Drs. Margulies, Smallwood and Keilholz
Special-Issue-Editors NeuroImage,

Cambridge, February 27, 2020

Dear Drs. Margulies, Smallwood and Keilholz

We would like to submit our manuscript *"Dispersion of functional gradients across the lifespan"* by Bethlehem, Paquola et al. for publication in the *NeuroImage special issue: Gradients in brain organisation*.

Ageing is commonly associated with changes to segregation and integration of functional brain networks, but, in isolation, current network-based approaches struggle to elucidate changes across the many axes of functional organisation. In the present manuscript we utilized gradient connectivity mapping to characterize lifespan differences in functional topology in the Cambridge Centre for Ageing Neuroscience cohort (n=643). Building on the existing gradient framework we further propose an extension towards multi-dimensional connectivity space. Quantifying lifespan differences in this multi-dimensional space allowed us to capture behaviourally relevant and network specific differences. Specifically, we detected a strong shift of the visual network across the lifespan from an extreme to a more central position in the 3D gradient space. In contrast, the dispersion distance of transmodal communities (dorsal attention, ventral attention, frontoparietal and default mode) did not change. However, these communities were increasingly dispersed with increasing age, reflecting more dissimilar functional connectivity profiles within each community. Increasing dispersion of frontoparietal and ventral attention networks, in particular, was associated negatively with cognition, measured by fluid intelligence. By using a technique that explicitly captures the ordering of functional systems in a multi-dimensional hierarchical framework, we identified behaviorally-relevant age-related differences of within and between network organisation.

We believe this work to be of broad relevance to the neuroimaging community as it not only shows how gradient topology varies across the lifespan it also outlines a novel way of quantifying multidimensional connectivity changes. Given its focus on using gradient analyses as a cornerstone of our analyses and methods we believe this work to be of particular interested for the special issue on *gradients in brain organization*.

We confirm this work is not under consideration elsewhere and as always we provide full transparency on our analyses by sharing all code and data used in the project on GitHub.

Yours sincerely,

Drs. Richard A.I. Bethlehem, Casey Paquola, Boris Bernhardt & Kamen Tsvetanov