A map of mitochondrial biology reveals the energy landscape of the human brain

Mapping the density, molecular features and energy-transformation capacity of cell organelles called mitochondria in the brain reveals region- and cell-type-specific variability that tracks with evolutionary patterns. Correlations between mitochondrial and brain-imaging metrics could enable future non-invasive explorations of mitochondrial bioenergetics in the brain in health and disease.

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The problem

The transformation of biochemical energy from food and oxygen into electricity, and then into molecules of ATP, one of the cell's energy currencies, is done by organelles called mitochondria[1]. In the brain, energy transformation is crucial for normal brain function, cognition and consciousness, and its disruption is a potential driver of neurological and psychiatric illnesses.

One barrier to efforts to resolve the bioenergetic contributions to brain health and disease is a 'scale gap': mitochondrial diversity is typically studied at the sub-micrometre scale[2], whereas brain activity is typically studied using imaging techniques, such as magnetic resonance imaging (MRI), that have millimetre-scale resolution. To relate complex human brain dynamics to mitochondria, the spatial distribution of diverse, energy-transforming mitochondria must be mapped across the brain, which is a considerable technical challenge. Another barrier is the 'translatability gap', which arises from the absence of non-invasive methods to investigate mitochondria in healthy individuals and in people with various disorders. These problems have prevented scientists from exploring how bioenergetics contributes to human experiences and behaviours[3].

The solution

To bridge the scale gap, we cut a frozen brain slab into cubes called 'voxels' that measured 3 millimetres in each direction. In this project, MitoBrainMap v.1.0, we partitioned a single brain section into 703 of these voxels. We constructed a spatial map (Fig. 1a) by using biochemical and molecular techniques to determine the mitochondrial density and energy-transformation capacity of each voxel. For some voxels, we also profiled mitochondria by using single-nucleus RNA sequencing, showing that mitochondria differ not only by brain region, but also by cell type.

To resolve the translatability gap, we mapped mitochondrial features onto standardized coordinates used for whole-brain imaging and looked for correlations between the measured mitochondrial subtypes and standard brain-imaging data of different modalities collected from several hundred healthy individuals. By training a computational model to predict mitochondrial metrics from different modalities of MRI data, we were able to extend the predictions of this model from one brain slice to the entire brain (Fig. 1b).

Mitochondrial density and ATP-synthesizing capacity in the brain's grey matter (which contains neuronal-cell bodies) were almost double those in the white matter (which contains neural tracts), and they closely matched the estimated evolutionary age of different regions of grey matter. More-recently evolved brain regions that make humans different from other species contained more mitochondria, and these mitochondria were specialized for more-efficient energy transformation. This aligns with the high energetic costs of these regions compared with evolutionarily older regions[4]. We also identified distinct brain-region-specific signatures that reflect mitochondrial specialization at both regional and cellular levels.

The implications

MitoBrainMap v.1.0 and our predictive model mark a milestone towards understanding how brain mitochondria are linked to cognitive function and neurological health, opening exciting possibilities for medicine and diagnostics. If validated, the predictive model could estimate the abundance and functional properties of brain mitochondria using MRI scans from live individuals, enabling scientists to explore the relationships between mitochondrial function and brain activity during cognition, development, disease states and psychological states.

The main limitation of this work is that it comes from a single section of a single brain. We do not know by how much mitochondrial distribution and specialization patterns differ between people, and determining this will require the 'voxelization' of other donor brains. An ongoing study of nine regions in 500 human brains partly addresses this issue, but the question of plasticity — how the mitochondria might change with human experiences — will remain. Moreover, our neuroimaging model was constructed using average brain templates from several, but not all, brain-imaging modalities. Much work remains to be done to fully leverage this approach.

Once validated, our brain-wide mitochondrial-profiling approach could be integrated with other imaging modalities[5] and help to track the health of brain-mitochondria. Applications could include diagnostics and the tracking of the effects of strategies to improve brain function or to stall or treat neurological, psychiatric and neurodegenerative disorders.

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EXPERT OPINION

"The manuscript introduces MitoBrainMap v.1.0, a brain-wide map of mitochondrial distribution and specialization that can be used to explore the molecular energetic landscape that enables normal brain function. The paper presents unique and precious information that maps the subcellular energetic architecture of different cell types, in different brain regions. This information will be crucial to advancing our understanding of large-scale brain dynamics." (CC BY 4.0)

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FIGURE

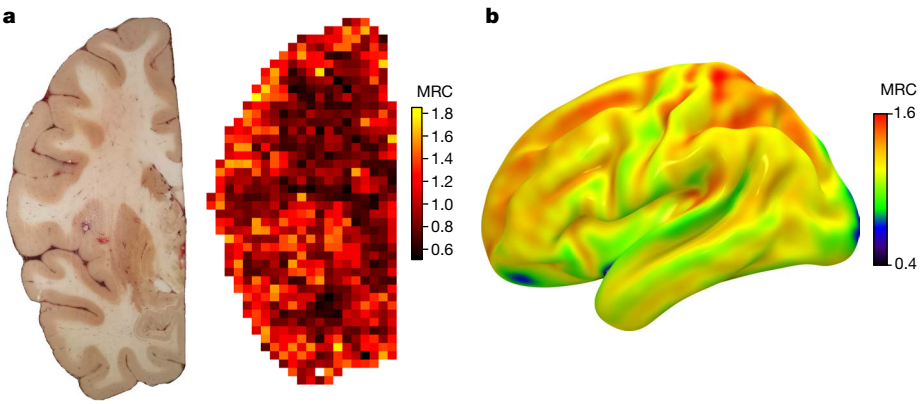

Figure 1 | Specialization and distribution of energy-transforming organelles called mitochondria across the human brain. a, This section of a 51-year-old man's brain (left) was cut into 703 voxels, each measuring 3 × 3 × 3 mm. The respiratory capacity of mitochondria in each voxel was assessed using biochemical techniques, and the values are represented by colour coding (right). Voxels with brighter colours contained mitochondria that are more highly specialized for energy transformation than were mitochondria in voxels with darker colours. **b**, A map of mitochondrial respiratory capacity across the brain, predicted from brain-imaging data of various modalities, including functional data (reflecting activity-associated changes in blood flow) and various types of structural data. MRC, mitochondrial respiratory capacity.

BEHIND THE PAPER

In 2020, first author Eugene Mosharov and M.P., inspired by the physics of brain imaging, imagined a way to turn a frozen brain slab into physical voxels. E.M., a chemist–engineer–neuroscientist polymath, programmed a cutting machine to voxelize frozen brain tissue from the Columbia BrainQUANT Institute's biobank. A few months later, M.P. met with M.T.d.S. on holiday in France, bonding over their love of energy, neuroimaging and the human mind. Two courageous students, Ayelet Rosenberg and Snehal Bindra, took on the challenge of analysing thousands of brain samples. E.M., M.T.d.S. and M.P. registered the mitochondrial data sets from Columbia and the Shirihai group at the University of California, Los Angeles, into standard neuroimaging space and developed a model to predict mitochondrial measures from MRI data. Bridging the scale and translatability gaps around human brain mitochondria has been an outstanding experience for everyone involved in MitoBrainMap v.1.0 — we are so grateful.

M.T.d.S. and **M.P.**

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