Human brain mapping

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Converging cortical axes

Konrad Wagstyl & Armin Raznahan

The cerebral cortex shows complex organization across diverse biological scales, from regional chemical and cellular specializations to macroscale functional networks. Zhang et al. report that macroscopic neuroimaging maps of cortical activity align with microscopic cellular features: sensory and association regions define opposing extremes for both. The consistent identification of a sensory–association axis across multiple scales and analytic approaches underscores it as a fundamental organizational principle that raises new challenges for the field.

From molecules to cells, through functional networks, to thought, our brains are beautifully complex at multiple levels of organization, but it is unclear how these levels relate to each other. Bold new efforts to compare brain maps from measures at diverse scales are giving us some surprising answers.

The structure of the cortex can now be analyzed using a wide array of techniques, which enables cortical cartography at multiple scales. These span from the cellular scale, which details morphology and cell-specific gene expression, through mesoscale descriptors of cellular density, cortical layering and architecture, to macroscale patterns that can be assessed via in vivo functional and structural measures from magnetic resonance imaging (fMRI and sMRI, respectively). A key goal of human brain mapping is to understand the connections between these diverse measures, which enables us to predict how variations in dendritic arborization might affect functional signals or, conversely, how differences in functional characteristics might reflect changes in the underlying cellular properties, for example. An increasingly popular strategy for tacking this challenging goal has been leveraging spatial covariation across the cortical sheet; this rests on the logic that cortical features that spatially covary are more likely to be mechanistically linked than those that do not.

The study from Zhang et al.[1] seeks to link up microscale and macroscale levels of cortical organization by using resting-state fMRI-derived connectivity as a starting point. These connectivity data can be used to represent the topography of cortical organization as a patchwork of discrete networks[2] or as a set of continuous gradients that capture common low-dimensional axes of regional variation in functional connectivity[3]. Zhang et al. used both of these representations, which identify maximally contrasting connectivity signatures in visual and somatosensory versus association cortices. In parallel, they estimated changes in the cellular composition of cortical areas by combining single-cell RNA-sequencing data from eight cortical areas[4] with bulk gene-expression data across the cortical sheet from the Allen Human Brain Atlas[5]. Using the cell-specific expression signatures to impute relative cellular abundance across the cortical sheet, Zhang et al. found that different functional connectivity gradients and networks exhibit distinctive cellular fingerprints. These gene-expression-based cellular fingerprints are maximally distinctive between those cortical regions that are also most functionally distinctive — namely, sensory versus association regions (Fig. 1).

The findings of Zhang et al. extend existing work on cortical organization by integrating new cellular phenotyping data and rooting this exploration in fMRI-derived cortical gradients. In doing so, the results add to a notable convergence (Fig. 1a) that is emerging across multiple recent studies that explore the topographical organization of the cerebral cortex through the integration of multimodal, multiscale data (Fig. 1b). Specifically, these diverse recent studies all reveal the same principal sensory–association axis of cortical organization defined by maximally distinct sensory versus limbic poles, regardless of whether the input data stem from measures of bulk expression data[6–8], neurotransmitter receptors[9], cell-type markers[1,4,6], fMRI measures of functional connectivity[3], or the temporal patterning of cortical development[10,11] and regional cortical changes in clinical groups[12].

The emerging fact that the sensory–association axis is a recurrent principal spatial gradient of cortical organization across this large set of cortical features dictates that there will be spatial coupling between most individual pairs of features from the set. As such, the field is now facing a transition point between describing pairwise alignments of cortical features along the sensory–association axis and understanding what these recurrent convergences mean for the future. This new phase of work poses several important challenges and opportunities.

First, it will be important to understand the mechanistic bases for pairwise convergence of diverse cortical measures along the sensory–association axis. Some mechanisms are clearly due to anatomical and methodological constraints: for example, cellular density, neuropil content, cell morphology and cytoarchitecture are perhaps deterministically linked, and bulk expression is a composite of the single-cell data. However, other mechanisms are less obvious, such as the spatial coordination between functional connectivity and single-cell phenotypes[1] or the recapitulation of topographic patterns across development[6,11]. These mechanisms cannot be understood by continued description of spatial covariation in the absence of orthogonal — and, ideally, experimental — data. However, the required experimental approaches are ethically and logistically difficult to implement in humans and will probably also pose challenges in those nonhuman animal models that are more experimentally accessible. Specifically, because the sensory–association axis reflects the integration and enmeshment of multiple complex biophysical processes over developmental time, attempting to manipulate any one feature pair will probably perturb this system in many ways. Experimental manipulations in the adult state may be easier, but will not be able to capture causal processes in development.

Second, it will be important to understand whether feature coherence along the sensory–association axis is as strong in individuals as it appears to be in group-level data. Postmortem measures are a particular concern here, because these often require aggregating measures

