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Reply to 'Issues of parcellation in the calculation of structure–function coupling'

We appreciate the thoughtful Correspondence from A. Turnbull, F. V. Lin and Z. Zhang about our recent Review (Fotiadis, P. et al. Structure–function coupling in macroscale human brain networks. *Nat. Rev. Neurosci.* **25**, 688–704; 2024)[1], in which we synthesized recent work assessing the dynamic relationship between structural and functional connectivity in the human brain, commonly referred to as structure–function coupling (SFC). We focused in the Review on studies that quantify this relationship by correlating each brain region's structural and functional connectivity towards all other brain regions. In their Correspondence, the authors emphasize an important methodological limitation of this approach, which is that it depends on the definition of brain regions — and by extension, the brain parcellation — used (Turnbull, A., Lin, F. V. & Zhang, Z. Issues of parcellation in the calculation of structure–function coupling. *Nat. Rev. Neurosci.* https://doi.org/10.1038/s41583-024-00877-z; 2024)[2]. To address this limitation, they propose an alternative methodology to quantify SFC that does not rely upon a pre-defined parcellation scheme. The proposed surface-based approach instead projects the structural and functional connectivity to the grey matter–white matter boundary, allowing the computation of SFC at a high spatial resolution[3].

Although there is merit to approaches that use few assumptions, there is also something to be learned by examining SFC using brain parcellations with different definitions of brain regions[4]. For instance, the use of a brain parcellation whose parcels (brain regions) have been defined using cyto-architectonic[5] or myelo-architectonic[6] features would allow us to study how structural connectivity shapes functional connectivity in the brain using established anatomical criteria, rather than imaging modality-defined features, such as voxel size. Beyond this point, examining SFC at different spatial scales, using brain parcellations of varying granularities, could also yield valuable intuitions. In a recent study, for instance, we investigated how intracortical myelination and excitation–inhibition balance collectively shape SFC across the cortical hierarchy; notably, we assessed this relationship at different spatial resolutions, ranging from the coarser atlas-based level to the substantially more fine-grained voxel-based level[7]. This approach allowed us to show that the relationship between the three variables remained qualitatively similar across scales, and thus did not depend on the spatial resolution used. More broadly, reporting on the potential dependence between SFC and the underlying spatial scale can provide critical information on whether this variable exhibits scale-free properties. Furthermore, such an exploration could elucidate how the dynamic coupling between structural and functional connectivity changes as we traverse from mesoscale to macroscale definitions of brain regions, enabling us to potentially pinpoint emergent dynamics. In the same vein, it would be particularly interesting to inspect whether SFC is more immune to the underlying spatial scale than its individual components: structural and functional connectivity. Such a finding could further identify SFC as a more robust marker of brain dynamics than structural or functional connectivity alone.

Designing dedicated studies that examine how (and whether) the relationship between structural and functional connectivity varies across different spatial scales could provide insight into the nature of their coupling. Harking back to the corresponding authors' astute point, however, studies that do use atlas-derived metrics of SFC could usefully also ideally compute the same variable using methodologies that do not rely on a priori parcellation choices, to be used as a reference. If the goal of the study is not to assess the variable's spatial dependence, however, we certainly concur with the authors that using a methodology that is not dependent on the choice of a brain parcellation would yield a compelling measure of SFC.

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Competing interests

The authors declare no competing interests.