Cambridge Quarterly of Healthcare Ethics (2023), 32: 4, 582–596
doi:10.1017/S096318012300021X

CAMBRIDGE UNIVERSITY PRESS

ARTICLE

Human Brain Organoids: Why There Can Be Moral Concerns If They Grow Up in the Lab and Are Transplanted or Destroyed

Andrea Lavazza[1,2] and Massimo Reichlin[3]

[1]University of Pavia, Pavia, Italy
[2]Centro Universitario Internazionale, Arezzo, Italy
[3]Vita-Salute San Raffaele University, Milan, Italy
Corresponding author: Andrea Lavazza; Email: lavazza67@gmail.com

Abstract
Human brain organoids (HBOs) are three-dimensional biological entities grown in the laboratory in order to recapitulate the structure and functions of the adult human brain. They can be taken to be novel living entities for their specific features and uses. As a contribution to the ongoing discussion on the use of HBOs, the authors identify three sets of reasons for moral concern. The first set of reasons regards the potential emergence of sentience/consciousness in HBOs that would endow them with a moral status whose perimeter should be established. The second set of moral concerns has to do with an analogy with artificial womb technology. The technical realization of processes that are typically connected to the physiology of the human body can create a manipulatory and instrumental attitude that can undermine the protection of what is human. The third set concerns the new frontiers of biocomputing and the creation of chimeras. As far as the new frontier of organoid intelligence is concerned, it is the close relationship of humans with new interfaces having biological components capable of mimicking memory and cognition that raises ethical issues. As far as chimeras are concerned, it is the humanization of nonhuman animals that is worthy of close moral scrutiny. A detailed description of these ethical issues is provided to contribute to the construction of a regulative framework that can guide decisions when considering research in the field of HBOs.

Keywords: neuroethics; sentience; consciousness; ectogenesis; hybridization

Introduction: Three Sets of Reasons for Moral Concern

Human brain organoids (HBOs) are three-dimensional biological entities grown in the laboratory in order to recapitulate the structure and functions of the adult human brain. Organoids originate from human pluripotent stem cells, either embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) derived from adult somatic cells (e.g., skin cells).[1,2,3,4,5] Currently, lab-grown organoids reach very small sizes (a few millimeters in diameter), but it is possible to join organoids that mimic different brain areas into assembloids.[6,7] In general, no blood vessels are formed in HBOs, and although HBOs have strong similarities to the adult human brain, they lack many features typical of it, nor can they develop into a human being as an embryo can.[8,9]

The purpose for which HBOs were created was initially, and still is primarily, clinical research. People in the biomedical field want to be able to study malformations, disorders, and diseases of the nervous system in a way that is not viable in human patients nor in animal models for both technical and ethical reasons. HBOs soon proved to be an excellent model for tracing the origin of diseases, observing their

development, and trying new treatments.[10,11,12] In addition, it is possible to personalize treatments, for example, against cancer, by creating organoids directly from the patient's diseased cells on which to test drugs to find the most suitable ones.[13,14]

Second, HBOs turn out to be very useful for the study of the physiology of the nervous system at the fine level, particularly regarding the development of the encephalon in the early stages and all processes of cell differentiation. These kinds of studies promise to have important spin-offs at the level of understanding our brain, but also for improving its well-being and efficiency since it is a fundamental organ, whose functioning is not yet fully understood.[15]

Recently, the technical feasibility and willingness of some researchers to grow HBOs as biological entities with specific features and functions increasingly similar to those of an adult human brain have emerged.[16,17,18,19,20] The goal here is to attempt to reproduce even the conscious phenomena that characterize human beings both to use them in an instrumental sense and to unravel the so-called mystery of human consciousness: its origin, its necessary and sufficient neuronal correlates, its evolution, and its disorders.[21,22]

This scenario primarily concerns biomedical research, with some spillover, as mentioned, into the area of the study of consciousness, which also involves cognitive scientists and philosophers. However, it was immediately apparent that ethical issues may arise from research on HBOs.[23,24,25] Prima facie, the idea of reproducing a human brain in the lab without a connected organism may elicit negative reactions, calling to mind the well-known brain-in-a-vat thought experiment devised by Hilary Putnam and some science-fiction movies that have envisioned dystopian futures based on this possibility.

Obviously, this initial emotional reaction should be compared with the extremely positive ones related to the extraordinary scientific, technological, and clinical advancements enabled by organoids, and HBOs specifically. Ten years after the publication of the first study regarded seminal to the field we are considering, a large and growing bioethical and neuroethical literature is accompanying research in laboratories around the world.[26,27,28,29,30,31,32,33]

With this paper, we wish to contribute to the ongoing ethical debate by trying to single out three strands of moral concern related to HBOs. Specifically, both drawing on the existing literature (to which one of us has contributed from the beginning) and trying to broaden to areas not yet well mapped, our aim is to give the coordinates of the issues at stake without claiming to give precise normative directions. Faced with the novelty of biological entities that could be considered of a special kind, other than a simple laboratory culture of human origin, we will try to specify what this special character of HBOs consists of and why it may give rise to moral concerns of different kinds.

In particular, we will consider the topics of the potential emergence of sentience/consciousness in HBOs and the associated moral status, of the analogy with artificial womb technology (AWT) and abortion, and of the hybridization of cellular lines derived from humans both with digital systems and with biological species. Preliminarily, it should be made clear that we will not deal in depth with epistemic issues that may be preparatory to ethical issues. For example, ascertaining the presence of consciousness in an entity that has no relationship with the external environment may be particularly challenging, yet the presence of consciousness constitutes an ethically sensitive issue. Nor are we going to deal in depth with technical issues that may be the premise of the feasibility of a certain moral scenario. For example, an entirely ectodermal pregnancy is not yet feasible; nevertheless, it makes sense to consider it as a realistic benchmark for moral analysis.

Therefore, we will not address other purely bioethical issues that are not typical of HBOs even though they have considerable relevance; these are the use of ESCs, the informed consent required for the donation of cells to produce HBOs, the patentability of lab-grown organoids, and the allocation of resources to organoid research.[34,35,36]

Before delving into the three above-mentioned strands of moral concern that can be distinguished concerning HBO research, it is important to clarify what we mean here by moral concern. It can be said that in the absence of moral concern, it is possible for agents who have no special constraints in their behavior to freely dispose of a certain entity. On the other hand, in the absence of moral concerns, that entity has no rights not to be treated as an object, that is, it is without protections or special prerogatives given by its nature, constitution, or social attributions.