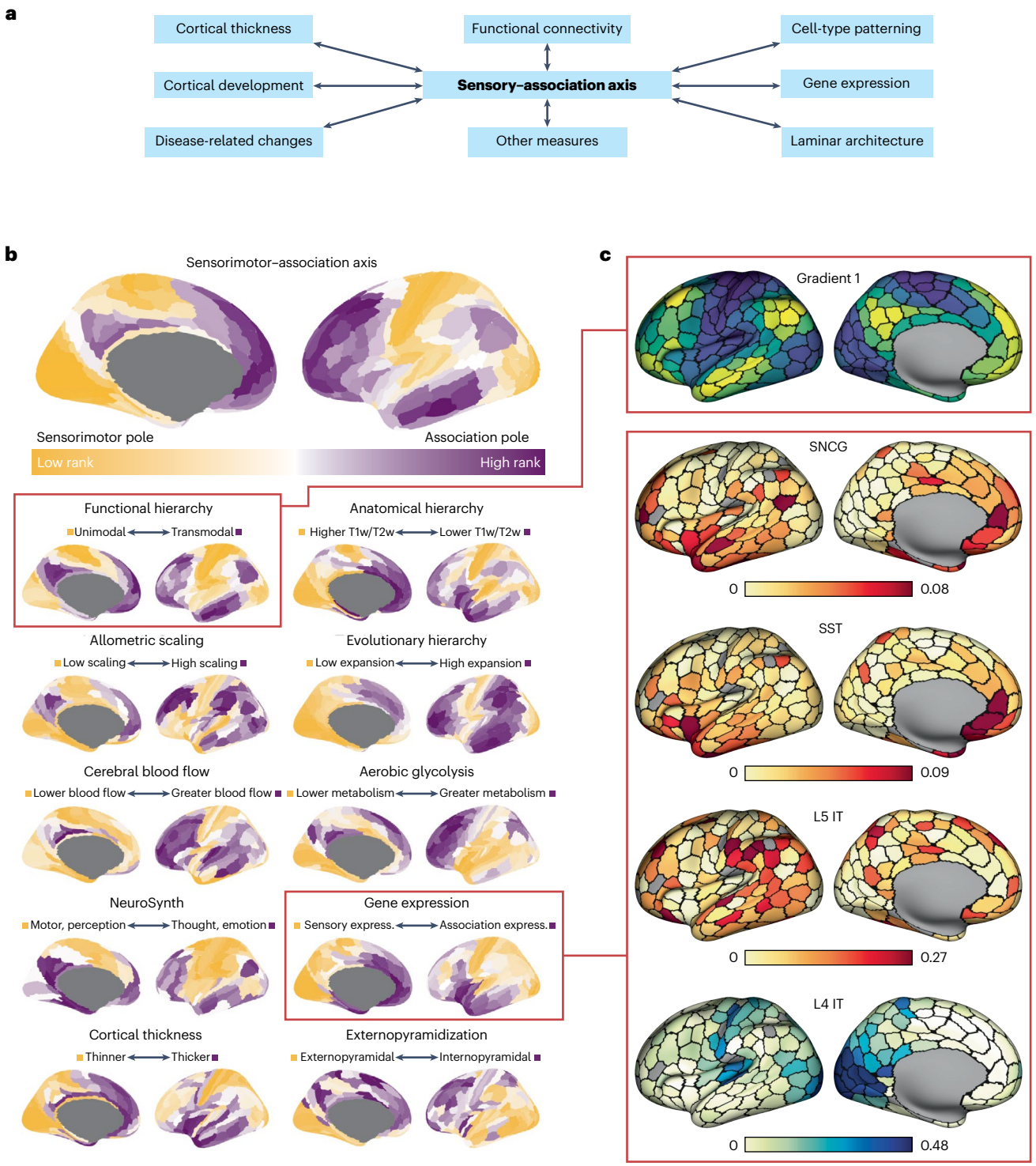

Fig. 1 | Converging cortical axes highlight sensory and association areas as maximally distinct poles across diverse measurement modalities. a, Schematic showing coalignment of diverse cortical features with the sensory–association axis. **b**, The principal spatial component of the sensory–association (or more fully, sensorimotor–association) axis (top), derived from many individual feature maps that show pairwise alignment along it. Reproduced with permission from ref. 11, Elsevier. **c**, Zhang et al. found that fMRI-derived functional connectivity gradients are topographically co-organized with specific transcriptomically defined neuronal cell types. Adapted from ref. 1, Springer Nature America, Inc. Red boxes: the functional hierarchy map (in **b**) and gradient 1 map (in **c**) both show the first principal component of interregional cortical functional connectivity from resting state fMRI. The cell-type-specific expression maps in **c** are derived by deconvolution of bulk RNA-sequencing data that have a first principal component as shown in the gene expression map (in **b**). Regions of extreme cell-type signatures tend to lie at the poles of the sensory–association axis. IT, intratelencephalic.

across subjects and then comparing the resultant average to an independently aggregated atlas. Under these conditions, universal axes may consistently emerge as the lowest common denominator across metrics and individuals, potentially at the cost of losing more subtle, unique topographies and connections. Addressing this issue will require the collection of matching data that capture multiple scales from the same individuals to directly probe these links, such as high-resolution structural and functional in vivo subject or spatio-cellular expression data capturing whole-brain patterning.

Third, dissecting the mechanisms for sensory–association convergence will require the development of new statistical methods. The field has already identified several challenges and solutions, including statistical null models to account for spatial autocorrelation[13] and background gene coexpression[14], alongside leveraging intersubject variability to link multimodal data[15]. However, such null models tend to be applied independently, and we may need additional innovations that are capable of testing for spatial association between one pair of cortical features while controlling for their co-occuring spatial associations with other cortical features.

Finally, owing to the inherent biophysical coexpression of many of our metrics, the question arises of how we identify the most statistically important or mechanistically meaningful level of explanation. For instance, the cortical topography of disease-related change might correlate with chemoreceptor concentrations, the regional neuronal subtypes and laminar architectures, owing to their own inherent biophysical coexpression. But questions of which of these best describes essential components of disease etiology, explains phenotypic change or identifies avenues for intervention remain open.

The Zhang et al. study advances our understanding of cortical topographic organization by characterizing new associations between cortical cellular subtypes and functional characteristics. It also highlights areas where our understanding of the multiscale organization of the cortex would be advanced through additional conceptual, methodological and experimental innovation.

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Competing interests

The authors declare no competing interests.