Review of: "Coupling between Human Brain Cortical Thickness and Glucose Metabolism from Regional to Connective level: a PET/MRI study"

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Potential competing interests: No potential competing interests to declare.

Introduction - In the absence of any cognitive outcomes or functional task activation, it is erroneous to talk about “connectivity” when discussing Cth-driven “structural connectivity”. It would be more apt to talk about “shared susceptibility” maps as this is, essentially, that which is being extracted from the Cth correlation matrices. A similar reasoning applies to FDG PET connectivity; what is being measured are correlated hypometabolic areas across aging, for example. That one wants to investigate if Cth and FDG PET areas are common however is a worthy goal, but “connectivity”, alas, it is not.

Methods – Provide the exact breakdown of the excluded group by exclusion criteria. Provide inclusion criteria: why were those participants scanned in the first place? What diagnostics warranted the investigation? Anything with a changed metabolism (e.g. cancer) or reduced blood flow (e.g. cardiovascular disease) would also be liable to affect FDG PET. Depending on the characteristics of this sample of convenience, this may invalidate the rest of the study.

Methods – Unclear if the slice thickness (0.67mm) and the space between slices (0.67mm) refer to the same thing, or is there really a space between slices? If so, how can the MR thickness estimates be reliable? Full 3D acquisition is necessary to extract thickness.

Methods – There seems to be no adjustment for head size for the T1w images; registration to the MNI space is not mentioned (it is for the PET)

Methods – There seems to be no adjustment of PET data to use SUVR? How were image intensities co-standardized between PET scans, given difference in dose/mass/counts?

Results – Other influences – e.g. sex, metabolic syndrome (high fasting glucose, hypertension, hypocholesterolemia, obesity, high triglycerides) – should be taken into account

Discussion – Again, when discussing “networks” and “efficiency” it should be widened to think in terms of susceptibility, barring functional (i.e. cognitive) evaluation.

Discussion – What is the influence of the partial volume correction of FDG PET on the results?

Discussion - Attention should be put as well to newer work (eg. Xiang Science Translational Medicine 2021) that shows

that the essence of the FDG PET signal may not, as has been widely believed previously, come from the neuronal population (due to synaptic activity) but rather from activated microglia. What is the impact on your findings?