# Ethical Aspects of Human Brain Organoids in Research

Anne Aukje Lankamp

2022

10-06-2022

Anne A. Lankamp, 6142869, a.a.lankamp@students.uu.nl

Master's Programme Cancer, Stem Cells & Developmental Biology

Utrecht University

Examiner: dr. Ghislaine van Thiel

Associate Professor at the UMC Utrecht

Second reviewer: dr. ir. Marc van Mil

Associate Professor at the UMC Utrecht

# Ethical Aspects of Human Brain Organoids in Research

**For about a decade, human brain organoids have been used in science to study the brain in health and disease. The translational implications of this improvement in our ability to model the human brain are huge, as many people are or will be affected by neurological disorders and neurodegenerative diseases. Because the brain holds a singular position amongst the organs as the seat of the mind, of personhood, generating organoids from the brain presents some unique ethical questions. This paper will focus on the ethical aspects at play in general when organoids are used in research, as well as those unique to brain organoids. It is the larger aim of this paper to help put a spotlight on what needs to be done, such that research with human brain organoids can progress ethically now and in the future, such that people may benefit from the large translational potential of this field.**

## What this paper adds

Previously known

- Organoids are ethically sensitive
- Brain organoids prompt some unique ethical considerations

What this paper adds

- An overview of ethical aspects of organoids in general, including donor consent
- Discussion of ethical aspects of human brain organoids, including potential for consciousness and moral status

Implications for the future

- Bioethicists and researchers should continue to work closely together going forward to ensure high ethical standards in this field
- Work to develop ways to evaluate or measure (potential for) consciousness in organoids has started, and should be done in parallel to work in refining brain organoid technology

## Introduction

Organoids are small collections of cells grown from stem cells, that self-organize until they somewhat resemble their tissue of origin in terms of cell types and three-dimensional organization (Clevers, 2016).

Brain organoids, therefore, self-organize into structures and cell types that recapitulate part of, or the whole brain. Organoids have been developed that resemble the cortical region, the midbrain, the cerebellum and hippocampus, and more, as summarized by Di Lullo and Kriegstein in 2017. They may, but do not have to, include synthetic bio(printed)materials, and they may be implanted into animal models. Lancaster et al. and Kadoshima et al. first described whole-brain organoids and multi-layered neocortex organoids, respectively, in 2013.

Many people are affected by neurological disorders and neurodegenerative diseases. Therefore, the translational potential of brain organoids in research is great, as they can be used to learn more about neurons and the structure of the brain on a small scale. Additionally, brain organoids can be used to study genetic disease, its origin or the biological mechanisms affected, and to test possible therapeutic agents (Wang, 2018). Brain organoid lines can even be made from specific individuals with rare diseases, for use in personalized medicine screening or development. Combining these potential applications and the large amount of people affected by neurological disorders and neurodegenerative diseases, there is certainly plenty of reason to move forward with research into the human brain, its disorders, and therefore brain organoids. Because of the potential for widely impactful therapeutic discovery, there is also plenty of interest from parties who may profit from these discoveries. All the more reason to continually examine the ethical aspects of research using brain organoid technology, which are inherent to the field as it progresses, to ensure high ethical standards. Additionally, there is the fact that, in most people's view, the brain holds a unique status among the organs as the seat of personality, of a person. Naturally therefore, brain organoids are viewed differently to many other types of organoids. This paper will cover the ethical considerations that organoids in research in general, as well as human brain organoids specifically, evoke, and how these (should) affect the use of organoids in research, now and moving forward.

As mentioned, the definition of human brain organoids could be expanded to organoids that include bio(printed)materials, and they may be implanted into animal models. Due to the limited scope of this study, ethical considerations that stem from these applications specifically, will be omitted. For this rapid review, searches for literature, often reviews, on relevant ethical aspects were performed in PubMed (https://pubmed.ncbi.nlm.nih.gov/). The snowballing method was then applied to identify further relevant literature and primary sources from the first articles and reviews found.

## Ethical aspects that affect all organoids

Before focusing in on the ethical considerations that affect specifically brain organoids, there are ethical components to all research with organoids to consider first. An important and intensely debated topic is informed consent. The declaration of Helsinki describes that consent in research should be "informed and voluntary" (World Medical Association, 1964). Consent to use a tissue donation for the generation of organoids should be "Explicit and contemporaneous" (Hyun et al., 2020). Of course consent from donors does not absolve scientists of their responsibility to do research ethically and with integrity in the first place, hence why research institutions have ethics boards to review research proposals.

