Brain Organoids, the Path Forward?

DOI: 10.52214/vib.v10i.12504

Ashley Diloreto

Keywords: Brain Organoids, In Vitro Modeling, Human Identity, Research Ethics, Animal Research

INTRODUCTION

The brain is one of the most foundational parts of being human, and we are still learning about what makes humans unique. Advancements in technology have allowed for the creation of miniature brain structures using pluripotent stem cells to mimic the embryonic human brain. These stem cells randomly accumulate into brain-like structures, consisting of tens of millions of cells spanning a few millimeters wide.[1] As brain organogenesis becomes more complex, these models may begin to exhibit consciousness, pain, and sentience. If these organoids become more complex, it is necessary to question the rights of brain organoids and the ethics of working with brain-like structures that begin to mirror our own identities. Overall, brain organoid usage has remarkable benefits that outweigh the negative outcomes. However, there must be continued exploration of the moral ramifications of greater levels of consciousness that brain organoids may exhibit in the future.

ANALYSIS

Knowing whether brain organoids should be used in research requires understanding what constitutes a conscious brain and how to classify a brain organoid. Due to its modeling of a human embryonic brain, it is helpful to explore the ethical considerations researchers should take both currently and as this field of research progresses. This philosophical question concerns the concept of self-identification and what it means to be human. It is also important to explore the levels of autonomy the brain should have due to its core role in how humans define themselves. As brain organogenesis technologies advance and facilitate the development of more complex brain organoids, this question becomes especially relevant. It blurs the line of ethical human subject research and has the power to alter the decisions that the scientific community makes about human-based research. In the brain organoid's current relatively undeveloped state, large bodies of evidence suggest that brain organoids are suitable and viable alternatives for research. Brain organogenesis research aids in various brain-based medical conditions, such as neurodegenerative diseases, developmental disorders, and Zika virus-infected fetuses.[2] Additionally, it allows for an alternative and potentially ethical approach to animal testing in research.[3]

I. Brain Organoids

Brain organoids are created from randomized self-clustering pluripotent stem cells using signaling factors, essentially modeling the human brain during its embryonic stage.[4] These models can aid in the understanding of both brain development and disorders. This includes a more comprehensive understanding of hereditary brain abnormalities, human evolution, neurological diseases, and psychiatric disorders.[5] Brain organoids replicate many features of human brain development during the embryonic stage, both structurally and functionally however, gyrification, cerebral cortex formation, and neuronal wiring are not fully developed.[6] This creates a relatively accurate novel model that is helping forge the field of neuroscience and strives toward a more accurate representation of the human brain.

II. Brain Organoids Deficiencies

Brain organoids provide an innovative way to enhance current neuroscience; however, opposing viewpoints would argue about the brain organoids deficiencies such as the several major differences between organoids and an embryonic brain. Firstly, this includes a lack of vascularization, causing cells to eventually die in the center.[7] Additionally, current methods only allow for the growth of neurons, excluding microglia, endothelial cells, blood cells, and immune cells, further altering an accurate neural environment.[8] Lastly, there is a significant amount of variation between the brain organoids based on the laboratory procedure and stem line used.[9] While brain organoids are excellent models, they are unable to accurately represent the adult human brain, and current research methods introduce a high level of mutations.[10]

III. Benefits of Brain Organoid Research

Brain organoid research should be pursued because it serves as an alternative to animal-based research, helps us understand the differences between hominid-like species, and advances the study of neurodegenerative diseases.[11] Moreover, while the formation of the brain is representative of the human brain, it lacks full complexity, including networking and complete vascularization.[12] This evidence suggests that brain organoids are not yet sentient, making them important replicas and alternatives to animal testing. Modern medicine research routinely uses animals as test subjects which is problematic because animals cannot provide informed consent, and guidelines often focus on harm minimization with little regard for animal welfare as long as it benefits human research.[13] Seeking alternatives, such as the development of brain organoids, could greatly minimize animal suffering and serve as ethical alternatives.

Brain organoids provide a way to study neurological disorders and diseases with a more physiologically accurate model. Currently, in the field of neurodegenerative diseases, many preclinical models fail to accurately represent the diseases they work with.[14] For instance, mouse models of Alzheimer's disease are genetically modified to overexpress high levels of human genetic mutations, however, the Alzheimer's phenotype is not expressed as expected.[15] Therefore, brain organoids have been considered the most ideal model for Alzheimer's disease because they allow researchers to observe Aβ deposits, Tau tangles, and neuronal degeneration.[16] Brain organoids have been far more accurate representations than both the mice and two-dimensional neuron models.[17] In addition to Alzheimer's studies, investigations about the Zika virus are better understood by examining the mechanisms in the brain organoids that resulted in microcephaly.[18] These studies more effectively capture the structure of the fetal brain during the first and second trimesters of pregnancy and more efficiently deconstruct the formation of microcephaly through the observation of neural progenitor cells and other cellular structures.[19]