There are no moral concerns in taking a stone from the ground and crumbling it or tearing up a book that legitimately belongs to us. There are no moral concerns about growing skin cells in the laboratory. The cultivation and use of HBOs, on the other hand, seem to have raised moral concerns and thus require evaluation and regulation of some kind if we are to take moral concerns into account, which is typical of ethically responsible research. Let us, therefore, see in order the three strands that give rise to moral concerns.

HBOs and the Emergence of Sentience/Consciousness

HBOs, as mentioned, can develop *in vitro* limited in both size and structure when compared to the *in vivo* development of a brain from fetal origins into an adult organ of an organism embedded in its environment. However, we know that any human nervous system taken as a whole, if not affected by congenital malformations or severe acquired pathologies, tends to develop what we call *phenomenal consciousness*. Consciousness amounts to the subjective experience, still difficult to treat scientifically, that appears upon waking and disappears during dreamless sleep. There is a tendency to regard consciousness as a fundamental characteristic of human beings, and the possibility of having subjective states that include experiencing suffering is generally held to be one of the minimum conditions for the attribution of moral status to an entity.[37,38,39]

In this sense, moral concerns are due to the potential emergence of states of consciousness in HBOs of larger size and more mature development than those currently being cultivated. Research progress in the field is very rapid, as is evident from the results achieved in the past three to four years. Two papers, one empirical and one theoretical, have recently been published, indicating that the goal of obtaining sentient entities from *in vitro* cultures of human neurons is already an achievable outcome, or at least in sight.[40,41] It is not of interest here to go into the details of those studies, because our purpose is to investigate moral concerns at the level of philosophical, social, and legal fallout. Nor, as mentioned above, do we want to delve into purely epistemic issues.

However, one cannot fail to mention a major problem at this stage of research on HBOs, namely that of ascertaining the presence in them of some form of subjective states. HBOs do not currently have effectors or other means of interacting or communicating with their environment. Yet, it is possible to make hypotheses using some indicator related to the presence of specific areas or specific electrical activities as proxies of the presence of some form of subjective states.[42] For example, based on the postulates of integrated information theory, one of the most widely discussed neuroscientific theories of consciousness on the market, it has been possible to obtain an index that seems to measure accurately the amount of consciousness remaining in patients with disorders of consciousness.[43,44]

Applying such an index to brain organoids is both a conceptual and a technological challenge due to the lack of adequate yardsticks for comparison. But it seems neither a foolish nor an impossible task. Therefore, the fact that an ascertainment, albeit still indirect, of the presence of consciousness in entities that have no way of actively expressing their subjective states is at least conceivable seems sufficient to reason about the consequences of the emergence of sentience/consciousness in HBOs.[45] First, sentience and consciousness should be distinguished. Sentience can be understood as the basic capacity to experience negative subjective states, such as physical pain and other forms of suffering, and positive subjective states such as pleasure (also basically expressed as removal/absence of suffering). Consciousness can be defined as the capacity to experience more complex subjective states concerning the self and one's environment.

It is well known that in biological entities very different from higher mammals (including human beings), pain manifested as an avoidance reaction cannot be assimilated with certainty to the deeply unpleasant sensations associated with suffering that are pivotal in our moral reasoning.[46] Secondly, consciousness can also come in degrees, and it cannot be ruled out, even based on the studies cited above, that the consciousness possibly manifested by HBOs at different levels of development is similar to "islands" of consciousness as have been diagnosed in patients with severe central nervous system injuries.[47]

Perhaps once one has succeeded in equipping them with sensory receptors, which does not seem so far off, it becomes plausible that specific HBOs begin to experience subjective states.[48] It would then make sense to speak of moral concerns. Indeed, the possibility of qualitative experiences is believed to be the basis for placing an entity in the moral circle to be accorded special consideration. Granting moral status to sentient or conscious HBOs would then be the step to lead them to become biological entities *sui generis*, ethically to be protected.[49,50,51]

They can be referred to as *sui generis* entities because they are organs or non-organisms, but they may have characteristics and capabilities typical of an organism, starting with the ability to experience subjective states and interact with the external environment. In addition, the brain is considered the key organ of the human being, as also indicated by the criteria for ascertaining death at the legal level.[52] The moral concern arises from the fact that HBOs share the possibility of experiencing subjective states as do the biological entities at the center of our moral circle, namely humans and some species phylogenetically closer to ours.

In this sense, the raising of a moral concern is not intended to equate an HBO with a healthy adult human being, nor with a nonhuman animal. The first kind of equating is implausible until there is no way to have direct manifestations by organoids of subjective states qualitatively comparable to those of an adult human being. The second type of equating is made difficult by the lack of a clear understanding of what subjective states are in nonhuman animals to which we nevertheless attribute sensations and emotions.[53,54]

We are thus faced with the fact that some HBOs might experience feelings of suffering or even higher-level subjective states. To what kind of moral status might they be entitled in that case? If one believes that full moral status is attributable only to a human being at least potentially capable of full consciousness and higher cognitive functions, the moral rank of an HBO can only be lower.[55] Indeed, from the standpoint of making decisions about research inspired by sound ethical guidelines, constructing a ranking of moral concerns associated with different entities used and the different contexts of use would be a significant step forward.[56]

First, it should be considered whether sentience justifies the attribution of moral status and moral concerns in HBOs. We can consider in this regard the epistemic objection that "derives from our profound uncertainty about sentience … we cannot use sentience as a criterion to ascribe moral status in practice because we won't know in the foreseeable future which animals and AI systems are sentient."[57] So, the proposal is to utilize another criterion, different from sentience. For example, the possession of desires or psychological equivalence to moral patiency has been proposed.[58,59] Moral patiency is defined as "a form of moral status that may arise in virtue of possession of specific psychological capacities such as sentience, autonomy, desires and so on."[60] In this vein, it has been proposed to recognize moral patiency in the presence of relations and interactions detectable as objectively as possible between the entity in question and subjects already endowed with moral status.[61] This leads to what is explicitly called *ethical behaviorism*.[62]

This form of behaviorism exposes itself to two kinds of objections. First, it unwarrantedly excludes entities such as HBOs that do not have direct and observable relationships with other moral subjects: that, in fact, does not imply that they should be considered devoid of sentience and consequently of moral status. Just as classical behaviorism excluded internal mental states from its explanatory horizon, failing to consider a part of the ontology and functioning of human beings—whether by choice or by epistemic insufficiency of the theory—so ethical behaviorism, on the basis of an epistemic criterion for ascertaining moral relevance, risks excluding entities for which other criteria can be used.

