



# Human cerebral organoids as a new legal and ethical challenge<sup>†</sup>

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## ABSTRACT

Human cerebral organoids (HCOs) are miniature brains cultivated in a dish using pluripotent human cells that, thanks to advanced technologies, tend to reproduce the development path of the brain of an embryo in the mother's uterus. Recent data from studies carried out in different laboratories have indicated that HCOs show complex electrical activity, are receptive to light stimuli, and can command a muscle connected to them. The presence of the main neuronal structures in them suggests that, despite currently lacking vascularization and sensory exchanges with the outside world, more developed HCOs could exhibit some rudimentary form of consciousness, specifically a minimal sentience with respect to the basic experiences of pain and pleasure. Faced with this possibility, which for many scientists is still a long way off, we have begun to reflect on how we could empirically investigate the presence of consciousness. If we were certain or had a reasonable belief that some types of HCOs are sentient, what kind of entity would we judge them to be? Would they have specific legal protection? Should they be attributed to a moral status? This article tries to give an initial answer to these two questions. On the one side, it seems that no special rights can be claimed for HCOs other than those relating to human biological material. On the other side, instead, a sentient HCO could aspire to having its moral status recognized. If this were the case, the law may have to adapt to this unprecedented situation.

**KEYWORDS:** brain activity, consciousness, legal protection, integrated information theory, moral status, personhood, neuroethics

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## WHAT ARE HUMAN CEREBRAL ORGANOIDS?

Even if researchers had long been trying to move from 2D to 3D cellular cultures, the term “organoid” was not used in scientific literature until ten years ago<sup>1</sup>. After the first cases of partial or almost complete growth of some human organs, in 2013, scientists achieved the first three-dimensional culture of an aggregate of human nerve cells guided by the same biochemical process that leads to the formation of the brain during gestation<sup>2</sup>. Over a few years, the cerebral or brain organoids cultivated in different laboratories worldwide have started exhibiting an increasing number of characteristics typical of the human brain. This has attracted the attention not only of neuroscientists and those who could benefit from this discovery—specifically patients and companies active in the biomedical sector—but also of neuroethicists<sup>3</sup>. In this article, besides the ethical aspects of the research on human cerebral organoids (HCOs), we want to also consider the legal and juridical aspects that could soon open up in this regard.

In this section, we wish to provide a sufficiently detailed scientific description of what HCOs are. In fact, we believe that any legal and ethical discussion cannot be conducted without solid and specific factual information on the topic in question. In the case of human cerebral organoids, moreover, this information is even more necessary because they are the result of new and complex biomedical techniques, and some uncommon emerging features of laboratory-grown entities are precisely what require careful legal and ethical scrutiny. Those who are already familiar with organoid biology and the latest literature are welcome to quickly scroll through this section.

So, what is a brain organoid? “A human cerebral organoid is described as a group of cells that dynamically self-organize into structures containing different cell types that resemble some aspects of the fetal brain. Human brain organoids can be used to study early stages of neural development. Neurons in brain organoids can connect and

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- 1 Toshiro Sato, Robert G. Vries, Hugo J. Snippert, Marc van de Wetering, Nick Barker, Daniel E. Stange, Johan H. van Es, Arie Abo, Pekka Kujala, Peter J. Peters, Hans Clevers, *Single Lgr5 Stem Cells Build Crypt-Villus Structures In Vitro without a Mesenchymal Niche*, 459 *NATURE* 262 (2009).
- 2 Madeline A. Lancaster, Magdalena Renner, Carol-Anne Martin, Daniel Wenzel, Louise S. Bicknell, Matthew E. Hurler, Tessa Homfray, Josef M. Penninger, Andrew P. Jackson, Juergen A. Knoblich, *Cerebral Organoids Model Human Brain Development and Microcephaly*, 501 *NATURE* 373 (2013).
- 3 Andrea Lavazza, Marcello Massimini, *Cerebral Organoids: Ethical Issues and Consciousness Assessment*. 44 *J. MED. ETHICS* 606 (2018); Andrea Lavazza, Marcello Massimini, *Cerebral Organoids and Consciousness: How Far Are We Willing To Go?*, 44 *J. MED. ETHICS* 613 (2018); Nita A. Farahany, Henry T. Greely, Steven Hyman, et al., *The Ethics of Experimenting with Human Brain Tissue*, 556 *NATURE*, 429 (2018); Sorin Hostiuc, Mugurel Constantin Rusu, Ionuț Negoii, Paula Perlea, Bogdan Dorobanțu, Eduard Drimaf, *The Moral Status of Cerebral Organoids*, 10 *REGEN. THER.* 118 (2019).

make simplified, organized networks, eventually leading to the developmental steps that all human brains take”<sup>4</sup>. Or, to put it more briefly, “human brain organoids are stem cell-derived 3D tissues that self-assemble into organized structures that resemble the developing human brain”<sup>5</sup>.

Research on the so-called organoids involves pluripotent stem cells (embryonic stem cells and induced pluripotent stem cells) and organ-restricted adult stem cells. Its goal is to obtain three-dimensional models of tissues and organs both for disease modeling (thanks to HCOs it was possible to better understand how the congenital Zika syndrome acts on fetal neurodevelopment, while the first study by Lancaster was aimed at understanding microcephaly) and drug testing (it is possible to test both the toxicity and the effectiveness of new drugs)<sup>6</sup>. A future goal is to obtain portions of brain tissue that can replace (by transplantation) damaged parts of the brain in patients affected by trauma, strokes, or neurological diseases.

