



Review

The moral status of cerebral organoids

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ABSTRACT

Organoids are 3D biological structures constructed from stem cells *in vitro*. They partially mimic the function of real organs. Although the number of articles detailing this technology has increased in recent years, papers debating their ethical issues are few. In addition, many of such articles outline a mere summary of potential ethical concerns associated with organoids, although some have focused on consciousness assessment or organoid use in cystic fibrosis treatment. This article seeks to evaluate the moral status of cerebral organoids and to determine under which conditions their use should be allowed from a bioethical standpoint. We will present an overview of recent steps in developing highly advanced cerebral organoids, followed by an analysis of their ethics based on three factors: human origin, a specific biological threshold (which, once crossed, grants an entity moral status), and the potential to generate human beings. We will also make practical recommendations for researchers working in this biological field.

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1. Introduction

Organoids are 3D biological structures, constructed from stem cells and created *in vitro*, partially mimicking functions of real organs. As of now, organoids of the following types have been developed: gastrointestinal (intestinal, gastric, lingual, pancreatic,

hepatic), endocrine (testicular, thyroid), cardiac, kidney, and lung organoids, as well as gastruloids (embryonic organoids). There are two main varieties of organoids that differ depending on the cellular source, either pluripotent stem cells (PSCs) [1,2] or somatic stem cells [3,4].

While an increasing amount of articles have covered this technology, the number of studies debating their ethics remains low [5–14]. Moreover, most of them present an overview of the potential ethical issues associated with organoids; only a few highlighted specific problems, including ethical issues related to consciousness assessment [5,13,15] and the perspectives of patients and their parents regarding the use of intestinal organoids in cystic fibrosis treatment [11].

Currently, research on human embryos is limited by the so-called “14-day rule”, according to which experiments using complete human embryos should not use embryos more than 14 days old or that demonstrate a primitive streak [12]. Some bioethical committees identified this time frame as relevant primarily due to its close temporal connection to the beginning of neural development and to the embryo’s distinct identity (the embryo is unique after day 14 and cannot lead to twins) [16]. Some authors have debated the moral relevance of this rule for organoids [6,8,14,15,17]. If moral status is explicitly linked with neural development in complete embryos, one could easily question the morality of developing and using cerebral organoids in clinical research. The purpose of this article is to evaluate the moral status of cerebral organoids and to see in which conditions their use should be allowed from a bioethical standpoint.

2. A general overview of the brain (cerebral organoids)

Brain organoids are stem-derived 3D biological structures, which are self-organizing in morphological units resembling a developing brain [17]. In 2008, Gaspard et al. published an article describing an intrinsic mechanism of corticogenesis, using embryonic stem cells taken from mice [18]. Eiraku et al. showed that cortical progenitors generated in cultures by mouse- and human-derived embryonic stem cells can spontaneously form patterned structures, mimicking the early aspects of corticogenesis [19]. Building on these results, Lancaster et al. built the first human brain organoids from human pluripotent stem cells, which were shown to have the capacity to recapitulate specific features of human cortical development—such as progenitor zone organization—with an increased density of outer radial glial stem cells [17]. Since 2013, the year in which Lancaster et al. presented their initial findings, numerous papers have been published that discuss the development of more complete cerebral organoids. For example, Paşca et al. developed human cortical spheroids containing both deep and superficial cortical layer neurons. These spheroids exhibited spontaneous activity [20] and corresponded to a 19–24 week embryo. Qian et al. developed forebrain, midbrain, and hypothalamic organoids containing neurons corresponding to all six cortical layers of the human cortex [21]. Giandomenico et al. developed cerebral organoids able to generate nerve tracts with functional output, the axon bundles being capable of not only intracortical projection within and across the cerebral organoid, but also decussation and projection outside the organoid. Moreover, organoid stimulation was shown to cause muscle contractions [22]. Bagley et al. developed a co-culture technique that combined various brain regions within one organoid tissue, fostering complex interaction between different brain regions [23]. Matsui et al. identified the presence of mature oligodendrocytes, mature GAD-67-positive inhibitory neurons, and VGLUT-1 positive excitatory neurons in long-term cultured cerebral organoids induced from H9 human embryonic stem cells [24]. Quadrato et al. found that

organoids developed over an extended period exhibited mature neuronal features, such as the formation of dendritic spines, spontaneously active neuronal networks, and functional photosensitive cells [25]. This brief summary enables an understanding of this field’s rate of advancement, and, more importantly, serves as a reminder that matters such as human brain organoids interacting with the environment may become reality in the near future.

