

An intact, molecularly active postmortem whole human brain model for gene therapy development

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Introduction

The limited predictive power of preclinical models remains a critical challenge for advancing gene therapy vectors to the clinic, particularly for therapies targeting the brain. Animal models, including non-human primates, often fail to capture the unique aspects of human blood-brain barrier physiology due to species-specific biology. Meanwhile, human-derived in vitro systems lack the cellular maturity, tissue complexity, and aged brain phenotypes relevant for evaluating vector performance. To overcome these barriers, Bexorg has developed **BrainEx**, a platform that restores molecular and cellular integrity in whole postmortem human brains. The blood-brain barrier remains intact and capable of supporting normal transcytosis on the BrainEx system. This enables testing of gene therapy vectors in the human brain, allowing for rigorous brain penetration, vector tropism, transduction efficiency, and dose optimization studies. By bridging the gap between traditional models and the human brain, BrainEx provides a transformative approach for advancing safer and more effective gene therapy strategies.

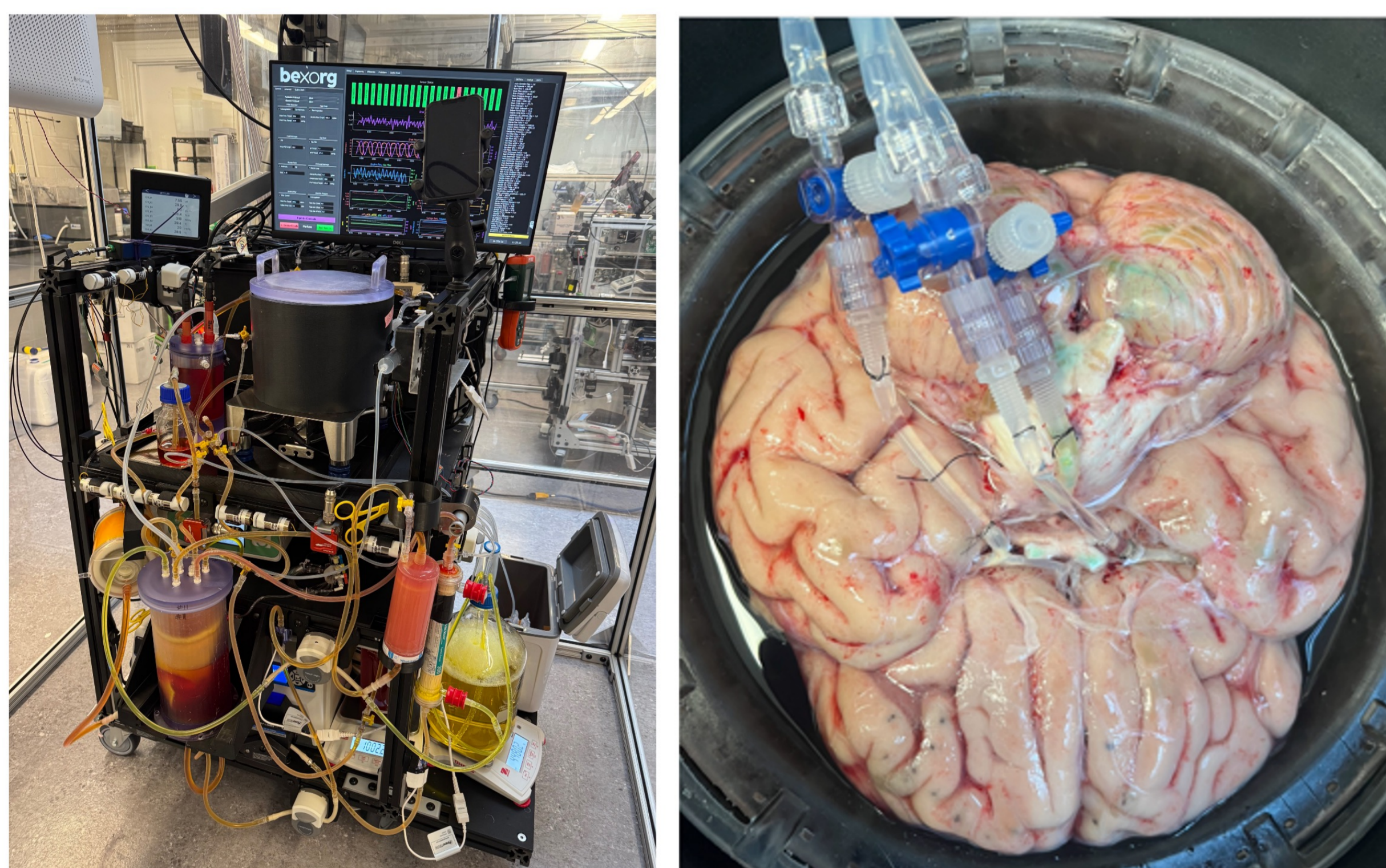
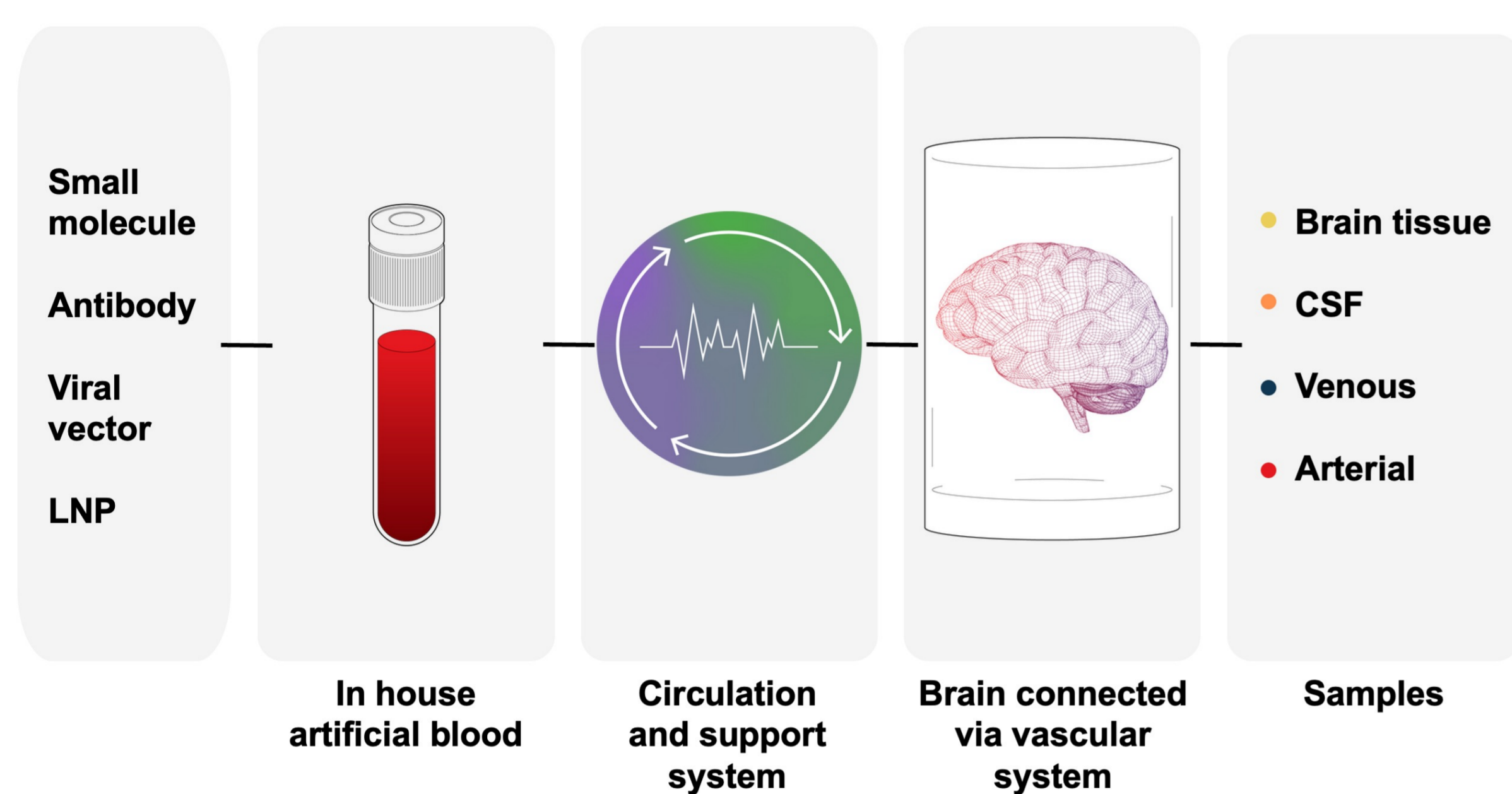


