

**Neurometabolic Resting-State Networks Derived from Seed-Based Functional Connectivity Analysis**

**TO THE EDITOR:** We read with great interest the paper by Savio et al. (1) on the imaging of resting-state networks (RSNs) from simultaneous <sup>18</sup>F-FDG PET/functional MRI (fMRI) data. The authors applied an independent component analysis (ICA) commonly used in fMRI and reported fair cross-modality agreement for several RSNs. In view of the distinct nature of the neurovascular and neurometabolic couplings, this tends to confirm the neural basis of RSNs, in line with recent magnetoencephalographic studies. Interestingly, some networks were only identified in one modality or the other, for example, the <sup>18</sup>F-FDG PET ICA reported by Savio et al. (1) failed at detecting the salience/insular or temporopolar RSNs disclosed in the corresponding fMRI ICA. This leaves the question of their neural underpinning pending.

Methodologically, this study focused on the ICA technique. A complementary approach is seed-based functional connectivity (sbFC) whereby a seed location is selected a priori as part of the sought network, and correlation maps are estimated between the seed and all other voxel activities. Compared with ICA, sbFC is straightforward to interpret and avoids the issues of selecting the number of components (which affects ICA decompositions) and visually discriminating between physiologic and noise components. Furthermore, sbFC can be subjected to the rigorous statistical framework of random field theory (RFT) (2), henceforth eliminating the usage of somewhat arbitrary thresholds. Supplementing ICA with sbFC thus appears necessary for robust inferences about RSNs.

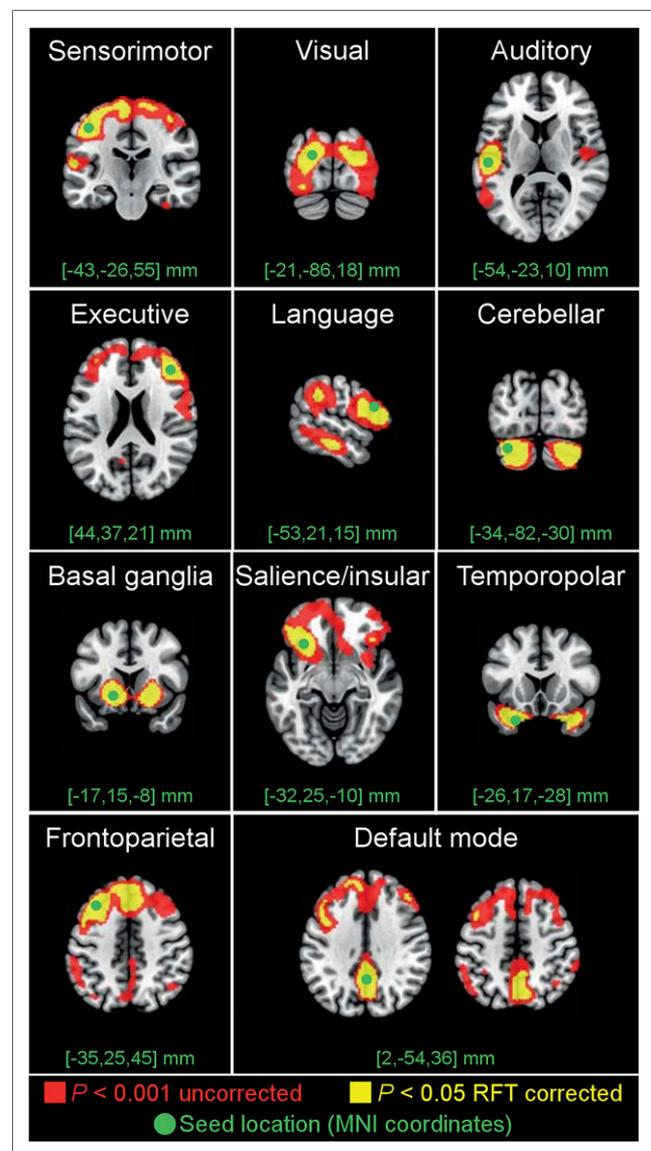
We hereby report that sbFC analysis of <sup>18</sup>F-FDG PET data do allow statistical mapping of most RSNs, including those unidentified from the <sup>18</sup>F-FDG PET ICA (1).

Specifically, we considered a resting-state (eyes closed) <sup>18</sup>F-FDG PET dataset of 50 healthy adults (27 women; age range, 18–43 y) whose acquisition and preprocessing procedures have been detailed in a previous publication (3). We used SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>, Wellcome Trust Centre for Neuroimaging) to design voxelwise general linear models of the <sup>18</sup>F-FDG PET images with metabolism at the seed location as covariate of interest. One-sided *t* tests were then applied to identify significantly positive sbFC, both at *P* < 0.05 with the whole-brain familywise error rate controlled by RFT and at *P* < 0.001 uncorrected.