3. An overview of the embryo’s moral status

Moral status is one of the most important ethical concepts in reproductive and regenerative medicine; if the subject of biomedical research possesses moral status, he/she has specific rights, and the investigators thereby have obligations that can significantly impact their research protocol. Baertschi classified moral status into four main types: complete (the subjects possess moral status and therefore all rights and duties associated with it), incomplete (subjects have entire or partial moral rights, but only some or none of the obligations associated with it), intrinsic (moral status is given based on intrinsic value or potentiality), and conferred (subjects are awarded moral status based on specific characteristics or properties) [26]. According to many research ethics guidelines, early human embryos do not have definite moral status; however, they do have to be respected based on their intrinsic potential to generate other human beings (and subsequently moral agents). This value was prescribed by the Warnock Committee as “respect for the embryo” [16,27,28] and it is conferred to embryos up to 14 days old (hence the 14-day rule) [29]. This time limit was selected because the embryo develops a primitive streak on day 15, which marks the beginning of gastrulation, the moment in which embryonic cells start to differentiate. The first pre-neural cells are identifiable soon after this stage, allowing for the embryo’s potential to feel pain: “the ethics of experiments on embryos must be determined by the balance of benefit over harm, or pleasure over pain. Therefore, as long as the embryo is incapable of feeling pain, it is argued that its treatment does not weigh in the balance” [30]. Therefore, according to the Warnock Report, the attribution of moral status to embryos is based on three main elements: their human origin, their potential to feel pain (the Warnock Committee selected a time earlier than the beginning of neurulation to ensure zero possibility of the embryo feeling pain) [30], and their potential to generate individual human beings. Based on this rule, research on human embryos is allowed in the first two weeks after conception, with some limitations. As a rule, it is forbidden any time after that. In recent decades, numerous researchers have argued for this rule to be revisited based on recent developments in reproductive and regenerative medicine. For example, Appleby and Bredenoord argued that, as embryos used in research are pre-designed to be destroyed at 14 days, they have no potential of personhood [31]. Hurlbut et al. emphasized the fact that extending this rule would allow greater insight into early human organogenesis [32], while Aach et al. argued that this rule is only applicable to conventional embryos. However, with the advent of organoids (especially gastruloids), recent advances in cell biology make this timeline completely irrelevant, as synthetic embryos can now be developed to skip some steps in embryogenesis [12], which was highly relevant in establishing the 14-day rule. As such, there is now a need to not only reassess relevant determinants of moral status in both research and clinical practice, but to reconceptualize moral status.

4. Moral status of cerebral organoids

To establish if and what kind of moral status can be attributed to cerebral organoids, we will follow the three elements presented in the abstract above: human origin, a biological threshold that grants

moral status to an entity and the potential to generate human beings (or procreation potential).

The human origin of cerebral organoids is non-disputable; since they consist of human-derived cells (either embryonic or adult), they should be considered as having a human origin. A potential issue complicating the human origin of cerebral organoids is the possible use of techniques that could alter it, such as creating chimeras or changing a specimen's genetic code using technology such as CRISPR-Cas9 [33]. Human-animal chimeric organoids have already been developed [34], and chimeric cerebral organoids could be a logical next step. According to Karpowicz et al., the ethical viability of neural chimeras should be allowed provided the following guidelines are respected: (1) researchers should be required to use a minimum number of stem cells from the human brain to make reliable scientific conclusions; (2) the host animal should not be too morphologically or functionally similar to humans (to mitigate the risk of developing human-like neurological networks), and (3) dissociated human stem cells should be used exclusively to avoid the manifestation of human characteristics in the specimen, such as dignity [35]. Regarding genetic engineering technologies, we recommend implementing minimal changes to support a specific research protocol [33] that neither visibly alters human morphology/physiology into that of another species nor causes human augmentation [36]. These criteria can be used not only to limit the development of chimeras/genetic engineering technologies, but as a threshold for establishing the human origin of organoids (in this case, cerebral organoids).

