A Means to an End: The Use of Brain Organoids in Research

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Brain organoids, also referred to as mini-brains, currently resemble pale pink miniature egg yolks. They lack sulculi and gyri and are quite small in size, not even approaching the intricate complexity of the brains of commonly used experimental animal models such as rats. However, many experts are already debating the ethical repercussions of further developing brain organoids. To be able to use brain organoids in research to their full potential, they must have resemblance to human brains. In this process, brain organoids may exhibit not only structural similarities to human brains but also functional ones, such as a sense of consciousness.

Assuming accurate tests to measure consciousness were developed and brain organoids showed responses, the perception of a brain organoid suddenly shifts from an inanimate piece of tissue in a petri dish to a biological entity that may be capable of thought. Despite being manufactured in a lab, we must determine if brain organoids warrant ethical consideration. To best address this area of ethical contention, I first establish a picture of current research and then, examine the ethics of brain organoids. The ethical question my paper seeks to address is whether it is permissible to use brain organoids with advanced, human-like functions in research. I will employ two ethical frameworks to explore this question at varying magnitudes. Through a macro utilitarian perspective, the benefits, such as better development of current and new treatment methods, and the mitigation of animal testing outweigh the possible suffering induced in a brain organoid. Through a micro Kantian perspective, brain organoids do not necessitate the same moral consideration as other conscious beings due to artificial and passive development. As part of this inquiry, I explore under what conditions brain organoids could be considered conscious. While brain organoids may develop sentience and sapience, qualifications for moral status, their heteronomous nature negates the need for moral consideration. On the grounds of the utilitarian and Kantian frameworks, I propose that the use of brain organoids in research is ethically permissible.

Overview

Seemingly out of science fiction, organoids are being grown in many labs around the world to mimic the function of natural human organs. By using stem cells, researchers have been able to synthesize specific organs ranging from kidneys to stereocilia in the inner ear. Many are hopeful that these lab grown organs will replace many models currently used in research. What makes organoids special is their ability to self-differentiate in a fashion similar to the development of normal tissues. Like seeds to a tree, researchers could plant stem cell clusters and theoretically, allow them to grow into complex structures, thus facilitating organoid harvest for research.

In 2005, Yoshiki Sasai and his team were the first group successful in synthesizing 3-d neural tissue from rodent stem cells (Watanabe et al., 2005). In 2008, the same group used human embryonic stem cells to grow cerebral neural tissue (Eiraku et al., 2008). These foundational studies paved the way for improvements in supporting neurogenesis and corticogenesis, specifically by ameliorating suspension cultures. Since then, researchers have been able to create neural areas such as parts of the thalamus, cerebral cortex and hippocampus (Shiraishi et al., 2017, Muguruma et al., 2015, Sakaguchi et al., 2015).

The main roadblock moving forwards is devising systems akin to the roles of our ventricular and circulatory systems that can nourish the growth of brain organoids. Without proper supporting systems, brain organoids are arrested in their capacity to develop further. When this challenge is circumvented, brain organoid structure can be expected to develop exponentially; with sophistication in structure, functionality will be the next issue. Researchers must be able to assess the activity of neural networks in comparison to human brains. Current techniques such as electrode recording, calcium imaging, fluorescent tagging and gene studies could help researchers map the functionality of a brain organoid.

If functional similarities to human brains are discovered in brain organoids, it would be imperative to assess if there is consciousness and the degree in which it is present. This will provide a better picture of the brain organoid's sophistication and level of similarity to a human's brain. As research studies are uncovering many more stages of consciousness than previously thought, determining a precise state of consciousness will pose a challenge. The recent findings that patients with neurologically "locked in" conditions resembling coma are still able to communicate illustrates that consciousness is not binary, aware or not, but a spectrum of different levels (Owen, 2017). Thus, the issue of testing consciousness alone raises a slew of concerns, both scientific and ethical. Currently, there are several different ways to assess consciousness including fMRIs[1], basic reflex tests and the interrogation of the subject. Since brain organoids would be without their own sensory system, many routine tests will not be applicable. One possible method is the Perturbation Complexity Index (PCI). This index measures the electrical response of perturbing the cerebral cortex with transcranial magnetic stimulation (Lavazza, 2018). In result, the integration of information, the perturbation signal, can be used to quantify how neural structures communicate (Lavazza, 2018). This approach is independent of sensory systems and has been shown to correlate with consciousness levels in unresponsive subjects (Lavazza, 2018). These techniques, increasingly refined to measure the

[1] A technique called functional magnetic resonance imaging that is used to measure brain activity via changes in blood flow.

consciousness of brain injured humans, will help set the stage to evaluate the consciousness of brain organoids and allow a more informed discussion of their use in research.

