Mounting brain organoid research reignites ethical debate

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As research involving the transplantation of human "mini-brains"—known as brain organoids—into animals to study disease continues to expand, so do the ethical debates around the practice. One concern is the possibility, however minute, that the grafted organoids may one day induce a level of consciousness in host animals, as models evolve to resemble the human brain more closely.

A new paper published today in *Cell Stem Cell* by researchers from Penn Medicine and the Department of Veterans Affairs sought to address this dilemma by clarifying the abilities of brain organoids and suggesting an ethical framework that better defines and contextualizes these organoids and establishes thresholds for their use. Their paper accompanies another study in the same journal that reported the presence of brain wave patterns, known as oscillatory activity, in brain organoids, which brought fresh attention to the overall research and ethical discussion.

"Due to their ability to mimic certain brain structures and activity, human brain organoids—in animal models—allow us to study neurological diseases and other disorders in previously unimaginable ways," said the study's first author H. Isaac Chen, MD, an assistant professor of Neurosurgery at Penn's Perelman School of Medicine and the Corporal Michael J. Crescenz VA Medical Center. "However, the field is developing quickly, and as we continue down this path, researchers need to contribute to the creation of ethical guidelines grounded in scientific principles that define how to approach their use before and after transplantation in animals. Such guidelines can help avoid confusion for scientists, especially when communicating with the public, and clearly lay out the benefits of this research, against which any ethical or moral risks can be weighed."

Lab-grown brain organoids—which are derived from human pluripotent stem cells and grown to a size no bigger than a pea—can recapitulate important brain architecture and several basic layers of the human cortex. Some resemble the midbrain, hippocampus, and the hypothalamus, and have genetic similarities to the human brain. There is also preliminary evidence suggesting that neurons within transplanted organoids respond to light stimulation of the host animal's eye, results which were presented in a Penn Medicine abstract at the Society for

Neuroscience meeting in November 2017.

Still, today's brain organoids remain distinctly different from the actual human brain, the authors note. Their maximum size remains small (measured in millimeters) due to inadequate nutrient, gas, and waste exchange which limits development. Organoids also lack endothelial cells, microglia cells (key cells in overall brain maintenance), and other cell types that contribute to the brain's microenvironment. Furthermore, organized structural nodes and the white matter connections among these cells are absent—which are both necessary for higher brain function.

Work on developing a "better" brain organoid, however, continues to make strides. And with that, the question of the host animal becoming more "human" remains at the forefront of the ethical debate. One particular outcome that has raised concerns is the potential appearance of self-awareness and consciousness in the animals, but authors note that this is unlikely for several reasons.

"Current brain organoid transplantation is more likely to worsen brain function than improve it," the authors wrote, "because transplantation involves the creation of a surgical cavity that likely leads to loss of function and a lack of connectivity." The authors also note that transplantation of brain organoids is only impactful in local areas where immediate connections are made, which means it's unlikely to generate brain functions across many brain regions, like consciousness.

The more relevant questions, the authors believe, should be around the enhancement of specific brain functions, rather than determining if the host animal is becoming more human. The host animal is also called the "chimera," which describes any animal injected or grafted with human cells or genes.

"We argue that determining the degree to which an animal is similar to a human is less constructive than considering the possibility of specific brain enhancements and how these enhancements could influence an animals' moral status," the authors noted. In other words, an important step is developing a better understanding of what types of brain functions could be impacted by brain organoid transplantation and establishing which of those enhancements would be considered harmful or unethical. At that point, rational "thresholds of concern" could be debated, and methods for measuring such enhancement could be developed.

One way to determine whether higher-order brain functions may arise is to conduct a thought experiment, specifically to compare a theoretical brain organoid chimera with a known animal species with documented features of self-awareness. An example of this is the so-called "mirror test," which measures self-awareness if/when certain animals are capable of recognizing themselves when observing their reflection in a mirror.

The authors note that regardless of the functional outcome of brain organoid transplantation, consideration for the host animal's well-being and other socio-legal matters stemming from the transplantation, would need to take place as part of this ongoing research.

"While today's brain organoids and brain organoid hosts do not come close to reaching any level of self-awareness," Chen said, "there is wisdom in understanding the relevant ethical considerations in order to avoid potential pitfalls that may arise as this technology advances."

Provided by Perelman School of Medicine at the University of Pennsylvania

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