Organoids are therefore biological entities produced *in vitro* from stem cells whose differentiation can be oriented towards the typical organization (architecture and physiology) of a human adult organ within a specially prepared environment: usually Matrigel (a mixture of protein from mouse sarcomas) and an adequate scaffolding (made by 3D support matrices). They are placed in a specific broth and in special reactors and are “guided” in their cell differentiation and in their initial development from totipotent stem cells to nerve cells; their subsequent development is autonomous at different degrees based on specific culture. The term “organoid” comes from their being miniaturized and simplified versions of an organ, although often endowed with many of its structural and functional features.

Indeed, the goal for an organoid in a 3D *in vitro* culture is to “replicate not only the complexity of the cell types present in the organ and the processes of self-organization of the tissue, but also the main organization of the whole organ”<sup>7</sup>; as for cerebral organoids, they ought to replicate “the appearance of different brain regions”. The key aspects here are self-assembly and differentiation, which are the outcome of “instructive signaling cues given to the cells by the extracellular matrix (ECM), the medium, and also, once the 3D structure assembles, the cell types present in the organoids themselves”<sup>8</sup>.

Today the term “organoid” is used both for “the isolation and propagation of adult stem cell niches in 3D and for the adoption of 3D culture conditions for the directed differentiation of pluripotent stem cell lines towards specific developing tissues”<sup>9</sup>. The organoids available today reproduce the retina, intestine, kidney, pancreas, liver, inner ear, thyroid, and so forth. But when it comes to ethical issues, the most relevant ones

4 Harpreet Setia, Alysson R. Muotri, *Brain Organoids as a Model System for Human Neurodevelopment and Disease*, SEMIN. CELL DEV. BIOL., Doi: [10.1016/j.semdb.2019.03.002](https://doi.org/10.1016/j.semdb.2019.03.002) (2019).

5 Xuyu Qian, Ha Nam Nguyen, Fadi Jacob, Hongjun Song, Guo-li Ming, *Using Brain Organoids to Understand Zika Virus-Induced Microcephaly*, 144 DEVELOPMENT 952 (2017).

6 Elizabeth Di Lullo, Arnold R. Kriegstein, *The Use of Brain Organoids to Investigate Neural Development and Disease*, 18 NAT. REV. NEUROSCI. 573 (2017).

7 Ida Kelava, Madeline A. Lancaster, *Stem Cell Models of Human Brain Development*, 18 CELL STEM CELL 736 (2016).

8 Meritxell Huch, Juergen A. Knoblich, Matthias P. Lutolf, Alfonso Martinez-Arias, *The Hope and the Hype of Organoid Research*, 144 DEVELOPMENT 938 (2017).

9 Melissa H. Little, *Organoids: A Special Issue*, 144 DEVELOPMENT 935 (2017).

seem to involve brain organoids, which include cerebral organoids and region-specific organoids.

The seminal study in this field was carried out by Lancaster and colleagues, who started with human adult skin cells reprogrammed as induced pluripotent stem cells so as to create a brain organoid as a model for the study of microcephaly. The cells taken from a microcephaly patient were used to form cerebral organoids with characteristics similar to those of the patient's brain. Then, thanks to the identification of a defective protein that is supposed to be related to microcephaly, the researchers replaced it by creating organoids that seemed to be at least partially protected from microcephaly. The study by Lancaster and colleagues has shown distinct and interdependent brain regions with interneural connections and a high level of similarity on a cellular level<sup>10</sup>. In the research, organoids of about 4 mm replicated *in vitro* the development *in vivo* at least up to the late mid-fetal period (19–24 weeks of gestation), with differences in gene expression.

Another successful study was conducted by Qian et al., who have obtained neurons corresponding to all six layers of the cerebral cortex, but without fully developed and stable synapses or circuitry<sup>11</sup>. A further issue, in addition to the underdevelopment of organoids, is the absence of blood vessels. In order to feed internal cells, Lancaster and colleagues encapsulated each organoid into a matrix of nutrients and immersed it in a nutrient bath while the organoids were rotated to assimilate as much food as possible. But, in general, organoids have a nucleus of cells that tend to rot in a short time due to lack of vascularization. Also, they are devoid of surrounding embryonic tissues, glial cells, meninges, and immune cells. Finally, organoid models are also limited by the great variability among organoids and by the absence of a predefined axis.

One way to achieve vascularization of brain organoids has been tested by implanting human cerebral organoids at an early stage of their development into an adult mouse brain. In this way, there was a “fusion” between the host tissues and the human brain organoid, which was able to develop functional neuronal networks and blood vessels in the grafts<sup>12</sup>.

Despite these difficulties, Lancaster and Knoblich have described a protocol for “generating 3D brain tissue (...) which closely mimics the endogenous developmental program. This method can easily be implemented in a standard tissue culture room, and can give rise to developing cerebral cortex, ventral telencephalon, choroid plexus,

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10 Cf. Anca M Paşca, Steven A Sloan, Laura E Clarke, Yuan Tian, Christopher D Makinson, Nina Huber, Chul Hoon Kim, Jin-Young Park, Nancy A O'Rourke, Khoa D Nguyen, Stephen J Smith, John R Huguenard, Daniel H Geschwind, Ben A Barres, Sergiu P Paşca, *Functional Cortical Neurons and Astrocytes from Human Pluripotent Stem Cells in 3D Culture*, 12 NAT. METHODS 671 (2015).

11 Xuyu Qian, Ha Nam Nguyen, Mingxi M. Song, Christopher, Hadiono, Sarah C. Ogden, Christy Hammack, Bing Yao, Gregory R. Hamersky, Fadi Jacob, Chun Zhong, Ki-jun Yoon, William Jeang, Li Lin, Yujing Li, Jai Thakor, Daniel A. Berg, Ce Zhang, Eunchai Kang, Michael Chickering, David Nauen, Cheng-Ying Ho, Zhexiong Wen, Kimberly M. Christian, Pei-Yong Shi, Brady J. Maher, Hao Wu, Peng Jin, Hengli Tang, Hongjun Song, Guo-li Ming, *Brain-Region-Specific Organoids Using Mini-Bioreactors for Modeling Zikv Exposure*, 165 CELL 1238 (2016).