Second, as argued by Leonard Dung, there is confusion between what determines moral status and what criteria should be used for moral status ascription.[63] Even proponents of ethical behaviorism seem to consider sentience as at least one of the foundations of an entity's moral relevance in agreement with a large body of recent literature.[64,65] As noted above, the epistemic problem of ascertaining the presence of sentience in HBOs does not invalidate moral concerns about their use in the lab. What grounds the potential moral status of HBOs are the subject states they may experience, and not the external behaviors or criteria for ascertaining the presence of sentience.

Another objection concerns the intrinsic value of pure sentience. Indeed, it can be argued that what should drive our moral concerns is the presence of higher cognitive abilities, such as the ability to have desires and make plans for one's life.[66] This perspective values intelligence more highly than phenomenal consciousness and, therefore, tends to minimize moral concerns referring to potentially conscious HBOs. An answer to this objection is that it seems very difficult to experience subjective states that are not valenced, that is, not characterized by a special positive or negative coloring or sensation, which descends from the possession of phenomenal consciousness. Otherwise, even a computer could be granted moral status by virtue of "cold" cognitive abilities alone.[67]

Yet, human zombies, although conceptually possible, do not seem to be on the horizon, and, therefore, phenomenal consciousness is fundamental to our orientation in the world, and it is hard to see how it could not be considered the basis of our existence and of what is of value to us. Finally, one can respond to the above-mentioned objection by showing that it is a form of super-speciesism, because it not only excludes from the primary moral circle those nonhuman animals that can experience pain and suffering but cannot exhibit higher cognitive functions, but also risks excluding those human individuals who do not possess or have lost, for various reasons, the abilities to have desires and make plans for their own lives.

That argued, however, the position of sentient HBOs in the ideal ranking of moral status remains to be established. They seem to rank below human individuals and probably below higher mammals capable of both intraspecific and interspecific relationships (mainly with humans). As for other species that, with good confidence, we may consider capable of subjective states, at least of suffering and pleasure, it seems more difficult to adjudicate the issue.[68] Indeed, just as we generally regard a human individual as more deserving of moral concerns than an individual of a nonhuman species, so we might regard a sentient HBO endowed with subjective states—although not well understood yet—as having a higher moral status than a mouse or parrot. But, in such cases, additional factual elements might help to overcome the uncertainty.

Considerations untethered from the ordinal conception of moral status, on the other hand, are in order when considering how to proceed in research in which HBOs appear to be more suitable and effective entities than animal model studies or *in silico* simulations. A utilitarian criterion has been proposed in this case, whereby the maximum reduction of suffering of the HBOs used and the minimum use of them are considered. This means that in order to obtain predictable important benefits for understanding and treating serious diseases of the nervous system, it is possible to grow and destroy human cerebral organoids. In this utilitarian view, the entire research should be aimed at the welfare of human organisms, for which it remains permissible to sacrifice animal models and, in this case, HBOs, with an implicit harm–benefit calculation based on the value placed on the suffering of each entity involved in the calculation.[69]

It is different if one assumes a deontological principle for the protection of what is human. No experiment is permissible that has an individual treated as a mere means and does not involve an informed and consenting subject capable of adhering to the purpose of the research (in some cases, such a decision is made by those who have legal guardianship of the individual and are presumed to be acting in their best interests). In this sense, the 14-day rule for the use of embryos in destructive scientific experiments is accepted in many legislations. This is based also on the fact that, since up to that stage of development, the embryo has not yet started the process that will lead it to have a nervous system and consequent states of pain.[70]

It has recently been questioned whether, even at a more advanced stage of development, the fetus can experience real suffering, which is often pointed out as a reason for banning abortion beyond a certain stage of development.[71] In any case, the 14-day rule could be adapted and prolonged (with some technical complexities) to sentience-capable HBOs. However, the analogy is not quite fitting because the embryo tends to develop into an organism with full consciousness, while the HBO is destined to remain in the condition of a *sui generis* entity with presumably limited subjective states.

A recommendation consistent with the moral concerns considered so far is that HBOs that reach a stage of development such that subjective states emerge should not be used in research. While more complex organoids, called *assembloids*, may be needed for some types of clinical studies, the technology is

sufficiently developed to make it possible to grow HBOs lacking some key structures for consciousness. Given the still-incomplete knowledge of the mechanisms of consciousness, there may not be certainty of outcome but a good chance. When some brain areas thought to be relevant to consciousness are integrally present, for example, the prefrontal cortex and occipital lobe,[72] the production and destruction of brain organoids should probably be kept to a minimum and all the precautions that are already taken today for animal experimentation, such as the use of sedation, should be taken.

It is therefore granted that experiments with sentient HBOs would exceed moral concerns when it comes to medical research aimed at cures. Instead, if it were assumed that conscious HBOs would be researched and cultivated and made to suffer for the purpose of studying the mechanisms of consciousness that we do not yet understand, such use of HBOs might be considered morally problematic because of the moral concerns raised by the suffering and destruction of conscious entities of human origin.

HBOs, Abortion, and AWT

Moral concerns are justified when dealing with individuals endowed with moral status. Several debated issues in bioethical reflection spring from the fact that they deal with entities whose moral status is controversial: Relevant examples are anencephalic newborns, people in a vegetative state, and nonhuman animals. The reason that makes these topics perplexing is that plausible indicators of moral status come in degrees, and this makes it reasonable to suppose that moral status admits degrees just as well.[73,74] In these cases, therefore, we are confronted with entities that display partial similarities with individuals endowed with full moral status, such as normal human adults, and partial similarities with entities clearly lacking a moral status, such as rocks or technological objects; the more we incline toward granting substantial or full moral status to these entities, the more substantial we will consider the moral concerns.

Abortion is one of the topics in which the discussion on moral status has been at the same time inevitable and inconclusive. Confronted with this situation, authors such as Judith Thomson and Don Marquis have attempted to provide new insights on the topic by shifting the focus from the seemingly irresolvable topic of the moral status of the fetus to the consideration of what follows once a certain status is attributed; in particular, Thomson tried to show that abortion may be permissible in many circumstances even if the fetus is granted full moral status, while Marquis attempted to demonstrate that it can be impermissible in several cases, even if the fetus has little or no moral status. In recent years, there have been some suggestions that the present discussion on HBOs may find some analogies with the abortion controversy. Referring to Thomson's and Marquis' strategy,[75,76] Andrew Barnhart and Kris Dierickx have suggested that "ethical debates about organoid-entities could make similar use of their philosophical methodology"[77]; the suggestion, in other words, is that we make assumptions on the controversial issue of moral status and then explore possible lines of inquiry that follow from them.