Figure 1 illustrates the statistically masked sbFC *t*-maps obtained from selected seeds. Several RSNs emerged at RFT significance, from low-level (e.g., sensorimotor, visual) to cognitive (e.g., language, executive) and subcortical (e.g., cerebellar, basal ganglia) networks. Other RSNs were identified only partially but recovered at *P* < 0.001 uncorrected (e.g., auditory, default-mode, and frontoparietal networks). In line with the discussion in Savio et al. (1), this may be due to the nondynamic nature of our <sup>18</sup>F-FDG PET data. Indeed, compared with fMRI, the loss of temporal samples strongly limits the sensitivity of correlation estimates. Importantly, the salience/insular and temporopolar RSNs missing in the <sup>18</sup>F-FDG PET ICA (1) were identified as well. The

reason may simply be that our dataset contains approximately 2.3 times more subjects, leading to approximately 33% less correlation noise. Indeed, repeating our sbFC analyses on half our population failed at revealing these 2 RSNs. Besides, this increase in sampling size would enable computing extra <sup>18</sup>F-FDG PET ICA components possibly disclosing these RSNs.

Together with previous seminal studies that had some shortcomings limiting the interpretations of their results (4,5), Savio et al.'s study (1) and our <sup>18</sup>F-FDG PET data obtained by statistical sbFC mapping bring novel evidence that the field of RSNs—up to now exclusive to fMRI and to a lesser extent extracranial electrophysiology—can be expanded to the realm of neurometabolism and thus pervades all functional neuroimaging. In particular, the combination of sbFC with ICA applied to resting-state <sup>18</sup>F-FDG



**FIGURE 1.** Statistically masked sbFC *t*-maps obtained from selected seeds.

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.

## REFERENCES

1. Savio A, Fänger S, Tahmasian M, et al. Resting state networks as simultaneously measured with fMRI and PET. *J Nucl Med*. 2017;58:1314–1317.
2. Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC. A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp*. 1996;4:58–73.
3. Trotta N, Archambaud F, Goldman S, et al. Functional integration changes in regional brain glucose metabolism from childhood to adulthood. *Hum Brain Mapp*. 2016;37:3017–3030.
4. Di X, Biswal B. Metabolic brain covariant networks as revealed by FDG-PET with reference to resting-state fMRI networks. *Brain Connect*. 2012;2:275–283.
5. Horwitz B, Duara R, Rapoport SI. Intercorrelations of glucosemetabolic rates between brain regions: application to healthy males in a state of reduced sensory input. *J Cereb Blood Flow Metab*. 1984;4:484–499.

**Nicola Trotta  
Kristof Baete  
Koen Van Laere  
Serge Goldman  
Xavier De Tiège  
Vincent Wens\***  
\*CUB—Hôpital Erasme  
808 Route de Lennik  
Brussels, Belgium 1070  
Email: vwens@ulb.ac.be

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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 <sup>18</sup>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 <sup>18</sup>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 <sup>18</sup>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 <sup>18</sup>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.

## REFERENCES

1. Trotta N, Baete K, Van Laere K, Goldman S, De Tiège X, Wens V. Neurometabolic resting-state networks derived from seed-based functional connectivity analysis [letter]. *J Nucl Med*. 2018;59:1642–1643.
2. Savio A, Fänger S, Tahmasian M, et al. Resting-state networks as simultaneously measured with functional MRI and PET. *J Nucl Med*. 2017;58:1314–1317.
3. Yakushev I, Drzezga A, Habeck C. Metabolic connectivity: methods and applications. *Curr Opin Neurol*. 2017;30:677–685.
4. Iraj A, Calhoun VD, Wiseman NM, et al. The connectivity domain: analyzing resting state fMRI data using feature-based data-driven and model-based methods. *Neuroimage*. 2016;134:494–507.
5. Yakushev I, Chételat G, Fischer FU, et al. Metabolic and structural connectivity within the default mode network relates to working memory performance in young healthy adults. *Neuroimage*. 2013;79:184–190.
6. Allen EA, Erhardt EB, Damaraju E, et al. A baseline for the multivariate comparison of resting-state networks. *Front Syst Neurosci*. 2011;5:2.

**Isabelle Ripp\*  
Alexandre Savio  
Igor Yakushev**  
\*Technische Universität München  
Einsteinstrasse 1  
München, D-81675, Germany  
E-mail: isabelle.ripp@mri.tum.de

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## Semiquantification Limitations: FMTVDM<sup>®</sup> 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