The material from which organoids and organoid lines are generated should be donated with such consent for their use. When induced pluripotent stem cells (iPS cells) from decision-competent adult somatic cell donors are used to generate organoids, explicit consent can be obtained in a timely (contemporaneous) manner through thoroughly informing donors of the application their donated cells will be used for in the research (ISSCR, 2016). If a potential donor is not decision-competent, their legal guardian must be fully informed of the (potential) uses of any donation to be made, and thus consent for the donation and its use in research can be given (ISSCR, 2016). Regardless of who makes the decision to consent to donate material for research, in this case organoid generation, all must understand what is being consented to, and the fact that incidental findings which are clinically relevant to the donor may occur. There should be an established process in place for the returning of these findings to donors should they occur, or if there is no such protocol, the absence of this should be noted in the explanation of what is being consented to (ISSCR, 2016).

Material for the generation of organoids is not always procured through research-project specific donations however. Occasionally, material from anonymized tissue banks is used to generate iPS cell lines and/or organoids (Hyun et al., 2020). It is currently not part of the standard process to disclose or explain the possibility of tissue donations being used for organoid generation to these anonymous tissue bank donors. As a consequence of this, there is no information available about the opinions of these donors on this potential use of their donation, or their consent to it occurring (Hyun et al., 2020). Seeing how vast and widely spread the production of successful cell and organoid lines can become, we find it ethically concerning that these donors, though they are anonymized, are not informed of this potential use of their donation, and given the opportunity to object to it. Further concern is sparked by the fact that the privacy of the donors cannot be guaranteed, as the genetic material in the organoids generated can always be matched back to a DNA sample from the donor (Hyun et al., 2020).

The stem cells required for the generation of organoids can also be obtained in other ways. For example, human embryonic stem cells can be collected from material donated by third-party gamete donors. Informed, explicit consent for the generation of organoids should also be obtained from these donors, as they may object to the use of their donation in human embryonic stem cell research. This consent should be separate from the consent to apply the donation for its originally intended use in reproductive health (Hyun et al., 2020).

According to the guidelines of the International Society for Stem Cell Research (ISSCR), it is important not to exaggerate the potential benefits of the research in which any donated materials would be used, when informing potential donors. In cases excluding the generation of organoids for use in personalized medicine, it should be clear that research conducted using the donated materials will not directly benefit the donor, nor anyone they know (ISSCR, 2016). This ensures that the donation is made with the right motivations, namely for the progression of research, not individual benefit.

In our opinion, consent to disseminate organoids generated from tissues or cells donated for research to other groups should be separate from the initial consent to generate organoids for a specific project. This is because once a successful and very useful organoid line starts to be dispersed amongst the scientific community, the original donor loses any idea they may have had about what the organoids are being used for and how many are being produced. With this, the donor gives up control over what research the organoids are being used for, even if it is research the donor objects to. Therefore, explicit consent should be obtained for the dissemination of organoids.

Additionally, further and separate consent should be obtained from a donor for commercialization of organoids produced from their donation. This is to avoid any possible conflict of interest, which could lead to unethical recruitment practices or exploitation. Especially in circumstances where consent to generate organoids is given in order to develop personalized medicine, these levels or tiers of consent must be firmly separated. Envisage a potential donor who can only take part in a study, which aims to develop or test medicine personalized to this person via the generation of organoids, if they also consent to the dissemination or even sale of those organoids. There is a clear imbalance of power between the potential donor (who is more incentivized to donate than the average donor because of the potential individual benefits) and the group or company developing the personalized medicine, and generating the organoids to that end. For this reason, it would be unethical to bundle consent to generate, consent to disseminate and consent to profit off of organoids together, or to impede the donor from taking part in the personalized medicine platform if they do not wish to consent to more than the limited generation of organoids required for taking part in the platform.

Finally, all potential donors should be made aware that if they consent to the generation of cell or organoid lines from their biological material, their privacy cannot be guaranteed. The genetic material in any generated cell or organoid line will unavoidably be possible to match to another sample from the same donor. Therefore, their privacy cannot be guaranteed (Hyun et al., 2020).

The application of personalized medicine also raises ethical considerations to be aware of as scientists. These are not as pronounced when the generation of organoids only serves as a way to select among established, tested and safe potential therapies. However, it is highly likely that organoids generated from people with rare diseases for example, may be generated with the intent to develop novel therapies. In the case of ultrarare diseases, if a novel potential therapy is found, it may not be possible to test its safety and efficacy following the usual protocols because the group of people whom it may benefit is so small. In this case, administering an untested therapy can be ethically done only as an absolute last resort (Hyun et al., 2020). Nevertheless, the ability to identify and select between untested therapies for such cases is a great benefit which we owe to organoid technology, as it enables another layer of investigation and testing prior to first-in-human administration.