Furthermore, studying brain organoids enhances our understanding of human brain development in comparison to other hominid-like species, such as one of our closest relatives – Neanderthals. It reveals some of the underpinnings of human evolution and the brain-based advantages that gave humans survival advantages over other hominid-like species. Neanderthal brain organoid research has shown that Neanderthal organoids have an irregular "popcorn-like" shape compared to the spherical shape of human brain organoids.[20] The differences in organoid shape suggest contrasts in their neuronal networks, potentially altering social abilities.[21] This research solidifies the role of the NOVA1 gene in socialization and provides further insight into both autism and schizophrenia.[22]

IV. Brain Organoids Consciousness

As technology becomes more advanced, brain organoids may eventually exhibit a higher level of consciousness, intelligence, and sentience. Currently, the use of brain organoids is regulated by the Embryonic/Human Stem Cell Research Oversight Committee (E/HSCRO) due to the stem cells used to generate them.[23] If brain organoids become more complex, ethical considerations will need to be expanded.[24] It can be inferred that researchers currently treat brain organoids similar to animal research, as both have reduced abilities to consent to research, allowing greater research freedom. Recent studies indicate that human cerebral organoids exhibit the same brain neuron connectivity and electroencephalogram (EEG) patterns as those collected from preterm babies.[25] This data supports the idea that brain organoids may eventually experience pain or even basic forms of consciousness.[26]Those in opposition to brain organoid research would argue that research supports the claim that brain organoids have achieved a high level of sentience and that experimental research, even at this stage, may be considered unethical.

Defining the concept of self is crucial for classifying brain organoids and distinguishing the line between ethical and unethical research. Examining how we perceive self allows us to understand how research will be conducted with brain organoids. In *Being and Nothingness*, Jean-Paul Sartre states that when someone looks at him, it supports the idea of his existence and sense of self.[27] Since the body would need to be seen within the gaze of another person, it also suggests that people would need to have a body to have an existence or an identity. Therefore, while this primitive brain state may have rudimentary consciousness, it does not have true existence due to a lack of a body. This would exclude the regulations imposed on human and animal research and allow for a laissez-faire approach to the research aside from stem cell regulation. In opposition, Schermer argues that “When we give up mind, as if that is even possible, we are nothing and nowhere.”[28] The creation of a brain organoid is the creation of a mind and therefore even the potential creation of the human self. Human research regulations would then be responsible for brain organoids in their more developed states.

CONCLUSION

The use of brain organoids is promising and expands our understanding of the brain and how it is affected by other neurological factors, such as disease or genetics. There are significant benefits in advancing our comprehension of neurodegenerative diseases such as Alzheimer’s, the Zika virus, and its effect on the fetus, and gaining a better understanding of our prehistorical brain evolution and development. Moreover, creating brain organoids is an efficient and potentially ethical alternative to animal testing. However, further research into brain organoids has suggested that there is a baseline level of consciousness that mirrors a human embryo, and there are still deficiencies in brain organoids that don’t perfectly replicate the human brain. Considering the rapidly progressing technology, ethical principles must also be evaluated to determine what it means to be human and where to draw the line of ethical research on more developed brain-like models. Overall, in the current state of brain organoids, researchers should work to harness brain organoids to their fullest potential to further contribute to the fields of neuroscience.

[1] Chan, W. K., Griffiths, R., Price, D. J., & Mason, J. O. (2020). Cerebral organoids as tools to identify the developmental roots of autism. *Molecular autism*, 11(1), 58. https://doi.org/10.1186/s13229-020-00360-3; Lavazza A. (2020). Human cerebral organoids and consciousness: a double-edged sword. *Monash bioethics review*, 38(2), 105–128. https://doi.org/10.1007/s40592-020-00116-y

[2] Chan, W. K., Griffiths, R., Price, D. J., & Mason, J. O. (2020). Cerebral organoids as tools to identify the developmental roots of autism. *Molecular autism*, 11(1), 58. https://doi.org/10.1186/s13229-020-00360-3

[3] Qian, X., Nguyen, H. N., Jacob, F., Song, H., & Ming, G. L. (2017). Using brain organoids to understand Zika virus-induced microcephaly. Development (Cambridge, England), 144(6), 952–957. https://doi.org/10.1242/dev.140707

[4] Lavazza A. (2020). Human cerebral organoids and consciousness: a double-edged sword. *Monash bioethics review*, 38(2), 105–128. https://doi.org/10.1007/s40592-020-00116-y

[5] Chan, W. K., Griffiths, R., Price, D. J., & Mason, J. O. (2020). Cerebral organoids as tools to identify the developmental roots of autism. *Molecular autism*, 11(1), 58. https://doi.org/10.1186/s13229-020-00360-3

[6] Chan, W. K., Griffiths, R., Price, D. J., & Mason, J. O. (2020). Cerebral organoids as tools to identify the developmental roots of autism. *Molecular autism*, 11(1), 58. https://doi.org/10.1186/s13229-020-00360-3