Figure 1. The BrainEx platform enables drug discovery in whole human disease brains. Bexorg has established a platform that maintains intact, molecularly and cellularly active postmortem human brains. The brain is connected to the BrainEx device via its endogenous vascular system. An acellular artificial perfusate supplies the brain with oxygen and nutrients, while a real-time operating system regulates physiological homeostasis. Viral vectors can be administered to the brain systemically.

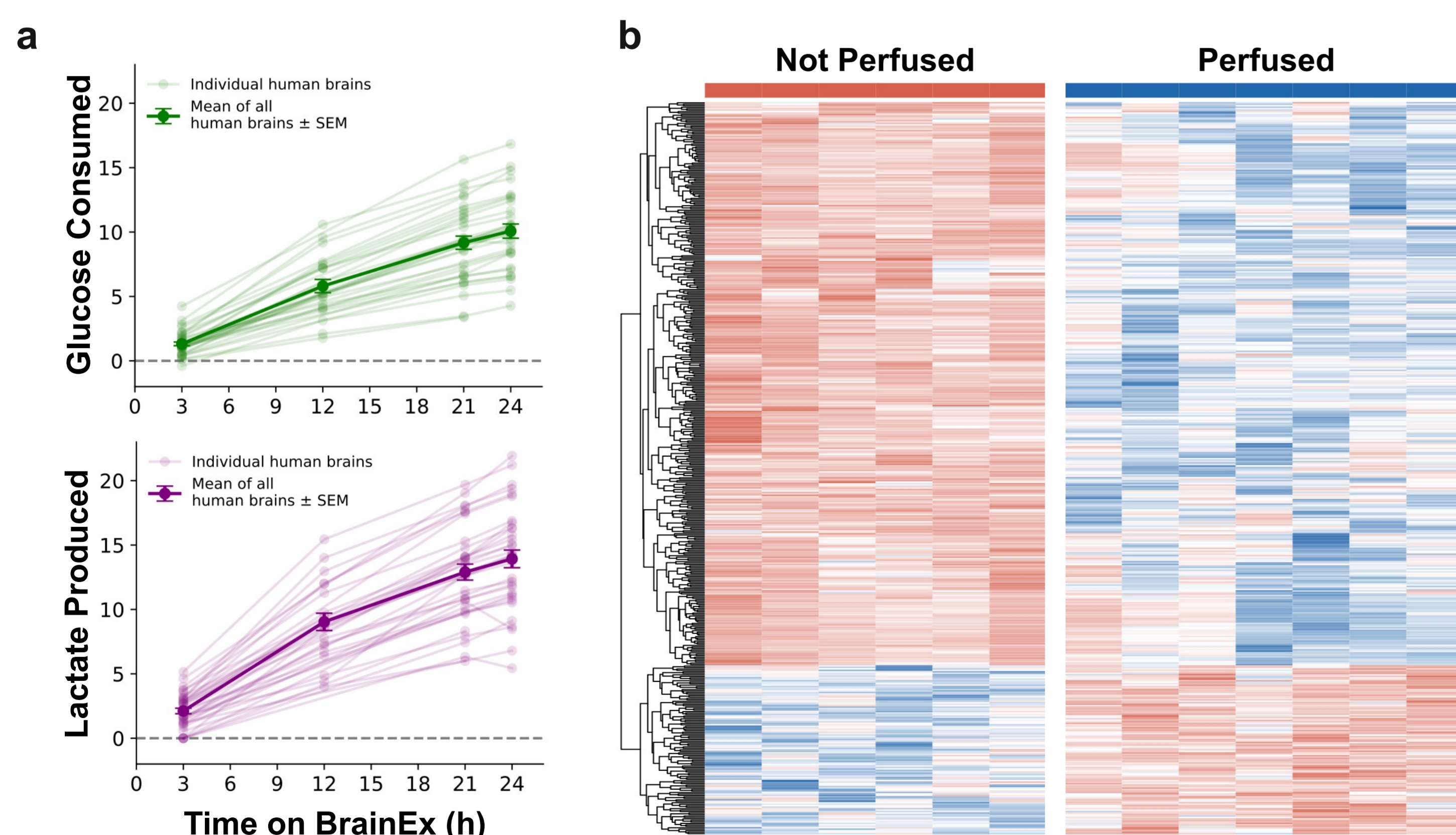


Figure 2. BrainEx perfusion restores cellular activity and drives growth and repair. **a**, Perfusate measurements show that glucose is consumed, and lactate is produced by the brain, indicating active metabolism. **b**, Proteomics comparing perfused versus non-perfused brains reveals that BrainEx reduces neuroinflammation, and activates transcription, translation, DNA repair, and synapse and membrane repair.