The ongoing discussion on the ethics of using HBOs indisputably shares with the abortion controversy the difficulty of finding common grounds on which to establish a conclusion on the moral status of the entities in question, and this may suggest the relevance of finding alternative routes to tackle the issue. However, it can also be noted that relevant disanalogies exist between the abortion context and the discussion on HBOs.

Two main facts characterize HBOs: First, unlike the abortion case, we are dealing not with an organism but with an organ or entity that mimics a human organ; second, the aim of developing HBOs is not to generate a new human individual but to provide an experimental model either for therapeutic goals or for merely scientific reasons. Arguably, therefore, the analogy with abortion may lead us partly astray, in that any moral evaluation on abortion cannot fail to consider the relevance of the result of the generating process, while, in the case of HBOs, there is no living organism that will result from the procedure.

A slightly different analogy may be of some more help: the one with AWT, or ectogenesis, that is, the situation in which pregnancy is carried out entirely outside the woman's body. This situation is more like HBOs, because, in this case, also, we have an entity whose moral status is inherently controversial, which is created and raised entirely in a technological environment, for reasons that—up to now, and for the

foreseeable future—are basically scientific. It is true that some people envisage not-so-far future times when the generation of a new human individual through this process will be a reality[78]; for the moment, however, it seems more sensible to believe that "the promise of a genuine artificial womb remains sci-fi,"[79] and that "complete ectogenesis," that is, a gestation that happens completely outside a woman's body, is not in the offing.

As a matter of fact, those who have recently developed extrauterine supportive systems have insisted on remarking that the goal of such experiments is "not to extend the current limits of viability, but rather to offer the potential for improved outcomes for those infants who are already being routinely resuscitated and cared for in neonatal intensive care units."[80] Further potential applications of these techniques are related to the treatment of fetal growth retardation related to placental insufficiency, the support of preterm infants threatening to deliver after fetal intervention, and, more generally, the advancement of fetal medicine.[81] It seems reasonable, therefore, to reflect on this practice as a merely experimental model.

This creates a potentially illuminating analogy with the case of HBOs: Here, we also deal with the artificial creation in the lab of an entity of uncertain moral status, for purposes of scientific research. As in AWT, and unlike the standard abortion situation, HBOs are not intended—nor do they presently have the potential—to give rise to new human (or human-like) individuals but only to provide a useful model for the study of the human brain and of possible therapeutic strategies.

This may suggest ethical concerns that do not directly hinge on the all-too-intricate topic of moral status but refer to other values that may be at stake in this domain. In the case of AWT, apart from its possible impact on the morality of abortion, the scope of abortion rights, and the safety of the procedure, moral concerns have concentrated on the possible effects of this procedure on other human values, such as those tied to the practice of uterine gestation. It has been noted that AWT may deprive fetuses not gestated in utero of basic psychological experiences that take place during pregnancy. Lacking an early exposure to emotionally laden relationships with their mothers, the psychological and emotional development of fetuses raised through AWT may be impaired.[82]

A relative consideration is women being deprived of the fundamental experience of pregnancy, with relevant consequences on the strength of the mother–child bond, also in later moments; the role played by oxytocin during pregnancy and delivery in promoting maternal behavior has been particularly studied in this area.[83] We could summarize such concerns by saying that AWT may risk "dehumanizing" the practice of gestation, leading to conceiving the child as the sterile output of a mechanical procedure, liable to external, impersonal quality control. This may be true even if we accept that the possibility of "complete ectogenesis" is remote to the full: The mere fact that a human fetus is created and raised in a technological environment for purposes of scientific research may give rise to ethical concerns, although no human being will exist as a result of this procedure.

Something similar may be hypothesized also for HBOs. While these entities are not human organisms but artificially constructed entities resembling a human organ, they may be regarded as more than mere conglomerates of human cells. First, because they are not artificial entities but made up of human neural cells and mimic elements and functions of the most important human organ, the one to which human distinctiveness is most frequently tied. Second, because the possibility that some HBOs can experience negative subjective states, some primitive kinds of emotions, and perhaps even some slight consciousness of themselves ensures that asking whether they should be accorded moral status is at least a meaningful question.

Indeed, it seems reasonable to adopt a precautionary principle regarding HBOs, that is, to err on the liberal side in the attribution of consciousness and therefore to act as if they did in fact have consciousness, lest we inflict harm on sensible entities.[84] As noted by Julian Koplin and Julian Savulescu, "We should not treat brain organoids as mere biological material if they could plausibly be conscious, even if we are not certain whether they possess consciousness."[85]

Acknowledging the possibility of sentience and consciousness, of course, does not amount to providing an answer to the question of their moral status and of its rank (as seen in Section 2); however, it seems to justify the conclusion that treating HBOs as mere clusters of cells risks endangering important values. If HBOs have some forms of sentience, like fetuses in AWT, then they can be harmed during

scientific studies in which they are used. Even if their moral status remains disputable, a disposition to treat HBOs in a merely instrumental manner may express disrespect for the human capacity for sentience and consciousness; although the relevant capacities are likely to be minimal in these entities, such a disposition may convey and reinforce a lack of consideration for the possible harms inflicted to human-like entities with at least a potential for consciousness.

If these concerns can be somewhat traced back to the first set seen above, albeit with different nuances, the analogy with AWT makes it possible to identify a specific set of moral concerns. Indeed, a "technological" pregnancy that is not strictly related to human physiology and all the symbolic practices—albeit varying in different eras and cultures—that accompany the nine months of gestation also risks reinforcing a manipulatory attitude. It can manifest itself concretely toward other human entities with a similar uncertain moral status, such as embryos and fetuses, either in vitro or in the context of AWT. But, in general, it represents a detachment of new living entities from their origin and diminishes sensitivity to their merely instrumental use.

In other words, as in AWT, the fact that no living entity will be the result of the procedures conducted on neural cultures does not remove the moral concerns the performance of these studies may legitimately raise. In particular, as we will highlight below, the use of human material mimicking pregnancy within an inanimate artifact, on the one hand, and an intelligent brain in a hybrid computer, on the other, may raise unease and somewhat weaken the framework of values and principles that protect what is human as something important and to be safeguarded. Such concerns may justify a degree of prudence by ethics committees in approving such studies and the definition of some conditions for their performance.[86,87]

Human Origins of HBOs, Relationships, and Interspecies Hybridization

An HBO is a human entity by genetic makeup that is proving capable of interaction with the environment albeit in a still rudimentary way. A recent experiment showed the ability of groups of neurons connected to an electronic device to learn to play Pong, a first-generation video game, simply by reinforcement and reward mechanisms at the level of electrical impulses.[88] One of the indications of this study (though controversial)[89] is that hybrid devices of carbon and silicon can be very effective tools, capable of performances that digital electronic devices cannot achieve or can achieve only at the great expense of computational capacity. This is because the brain is a sequential processor, whereas computers work in parallel.