12 Abed AlFatah Mansour, J Tiago Gonçalves, Cooper W Bloyd, Hao Li, Sarah Fernandes, Daphne Quang, Stephen Johnston, Sarah L Parylak, Xin Jin, Fred H Gage, *An In Vivo Model of Functional and Vascularized Human Brain Organoids*, 36 NAT. BIOTECHNOL. 432 (2018).

and retinal identities, among others, within 1-2 months<sup>13</sup>. But there are also layers of cortex, the hippocampus (a crucial area for memory) and the spinal cord. And organoids, according to the authors, can be maintained for more than a year in long-term cultures. Along the same lines, Kelava and Lancaster claim that human pluripotent stem cells can be used to produce “organoids which faithfully recapitulate, on a cell-biological and gene expression level, the early period of human embryonic and fetal brain development”<sup>14</sup>.

In this vein, Birey and colleagues have produced “three-dimensional spheroids from human pluripotent stem cells that resemble either the dorsal or ventral forebrain and contain cortical glutamatergic or GABAergic neurons”, thus recapitulating the saltatory migration of interneurons in the fetal forebrain. They also showed that after migration, interneurons functionally integrate with glutamatergic neurons to form a microphysiological system<sup>15</sup>. And “spheroids cells were remarkably similar to those from corresponding regions of the human fetal brain”, with “both excitatory and inhibitory neuronal activity”<sup>16</sup>.

Although brain organoids still have strong limitations in terms of reproducing an *in vivo* brain *in vitro*, attempts are being made to solve the so-called plumbing and scaffolding problems, that is, how to bring oxygen and nutrients (so as to keep the cells alive) and grow organoids beyond the current millimeter scale. However, it is not to be forgotten that the *in vivo* organs dynamically develop their final form through growth, reorganization, and differentiation of cellular material, which are genetically regulated and in turn regulate themselves epigenetically, depending on the biochemical signals they receive from their surroundings, the activation or deactivation of specific genes. Thus, the so-called mini-brains that grow *in vitro*, isolated from a complete embryo and without interaction with the environment, may not be able to fully develop as happens *in vivo*.

Indeed, since the breakthrough of the first study by Lancaster and colleagues, there has been rapid and considerable progress in the attempt to create HCOs capable of recapitulating the characteristics of the brain; even if, as mentioned, there are still strong limitations, including the absence of vascularization which makes it impossible to nourish the central layers of cerebral organoids<sup>17</sup>. Nevertheless, some important features of the nervous system have recently been observed in brain organoids. HCOs manifest specific and autonomous electrical activity (i.e. communication between neurons) and

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13 Madeline A. Lancaster, Jürgen A. Knoblich, *Generation of Cerebral Organoids from Human Pluripotent Stem Cells*, 9 NAT. PROT. 2329 (2014).

14 *Supra* note 7.

15 Fikri Birey, Jimena Andersen, Christopher D. Makinson, Saiful Islam, Wu Wei, Nina Huber, H. Christina Fan, Kimberly R. Cordes Metzler, Georgia Panagiotakos, Nicholas Thom, Nancy A. O'Rourke, Lars M. Steinmetz, Jonathan A. Bernstein, Joachim Hallmayer, John R. Huguenard, Sergiu P. Pașca, *Assembly of Functionally Integrated Human Forebrain Spheroids*, 545 NATURE 54 (2017).

16 J. Gray Camp, Barbara Treutlein, *Human Development: Advances in Mini-Brain Technology*, 545 NATURE 39 (2017).

17 Cf. Missy T. Pham, Kari M. Pollock, Melanie D. Rose, Whitney A. Cary, Heather R. Stewart, Ping Zhou, Jan A. Nolte, Ben Waldau, *Generation of Human Vascularized Brain Organoids*, 29 NEUROREPORT 588 (2018). Recent studies have shown that this limit could be exceeded.

are sensitive to light stimulation<sup>18</sup> and capable to connect to a spinal cord by sending nerve impulses that make a muscle contract<sup>19</sup>.

A recent study demonstrates for the first time that cortical organoids generated from induced pluripotent stem cells can spontaneously develop periodic and regular oscillatory network electrical activity, which resembles the EEG patterns of preterm babies. This means that, even in the absence of external or subcortical inputs, ten-month-old HCOs can develop according to a specific genetic program, like all human beings, and manifest a complex brain activity. “The spontaneous network formation displayed periodic and regular oscillatory events that were dependent on glutamatergic and GABAergic signaling”<sup>20</sup>. The firing rate, up to two or three per second, and the kind of waves—gamma, alpha, and delta waves—are all a hallmark of a vital human brain. Indeed, a machine-learned model based on a preterm newborn’s EEG features was able to predict the organoid culture’s age based on the electrical activity of the organoid itself.

These are extremely significant steps forward as regards the functionality exhibited by cerebral organoids. It could therefore be deduced that HCOs have the minimum organic capacities to use receptors and effectors and to process the received stimuli and the feedback of the impulses sent, even if this does not mean that this basic processing might take the form of a rudimentary consciousness. Indeed, the judgment of neuroscientists working with cerebral organoids seems to be skeptic about the possibility that current (and future) HCOs are capable to develop a minimal mental life<sup>21</sup>. However, we still know too little about the mechanisms that trigger human consciousness and about the sentience of many nonhuman species to be able to make univocal scientific statements in one direction or another.

