary as mentioned by the authors (*1*). In addition, each network is represented as a single loading parameter, so the number of tests/comparisons is much lower compared with the sbFC analysis, which requires a test at every voxel. Given the format of the letter, details on this analysis such as size and choice of the seed location are not reported (*1*). We think, however, that caution should be taken when examining RSNs in PET data using seeds derived from fMRI-based networks. In particular, as shown in fMRI studies, minor changes in the seed location or size result in spatially varying functional maps (*4*). This limitation is expected to be even more critical for a cross-modality approach. For example, parietal clusters of the default mode network are localized in ^{18}F-FDG PET data more superiorly than in fMRI data, both according to Figure 1 in Trotta et al. (*1*) and to our experience (*5*). So far, data on spatial similarity between peak regions/coordinates within RSNs derived from fMRI and ^{18}F-FDG PET data in the same subjects are missing. Furthermore, the colleagues raise an important issue of the sample size (*1*). Namely, they could detect more RSNs with more study subjects. In line with this observation and in comparison to Savio et al. (*2*), we did identify the salience network in another study with a larger group of subjects (unpublished data). The impact of the sample size on the network detectability should be systematically addressed by future studies.

To facilitate the contribution of PET in understanding principles of brain connectivity, we propose to develop an atlas of RSNs on the basis of a large ^{18}F-FDG PET dataset, similar to Allen et al. (*6*). Such PET-based templates of RSNs may be also of value in characterizing disease-specific alterations at the metabolic network level.

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Semiquantification Limitations: FMTVDM©℗ Demonstrates Quantified Tumor Response to Treatment with Both Regional Blood Flow and Metabolic Changes

TO THE EDITOR: True quantification (*1–6*) is the actual measurement of material within a tested region. In molecular imaging, the ability to accurately measure isotope accumulation is dependent on the demonstration that the measuring device, be it a SPECT or PET camera, is accurately calibrated, is measuring the correct isotope, and can be counted and reproduced serially.

The publication by Humbert et al. (*7*) is important because it raises the question of whether PET cameras can detect actual changes in disease after treatment. To accurately measure changes in regional blood flow and metabolism it is necessary to rely on a truly quantified (*1–6*) method and not on a method that produces only a calculated value. The Humbert et al. (*7*) method makes 2 flawed presumptions. First, it applies the wrong pharmacologic kinetic model that the isotope absent from the arterial bed traveled only to the site of interest. Second, it uses a matrix setting, which has

been demonstrated to produce a loss of signal data, which produces a significant error rate (*2–6*). This method produces a *semi*quantified value derived from "first-pass extraction," not an accurate measurement of the amount of isotope within the tissue of interest.

We have demonstrated that using a true quantification method provides an actual measurement of change in regional blood flow and metabolism, which is useful in assessment of treatment response.

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REPLY: We thank Dr. Fleming for the interest shown to our paper (*1*).

In the present clinical research article, we applied a first-pass PET kinetic model that was developed and validated for blood flow (BF) measurement many years ago by Mullani et al. (*2,3*).

Kinetic modeling of ^{18}F-FDG in tissue assumes that there is a large influx of ^{18}F-FDG into tissue during the first pass of the tracer that is delivered as a function of the BF to the tissue. The input of this model is the arterial concentration of ^{18}F-FDG. The tracer then diffuses across the capillary wall into the extravascular space and washes out of the tissue at a slower rate without being metabolically trapped in the cell. The model of Mullani et al. postulates that during the first pass of a highly extracted tracer through the tumor, most of it is retained in the tissue and the venous egress of the tracer is delayed by some time. BF can be calculated during this delay time by using a simple 1-compartment kinetic model.

We do not think that this method relies on a wrong pharmacokinetic model. As it is the case in most of the models, it relies on some assumptions, which may not be fulfilled. Because of incomplete tumor extraction of ^{18}F-FDG, this simple pharmacokinetic model provides only an estimation of the BF. Regarding ^{18}F-FDG uptake quantification, our PET systems complies with the European Association of Nuclear Medicine ^{18}F-FDG PET/CT accreditation program, which is also endorsed by the European Organization for Research and Treatment of Cancer Imaging Group. Importantly, Mullani et al. validated their model by demonstrating that the estimated BF obtained with first-pass ^{18}F-FDG measurement was linearly and highly correlated with BF determined with ^{15}O-H_2O PET, the reference standard (*3*). Later, Cochet et al. demonstrated that, in breast cancer, BF calculated with this model was associated with tumor angiogenesis biomarkers (*4*).

In our work, we did not aim to raise whether ^{18}F-FDG PET can detect tumor changes during treatment (*1*). This has already been demonstrated decades ago. We aimed to evaluate the clinical usefulness of ^{18}F-FDG PET in the neoadjuvant setting of breast cancer. We assessed whether these changes can predict pathologic complete response at the end of treatment, which is the only validated surrogate marker of improved survival in this setting. For this purpose, tumor metabolic changes clearly outperformed changes of the estimated tumor BF changes, obtained from the first-pass dynamic images.

We recognize that developing improved imaging approaches to measure tumor BF more accurately, including SPECT imaging, might modify our conclusions in the future. Nevertheless, these new methods require comparison with the more routinely available technique we have used to prove their superiority and moreover their ability to improve patients' care. Contrary to what is written, Fleming et al. have not yet demonstrated in their previous paper the clinical usefulness of their method to predict breast cancer histologic response to chemotherapy (*5*).

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