ISSCR guidelines do not currently address any ethical considerations concerning specifically brain organoids, though these are certainly present. The ethical aspects relevant to the use of brain organoids specifically will be the topic of the next sections.

## Ethical aspects that affect brain organoids specifically: Consciousness

### Human brain organoids in science at present

Brain organoids have an edge on other model systems in multiple ways. Compared to cell lines for example, the three dimensional organization of organoids means that they more closely resemble the tissue they stem from, thus modelling it better. At this point in time however, brain organoids do not nearly recapitulate the complexity of the entire brain (Di Lullo and Kriegstein, 2017). However, they do reproduce the human brain in terms of epigenomic and transcriptional programs (Luo et al., 2016; Xiang et al., 2017). In addition to tissue organization, organoids more closely represent tissues because of their more complete set of cell types present, when compared to cell lines for example. Furthermore, organoids may include cell types completely absent from some animal models, such as is the case for outer radial glial cells, which are crucial to the development of the size and complexity of the brain (Fish et al., 2008). The fact that these decisive cells are absent from animal models illustrates the advantages of human organoids that can contain all relevant cell types, if given the optimal culture and differentiation conditions. However, these optimal conditions have not yet been fully elucidated in many cases. Because of this, there is currently some amount of variation in the cell type composition of brain organoids differentiated within a single experiment. The amount of variation in composition differs depending on the protocol and type of brain organoids. The variation is expected to lessen as culture conditions and differentiation media are refined, which could also lead to progression in the complexity of the organoids (Di Lullo and Kriegstein, 2017). Work to increase differentiation of cell types that are currently missing, which includes some cell types shown to affect development, is ongoing (Di Lullo and Kriegstein, 2017).

The size and thus development of brain organoids is also limited by the current lack of vascularization in organoid culture technology. Oxygen and nutrients can only reach cells in organoids by diffusion. As a result, necrosis occurs at the centre of organoids that grow too large, specifically when the number of cell layers prevents diffusion of oxygen and nutrients to the centre of the organoid. If or when a protocol for vascularization of organoids is established, this will allow for larger and more mature (brain) organoids (Hyun et al., 2020). Additional experimental progress is being made, e.g. the innervation of a mouse spinal cord, causing connected muscle cells to contract, through brain organoids (Giandomenico et al., 2019).

It is important to keep in mind as work to improve brain organoids goes on, that they must be validated as accurately representing the (intended region and developmental stage of the) brain, our knowledge of which is certainly incomplete. Therefore, paradoxically, our knowledge of how well the organoids recapitulate the (development of the) brain is currently limited by our knowledge of the real thing.

**Why does the potential for consciousness in human brain organoids matter?**

When the concept of brain organoids is introduced to most lay people, their first concern is often what these ‘mini-brains’ are doing exactly, whether they could possibly be conscious or thinking? Before we examine these possibilities, we can reflect on why it matters. Why would it matter if the ‘mini-brains’ used for research were conscious? After all, the other organisms used in research possess almost all of the cognitive capabilities which the human brain does. Mice used for research can suffer and experience pain, so why would it be different if there were a human brain organoid with these capabilities used for research purposes under the same rules and justifications? The true ethical worry lies not in general consciousness or the lower cognitive capabilities animals such as mice share with people (Hyun et al., 2020). Where conscious brain organoids would become morally very significant is at the level of personhood, at the level of self-awareness, the sense of one’s identity (Koplin and Savulescu, 2019). Naturally, we associate a conscious (adult) human with personhood. This is why consciousness in human tissues seems more significant than in e.g. laboratory mice, because of the association with and potential for self-awareness and personhood. Lower consciousness would be the first stepping stone towards brain organoids capable of morally significant self-awareness in the future. Therefore, as brain organoid technology is progressing, we must keep an eye on the development of potential for different levels of consciousness in the organoids.

**When do we assign moral status to brain organoids?**

Moral status indicates that a being matters for its own sake (Jaworska and Tannenbaum, 2021). The first moral line that, if it is reached, will be relevant to human brain organoids concerns the ability to perceive, which harbours the potential to suffer (Koplin and Savulescu, 2019). While the brain contains no pain receptors, brain organoids might advance to include tissues like meninges, which do. At this point there might be concern for the organoids experiencing pain (Koplin and Savulescu, 2019). However, it is also possible to suffer from lack of sensory stimulation. Therefore it is a false assumption that brain organoids that contain no other tissues would be invulnerable to suffering due to the absence of pain receptors. At the point of developing perception, human organoids may be assigned partial moral status. Accordingly, they may be granted some claim to protection from unnecessary suffering, like other perceptive animals used for research purposes (Koplin and Savulescu, 2019).

