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Issues of parcellation in the calculation of structure–function coupling

In their recent Review, Fotiadis and colleagues expertly summarized recent research on structure–function coupling (SFC), a neural marker representing the correspondence between structural and functional neural connections (Fotiadis, P. et al. Structure–function coupling in macroscale human brain networks. *Nat. Rev. Neurosci.* **25**, 688–704; 2024)[1]. They outlined how this marker is important for understanding ageing and neurological and psychiatric disorders, providing an invaluable resource for researchers interested in SFC. The authors identified that most studies calculate macroscale SFC by correlating structural connectivity (SC) and functional connectivity (FC) matrices. They also highlighted several methodological considerations; however, we think that there is a critical issue with SFC calculation from SC and FC that was not mentioned in this Review. Given the growing interest in this marker, we hope to highlight this issue alongside this trailblazing Review, to improve research on SFC moving forward.

FC and SC matrices are produced from data that capture different aspects of brain organization. Diffusion tensor imaging (DTI) data can provide an estimate of white matter tracts that connect two different regions (SC). Functional MRI (fMRI) data measure changes in the blood-oxygen-level-dependent signal as an indirect measure of brain activity, which can be correlated between regions to provide a measure of FC. Both measures can be averaged within specific brain regions, or parcels, to provide a shared space to correlate FC and SC to produce SFC. This is necessary because, at a more precise level, FC (reflecting brain activity) emerges from the cortical grey matter and SC (reflecting brain structure) exists in the white matter.

This requirement is problematic for several reasons. The lack of overlap forces researchers to pick a parcellation within which to average FC and SC. There are many parcellations[2], comparison across studies using different parcellations is a challenge[3], and parcels may vary depending on the population (for example, older versus younger adults[4]). Parcellation approaches aim to divide the brain into specialized units that contain similar brain regions in terms of either function (for example, their activity) or structure (for example, their shape and/or where they connect to), and parcellations are therefore usually either functional or structural. This means that there is a need to compromise by averaging SC or FC within parcels that may not represent homogenous units for that particular methodology, potentially leading to a loss of meaningful signal. Even parcellations that are made from multimodal data[5] are rarely designed to best capture both SC and FC. Using parcellations also removes the ability of researchers to look at local differences in SFC with a spatial precision that is smaller than the size of the parcels. Together, these issues may explain why a recent approach that projects FC and SC to the grey matter–white matter boundary showed improved discriminability for sex differences in SFC[6]. This approach also removes the requirement of researchers to choose a parcellation as well as allowing them to look at local SFC at a higher spatial precision. This sort of approach may be necessary to maximize the predictive power of SFC when using it to understand ageing as well as neurological and psychiatric disorders.

There is a reply to this letter by Fotiadis, P. & Bassett D. S. *Nat. Rev. Neurosci*. https://doi.org/10.1038/s41583-024-00878-y (2024).

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Competing interests

The authors declare no competing interests.