It is not a far-fetched prediction to speculate that human brain assemblies connected to more advanced effectors may develop the ability to interact with human individuals even if not consciously, for example, by playing Pong against real opponents or by performing other tasks. In a very recent collective paper, a group of prominent researchers in the field coined the term "organoid intelligence" (OI) "to describe an emerging field aiming to expand the definition of biocomputing toward brain-directed OI computing, i.e., to leverage the self-assembled machinery of 3D human brain cell cultures (brain organoids) to memorize and compute inputs."[90]

New miniaturized instruments and an increase in the size of HBOs will, according to the authors, allow for "novel biocomputing models *via* stimuli-response training and organoid-computer interfaces." In these "complex, networked interfaces … brain organoids are connected with real-world sensors and output devices."[91] They could be faster than current computers in decision-making, display continuous learning during tasks, and have greater energy and data efficiency. In summary, it is a "new frontier in biocomputing and intelligence-in-a-dish."

It is not necessary to consider the possibility of hybrid devices being conscious in order to assess the ethical implications and possible moral concerns of cognitively efficient devices. In fact, purpose-oriented interaction with an entity may generate in the human agent a habit and even an affection toward the entity.

If this entity is an artifact, the instrument can take on a very high emotional and personal value. It ranges from the skis of an amateur hiker to the violin of a professional musician. Of course, very strong bonds are established between human beings and pets. In between are cases such as those recounted in

the movie *Her*, in which the protagonist purchases an operating system that includes a virtual assistant with artificial intelligence, chooses the feminine-voiced AI, and eventually falls in love with the operating system because of the responses he receives in long conversations.[92]

Carbon–silicon hybrid devices are unlikely to have the features of that operating system—in the age of ChatGPT, generative AI is sufficiently developed to make many people fall in love with it—but other applications could enter the daily routine of individuals involved in specific activities. In that case, tools made up of human brain matter, with precise DNA belonging to a living or deceased human being, could be a factor in moral concerns. It is not primarily a concern in this case about the brain organoids involved, which would not be conscious. Rather, it is the emotional reaction of the users—who would be aware that they are interacting with a device that is partly activated by a human "mini-brain" grown from the cells of a donor—that is at stake.

We are faced with partly unprecedented scenarios with which we must reckon leaning on the innate and rationally developed moral sensibility that characterizes us. Cannibalism is not only a strongly blamed practice, but it also arouses instinctive horror in the vast majority of people, even if the body offered as food has ceased to live from natural causes.[93] We know that it is possible to debunk some moral taboos evolution has constructed, showing their ethical irrelevance under rational scrutiny (think of incest without offspring between brother and sister).[94]

However, would it be desirable to propose dating sites aimed at promoting sexual encounters between relatives? Or produce lab-grown human meat to replace intensive livestock farms that make animals suffer and harm the environment? While it may be acknowledged among scholars of philosophy that it is difficult to produce a good argument in favor of banning incest without offspring between brother and sister, this does not mean that all members of society should immediately acquiesce in debunking moral taboos if their persistence does not result in discrimination.

One should remove the taboo of interracial unions as a racist legacy, but there is no urgency to impose moral paternalism in favor of lab-grown human meat if it is ascertained that most people are strongly uncomfortable with this food and prefer not to eat it. The same, therefore, could apply to carbon–silicon devices where the human biological component is relevant. There is no moral argument per se against using lab-grown human cells to improve the performance of an artifact. One can perhaps invoke reasons of dignity and respect in a general sense for what is human in a biological sense.[95] But these arguments seem easily overcome. One could, for example, modify the DNA of cells from which HBOs are grown so that they have a genetic profile different from the donor and from any individual who has ever lived.

The strongest argument remains that of the moral sensitivity of most users, who would have moral concerns in knowing about the commercial and purely instrumental use of complex HBOs. Of course, it is possible that appropriate philosophical pedagogy or simple habit, after initial resistance, might in the long run lead to a reduction in the moral concerns of the scenario hypothesized thus far.[96] In the short and medium term, however, such moral concerns should be taken into account, also in light of those related to interspecies hybridization.

HBOs have been grafted to or transplanted into rodent brains in numerous experiments to ensure vascularization and a more suitable growth environment.[97,98,99] Some recent studies have shown how HBOs transplanted into the brain of a host not only lived a long time and integrated into the brain environment without harming the animal but also integrated structurally and functionally into it while also contributing to the perceptual process.[100] This does not mean for now that human cells have altered or "enhanced" the brain of the host animal, but this possibility cannot be ruled out and, indeed, should be considered likely in light of current scientific knowledge.

As was appropriately pointed out, "chimeric cerebral organoid animals … if somehow 'brain enhanced' … might experience the stress exposure even more seriously than typical experimental animals."[101] The point of interest here, however, is not the protection of animal models used in experiments, which is certainly an issue of great importance. Our interest focuses on the moral concerns that may arise from interspecies hybridization between HBOs and nonhuman animals. While it is certainly true that nonhuman animals that are more sensitive to pain and suffering should not be created, or in any case their use should be minimal and commensurate with the expected utility of their use, we are considering moral concerns related to HBOs.

Such moral concerns might arise from humanizing the chimeras thus created. Could the transplantation of HBOs into higher mammals produce phenomena of thinking typical of humans in such nonhuman animal models that already have strong similarities to human behavior? The hypothesis formulated by Benjamin Capps is not supported by experiments or other scientific evidence as yet, but it serves to formulate an argument for extending protection and rights toward such chimeras.[102]

From our point of view, if an HBO were transplanted into the brain of a nonhuman animal and gave rise to a brain chimera of enhanced cognitive abilities, this might raise moral concerns about its fate even if it did not expand the sentience of the host animal. A companion animal with a more intelligent behavior would undoubtedly be widely requested on the market and this would increase the demand and "production" of these chimeras. We can then ask: what kind of chimera with respect to subjective states would the one thus created be?

On the one hand, it can be argued that it is a better fate for an HBO to be transplanted into the brain of a dog that will be welcomed and loved by someone than to live only a few months in a lab or be destroyed in an experiment. Obviously, a non-sentient HBO has no interests or preferences, but once implanted into a sentient animal, would it somehow become one? On the other hand, one may ask whether it is recommendable that an HBO, although not yet sentient, be transplanted into a nonhuman animal. The considerations made for the biological–electronic hybrids described above apply in this regard, although the contextual conditions are somewhat different. In this sense, it would be preferable to use organoids with modified DNA because they do not resemble in their genetic characteristics any specific individual.