Establishing a specific threshold whose presence would potentially generate moral status for cerebral organoids is much more difficult. Until now, most authors have used criteria pertaining to conventional/biological embryogenesis to determine moral status: the presence of human genetic material, the appearance of the zygote, a primitive streak, a functional heart, sensitivity, the visualization of EEG patterns, the presence of a viable fetus, the moment of birth, or even the moment when the person becomes an adult from a legal standpoint [37,38]. However, when dealing with “non-conventional” biological structures or entities with synthetic human embryo-like features, such as cerebral organoids, such thresholds are not very useful; various authors now seek alternative approaches. For example, Aach et al. presented a four-step algorithm for seeking characteristics that could generate moral status, namely: (1) cataloging morally significant events in canonical embryogenesis, (2) determining the applicability of the catalog to the entities with synthetic human embryo-like features, (3) identifying the substrates of features signifying moral status, and (4) organizing inquiries [12]. In a highly debated article [5,13,15], Lavazza tried to link ethical issues associated with cerebral organoids to the assessment of consciousness by using a specific tool (Perturbational Complexity Index) [5]. This tool was used for the clinical assessment of brain-injured, unresponsive patients, and is independent upon the ability of the subject to interact with the external environment [39]. Therefore, it is applicable to fully developed human brains, even though in a very particular, basal state, and we believe it is too advanced for the evaluation of the moral status of cerebral organoids, at least if we were to take the same precautions as the Warnock Committee. When establishing possible criteria, we should consider that they must be as primitive as possible to minimize the risk of harming moral entities (regardless of their type of moral status), but also as advanced as possible to maximize their utility. We must also consider that this entity will develop outside a complete body; as such, some of the above-mentioned criteria cannot be employed while others can easily be circumvented. Lavazza and Massimini argued that, from a consequentialist view, an entity that is sentient might have interests and can be included in a consequentialist calculation, which

should be done using a risk-benefit analysis [5,15]. Therefore, moral status could be attributed to any cerebral organoid that is sentient, even if in the most minimal sense. We would refrain from adopting this approach because sentience is not a uniquely human characteristic, but is rather used as an argument for granting certain rights to animals based on their ability to suffer or feel pain [40]. Moreover, if we decide the threshold for obtaining moral status entails the capacity to feel pain, it is entirely possible to develop, *in vitro*, a fully mature brain that can reason but cannot feel pain due to a lack of nociceptors. Also, again, using the precautions of the Warnock Committee, the sentience capacity would be too advanced as a criterion for establishing moral status, as the capacity to feel pain would be attributed to a biological construct with human-like characteristics. Therefore, the attribution of moral status to cerebral organoids must rely on criteria that are specific to humans (such as speech or abstract thought) or that are too multifaceted to be circumvented once the brain organoid reaches a certain level of complexity. We believe that the first approach (human-specific criteria) is not morally acceptable, as it could yield the creation of actual human brains in a dish [41]. This would contradict one of the fundamental principles in the Helsinki Declaration, namely that “it is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects” [42]. Protecting the dignity of research subjects implies protecting their free choice of telos [43], which cannot be done through their creation solely for scientific purposes.

The second approach is more feasible in practice, but the challenge would be quantifying it using the available techniques [5]. We recommend learning capacity as a specific criteria in this regard; an entity that is capable of learning can self-develop, interact with the environment, and can be considered as more than a mere mass of cells in a 3D matrix. Learning capacity is not unique to human beings, but is specific enough to differentiate between biological structures that are capable or incapable of interacting with the environment or understanding it. However, humans have an increased learning capacity compared to other beings; this, associated with the biological foundation of human cerebral organoids (human cells/human genetic material), would be specific enough to grant moral status. The quantification of learning ability can be made using techniques such as single-photon emission tomography [44], microRNAs [45], biochemical markers [46], etc.