Like previously mentioned, there is no need to halt work with human brain organoids purely at the point of developing consciousness, as other animals used for research are also conscious and capable of suffering. Morality, which forbids harming or killing of a being without their consent, applies only in full to persons (Koplin and Savulescu, 2019). Personhood involves advanced cognitive capabilities, including refined self-awareness, rationality and autonomy (Tooley, 2009). As such, personhood applies only to humans from birth, at this point. In many jurisdictions, abortions are legal even after the estimated onset of consciousness, reiterating the fact that consciousness and the potential to become a person do not provide an absolute right to come to no harm or to life, personhood does (Koplin and Savulescu, 2019). Human brain organoids are thought to be very unlikely to reach the level of full personhood, because it is accepted that personhood does not develop without meaningful interactions with others, developing social interactions and language (Koplin and Savulescu, 2019; Hyun et al., 2020).

**What is consciousness?**

To continually examine the potential for consciousness in brain organoids, a consensus will need to be reached on the definition(s) of consciousness itself, and how to measure or evaluate it. At present, there is no overarching consensus definition of consciousness itself or levels thereof.

If we are considering basic electrical and neuronal activity in a brain organoid following stimulation, we are seeing simple brain mechanics. So long as there is no awareness of the sensory input, this is ethically irrelevant, as it is just a physiological chain reaction (Hyun et al., 2020). Multiple ways of defining consciousness have been put forth. Ankeny and Wolvetang described the recognized aspects of consciousness as first awareness of the environment through connection with it, including the ability to experience pain. Then, phenomenal consciousness, which encompasses reason and recollection of past events, and finally self-consciousness, where a being possesses a sense of self and identity (Ankeny and Wolvetang, 2020). Hyun et al. place different aspects of consciousness in order of ascending complexity as such; awareness of sensory stimulation, wakefulness, alertness, focus, sentience, and finally self-consciousness (Hyun et al., 2020). These facets are also positioned in decreasing likelihood of occurring in brain organoids, in their opinion.

**How close or remote is the possibility of conscious organoids?**

Before looking further into how consciousness in organoids may be measured in the future, it is important to keep the correct perspective by considering how close or remote the possibility of conscious organoids is considered to be at this point. In general, it is agreed that brain organoids will probably not gain significant potential for consciousness in the near future. Consciousness in complex assembloids of multiple cell types is considered to be in the far future (Hyun et al., 2020). Hyun et al. consider the previously described levels of consciousness as decreasing in probability of occurring, as advanced cognitive capabilities such as higher forms of consciousness are thought impossible without complex neural networks and activation of multiple brain regions, which is not possible in brain organoids with only one cell type (Hyun et al., 2020). It has been reported that cortical organoids may exhibit electroencephalogram activity similar to those of a 25-39 week premature neonates after six months of culture, which sparked some concern that this may be the first sign of potential for consciousness (Trujillo et al., 2019). However, it is currently not possible to assess what this similarity could mean for the potential for consciousness (which, as discussed, is itself not clearly defined), because not enough is understood about the brain waves of premature babies in the first place (Reardon, 2018). Again, our knowledge and understanding of what is taking place in the model system is limited by our understanding of the real thing.

Development of neural networks with higher cognitive capabilities is thought to require both stimulation, and therefore input into the system, and output (Koplin and Savulescu, 2019). Researchers are pushing these boundaries by, amongst other things, creating 'assembloids' of brain organoids and muscle tissue, such that the muscle in innervated and affected by signals stemming from the brain tissue (Giandomenico et al., 2019). Conversely, testing of brain organoids to monitor for progression in cognitive capabilities may involve stimulating them in different ways. As a result, attempts to monitor progression of potential consciousness going forward may indeed further that progression (Koplin and Savulescu, 2019).

So long as consciousness is not clearly defined and therefore not measurable in an empiric way, it will be best to treat brain organoids in a way that considers their potential for consciousness. After all, their capabilities cannot be exactly evaluated, and therefore the possibility of certain levels of consciousness cannot be eliminated. It is therefore safest to work with these organoids keeping in mind their possible levels of consciousness, erring on the side of generosity (Koplin and Savulescu, 2019).