[7] Chan, W. K., Griffiths, R., Price, D. J., & Mason, J. O. (2020). Cerebral organoids as tools to identify the developmental roots of autism. *Molecular autism*, 11(1), 58. https://doi.org/10.1186/s13229-020-00360-3

[8] Chan, W. K., Griffiths, R., Price, D. J., & Mason, J. O. (2020). Cerebral organoids as tools to identify the developmental roots of autism. *Molecular autism*, 11(1), 58. https://doi.org/10.1186/s13229-020-00360-3

[9] Chan, W. K., Griffiths, R., Price, D. J., & Mason, J. O. (2020). Cerebral organoids as tools to identify the developmental roots of autism. *Molecular autism*, 11(1), 58. https://doi.org/10.1186/s13229-020-00360-3

[10] Hyun, I., Scharf-Deering, J. C., & Lunshof, J. E. (2020). Ethical issues related to brain organoid research. Brain research, 1732, 146653. https://doi.org/10.1016/j.brainres.2020.146653

[11] Chan, W. K., Griffiths, R., Price, D. J., & Mason, J. O. (2020). Cerebral organoids as tools to identify the developmental roots of autism. *Molecular autism*, 11(1), 58. https://doi.org/10.1186/s13229-020-00360-3

[12] Lavazza A. (2020). Human cerebral organoids and consciousness: a double-edged sword. *Monash bioethics review*, 38(2), 105–128. https://doi.org/10.1007/s40592-020-00116-y

[13] Gerakis, Y. (2019). Hetz, C. Brain organoids: a next step for humanized Alzheimer's disease models?. Mol Psychiatry 24, 474–478. https://doi.org/10.1038/s41380-018-0343-7

[14] Qian, X., Nguyen, H. N., Jacob, F., Song, H., & Ming, G. L. (2017). Using brain organoids to understand Zika virus-induced microcephaly. Development (Cambridge, England), 144(6), 952–957. https://doi.org/10.1242/dev.140707

[15] Qian, X., Nguyen, H. N., Jacob, F., Song, H., & Ming, G. L. (2017). Using brain organoids to understand Zika virus-induced microcephaly. Development (Cambridge, England), 144(6), 952–957. https://doi.org/10.1242/dev.140707

[16] Qian, X., Nguyen, H. N., Jacob, F., Song, H., & Ming, G. L. (2017). Using brain organoids to understand Zika virus-induced microcephaly. Development (Cambridge, England), 144(6), 952–957. https://doi.org/10.1242/dev.140707

[17] Gerakis, Y. (2019). Hetz, C. Brain organoids: a next step for humanized Alzheimer's disease models?. Mol Psychiatry 24, 474–478. https://doi.org/10.1038/s41380-018-0343-7

[18] Cohen J. (2018),Neanderthal brain organoids come to life. *Science,* 360,1284-1284.DOI:10.1126/science.360.6395.1284

[19] Qian, X., Nguyen, H. N., Jacob, F., Song, H., & Ming, G. L. (2017). Using brain organoids to understand Zika virus-induced microcephaly. Development (Cambridge, England), 144(6), 952–957. https://doi.org/10.1242/dev.140707

[20] Hyun, I., Scharf-Deering, J. C., & Lunshof, J. E. (2020). Ethical issues related to brain organoid research. Brain research, 1732, 146653. https://doi.org/10.1016/j.brainres.2020.146653

[21] Cohen J. (2018),Neanderthal brain organoids come to life. *Science,* 360,1284-1284.DOI:10.1126/science.360.6395.1284

[22] Hyun, I., Scharf-Deering, J. C., & Lunshof, J. E. (2020). Ethical issues related to brain organoid research. Brain research, 1732, 146653. https://doi.org/10.1016/j.brainres.2020.146653

[23] Sartre, Jean Paul. Being and Nothingness, 1943. https://dx.doi.org/10.4324/9780203827123.

[24] Hyun, I., Scharf-Deering, J. C., & Lunshof, J. E. (2020). Ethical issues related to brain organoid research. Brain research, 1732, 146653. https://doi.org/10.1016/j.brainres.2020.146653

[25] Lavazza A. (2020). Human cerebral organoids and consciousness: a double-edged sword. *Monash bioethics review*, 38(2), 105–128. https://doi.org/10.1007/s40592-020-00116-y

[26] Lavazza A. (2020). Human cerebral organoids and consciousness: a double-edged sword. *Monash bioethics review*, 38(2), 105–128. https://doi.org/10.1007/s40592-020-00116-y

[27] Sartre, Jean Paul. Being and Nothingness, 1943. https://dx.doi.org/10.4324/9780203827123.

[28] Schermer, V. I. (2002). Spirit and psyche: A new paradigm for psychology, psychoanalysis and psychotherapy. Jessica Kingsley Publishers