But this expedient may not be enough, and the use of HBOs may end up populating our environment with sentient entities in varying degrees experiencing a different condition than they would have experienced otherwise. This would be due to the insertion in their brains of an HBO, whose fate would remain unknown to us, just as the valence of the altered subjective states of hybridized animals might remain unknown. This uncertainty would seem to configure moral concerns and tilt toward a precautionary principle calling for the avoidance of interspecies hybridization, except with rodents and for specific experiments aimed at the study and treatment of severe diseases.

In the field of biomedical experimentation, the use of chimeras enhanced through the engraftment of HBOs configures a programmatic negative instrumental use of HBOs. In this case, they are considered useful only to make animal models more like sick and suffering individuals and to make them entities to be treated and dissected for the sole purpose of testing their reaction to adverse events.

Conclusion

HBOs are novel living entities that can raise certain sets of moral concerns, in themselves and in relation to the humans with whom they might interact. In this paper, we have identified three sets of moral concerns. The first set of reasons for moral concern regards the potential emergence of sentience/consciousness in HBOs that would endow them with a moral status whose perimeter should be established. The second set of moral concerns has to do with the analogy with AWT. The technical realization of processes that are typically connected to the physiology of the human body can create a manipulatory and instrumental attitude that can undermine the protection of what is human. The third set concerns the new frontier of biocomputing and the creation of chimeras. As far as the new frontier of OI is concerned, it is the close relationship with humans of new interfaces with biological components capable of mimicking memory and cognition that raises ethical issues. As far as chimeras are concerned, it is the humanization of nonhuman animals that is worthy of close moral scrutiny.

As the proponents of OI note, moral attitudes "may depend … on ontological arguments of what constitutes a human being."[103] In this vein, decisions on the ethical permissibility of the laboratory cultivation of HBOs, their transplantation, and their destruction are particularly complex in contrast to what the current lack of specific regulation seems to suggest. In light of the three sets of moral concerns we have identified—in addition to the more classical bioethical topics of informed consent of donors, commercialization, and patentability—a broad involvement of all stakeholders and the public is certainly

desirable in order to create a comprehensive framework. Within this framework, institutional review boards can then make specific choices on each research protocol.

Devising such a framework is a difficult task that requires careful clarification of concepts and procedures and a sensible balance of interests, values, and principles. The whole extended scientific community engaged in the field of HBOs is called to contribute to this effort, together with neuroethicists and other relevant experts, always in dialogue with society and policymakers.

Competing Interest. The authors declare that they have no conflict of interest

Notes

1. Lancaster MA, Renner M, Martin C-A, Wenzel D, Bicknell LS, Hurles ME, et al. Cerebral organoids model human brain development and microcephaly. *Nature* 2013;**501**(7467):373–9.
2. Pacitti D, Privolizzi R, Bax BE. Organs to cells and cells to organoids: The evolution of in vitro central nervous system modelling. *Frontiers in Cellular Neuroscience* 2019;**13**:129.
3. Giandomenico SL, Sutcliffe M, Lancaster MA. Generation and long-term culture of advanced cerebral organoids for studying later stages of neural development. *Nature Protocols* 2021;**16**(2):579–602.
4. Puppo F, Muotri AR. Network and microcircuitry development in human brain organoids. *Biological Psychiatry* 2023;**93**(7):590–3.
5. Chiaradia I, Lancaster MA. Brain organoids for the study of human neurobiology at the interface of in vitro and in vivo. *Nature Neuroscience* 2020;**23**(12):1496–508.
6. Pașca SP. Assembling human brain organoids. *Science* 2019;**363**(6423):126–7.
7. Miura Y, Li MY, Revah O, Yoon SJ, Narazaki G, Pașca SP. Engineering brain assembloids to interrogate human neural circuits. *Nature Protocols* 2022;**17**(1):15–35.
8. Matsui TK, Tsuru Y, Hasegawa K, Kuwako KI. Vascularization of human brain organoids. *Stem Cells* 2021;**39**(8):1017–24.
9. Miura Y, Li MY, Revah O, Yoon SJ, Narazaki G, Pașca SP. Engineering brain assembloids to interrogate human neural circuits. *Nature Protocols* 2022;**17**(1):15–35.
10. Qian X, Nguyen HN, Jacob F, Song H, Ming G. Using brain organoids to understand Zika virus-induced microcephaly. *Development* 2017;**144**(6):952–7.
11. Bubnys A, Tsai LH. Harnessing cerebral organoids for Alzheimer's disease research. *Current Opinion in Neurobiology* 2022;**72**:120–30.
12. Ostermann PN, Schaal H. Human brain organoids to explore SARS-CoV-2-induced effects on the central nervous system. *Reviews in Medical Virology* 2023;**33**:e2430.
13. Ye E, Lee, JE, Lim YS, Yang SH, Park SM. Effect of duty cycles of tumor-treating fields on glioblastoma cells and normal brain organoids. *International Journal of Oncology* 2022;**60**(1):1–12.
14. Raue KD, Duffy JT, Babak MV, Balyasnikova IV. Modeling glioblastoma complexity with organoids for personalized treatments. *Trends in Molecular Medicine* 2023;**29**:282–96. doi:10.1016/j.molmed.2023.01.002.
15. Uzquiano A, Arlotta P. Brain organoids: The quest to decipher human-specific features of brain development. *Current Opinion in Genetics & Development* 2022;**75**;101955.
16. Giandomenico SL, Mierau SB, Gibbons GM, Wenger LMD, Masullo L, Sit T, et al. Cerebral organoids at the air-liquid interface generate diverse nerve tracts with functional output. *Nature Neuroscience* 2019;**22**(4):669–79.
17. Quadrato G, Nguyen T, Macosko EZ, Sherwood JL, Min Yang S, Berger DR, et al. Cell diversity and network dynamics in photosensitive human brain organoids. *Nature* 2017;**545**(7652):48–53.
18. Sakaguchi H, Ozaki Y, Ashida T, Matsubara T, Oishi N, Kihara S, et al. Self-organized synchronous calcium transients in a cultured human neural network derived from cerebral organoids. *Stem Cell Reports* 2019;**13**(3):458–73.

