BRAIN IMAGING

Mapping gradients in the mouse cortex

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The cerebral cortex processes incoming sensory information by following a functional hierarchy: the cortical areas that are lower in this hierarchy—the early sensory areas—are involved in fast responses to incoming stimuli, whereas higher-order association areas at the top of the hierarchy can integrate multiple sources of information over longer timescales. Studies in monkeys and humans have shown that in primates, this functional hierarchy in sensory processing is underpinned by corresponding changes in brain structure: across the cortex, the structure of the microcircuits varies along spatial gradients that contribute to the specialization of cortical function. According to a new study, the mouse cortex is also organized in large-scale gradients of structural properties, indicating that the hierarchical specialization of the brain may be conserved among mammals.

“We wanted to investigate whether a similar principle of brain organization holds in the mouse cortex, which has been shown to be relatively uniform in comparison to the highly specialized primate cortex,” says study investigator Ben Fulcher, from Sydney University. The project started when Xiao-Jing Wang, a researcher at NYU and at the Shanghai Research Center for Brain Science, saw a connection between his work on gradients of interneuron cell densities in the mouse cortex and Fulcher’s work on gradients of gene expression across the mouse brain. “This finding gave us a foundation to bring lots of diverse and independently analyzed measurements of the mouse cortex from diverse available databases together for the first time,” explains Fulcher.

When John Murray from Yale University joined the research team, he was investigating how T1-weighted (T1w)/T2-weighted (T2w) ratio maps created from MRI images correlated with structural and transcriptional variations across the primate cortex. T1w/T2w is a noninvasive measurement, interpreted as a marker of intracortical myelin content that has been used in mice, macaques, and humans to map cortical areas. Therefore, the investigators thought to use T1w/T2w in this study as a common spatial reference to compare the organization of the brain across species.

Variation in T1w/T2w across mouse cortical areas. Reprinted with permission from Fulcher et al. (2019). National Academy of Sciences.

Murine MRI data were obtained from the scalable brain atlas in Waxholm Space (<https://www.nitrc.org/projects/incfwhsmouse>) and Valerio Zerbi from ETH Zürich reconstructed the T1w/T2w maps across 40 cortical areas of the Allen Reference Atlas. The results showed that T1w/T2w decreased across the main connectivity areas of the mouse cortex, from somatomotor to prefrontal areas (somatomotor>medial>temporal>visual>anterior>prefrontal). These results are consistent with previous studies in macaques and humans, in which T1w/T2w decreases from unimodal areas to transmodal areas, along a hierarchy of increasing functional integration. The analysis also revealed that T1w/T2w correlated with changes in several structural properties of the cortex such as cytoarchitecture, interneuron density, and axonal connectivity, similar to what has been shown in primates.

Next, using data from the Allen Mouse Brain Atlas (<http://mouse.brain-map.org/>), the investigators established the expression profile of 4,181 genes across the mouse cortex and selected a set of 86 receptor subunits and cell-type marker genes for further analysis. The result showed that 24 genes, including glutamate receptor subunits, serotonin receptor subunits, and interneuron cell-type markers, significantly correlated with T1w/T2w. Principal Component Analysis (PCA) of 1,055 brain-expressed genes organized the different cortical areas along intuitive primary–transmodal processing streams.

The investigators then combined the structural properties and gene-expression profiles to understand the relationships

between the different gradients of variation for each type of data across the cortex. “By bringing together measurements of cell-type densities, gene expression, axonal connectivity, cytoarchitecture, and structural MRI maps, we found a common gradient of variation along which all of these measurements covary,” says Fulcher. “This axis captures a functional hierarchy of mouse brain areas, matching the results in primate; these results highlight a previously unappreciated level of structural heterogeneity of mouse cortical circuits,” he adds.

Next, to assess the consistency between mouse and human brain organization, the investigators compared the transcriptional gradients in the mouse to those in human cortex (<http://human.brain-map.org/>), using T1w/T2w as a common spatial reference. Analysis of the gene-expression profiles of 70 brain-related mouse genes and their human orthologs highlighted a significant interspecies correspondence of transcriptional gradients.

“Our results suggest that a common spatial variation in microcircuit properties may underpin functional specialization across the hierarchy in both mouse and human, providing new understanding of how the neural architecture of the brain has evolved to process information efficiently,” says Fulcher.

Fulcher adds that future studies will investigate microstructural variations across the brain more closely, using computational neuroscience and simulations to link microscale structure to macroscale functional brain dynamics.

“Through tight integration between theory and experiment, we hope to draw closer to understanding how the brain’s structure facilitates the diverse range of complex cognitive functions we are able to perform, and thus move towards a future in which we might be able to emulate these architectures for building new artificial intelligence algorithms,” he concludes.

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