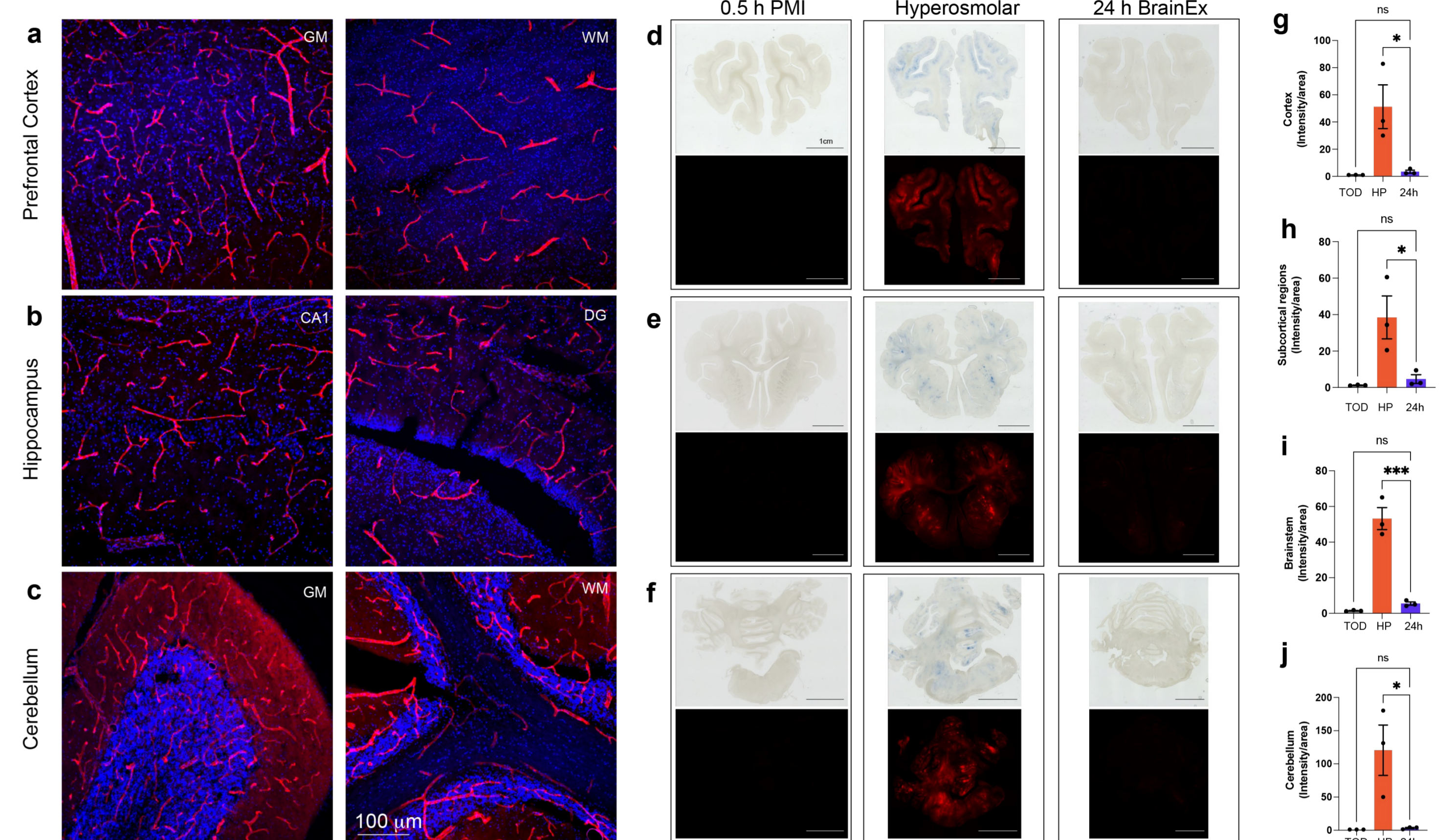


Figure 3. Preservation of the microcirculation and blood-brain barrier. **a-c**, Representative images of labeled vasculature by lectin during the perfusion in the prefrontal cortex (**a**), hippocampus (**b**), and cerebellum (**c**). GM, grey matter; WM, white matter; CA1, cornu ammonis 1; DG, dentate gyrus. **d-f**, Representative images of the infiltration of Evans blue-albumin in different brain regions (from anterior to posterior) in the wide field (top) and under fluorescence (bottom). **g-k**, Quantitation of the infiltrated Evans blue-albumin complex into the brain tissue in cortex (**g**), subcortical regions (**h**), brain stem (**i**), and cerebellum (**j**). HP, hyperosmolar.