On the one hand, for now, HCOs do not grow beyond a very small size compared to an adult human brain; unlike the latter, they lack spatial organization, differ in the number, complexity, and maturity of neurons, do not have the organic feedback typical of an entire organism and do not have any input and output exchange with an external environment. On the other hand, as said, HCOs possess the ability to react to sensory inputs. Also, whole-brain organoids (the only ones dealt with here, as opposed to brain organoids that aim to reconstruct only specific portions of the brain, such as the forebrain or cerebellum) show an electrical activity that is very similar to that of a preterm infant’s brain.

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18 Giorgia Quadrato, Tuan Nguyen, Evan Z. Macosko, John L. Sherwood, Sung Min Yang, Daniel Berger, Natalie Maria, Jorg Scholvin, Melissa Goldman, Justin Kinney, Edward S. Boyden, Jeff Lichtman, Ziv M. Williams, Steven A. McCarroll, Paola Arlotta, *Cell Diversity and Network Dynamics in Photosensitive Human Brain Organoids*, 545 NATURE 48 (2017).

19 Stefano L. Gandenico, Susanna B. Mierau, George M. Gibbons, Lea M. D. Wenger, Laura Masullo, Timothy Sit, Magdalena Sutcliffe, Jerome Boulanger, Marco Tripodi, Emmanuel Derivery, Ole Paulsen, Andrés Lakatos, Madeline A. Lancaster, *Cerebral Organoids at the Air-Liquid Interface Generate Diverse Nerve Tracts with Functional Output*, 22 NAT. NEUROSCI. 669 (2019).

20 Cleber A. Trujillo, Richard Gao, Priscilla D. Negraes, Jing Gu, Justin Buchanan, Sebastian Preissl, Allen Wang, Wei Wu, Gabriel G. Haddad, Isaac A. Chaim, Alain Domissy, Matthieu Vandenberghe, Anna Devor, Gene W. Yeo, Bradley Voytek, Alysson R. Muotri, *Oscillatory Waves Emerging from Cortical Organoids Model Early Human Brain Network Development*. Cell Stem Cell. <https://doi.org/10.1016/j.stem.2019.08.002> (2019).

21 Ian Stevens, *Human Brain Organoids: the Science, the Ethics*, <https://www.neuroethicssociety.org/oxford-meeting-2018> (2018).

Recently, laboratory-cultivated models of the cerebral cortex have exhibited a synchronized neural activity, which is a hallmark of the main brain functions, including memory<sup>22</sup>. Also, the HCOs' neurons fire spontaneously, indicating that even this type of nerve cells grown *in vitro* show the typical activity of human neurons, allowing for the development and creation of new connections.

All this can raise ethical issues that *prima facie* deal with the possibility of creating sentient entities of human origin that could have a moral status. But before addressing this issue, which has already been the subject of some reflections<sup>23</sup>, we want to consider some legal aspects that may instead be completely unprecedented.

### FROM THE LAB TO THE COURT: A HYPOTHETICAL LEGAL SCENARIO

As we have seen, ethical issues concerning HCOs are already on the agenda. The rapid progress of the research could lead, in a relatively short time, to the creation of human cerebral organoids that have a larger size than the current ones, are connected both to sensory receptors and to organic (muscle) or artificial effectors, and manifest a coordinated electrical activity quite similar to that of a newborn's brain, despite the morphological and functional differences mentioned. This being the case, one can hypothesize a scenario that, as we shall see shortly, is certainly imaginative but can be used to introduce very relevant legal issues.

We are aware that discussing the following scenario paradoxically brings us closer to its realization, both because it constitutes a possible suggestion for those who wish to implement it, and because the argument we develop gives plausibility to the issues raised. However, we believe that it is the task of biomedical ethics—and specifically neuroethics in the case in question—to address potential ethical concerns even before the research makes them urgent, if the expected findings are relevant both in themselves and in terms of their impact on society<sup>24</sup>. Yet, discussing potential risks or suggesting caution in conduct does not mean damaging the research or hindering its benefits. In fact, if there are no particularly strong concerns or objections and if the research is carried out according to shared ethical rules of nonmaleficence, beneficence, justice, and autonomy of the subjects involved, one should not introduce obstacles related to prejudice or to preference for the status quo. But this does not exclude that research on HCOs may have potential consequences that have not been sufficiently considered or completely overlooked and that deserve further in-depth evaluation, as we'll explain below.

So, let's come to the hypothetical scenario. Consider a neurobiology laboratory where brain organoids are grown with all the characteristics listed above: as said, the goal of the research is to make them more and more similar to a typical human brain. Indeed, one may well think that a human cerebral organoid shares some relevant

22 Hideya Sakaguchi, Yuki Ozaki, Tomoka Ashida, Takayoshi Matsubara, Naotaka Oishi, Shunsuke Kihara, Jun Takahashi, *Self-Organized Synchronous Calcium Transients in a Cultured Human Neural Network Derived from Cerebral Organoids*, 13 STEM CELL REP. 1 (2019).

23 Megan Munsie, Insoo Hyun, Jeremy Sugarman, *Ethical Issues in Human Organoid and Gastruloid Research*, 144 DEVELOPMENT 942 (2017).

24 Adina Roskies, *Neuroethics*. The Stanford Encyclopedia of Philosophy, E. N. Zalta (ed.), URL = <https://plato.stanford.edu/archives/spr2016/entries/neuroethics/> (2016); Andrea Lavazza, *Neuroethics: A New Framework—From Bioethics to Anthropology*. In: Id. (ed.), FRONTIERS IN NEUROETHICS (2016).

features with a human being and cannot be treated as simple lump of biological material. Now, imagine that a researcher questioned the ethical correctness of such practices, on grounds that the brains thus created might have a glimpse of sentience (understood as the minimal degree of consciousness, i.e. the ability to experience basic phenomenal states such as pain and other sensations related to physical homeostasis, such as lack of vital resources)<sup>25</sup>. This researcher, unable to raise the case inside the laboratory, could go to the local police department or directly to the relevant judicial authority and report the fact that destructive experiments are being carried out on quasi-brains grown in a dish from human tissues.