19. Trujillo CA, Gao R, Negraes PD, Gu J, Buchanan J, Preissl S, et al. Complex oscillatory waves emerging from cortical organoids model early human brain network development. *Cell Stem Cell* 2019;**25**(4):558–69.e7.
20. Gabriel E, Albanna W, Pasquini G, Ramani A, Josipovic N, Mariappan A, et al. Human brain organoids assemble functionally integrated bilateral optic cups. *Cell Stem Cell* 2021;**28** (10):1740–57.
21. Lavazza A. 'Consciousnessoids': Clues and insights from human cerebral organoids for the study of consciousness. *Neuroscience of Consciousness* 2021;**2**:niab029.
22. Pereira JRA, Garcia JW, Muotri A. Neural stimulation of brain organoids with dynamic patterns: A sentiomics approach directed to regenerative neuromedicine. *NeuroScience* 2023;**4**(1):31–42.
23. Lavazza A, Massimini M. Cerebral organoids: Ethical issues and consciousness assessment. *Journal of Medical Ethics* 2018;**44**(9):606–10.
24. Lavazza A, Massimini M. Cerebral organoids and consciousness: How far are we willing to go? *Journal of Medical Ethics* 2018;**44**(9):613–4.
25. Farahany NA, Greely HT, Hyman S, Koch C, Grady C, Pașca SP, et al. The ethics of experimenting with human brain tissue. *Nature* 2018;**556**:429–32.
26. Koplin JJ, Savulescu J. Moral limits of brain organoid research. *Journal of Law, Medicine & Ethics* 2019;**47**(4):760–7.
27. Hyun I, Scharf-Deering JC, Lunshof JE. Ethical issues related to brain organoid research. *Brain Research* 2020;**1732**:146653.
28. Lavazza A. Potential ethical problems with human cerebral organoids: Consciousness and moral status of future brains in a dish. *Brain Research* 2021;**1750**:147146.
29. Niikawa T, Hayashi Y, Shepherd J, Sawai T. Human brain organoids and consciousness. *Neuroethics* 2022;**15**(1):1–16.
30. Sawai T, Hayashi Y, Niikawa T, Shepherd J, Thomas E, Lee T, et al. Mapping the ethical issues of brain organoid research and application. *AJOB Neuroscience* 2022;**13**(2):81–94.
31. Lavazza A. Human cerebral organoids and consciousness: A double-edged sword. *Monash Bioethics Review* 2020;**38**(2):105–28.
32. Jeziorski J, Brandt R, Evans JH, Campana W, Kalichman M, Thompson E, et al. Brain organoids, consciousness, ethics and moral status. *Seminars in Cell & Developmental Biology* 2023;**144**:97–102. doi:10.1016/j.semcdb.2022.03.020.
33. Greely HT. Human brain surrogates research: the onrushing ethical dilemma. *The American Journal of Bioethics* 2021;**21**(1):34–45.
34. Haselager DR, Boers SN, Jongsma KR, Vinkers CH, Broekman ML, Bredenoord AL. Breeding brains? Patients' and laymen's perspectives on cerebral organoids. *Regenerative Medicine* 2020;**15** (12):2351–60.
35. Bollinger J, May E, Mathews D, Donowitz M, Sugarman J. Patients' perspectives on the derivation and use of organoids. *Stem Cell Reports* 2021;**16**(8):1874–83.
36. de Jongh D, Massey EK, Bunnik EM. Organoids: A systematic review of ethical issues. *Stem Cell Research & Therapy* 2022;**13**(1):337.
37. Nagel T. What is it like to be a bat? *The Philosophical Review* 1974;**83**(4):435–50.
38. Kriegel U. The value of consciousness. *Analysis* 2019;**79**(3):503–20.
39. Jaworska A, Tannenbaum J. The grounds of moral status. In: Zalta EN, ed. *Stanford Encyclopedia of Philosophy*; 2021; available at https://plato.stanford.edu/archives/spr2021/entries/grounds-moral-status/ (last accessed 1 Mar 2023).
40. See note 22, Pereira et al. 2023.
41. Kagan BJ, Kitchen AC, Tran NT, Habibollahi F, Khajehnejad M, Parker BJ, et al. In vitro neurons learn and exhibit sentience when embodied in a simulated game-world. *Neuron* 2022;**110** (23):3952–69.
42. Birch J, Browning H. Neural organoids and the precautionary principle. *The American Journal of Bioethics* 2021;**21**(1):56–8.

43. See note 23, Lavazza, Massimini 2018.
44. Casali AG, Gosseries O, Rosanova M, Boly M, Sarasso S, Casali KR, et al. A theoretically based index of consciousness independent of sensory processing and behavior. *Science Translational Medicine* 2013;**5**(198):198ra105.
45. Zilio F, Lavazza A. Consciousness in a rotor? Science and ethics of potentially conscious human cerebral organoids. *AJOB Neuroscience* 2023. doi:10.1080/21507740.2023.2173329.
46. Salomons TV, Iannetti GD. Fetal pain and its relevance to abortion policy. *Nature Neuroscience* 2022;**25**:1396–8.
47. Bayne T, Seth AK, Massimini M. Are there islands of awareness? *Trends in Neurosciences* 2020;**43**(1):6–16.
48. Cowan CS, Renner M, De Gennaro M, Gross-Scherf B, Goldblum D, Hou Y, et al. Cell types of the human retina and its organoids at single-cell resolution. *Cell* 2020;**182**(6):1623–40.
49. Lawrence DR, Morley S. Regulating the Tyrell Corporation: The emergence of novel beings. *Cambridge Quarterly of Healthcare Ethics* 2021;**30**(3):421–34.
50. Lavazza A. Human cerebral organoids: Evolving entities and their moral status. In: Dederer HG, Hamburger D, eds. *Brain Organoids in Research and Therapy: Emerging Ethical and Legal Issues*. Cham: Springer; 2022:65–95.
51. Chinaia AA, Lavazza A. Cerebral organoids and biological hybrids as new entities in the moral landscape. *AJOB Neuroscience* 2022;**13**(2):117–9.
52. Lavazza A, Pizzetti FG. Human cerebral organoids as a new legal and ethical challenge. *Journal of Law and the Biosciences* 2020;**7**(1):lsaa005.
53. Birch J, Schnell AK, Clayton NS. Dimensions of animal consciousness. *Trends in Cognitive Sciences* 2020;**24**(10):789–801.
54. Edelman DB, Seth AK. Animal consciousness: A synthetic approach. *Trends in Neurosciences* 2009;**32**(9):476–84.
55. Shepherd J. Ethical (and epistemological) issues regarding consciousness in cerebral organoids. *Journal of Medical Ethics* 2018;**44**(9);611–2.
56. See note 50, Lavazza 2022.
57. Dung L. Why the epistemic objection against using sentience as criterion of moral status is flawed. *Science and Engineering Ethics* 2022;**28**(6):1–15.
58. Danaher J. Welcoming robots into the moral circle: A defence of ethical behaviourism. *Science and Engineering Ethics* 2020;**26**(4):2023–49.
59. Shevlin H. How could we know when a robot was a moral patient? *Cambridge Quarterly of Healthcare Ethics* 2021;**30**(3):459–71.
60. See note 59, Shevlin 2021.
61. Gunkel DJ. No brainer: Why consciousness is neither a necessary nor sufcient condition for AI ethics. In: *AAAI Spring Symposium: Towards Conscious AI systems*; 2019; available at https://ceur-ws.org/Vol-2287/paper9.pdf (last accessed 13 Mar 2023).
62. See note 58, Danaher 2020.
63. See note 57, Dung 2022.
64. Singer P. *Practical Ethics*. 3rd ed. New York: Cambridge University Press; 2011.
65. Nussbaum MC. *Frontiers of Justice: Disability, Nationality, Species Membership*. Cambridge, MA: Harvard University Press; 2006.
66. Levy N. The value of consciousness. *Journal of Consciousness Studies* 2014;**21**(1–2):127–38.
67. Koch C. *The Feeling of Life Itself: Why Consciousness Is Widespread but Can't Be Computed*. Cambridge, MS: The Mit Press; 2019.
68. Dawkins MS. *The Science of Animal Welfare: Understanding What Animals Want*. New York: Oxford University Press; 2021.
69. See note 26, Koplin, Savulescu 2019.
70. Pera MF. Human embryo research and the 14-day rule. *Development* 2017;**144**(11):1923–25.
71. See note 46, Salomons, Iannetti 2022.