**How might consciousness be measured?**

In order to monitor the progression of potential for consciousness in organoids in the future, protocols and techniques for assessing this potential will need to be developed and standardized in advance. This need to establish evaluation protocols in advance is one of the reasons why it is important to consider now, what will be needed to continue ethical research in the future. If there is no progress made in the establishment of these protocols before they are needed, the risk of science progressing regardless, and therefore possibly unethically, is unfortunately heightened. To prevent this, suggestions are being put forth as to what techniques may be used for evaluation of potential for consciousness in human brain organoids, and when it might be time to apply them.

A logical place to start is to examine what we know of the emergence of consciousness in humans in general. If an organoid resembles the brain of a fetus that is estimated to harbour a certain level of consciousness, it follows to consider the possibility of consciousness occurring in the organoid (Koplin and Savulescu, 2019). It is predicted that the start of fetal consciousness at the level of the ability to experience pain may be as early as 20 weeks' gestation (Christian Brugger, 2012). Therefore, if and when human brain organoids reach a stage of complexity and development that resembles that of a fetus at 20 weeks' gestation, there would be sufficient grounds to seriously look into the possibility of that level of consciousness in the organoids (Koplin and Savulescu, 2019).

Multiple methods have been put forth concerning how consciousness might be observed, if some level of it were to occur in human brain organoids. For example, using electroencephalography (EEG) to detect low-amplitude activity, which is associated with consciousness (Ankeny and Wolvetang, 2020). EEG could be expanded with transcranial magnetic stimulation, which would make it possible to determine the Perturbational Complexity Index, which reliably predicts consciousness (Massimini et al., 2009). The detection of synchronized gamma waves between multiple brain regions using multi-electrode arrays is also associated with consciousness (Ankeny and Wolvetang, 2020). Alternatively, protocols used to measure activity in vegetative and minimally conscious patients may be used to evaluate potential for consciousness. An example would be the bispectral index, which measures anaesthetic depth during procedures requiring full anaesthesia (Myles et al., 2004). Similarly, magnetoencephalography could be used to compare the magnetic fields generated from electrical activity in neural systems of future, potentially conscious organoids to those observed in fetuses or comatose patients (Gross, 2019).

Regardless of which methods will become established as the golden standard in the future, it is essential that we get to it in time, before the progress in brain organoid development reaches the point where it is needed. The gold standard will need to be non-invasive, work on a very small scale, be accurate and standardizable to offer the field an objective tool for assessing (potential for) consciousness in human brain organoids, such that the research can progress ethically past the point where such assessments would become necessary (Ankeny and Wolvetang, 2020).

**How do these aspects affect the research?**

How then, do or should the ethical considerations discussed so far, affect research involving human brain organoids? At present, the field is at a place where the work with the current organoids does not cause immediate or short-term concern with regards to the potential for consciousness. While intervention or halting of progress in the field is not currently needed, it is important to look ahead. By doing so, necessary steps and preparations can be made, before they become time-critical, before there is a risk of the research starting to progress in an unethical manner. Such preparations might be imagined to include things like public discourse and academic debate to establish consensus on ethical issues that may come up as the research progresses. Additionally, development of and field-wide acceptance of a gold standard method for testing consciousness levels that may affect the way research is conducted when using brain organoids will need to occur alongside the development of the organoids. Of course, to develop such tests, the field will also have to reach a consensus definition of consciousness itself. Overall, these necessary steps are certainly not insurmountable, especially when work on them is started on time, as it has already. Cooperation between scientists and ethicists in debate and at the benchside will ensure timely identification and discussion of ethical issues before and as they may appear (Hyun et al., 2020).

As the field looks to prepare for future progression in the cognitive capabilities of human brain organoids, the first proposals for how to react to significant progression are being presented, such as by Koplin and Savulescu in 2019. In general, they propose to expand the classic Russell and Burch principles (Reduce the number, Refine to reduce harm done and Replace where possible) with several principles formulated by Beauchamp and DeGrazia in 2019, specifically the principles of sufficient value to justify harm, of no unnecessary harm, of basic needs and of upper limits to harm. These principles describe how researchers should adequately justify the necessity of certain research being performed as opposed to the harm to (potentially) conscious organoids that would be done, and how that harm should be minimized, including studying which organoids probably experience the least harm and potentially genetically altering organoids to limit their levels of consciousness to only what is absolutely necessary for the study. The principle of basic needs dictates that the researchers should fulfil the organoids' basic needs, just like any other being used for research purposes. Finally, similar to the principle of sufficient value to justify harm, the principle of upper limits to harm establishes that severe, extended suffering should be prevented, unless essential to absolutely crucial research. In order to accurately weigh possible harm against potential benefit from proposed research, researchers need to be able to evaluate the cognitive capabilities the intended brain organoids have or may develop, as higher cognitive capabilities and therefore potential vulnerability to suffering requires greater justification of the intended research. Additionally, accurate evaluation of the cognitive abilities of the organoids will enable researchers to better meet their welfare needs (Koplin and Savulescu, 2019).