Such a situation should be considered as totally new and unprecedented. Therefore, it is difficult to foresee the legal framework in which it would be dealt with. Probably in every country, there would be a somehow different procedure for filing such a complaint. In fact, one should wonder in what legislative framework this “complaint” should be placed. Would there be the conditions for some judicial intervention? The fact that brain death has become the criterion to establish a person’s death seems to entail that the brain is the central and (perhaps) identifying organic element of the person also in a legal sense. So, does the existence of human cerebral organoids have any implications about the legal definitions of the beginning and end of life? And if it were established that organoids do have a minimum level of sentience, or that they can experience pain as some animals do, would this have some legal significance?

Potential answers to such highly problematic and sophisticated questions need to consider the current legal framework. In this sense, to answer the question whether there should be some special protection for human brain organoids, broadly understood as vital biological structures of human origin cultivated *in vitro*, we believe that it is useful to discuss how the Italian system (and also the European system, as a superordinate) might address the legal status of human cerebral organoids (albeit with the specificity of each individual legal system). So, on the basis of our specific knowledge of the Italian legal system, which is traditionally very “protective” of human life and is considered rather conservative in terms of bioethics, we will now carry out an analysis of how the Italian law could address the scenario hypothesized above. We will do so in the belief that, despite some secondary differences, the Italian and European legislations and the related jurisprudence can be seen as illustrative of most legal systems of the Western world and also of several countries of other legal traditions.

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25 It is sometimes argued that since there are no pain receptors in the brain itself, an HCO is probably not vulnerable to pain. That may be true but consider the phenomenon of phantom limbs: individuals sometimes report feeling pain in a limb that has been amputated, and that pain is “experienced” in the brain in the absence of any actual peripheral stimulation. Now, it cannot be excluded that the phantom limb phenomenon is possible precisely because there previously *was* peripheral stimulation, something that is impossible in the case of HCOs. Nevertheless, it can be hypothesized that a conscious entity without connections to the external environment may suffer from this “unnatural” condition compared to the normal development of a human brain, even if an HCO would not be aware of the difference between its own situation and that of a human being whose brain is connected to the body. There is a wide debate about the quality of life of people suffering from locked-in syndrome or believed to be in a persistent but actually conscious vegetative state. What we observe in nature is that all living beings tend to avoid environments or situations that are supposed to be distressing for them, so it would be strange if HCOs were the only conscious entities without the ability to experience suffering in a broad sense.



In Italy, as in the rest of Europe (as well as in the U.S.<sup>26</sup>, with the exemption of New Jersey<sup>27</sup>), legal death coincides with the irreversible termination of *all the activities of the brain* (Article 1 of the L. n. 578/1993 (It.))<sup>28</sup>. As the Italian Constitutional Court stated, that criterion should be respectful of both the popular sentiment and the scientific framework, in compliance with the constitutional principles<sup>29</sup>. Now, to be coherent with the fundamental constitutional principles, the legal death criterion chosen by the law must be (in general) respectful of life, unique, robust in its irreversibility, and referred to the extinction of the person as a whole<sup>30</sup>.

In fact, it would go against the essential content of human dignity to have a legal discipline that reduces the human being to one of its constituent parts instead of the whole that ontologically characterizes it, if that part does not perform any essential and irreplaceable function of integration of the different organs and tissues in a “coordinated whole”. On the other hand, however, it cannot be permitted to keep a body in an intensive care unit if this body is only a set of isolated anatomical parts, kept in operation by machines, without any possibility of restoring the systemic unity that creates the person. Such “*ad infinitum*” deferment of the funeral, in fact, would trample the dignity of the deceased, preventing the body to reach the peace of the cemetery at the end of life. Moreover, waiting too long will hinder the possibility of transplanting the organs and tissue “*ex mortuo*”, before necrosis, thus affecting the principle of social solidarity, which underlies the promotion and development of transplantation medicine.

In the light of what is assured by current scientific medical acquisitions, the *irreversible loss of brain function*—as the Italian Constitutional Court affirms—guarantees that the organic unity of the body as an integrated system of anatomic parts is lost forever<sup>31</sup>. Of course, the disappearance of legal personhood after brain death does not mean that the corpse should be considered a simple “object,” deprived of dignity and legal protection. In fact, the corpse and its parts cannot be traded or disposed of as waste and shall be preserved carefully in cemeteries by inhumation, which is specifically regulated by mortuary rules (D.P.R. n. 285/1990 (It.))<sup>32</sup>. Moreover, the

26 Thaddeus M. Pope, *Brain Death and the Law: Hard Cases and Legal Challenges*, 48 HASTINGS CTR. REP. S46 (2019); Winston CHIONG, *Brain Death without Definitions*, 35 HASTINGS CTR. REP., 20 (2005); Robert D. Truog, *Is It Time to Abandon Brain Death?*, 27 HASTINGS CTR. REP., 29 (1997); Thomas Brante, Margareta Hallberg, *Brain or Heart? The Controversy over the Concept of Death*, 21 SOC. STUD. SCI. 389 (1991); Andra le Roux-Kemp, *The Moment of Death: Law, Society and Science*, 29 OBITER 260 (2008); D. Alan Shewmon D.A., *Brain Death: Can It Be Resuscitated?* 39 HASTINGS CTR. REP. 18 (2002); James L. Bernat, Charles M. Culver, Bernard Gert, *On the Definition and Criterion of Death*, 94 ANN. INTERN. MED. 389 (1981); Michael Near Collins, *Death, Brain Death, and the Limits of Science: Why the Whole-Brain Concept of Death is a Flawed Public Policy*, 38 J.L. MED. & ETHICS 667 (2010); Paul S. Rothstein, *Piercing the Veil: The Limits of Brain Death as a Legal Fiction* 32 U. FLA. L. REV. 275 (1979–1980).