The assessment of brain organoid functionality can be subdivided into determining the presence of phenomenal consciousness and self-consciousness to pinpoint the overall level of cognitive capacity. Most animals are thought to have a form of phenomenal consciousness, often described as a subjective experience in which pleasure and pain can be perceived (Sawai, 2019). Self-consciousness is the awareness of the self and is experienced by humans and human-like primates (Sawai, 2019). Self-consciousness signals higher cognitive ability and is thought to impart goals and desires - both of which are dependent on self-awareness. The presence of phenomenal consciousness could act as a baseline for basic brain organoids in which they could be compared to animals models. Self-consciousness is a marker of advanced consciousness and would require highly sophisticated brain organoids.

The Ethics of Brain Organoid Use in Research

The concept of moral status is used throughout the ethical discussion of brain organoids. Due to its omnipresence, I would like to preemptively define it as a benchmark at which an organism needs to be considered ethically. For the purposes of this paper, moral status is considered as a graded scale, such that an adult human has a higher moral status than a pigeon.[2] These comparisons are often made between species. A comatose or disabled human would have the same status as a normal human. The level of moral status can be attributed through the consideration of an organism's capacity to confer value and perceive (sentience) (Bostrum 2014). This can be further defined as the ability to hold values and interests (practical reason) and have

[2] This is comparable to McMahan's hierarchy of being i.e. based on a series of evaluations such as assessing the level of well-being, intrinsic potential, and psychological capacity, it is possible to rank the moral status of beings (2002).

morally relevant features like cognitive ability (sapience) (Bostrum 2014). Organisms have values and interests that greatly range in complexity from the simple perception of pain to the multilayered desires humans have. The intricacy of these values and interests often reflect the species' ability to pursue these goals and is a marker of higher intelligence, rationality and self-awareness. There are various other criteria philosophers have used to accord moral status such as the sense of justice and a conception of good but these criteria are the most consistent and relevant across brain organoid research (Rawls, 1993).

As it is an indication of sapience and sentience, the predominance of a consciousness type bears significant influence on an organism's moral status. Animals with lower consciousness[3] such as possessing phenomenal consciousness but not self-consciousness are deemed of a lower moral status and are commonly used in lab experiments (Sawai, 2019). More moral consideration is given to those possessing self-consciousness followed by beings with solely phenomenal consciousness. The definition of consciousness differs but it is often centered around the concept of awareness. Awareness is critical for responsiveness, this has a direct influence on an organism's capacity for decision-making and self-government. Thus, consciousness, in some capacity, is necessary but not sufficient for autonomy. While the methods to test consciousness are incomplete, they could eventually be used to attribute moral status.

There are significant challenges and areas of uncertainty to overcome to develop a sophisticated brain organoid. Regardless, due to the current primacy of the field coupled with a high rate of growth, it seems likely that brain organoids will greatly improve. To explore the ethics and argue the permissibility of using brain organoids in research, I aim to apply two

[3] While there is no consensus regarding the consciousness of animals, this categorization is based on cognitive abilities that are thought to reflect consciousness such as goal-setting/recognition tests used to measure self-consciousness.

frameworks, utilitarianism and Kantianism. Through addressing opposition via the combination of these frameworks, it is clear that brain organoids should be used in research.

Utilitarianism is part of the teleological school of thought and is centered around the notion end goal/purpose something serves. Teleology is the idea that the means should be judged on the outcome they produce (The Editors of Encyclopaedia Britannica, 2009). Utilitarianism is a subdivision of this and defines an action as good or bad depending on whether it maximizes the greater good for the most people possible (The Editors of Encyclopaedia Britannica, 2009).

This framework is best suited to examine if the outcomes of inflicting suffering on a brain organoid are worth the negative consequences. It is highly likely based on current research that there will be many positive benefits of brain organoid research. As studies have shown, many researchers are overcoming the hurdles associated with brain organoid research and are producing results based on rudimentary non-conscious models. Discrete neural tissues have already been used to investigate diseases and disorders. For example, the effect of the Zika virus on neural development has been studied in greater depth. This allowed researchers to test drugs to combat Zika virus microcephaly by identifying the point of entry into neural stem cells that the virus exploits (Nowakowski, 2016). Other treatments have been explored in regards to Alzheimer’s disease and amyotrophic lateral sclerosis (Sawai, 2019). Evidently, a deeper look into human neural development will help answer many questions and provide insight into combatting many diseases and disorders. While benefits are speculative, conscious brain organoids with functioning neural circuits could help us better understand the mind-body connection, a preliminary step to more effectively treating psychological disorders, testing new medications and much more. These benefits each have the capacity to aid many at the cost of potentially harming one being. From a utilitarian perspective, the harm inflicted on a few, the brain organoids, is outweighed by the greater good of many.