72. Melloni L, Mudrik L, Pitts M, Bendtz K, Ferrante O, Gorska U. An adversarial collaboration protocol for testing contrasting predictions of global neuronal workspace and integrated information theory. *PLoS ONE* 2023;**18**(2):e0268577.
73. DeGrazia D. Moral status as a matter of degree? *The Southern Journal of Philosophy* 2008;**46**(2):181–98.
74. Kagan S. *How to Count Animals, More or Less*. New York: Oxford University Press; 2019.
75. Thomson JJ. A defense of abortion. *Philosophy and Public Affairs* 1971;**1**:47—66.
76. Marquis D. Why abortion is immoral. *The Journal of Philosophy* 1989;**86**(4):183–202.
77. Barnhart AJ, Dierickx K. Moving beyond the moral status of organoid-entities. *Bioethics* 2023;**37**(2):103–10.
78. Mychaliska GB. The artificial placenta: Is clinical translation next? *Pediatric Pulmonology* 2016;**51**:557–9.
79. Kingma E, Finn S Neonatal incubator or artificial womb? Distinguishing ectogestation and ectogenesis using the metaphysics of pregnancy. *Bioethics* 2020;**34**:354–63.
80. Partridge EA, Davey MG, Hornick MA, McGovern PE, Mejaddam AY, Vrecenak JD, et al. An extra-uterine system to physiologically support the extreme premature lamb. *Nature Communications* 2017;**8**(1):15112.
81. Segers S. The path toward ectogenesis: Looking beyond the technical challenges. *BMC Medical Ethics* 2021;**22**:59.
82. Sander-Staudt M. Of machine born? A feminist assessment of ectogenesis and artificial wombs. In: Gelfand S, Shook J, eds. *Ectogenesis: Artificial Womb Technology and the Future of Human Reproduction*. Amsterdam: Rodopi; 2006:109–28.
83. Brunton PJ, Russell JA. Endocrine induced changes in brain function during pregnancy. *Brain Research* 2010;**1364**:198–215.
84. See note 29, Niikawa et al. 2022.
85. See note 26, Koplin, Savulescu 2019.
86. See note 26, Koplin, Savulescu 2019.
87. See note 29, Niikawa et al. 2022.
88. See note 41, Kagan et al. 2022.
89. Balci F, Hamed SB, Boraud T, Bouret S, Brochier T, Brun C, et al. A response to claims of emergent intelligence and sentience in a dish. *Neuron* 2023;**111**(5):604–5.
90. Smirnova L, Caffo BS, Gracias DH, Huang Q, Morales Pantoja IE, Tang B, et al. Organoid intelligence (OI): The new frontier in biocomputing and intelligence-in-a-dish. *Frontiers in Science* 2023;**1**:1017235.
91. See note 90, Smirnova et al. 2023.
92. Available at: https://en.wikipedia.org/wiki/Her_(film) (last accessed 1 Mar 2023).
93. Schutt B. *Eat Me: A Natural and Unnatural History of Cannibalism*. London: Profile Books; 2017.
94. Haidt J. The emotional dog and its rational tail: A social intuitionist approach to moral judgment. *Psychological Review* 2001;**108**(4):814–34.
95. Kateb G. *Human dignity*. Cambridge, MA: Harvard University Press; 2014.
96. Inglese S, Lavazza A. Neuroethics as a new kind of scientific anthropology. *AJOB Neuroscience* 2022;**13**(1):40–3.
97. Mansour AA, Gonçalves JT, Bloyd CW, Li H, Fernandes S, Quang D, et al. An in vivo model of functional and vascularized human brain organoids. *Nature Biotechnology* 2018;**36**(5):432–41.
98. Vermaercke B, Bonin V, Vanderhaeghen P. Studying human neural function in vivo at the cellular level: Chasing chimeras? *Cell* 2022;**185**(26):4869–72.
99. Chen HI, Wolf JA, Blue R, Song MM, Moreno JD, Ming GL, et al. Transplantation of human brain organoids: Revisiting the science and ethics of brain chimeras. *Cell Stem Cell* 2019;**25**(4):462–72.
100. Revah O, Gore F, Kelley KW, Andersen J, Sakai N, Chen X, et al. Maturation and circuit integration of transplanted human cortical organoids. *Nature* 2022;**610**(7931):319–26.

101. Bassil K, Horstkötter D. Ethical implications in making use of human cerebral organoids for investigating stress—Related mechanisms and disorders. *Cambridge Quarterly of Healthcare Ethics* 2023. doi:10.1017/S0963180123000038.
102. Capps B. What do chimeras think about? *Cambridge Quarterly of Healthcare Ethics* 2023:1–19. doi:10.1017/S0963180122000780.
103. See note 90, Smirnova et al. 2023.

Cite this article: Lavazza A and Reichlin M (2023). Human Brain Organoids: Why There Can Be Moral Concerns If They Grow Up in the Lab and Are Transplanted or Destroyed. *Cambridge Quarterly of Healthcare Ethics* 32: 582–596, doi:10.1017/S096318012300021X