27 Michael A. Grodin, *Religious Exemptions: Brain Death and Jewish Law*, 36 J. CHURCH & ST., 357 (1994).

28 For a further analysis of the evolution of Italian legal framework about the definition of death and the related references, see (in Italian) Federico G. Pizzetti, *La morte e la legge. La disciplina sulla definizione di morte e l'accertamento della morte legale dall'Unità d'Italia a oggi (e a domani)*, in STORIA DELLA DEFINIZIONE DI MORTE 391 (F.P. de Ceglia ed., 2014). It should be pointed out here that the (few) references to works in Italian are included for scientific completeness and precision, but they are not decisive for the understanding of the subject we are discussing here.

29 Corte cost., 27 luglio 1995, n. 414, Giur. It. 1996, I, 26 (It.).

30 *Id.*

31 *Id.*

32 Cass., 17 maggio 1971, Riv. pen. 1972, 888 (It.); Cass., 2 febbraio 1960, Giust. pen. 1960, II, 354 (It.).

abuse of a corpse (even in cases of stillbirth, if the fetus has a “human figure”<sup>33</sup>), or the destruction, suppression or hiding of a dead body<sup>34</sup>, or else the use of a cadaver for scientific experiments or teaching without the regular permission are crimes punished by the law (articles 410-413 C.p. (It.)). Now, given that the brain and its complete and irreversible switch-off play a paramount role in ascertaining legal death—that is the extinction of a human legal person, the holder of dignity, rights, and duties—one may be tempted to use the same criterion with human cerebral organoids.

From this point of view, given that there is no specific law that regulates organoids, one may argue as follows. Since the human cerebral organoid presents some neuronal activity, and therefore is not dead according to the brain death criterion used for legal subjects, destroying that organoid would imply to breach the dignity and the rights—first and foremost the right to life—of a legal entity. This argument, however, does not seem robust enough from a legal perspective. In fact, as mentioned, the Italian Constitutional Court plainly affirms that the end point of a “legal person” is only reached with the irreversible loss of an organ which is able “*per se*” to “coordinate” and “integrate” in an organic “unity” all the several and different parts of the “entire human organism”<sup>35</sup>.

Human cerebral organoids do not seem to perform any activity of “coordination” and “integration” of an *entire human person*. As said before, in fact, those organoids are the result of reengineered adult stem cells and are genetically reprogrammed to “recreate” only pieces of neuronal tissues in a Petri dish—not an entire human being. Moreover, the organoids are by no means “*embodied parts*” of a complete human body, nor do they function as factors useful for maintaining the “systemic unity” of the several physical apparatuses of a real human being. Now, one may argue that, in a (remote?) future, cerebral organoids may develop enough as to generate patterns of sophisticated “mental” activity, and might also be connected to some other human bodily components (similar to the embodied human brain)<sup>36</sup>. But, even in this futuristic hypothesis, it remains highly questionable and rebuttable if those organoids will be legally equivalent to the human brain in the light of the *current* (Italian) normative provisions about human legal subjectivity and human legal personhood.

In fact, from a legal point of view, the application of the brain criterion to identify human death presupposes—of course—the legal existence of a human being (body and mind), who was *once* alive. According to article 1 of the Italian Civil Code, legal personhood starts with birth, i.e. with the complete detachment of the newborn from the mother’s womb (if the baby shows at least one vital sign). Moreover, according to

33 Cass., sez. I, 15 giugno 1959, Giust. Pen., 1960, II, 246 (It.) and Cass., sez. II, 2 December 1942, Giust. Pen., 1943, II, 306 (It.).

34 Stefano Biondi, *Property on Bodily Parts, Dignity and Sovereignty: Some Comparative Reflections on the English and Italian Law of Organ Transplantations*, 54 ACTA JUR. HNG. 90 (2013); in general Imogen Jones, *A Grave Offence: Corpse Desecration and the Criminal Law*, 37 LEGAL STUD. 599 (2017).

35 *Supra* note 28.

36 Yvonne Cripps, *The Global Person: Pig- Human Embryos, Personhood, and Precision Medicine*, 25 IND. J. GLOBAL LEGAL STUD. 701, 714 (2018), also quoting Paul Knoepfler, *Human Chimera Research’s Huge (and Thorny) Potential*, WIRED, <https://www.wired.com/2016/09/human-chimera-researchs-huge-thorny-potential/> (Sept. 19, 2016, accessed Aug. 1, 2019).

L. n. 40/2004<sup>37</sup>, the embryo, despite not being “born” yet, is nevertheless also a “legal subject” (though *not* a legal person)<sup>38</sup>: it is vested with human nature and dignity, and therefore holds the rights to life, health, and development.

The Italian and European case-law<sup>39</sup> specify that an embryo should be considered a “human subject”, and *not* merely a “possess”, if (and only if) it contains the “origin of human life”, which means that it must have the “intrinsic” ability to self-develop into a human being<sup>40</sup>. It can be said that a human cerebral organoid is a *never-born* entity: an HCO, in fact, was *not* born from a womb, and is also profoundly *different* from a human embryo. The cerebral organoid, in fact, is the product of sophisticated genetic techniques on *adult* (and not embryonal) stem cells, which does *not* show any aptitude to self-develop into a complete human being. As a conclusion, cerebral organoids cannot be considered, under any legal circumstances, as “subjects” or, *a fortiori*, as “persons.”