Finally, Koplin and Savulescu propose a tangible framework for how research with organoids that (may) experience certain levels of consciousness could be conducted (Koplin and Savulescu, 2019). For brain organoids that do not possess any level of consciousness and do not hold any potential to do so, no special regulation is needed beyond what is usually required for ethical handling of human biological material, such as proper donor consent. Brain organoids that possess a level of consciousness that enables them to experience in some way, and therefore suffer, should be protected from unnecessary suffering. Finally, cognitively sophisticated organoids that are capable of interaction ought to be monitored to establish more precisely what their exact capabilities are, and their wellbeing needs taken care of accordingly (Koplin and Savulescu, 2019).

## Immediate improvements and steps for the future

As discussed previously, the consensus in the field and amongst ethicists is that there is no immediate ethical concern grave enough to justify halting research in which human brain organoids are used. However, there are things to be improved upon now, and steps to be taken to ensure we are best prepared for the future of this field. For example, guidelines should be put in place that illustrate best practices in the case of organoid generation from donated materials. Consent should be obtained from donors who are anonymized and donors should consent to the generation of organoid lines specifically. Additionally, consent from donors, especially those whose material will be used for the generation of personalized therapies, should be separate from any consent to disseminate or sell the organoids generated. There should be guidelines for example on how informed consent should be obtained, how to handle the privacy of donors while acknowledging that it cannot be absolute. In short, a governance system or set of guidelines such as those suggested above, for example from the ISSCR, could assist in keeping high standards of conduct in the field.

In order to best prepare for the future, it is important that work is started on several aspects that may be necessary down the line. Work on developing consensus on the definition of consciousness and standardized methods of evaluating it in organoids must be done in parallel to progress in refining brain organoid development. These standardized methods must be ready in time for when brain organoids may develop cognitive capabilities that affect their moral status, and thus how they are treated. While this moment is estimated to be far away still, progress is also often surprisingly swift, and there is no such thing as being ready too early in this case. With standardized evaluation protocols, guidelines can also be developed that will cover ethical research practice, if and when organoids show relevant levels of consciousness in those evaluations. Early and continuous collaboration between scientists and bioethicists will be very helpful in bringing ethical issues to the attention of the field as they emerge, as suggested by Hyun et al. in 2020.

## Conclusion

In summary, the development of human brain organoids has certainly improved modelling, facilitating more accurate study of the development of the brain in health and disease by forgoing the uncertainty that comes with studying these phenomena through animal models. A large number of people globally are affected by neurological disorders and neurodegenerative diseases, therefore the translational potential of study through this model is great. Human brain organoids enable more direct study of mechanisms underlying disease as well as screening and testing of possible therapeutic agents. For this reason, every effort should be made to ensure that progress in refining these models and their use in research can continue. Those efforts include considering and preparing for current and especially future ethical challenges that may threaten to halt ethical research using these models, as described in the previous section. In highlighting these actions and ethical aspects in this paper, it is our hope to have contributed to the continued ethical use of human brain organoids in research.

## Layperson's summary

Organoids zijn kleine klompjes cellen die het weefsel waaruit ze afstammen zoveel mogelijk nabootsen. Dit doen ze door zich te organiseren in de ruimte zoals ze dat in het weefsel zouden doen, en door de verschillende typen cellen die in het weefsel voorkomen, aan te maken. Om deze redenen zijn organoids vaak meer representatief voor een weefsel dan een cellijn, die doorgaans zichzelf niet organiseert, en maar één celtype bevat. Organoids worden daarom steeds meer gebruikt voor celbiologisch onderzoek, onderzoek naar ziekten of zelfs het uittesten van mogelijke behandelingen. Het doel van deze schrijfopdracht was om de ethische kwesties die komen kijken bij onderzoek met menselijke organoids in kaart te brengen, in het algemeen en ook specifiek voor hersen-organoids. Onderzoek met hersen-organoids heeft een potentiële impact op grote patiëntengroepen zoals die van neurodegeneratieve ziekten. Hierom is het belangrijk om de ethische aspecten van dit veld voor ogen te houden, zodat het onderzoek op een ethische manier door kan gaan en deze grote patiëntengroepen er baat bij kunnen hebben.