Sentient brain organoids could have their nociceptors, sensory neurons that signal pain, removed so the harm that could arise through their use in research would pertain to their self-consciousness rather than their phenomenal consciousness. Specifically, the involuntary use of brain organoids may conflict with interests and desires resulting from self-awareness. Researchers have suggested that consent may be given through the stem cell donor. However, this indirect form of consent cannot not accurately convey the brain organoid's interests the same way a parent's do not always reflect the best interests of their child. Hence, in order to subject a conscious brain organoid to research, we must consider whether its moral status is significant or if there is a corresponding moral duty[4] towards it.

As well, while many could be aided by brain organoids, we must ask if it is more ethical to use brain organoids instead of other research models. Today, animals are often used in research as the best approximation of human physiological systems. If brain organoids develop advanced neural circuits, it is clear they would replace animal models in many areas of research. From a utilitarian perspective, this could limit the unethical use of animals in research - a greater good at the consequence of using a lab grown organism. From today's perspective, researchers have speculated the vast potential for specifically brain organoids. In the future, with other technological advancements, brain organoids may not be the only means to reach such ends. Current research is proof that progress in brain organoid research is achievable without a closer approximation to humans. Improvement of other methods such as virtual simulations,

[4] An obligation based on ethical motives (explained in greater depth below)

psychological assessments and imaging/scanning techniques, might be able to provide a lot of the similar benefits as if conscious brain organoids were used. Therefore, to permit use of brain organoids in research, they must have a moral status or moral duty that is equivalent or ideally, lower than currently used animal models.

Clearly, the utilitarian calculus of the cost-benefit of using brain organoids does not reveal the entire picture. To address the latter counter-points regarding the significance of a brain organoid's moral status, I applied the deontological Kantian framework. This framework allows a closer look at using brain organoids, the means, rather than placing emphasis on large scale-outcomes, the ends. Kantianism revolves around the concept of moral duty based on categorical imperatives - constant universal rules (Kant, 1785). Moral duty is the consideration of the needs and desires of others beyond treating them like means to an end (Kant, 1785). Moral duties arise from internal relations rather external responsibilities (Kant, 1785). For example, our duty to respect our peers stems from obligations to rational beings as a whole and not the intrinsic value of the beings themselves (Kant, 1785). These obligations are not unidirectional and depend on reciprocation of others who also have the capacity to oblige and fulfill obligations (Kant, 1785). This concept extends beyond Kantianism and the capacity to reciprocate often serves as a basis to attribute moral responsibilities. Non-rational beings such as plants and animals cannot uphold duties to humans and thus, do not have the corresponding capacity to obligate (Kant, 1785). There could be other indirect duties to plants and animals but they can be used as a means to an end. Ultimately, autonomy, self-government, allows incentive and willingness which are critical to enabling beings the ability to obligate and uphold maxims (Kant, 1785).

Before applying the Kantian framework, it is important to attribute a degree of moral status to brain organoids. This can be approximated through an examination of their consciousness and how it may arise. Due to a lack of subjective experiences, brain organoids will not be able to have any forms of consciousness on their own. The brains of human embryos receive stimulation allowing mature neurons to establish networks (Lavazza, 2018). Sensory input is needed to feel pleasure/pain and form a self-concept through awareness, each fundamental prerequisites for phenomenal and self-consciousness. Tests like PCI rely on the presence of pre-existing neural networks. These networks require stimulation during neuronal development to strengthen synapses that give rise to cognitive functions. Therefore, artificial inputs are necessary to make brain organoids conscious. In fact, it has recently been shown that brain organoids that do not exhibit consciousness on their own can contribute to the consciousness of the animal post transplantation (Sawai, 2019). More-so, many brain organoids are being grown past the 14 day cut-off for in vitro human embryo cultures as a reflection of the different developmental processes (Kadoshima et al., 2013). This further demonstrates that consciousness is a result of integration with sensory systems.