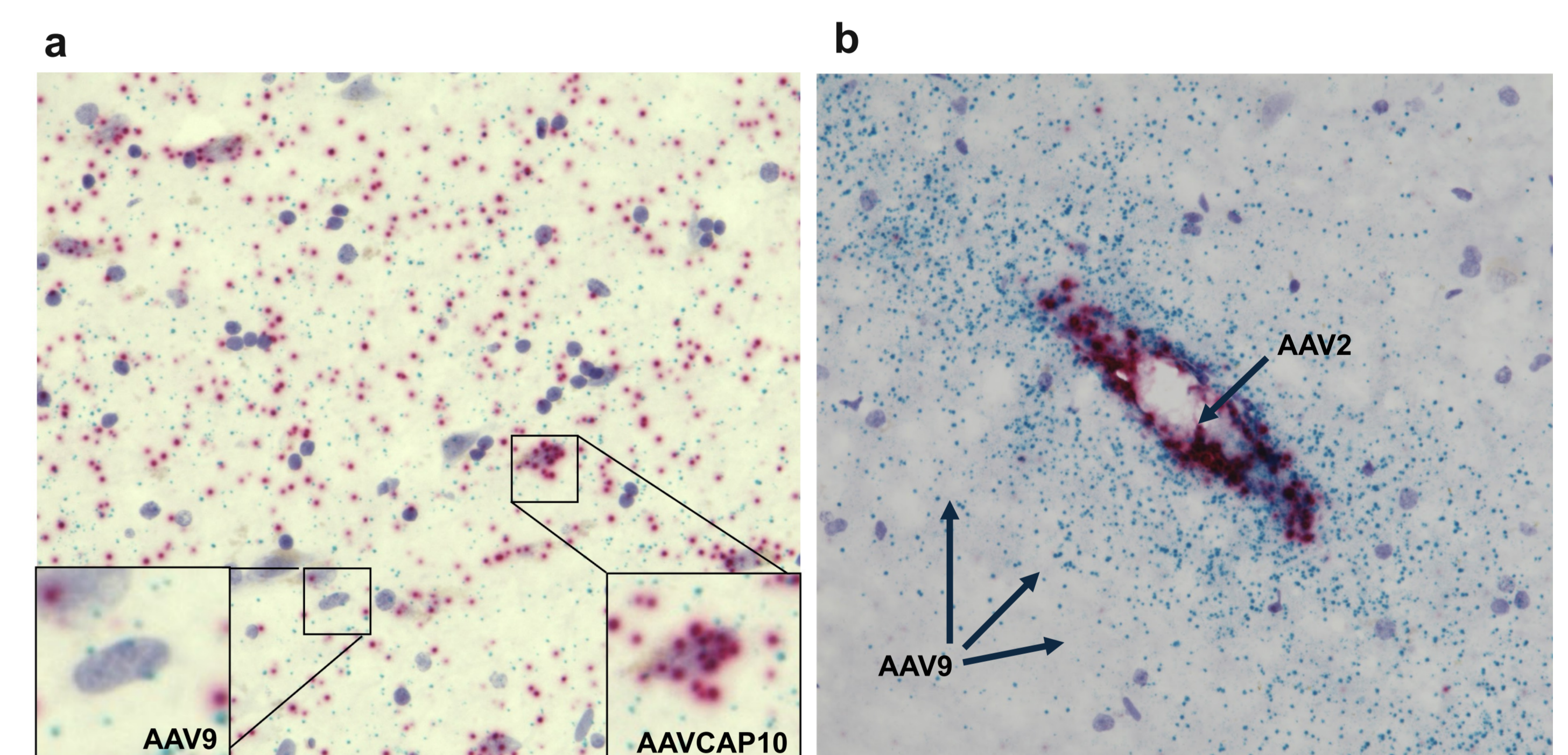


Figure 4. BrainEx faithfully predicts brain penetrance of gene therapy vectors. AAV viral vectors used for gene therapy were delivered systemically into human brains on BrainEx. After 24 h, expression of the AAV cargo was detected by RNAscope. **a**, AAV9 (blue) and AAVCAP10 (red), which cross the BBB, transduced cells in the brain parenchyma. **b**, AAV2 (red), which does not effectively cross the BBB, was detected primarily in the vasculature, whereas AAV9 (blue) was detected throughout the parenchyma.

Ethical considerations

Acquisition of postmortem human brains adheres to the highest possible ethical standards, overseen by an independent board of world-renowned bioethicists. Brains are procured through Organ Procurement Organizations (OPOs) with enhanced levels of consent from patients and families that specifically cover the BrainEx platform. Measures are taken on the BrainEx device to ensure that there is no possibility of coordinated network activity associated with consciousness.

Conclusions

- BrainEx establishes a transformative preclinical platform by maintaining intact, molecularly and cellularly active whole human brains postmortem.
- BrainEx preserves vascular integrity and blood-brain barrier function, enabling physiologically relevant delivery and evaluation of gene therapy vectors.
- BrainEx supports active metabolism, reduced neuroinflammation, and engagement of repair pathways, ensuring that vector performance is evaluated under conditions reflecting the human brain's native biology.
- By bridging the translational gap between animal models and human patients, BrainEx offers a rigorous and ethically grounded model to optimize vector design, tropism, dose, and safety before clinical application.

Overall, BrainEx provides a predictive, human-relevant tool to accelerate safer and more effective gene therapy development for neurological diseases.