In zijn algemeenheid liggen de voornaamste ethische kwesties bij gebruik van organoids in onderzoek rond consent. Immers, om de organoids te genereren is gedoneerd menselijk materiaal nodig. Donoren moeten consent geven om organoids te laten genereren van hun donatie, en daarbij moeten ze goed geïnformeerd zijn over waar ze precies toestemming voor geven. Bijvoorbeeld moet het duidelijk zijn dat absolute privacy niet mogelijk is, vanwege het feit dat de organoids genetisch materiaal van de donor zullen bevatten, en daardoor altijd terug te matchen zijn aan die persoon. Wanneer de donor zelf niet wilsbekwaam is, moet consent door de wettelijke vertegenwoordiger gegeven worden. Consent om de organoids voor ander onderzoek of zelfs voor commerciële doeleinden te gebruiken zou altijd apart moeten staan van de initiële consent om organoids te genereren. Dit omdat er anders een risico is op belangenverstrengeling, wat zou kunnen leiden tot onethisch handelen, bijvoorbeeld bij de werving van donoren. Het zou daarom ook onethisch zijn om de deelname van een donatie aan een onderzoek te weigeren op grond van het feit dat de donor verspreiding of verkoop van de organoids niet toestaat.

De hersenen hebben onder de organen een unieke status omdat ze de persoonlijkheid en alle cognitieve vaardigheden, zoals herinneren en redeneren, bevatten. Het gebruik van menselijke hersen-organoids in onderzoek roept dan ook unieke ethische vragen op. Ten eerste kunnen we bekijken waarom het überhaupt uit zou maken of menselijke hersen-organoids in onderzoek gebruikt worden. Zijn we bezorgd dat ze mogelijk zouden kunnen lijden? Aangezien de dieren die voor onderzoek gebruikt worden kunnen lijden en ervaren kan dit niet het probleem zijn. De wortel van deze zorgen over hersen-organoids ligt in het feit dat we bewuste, volwassen mensen associëren met persoonlijkheid, zelfbewustzijn. Persoonlijkheid, een zelfbewust persoon zijn, is moreel significant. Dat wil zeggen dat het immoreel is om iemand, een persoon, te doden zonder hun toestemming bijvoorbeeld. Bewustzijn in hersen-organoids roept om deze redenen bij de veel mensen ethische zorgen op. Onderzoekers en ethici in het veld zijn het eens dat het ontstaan van bewustzijn in hersen-organoids nog ver weg is. Desalniettemin is het belangrijk om vanaf nu te gaan voorbereiden op de toekomst van dit onderzoeksveld, zodat het hoge ethische standaarden in de toekomst zal hanteren. Ook ontbreken er op dit moment internationaal erkende handleidingen over ethisch handelen in onderzoek specifiek voor hersen-organoids. Hierdoor wordt bijvoorbeeld niet altijd aan de donor gevraagd of ze bezwaar hebben tegen het gebruik van hun donatie voor het maken van hersen-organoids. Dit is iets wat in het veld op dit moment verbeterd kan worden.

Beginnend bewustzijn in de organoids willen we opmerken zodat we weten hoe ver de ontwikkeling van de organoids is, en wanneer ze mogelijk een partiële morele status zouden moeten krijgen. Om de eerste tekenen van bewustzijn op te merken, zullen protocollen en meetmethoden ontwikkeld moeten worden. Zelfs het begrip bewustzijn zelf heeft nog niet een algemeen geaccepteerde definitie. Ook moeten er handleidingen opgesteld worden voor hoe we in onderzoek om moeten gaan met organoids, wanneer deze in de toekomst zouden beginnen bewust te worden. Werk aan al deze onderdelen is al begonnen, zodat het klaar staat op het moment dat het nodig zal worden om te toetsen in hoeverre organoids bewust geworden zijn. Door de ethische aspecten van hersen-organoids in onderzoek voor ogen te houden, en door meetprotocollen en handleidingen klaar te hebben staan, kunnen we er voor zorgen dat het onderzoek op een ethische manier door zal gaan, zodat zo veel mogelijk patiënten baat kunnen hebben bij het onderzoek, nu en in de toekomst.

## Bibliography


Ankeny RA, Wolvetang E (2020) Testing the Correlates of Consciousness in Brain Organoids: How Do We Know and What Do We Do? https://doi.org/101080/1526516120201845869 21:51–53 Available at: https://www.tandfonline.com/doi/abs/10.1080/15265161.2020.1845869 [Accessed March 25, 2022].

Christian Brugger E (2012) The problem of fetal pain and abortion: Toward an ethical consensus for appropriate behavior. Kennedy Inst Ethics J 22:263–287.