Therefore, the destruction of cerebral organoids should *not* be regarded as the suppression of “someone” (*a legal “subject” or a legal “person”: “homo/persona”*). Rather, it shall be legally evaluated as the destruction of “something” (*a legal object: “res”*)—i.e. biological material. Incidentally, it may be also noted that a cerebral organoid *cannot* be treated as the result of human reproductive cloning. So, manipulating organoids is not forbidden under article 3, section 2, letter *d*) EUCFR and under article 1 of the Additional Protocol to the European Convention on Human Rights and Biomedicine on the Prohibition of Cloning Human Beings.

HCOs share the same nuclear genetic set as an individual whose cells have been taken to be reduced at a staminal level. But they are the product of a manipulative technique, which does not end in the creation of a *human being*, genetically identical to the “original” cloned. The result, in fact, is “only” the development of a portion of (neuronal) tissue (we assume here that the rules governing donation, informed consent, conservation of biological material, and any intellectual property rights, which are not the focus of our discussion, are respected.)

37 Gianluca Montanari Vergallo, Simona Zaami, Valerio Bruti, Fabrizio Signore, Enrico Marinelli, *How the Legislation on Medically Assisted Procreation Has Evolved in Italy* 36 MED. & L. 5 (2017); Andrea Boggio, *The Legalisation of Gamete Donation in Italy*, 24 EUR. J. HEALTH L. 85 (2017).

38 Corte cost., 18 February 1975, n. 27, Giur. it. 1975, I, 1416 (It.).

39 E.C.J., 18 December 2014 n. C-364/13, International Stem Cell Corporation, 2014 E.C.R. 2451; Eur. Ct. H.R. 28 May 2013, n. 46470/11, Parrillo v. Italy, 249 Eur. Ct. H.R. (2015); Corte cost., 13 aprile 2016, n. 84, Foro It. 2016, 5, I, 1509.

40 Deryck Beyelle and Roger Brownsword, HUMAN DIGNITY IN BIOETHICS AND BIOLAW 197 (2001); Ali Seyhan Uğurlu, BIOETHICS AND THE PATENT ELIGIBILITY OF HUMAN EMBRYONIC STEM CELLS-RELATED INVENTIONS IN EUROPE 55–71 (2014); Timo Minssen and Ana Nordberg, *The Evolution of the CJEU’s Case Law on Stem Cell Patents: Context, Outcome and Implications of Case C-364/13 International Stem Cell Corporation*, 5 NORDIC INTELL. PROP. L. REV. 493 (2015); Alice Yuen-Ting Wong, Aurélie Mahalatchimy, *Human stem cells patents—Emerging issues and challenges in Europe, United States, China, and Japan* 21 J. WORLD INTELL. PROP. 326 (2018); Daniele D’Alvia and Angelo Vignalis Ferraro, *The (Legal) Qualification of the Embryo and Its Utilization for Scientific Research Purposes under the European Multilevel Protection System of Fundamental Rights*, 26 EUR. REV. PRIVATE L. 421 (2018); Palmer E. Hurst, Christina A. Hurst, *Baby Steps: The European Court of Human Rights Moves Closer to Protecting the Unborn in Parrillo v. Italy*, 2 J. GLOB. JUST. & PUB. POL’Y 155 (2015–2016); Robynson Robbie, *The Legal Nature of the Embryo: Legal Subject or Legal Object*, 21 POTCHEFSTROOM ELEC. L.J. 1 (2018); Amy Lai, *The Possible Impact of Legal Globalization on the ECJ Decision on Human Embryonic Stem Cell Patents and Its Implications*, 50 INT’L LAW. 261 (2016–2017).

All this being said, however, the law should deal with the development of human cerebral organoids, especially if they are to become, in the future, sophisticated sentient entities (and even more so if they are to acquire some conscious capabilities). As is well known, in fact, the law (in Italy and elsewhere) currently protects animals—which are *living but not human entities*, and which do *not have legal personhood*<sup>41</sup>—against torture, cruelty, severe suffering both in clinical and cosmetic trials (Dir. n. 2010/63/UE), and in everyday life (articles 544-ter and 727 C.p. (It.)). Further restrictions were introduced by the legislative decree (n. 26/2014). Such provisions reflect people’s general mercy (public feeling) towards living entities that may suffer distress (even if not consciously). But the same rules also protect the integrity and the well-being of animals (although animals *are not the holders* of rights because they do not have legal subjectivity<sup>42</sup>). From this point of view, therefore, it does not seem unreasonable to promulgate new rules for clinical trials to prevent “suffering” in human cerebral organoids, even if they are neither human legal subjects nor human legal person.

Those limitations should be justified on a double ground. On the one hand, banning the development and use of highly developed organoids is a way to protect the popular sentiment of mercy. Indeed, the public is likely to feel mercy (and to be scared) for those “*quasi-brains*” (developed cerebral organoids), so close to our brains as to have “*human-like*” feelings and emotions (and probably some form of blurred memories), living in laboratories and undergoing several experiments. That mercy, worthy of juridical appreciation, should prevent the realization of highly developed cerebral organoids, understood as entities able to generate “*human-like*” patterns and therefore to feel feelings in the above-mentioned conditions.

On the other hand, banning the development of highly sophisticated cerebral organoids will prevent those entities from severe suffering. Because the scientific and technological research for the promotion and safeguard of human health is a constitutional and European value (articles 9, 32 and 33 Cost. (It.); article 13 EUCFR; article 3 TUE; article 1 of the Convention on Human Rights and Biomedicine), the limitation should be reasonable and proportional. This means that the research on organoids and the development of cerebral organoids for health purposes (diagnosis, treatments) should not be impeded. The limitations should only apply to experiments aimed at “producing” highly developed and sophisticated brain organoids capable of mimicking human superior cognitive functions and human emotional feelings of pain and distress<sup>43</sup>.