To mimic these natural mechanisms, researchers could potentially use an advanced form of electrical stimulation. Similar techniques have already been used in a variety of technologies including cochlear and visual cortical implants to provide sensory information in the absence of functioning sensory organs. This concept of artificial neural stimulation extends beyond modern day brain organoid research. Philosopher Hilary Putnam proposed the brain vat experiment in 1981. Similarly to René Descartes' conception of a demon fabricating our world, this experiment was conducted to explore skepticism of reality. In this thought experiment, a fully functioning brain is placed in a vat (Putnam, 1981). Its nerves are attached to a computer and via electrical pulses, the brain has a complete sensory perception of reality (Putnam, 1981). For the brain, these artificial stimulations are indistinguishable from real sensory interactions (Putnam, 1981). While this scenario is farfetched from current research, it illustrates how consciousness akin to a human's could develop in a brain organoid via artificial stimulation. This example would produce a brain organoid with degree of cognitive ability beyond purely sentience.

In contrast to the previous definition of graded moral status, it is best to ascertain a range of moral statuses to a conscious brain organoids to address variations in development. This is further reinforced by the idea that consciousness testing like PCI may not be accurate or precise. Non-conscious brain organoids warrant a baseline moral status due to their human origins and potential. This would be similar to the moral status we attribute to cell-tissues and stem cells. This is how researchers currently treat brain organoids. If brain organoids are produced with a significant degree of cognitive capacity, they would adhere to at least one of the moral status criteria. The moral status of a rudimentary conscious brain organoid that is sentient could be compared to that of some non-primate animals (Sawai, 2019). In contrast, an organoid derived from Putnam's example would be able to demonstrate sapience and sentience. This organoid would satisfy the criteria of moral status at the human level.

Artificial programming of consciousness via stimulation of neural networks is a reflection of the total passivity of brain organoids, their heteronomy[5]. Unlike embryos that grow and develop active responses, the capacity of brain organoids to experience phenomena is limited to the period of stimulation. Without this input, brain organoids would lose consciousness,

[5] Rather than self-governed, other-governed (Kant, 1785, p. 32)

similar to how humans can lose sensory input in comas or death. This enduring passivity never allows for any degree of independence and autonomy. This is in direct opposition to Kant's definition of will - "a kind of causality that living beings exert if they are rational, and when the will can be effective independent of outside causes acting on it, that would involve this causality's property of freedom" (Kant, 1785, p. 41). Kant explained that for morality to be upheld as a maxim, freedom must be property of the rational beings (Kant, 1785, p. 42). Brain organoids are not equipped with freedom and the ability to act independently. In result, they cannot uphold and be held to maxims.

Moral duty and moral status work in tandem. Moral status is a requisite to having and owing moral duties. Likewise, having and owing moral duties can indicate moral status. Contrary to this norm, brain organoids have raised the possibility that while moral duty is often intertwined with moral status, they are not always in parallel. Specifically, conscious brain organoids are at the crux of this disjoint. They have some degree(s) of moral status but do not have moral duties associated with them. This is radically different from most beings such as animals, who have a lesser moral status and corresponding moral duties. Animals are autonomous and we have established rights that detail our moral duties to them. These rights are often transcended due to their lesser moral status provided that this violation is substantially beneficial. This justification applies to the use of animals in research and is the reason why scarifying rats to test remedies for Parkinson's is acceptable while using them to test nail polish is not. This balance of moral status with duty also extends to humans who, unless autonomy is severely compromised, have both moral duties and moral status. In cases with severely cognitively impaired people, a reduction in moral duty can be used to reflect limited autonomy while moral status is held constant within a species.

From a strictly Kantian perspective, brain organoids will not even qualify for a moral status as autonomy is a precursor to all things of value - “Autonomy is thus the basis for the dignity of human nature [moral status] and of every rational nature” (Kant, 1785, p. 34). Therefore, brain organoids should be treated as means in themselves as they do not possess moral status. If the common definition of moral status, one that is most often used in research, is applied with the concept of moral duty (while here it is defined through the Kantian framework, it is applicable on a broader scale), it is clear that either way brain organoids fail to meet criteria for moral consideration. Conclusively, whether the weight of autonomy is placed in the definition of moral status or moral duty or both, it is fundamental to the moral consideration of a being.

Due to the lack of a moral duty (and depending on the definition used, moral status as well) of brain organoids resulting from the absence of autonomy, and the potential benefits derived from their use, it is acceptable to use them in research. Notably, this conclusion is limited by the indirect effects that the use of brain organoids in research may cause such as a greater ease of biohacking, transplantation and consciousness transfer. These remain separate areas of ethical contention but in the grand scope, they are related to the implications of this paper and require a closer examination. Thus, based on research trajectories, the current state of our understanding of consciousness and direct effects of brain organoids, they will be a useful means in the future that should be used to help progress research.

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