The potential to generate human beings is not necessarily associated with cerebral organoids, since they cannot generate fully developed humans. However, two issues must be considered: first, if we were to develop a fully matured human brain in a Petri dish, it would possess all the morally relevant characteristics of a human being and would be considered a moral agent [38]. This can be demonstrated through a reductionist approach. If we were to take a fully developed adult human being and remove various organs/biological structures, we would still view the adult as an individual until removing the brain. A person without a limb is still an individual; one without a liver is still an individual; one without kidneys, a urethra, lungs—again, still individual human beings. Many human beings live without various body parts, some of which are replaced with synthetic or transplanted organs and tissues. However, nobody can live without a brain (or have a brain transplanted). Moreover, even if a human brain is theoretically transplanted into another body, the individuality of the newly-formed person would mostly be characterized by brain-related functions.

Second, in a recent decision from the Court of Justice of the European Union in a case about the patenting of neural precursor stem cells from embryonic stem cells, the ruling was as follows:

“The use of human embryos for scientific research purposes is not patentable. A ‘human embryo’ within the meaning of Union law is any human ovum after fertilization or any human ovum not fertilized but which, through the effect of the technique used to obtain it, is capable of commencing the process of development of a human being” [47]. Also, the ruling extended the applicability of any type of cell able to initiate the process of developing human beings and linked it with human dignity [37], thus inferring moral status: “the use of biological material originating from humans must be consistent with regard for fundamental rights and, in particular, the dignity of the person. It is from this perspective that the patentability of the human body is prohibited. As a result of this, in its opinion, the concept of human embryo, within the meaning of Article 6(2) (c) of the Directive, must be interpreted broadly as covering any cell capable of commencing the process of development of a human being. This includes, on the one hand, the human ovum as soon as fertilized and, on the other hand the non-fertilized human ovum into which the nucleus from a mature human cell has been transplanted and a non-fertilized human ovum whose division and further development have been stimulated by parthenogenesis” [48]. Based on this decision, as the cells used to initiate the development of brain organoids are either embryonic or induced pluripotent stem cells, cerebral organoids have, from a legal point of view, the potential to generate human beings—even if they are not necessarily human in the strict sense of the term.

5. Discussions

By considering the three characteristics outlined above, we can posit that human brain organoids have moral status. Research on them should be prohibited because they have the potential to generate human beings if (1) they are based on human genetic material that has not been significantly altered, and/or (2) they have reached a developmental threshold that is extremely difficult to overcome by simply manipulating genetic and epigenetic information (which we proposed as learning capacity). However, in the case of the second criteria, we would allow the development of advanced cerebral structures. Boers et al. found that people attribute a higher moral value to 3D organized structures containing human cells compared to ones associated with other types of cellular materials obtained through biopsy: “it is the transformation of the biopsy into a 3D immortalized cell line that is genetically and functionally similar to the donor that is considered meaningful, and to some extent as sensitive” [11]. This would be especially true for human brain-like 3D structures, and special safeguards should be imposed before performing studies on them—perhaps based on a concept like “respect for the embryo”. In this sense, we could distinguish between moral status and value. Steinbock argued that while some sentient beings can have a moral status, other entities, including stem cells or organoids, have the potential to bring forth something unique to moral agents; this might discourage people from considering them as mere objects [49]. According to the same author, moral value can be attributed to two main things: symbols (such as flags), and material things (such as human cells or human remains). Based on this distinction, we can use things with moral value for morally significant purposes, such as improving knowledge about a disease or finding a cure [37,49].

In conclusion, research on human cerebral organoids should be allowed, but only if such organoids are not developed enough to acquire moral status. Their moral value should be valued and respected by only using them in studies conducted with morally viable techniques.

Author's contributions

All authors participated equally in developing the ideas in this paper, drafting the manuscript, correcting it, and approving the final version.

Conflicts of interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.reth.2019.02.003>.

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