Clevers H (2016) Modeling Development and Disease with Organoids. Cell 165:1586–1597.

Di Lullo E, Kriegstein AR (2017) The use of brain organoids to investigate neural development and disease. Nat Rev Neurosci 18:573 Available at: /pmc/articles/PMC5667942/ [Accessed April 1, 2022].

Fish JL, Dehay C, Kennedy H, Huttner WB (2008) Making bigger brains–the evolution of neural-progenitor-cell division. J Cell Sci 121:2783–2793 Available at: https://journals.biologists.com/jcs/article/121/17/2783/30280/Making-bigger-brains-the-evolution-of-neural [Accessed April 1, 2022].

Giandomenico SL, Mierau SB, Gibbons GM, Wenger LMD, Masullo L, Sit T, Sutcliffe M, Boulanger J, Tripodi M, Derivery E, Paulsen O, Lakatos A, Lancaster MA (2019) Cerebral organoids at the air-liquid interface generate diverse nerve tracts with functional output. Nat Neurosci 22:669 Available at: /pmc/articles/PMC6436729/ [Accessed March 30, 2022].

Gross J (2019) Magnetoencephalography in Cognitive Neuroscience: A Primer. Neuron 104:189–204.

Hyun I, Scharf-Deering JC, Lunshof JE (2020) Ethical Issues Related to Brain Organoid Research. Brain Res 1732:146653 Available at: /pmc/articles/PMC7140135/ [Accessed March 24, 2022].

ISSCR IS for SCR (2016) Guidelines for Stem Cell Science and Clinical Translation.

Jaworska A, Tannenbaum J (2021) The Grounds of Moral Status (Stanford Encyclopedia of Philosophy). Available at: https://plato.stanford.edu/entries/grounds-moral-status/ [Accessed May 12, 2022].

Koch C, Massimini M, Boly M, Tononi G (2016) Neural correlates of consciousness: progress and problems. Nat Rev Neurosci 2016 175 17:307–321 Available at: https://www.nature.com/articles/nrn.2016.22 [Accessed March 30, 2022].

Koplin JJ, Savulescu J (2019) Moral Limits of Brain Organoid Research. J Law, Med Ethics 47:760 Available at: /pmc/articles/PMC7433685/ [Accessed April 5, 2022].

Luo C, Lancaster MA, Castanon R, Nery JR, Knoblich JA, Ecker JR (2016) Cerebral Organoids Recapitulate Epigenomic Signatures of the Human Fetal Brain. Cell Rep 17:3369 Available at: /pmc/articles/PMC5495578/ [Accessed April 11, 2022].

Massimini M, Boly M, Casali A, Rosanova M, Tononi G (2009) A perturbational approach for evaluating the brain's capacity for consciousness. Prog Brain Res 177:201–214 Available at: https://pubmed.ncbi.nlm.nih.gov/19818903/ [Accessed March 30, 2022].

Myles PS, Leslie K, McNeil J, Forbes A, Chan MTV (2004) Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet 363:1757–1763.

Reardon S (2018) Lab-grown “mini brains” produce electrical patterns that resemble those of premature babies. Nature 563:453.

Tooley M (2009) Personhood. In: A Companion to Bioethics (Kuhse H, Singer P, eds), pp 129–139.

Trujillo CA, Gao R, Negraes PD, Gu J, Buchanan J, Preissl S, Wang A, Wu W, Haddad GG, Chaim IA, Domissy A, Vandenberghe M, Devor A, Yeo GW, Voytek B, Muotri AR (2019) Complex oscillatory waves emerging from cortical organoids model early human brain network development. Cell Stem Cell 25:558 Available at: /pmc/articles/PMC6778040/ [Accessed March 30, 2022].

Wang H (2018) Modeling Neurological Diseases With Human Brain Organoids. Front Synaptic Neurosci 10 Available at: /pmc/articles/PMC6002496/ [Accessed April 4, 2022].

World Medical Association (1964) WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects – WMA – The World Medical Association. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ [Accessed May 25, 2022].

Xiang Y, Tanaka Y, Patterson B, Kang YJ, Govindaiah G, Roselaar N, Cakir B, Kim KY, Lombroso AP, Hwang SM, Zhong M, Stanley EG, Elefanty AG, Naegele JR, Lee SH, Weissman SM, Park IH (2017) Fusion of regionally-specified hPSC-derived organoids models human brain development and interneuron migration. Cell Stem Cell 21:383 Available at: /pmc/articles/PMC5720381/ [Accessed April 11, 2022].