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41 See Ani B. Satz, *Animals as Vulnerable Subjects: Beyond Interest-Convergence, Hierarchy, and Property*, 16 ANIMAL LAW 1 (2009); Cass R. Sunstein, *The Rights of Animals: A Very Short Primer*, 30 U. CHICAGO LAW SCHOOL PUBLIC LAW & LEGAL THEORY WORKING PAPERS (2002); Richard A. Epstein, *Animals as Objects, or Subjects, of Rights*, 171 U. CHICAGO LAW & ECONOMICS, OLIN WORKING PAPER (2002); Wendy A. Adams, *Human Subjects and Animal Objects: Animals as ‘Other’ in Law*, 3 J. ANIMAL L. & ETHICS 29 (2009); Richard L. Cupp, *Cognitively Impaired Humans, Intelligent Animals, and Legal Personhood*, 69 FLA. L. REV. 465 (2017); Reed Elizabeth Loder, *Animal Dignity*, 23 ANIMAL L. 1 (2016); Francis X. Shen, *Law and Neuroscience 2.0*, 48 ARIZ. ST. L. J. 1043, 1074–1075 (2017).

42 Cass., sez. III, 28 February 2019, n. 16039, Dir. & Giust. 2019.

43 It might be argued that the law (in Italy or elsewhere) has the power to extend the legal personhood—and therefore all the set of rights related to the legal personhood—to HCOs, even if HCOs cannot be considered as a “human person”. This scenario has some analogies with the ongoing debate about the recognition of a specific legal personhood to IA. For, like HCOs a instantiation of IA cannot be considered as a “human person”. For example, it has been reported that the Kingdom of Saudi Arabia has given “Saudi’s citizenship”—and,

## WHAT MIGHT BE THE MORAL STATUS OF HUMAN CEREBRAL ORGANOID?

The legal system does not seem to give special consideration or protection to human cerebral organoids as such. However, it can be assessed whether HCOs may acquire a moral status at a certain stage of their development and what kind of rights might result from this. It can be said that moral status is the condition by which a certain entity is considered morally as such and not in dependence on other entities<sup>44</sup>. *Status* is the condition of a certain entity within a system of evaluations, while the adjective *moral* specifies the type of relevant evaluations. This is not the same as saying that moral status is the moral value of a certain entity, since entities with the same moral status can have a different moral value.

Moral status is attributed to an entity on the basis of properties and relationships that the entity itself has or manifests, but which do not necessarily depend on the intention or will of the entity and which, on the contrary, may be independent of the entity's ability to have volitions, that is, be attributes related to its constitution as such. In this sense, the fundamental moral status defines the type of rights to which an entity is entitled and the weight of its interests, i.e. the set of appropriate practical and evaluative attitudes that other moral agents must have towards it.

There is a general consensus that only entities that have subjective interests can have a moral status, i.e. entities that can have some kind of subjective experience and can be

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therefore, it has also recognized the legal capacity insofar as the citizenship implies the legal personhood—to an android named “Sophia” (see for an analysis of the case: Federico G. Pizzetti, *The Robot Sophia as a “New Citizen” of Saudi Arabia: What About Granting Legal Personhood, “Citizenship” and Eventually Dignity to Non-Human Entities with Artificial Intelligence?*, 133 NOTIZIE DI POLITEIA 63 (2019)). The European Parliament resolution of February 16, 2017, with recommendations to the Commission on Civil Law Rules on Robotics (2015/2103(INL)), urged the Commission to explore the implications of “creating a specific legal status for robots” and of “applying electronic personality to cases where robots make smart autonomous decisions or otherwise interact with third parties independently”. However, there is a relevant difference between the possible recognition of legal personhood to an android and to HCOs. While a robot is made of inorganic material, HCOs are made of human cells. If HCOs were vested of legal personhood, that insulated part of human tissue, which will never become a human body, would be considered substantively as “equivalent” to a human entity, at least under the point of view of the legal framework. That sort of “equivalence” might raise serious questions; e.g. granting legal personhood to HCOs is, or not, fully consistent with the respect of the fundamental right of human dignity (article 1 of the EUCFR; article 1 of the Convention on Human Right and Biomedicine; article 1 of the UN Universal Declaration of Human Rights; article 2 and 3 Cost. (It.)). Under a specific viewpoint, equating the spare parts of human body to whole human body might represent a “reduction” or a “degradation” of human dignity, as a right is vested uniquely in the human entity “as a whole” (even if that human entity has not yet reached the stage of a human body like the embryos or the fetuses during the pregnancy). As to the possible transformation of the legal concept of personhood based on the evolution of biosciences and informatics, see Visa A.J. Kurki and Tomasz Pietrzykowski (eds), *LEGAL PERSONHOOD: ANIMALS, ARTIFICIAL INTELLIGENCE AND THE UNBORN* (2017); Tomasz Pietrzykowski, *PERSONHOOD BEYOND HUMANISM ANIMALS, CHIMERAS, AUTONOMOUS AGENTS AND THE LAW* (2018); Amedeo Santosuosso, *If the agent is not necessarily a human being. Some legal thoughts*, in *GENETICS, ROBOTICS, LAW, PUNISHMENT* 545–561 (D. Provolo, S. Riondato, F. Yenisey eds., 2014); Woodrow Barfield and Ugo Pagallo, *RESEARCH HANDBOOK ON THE LAW OF ARTIFICIAL INTELLIGENCE* (2018); Gunther Teubner, *Digital Personhood? The Status of Autonomous Software Agents in Private Law*, *ANCILLA IURIS* 107–149 (2018).

44 Agnieszka Jaworska, Julie Tannenbaum, *The Grounds of Moral Status*, *The Stanford Encyclopedia of Philosophy* (Spring 2018 Edition), Edward N. Zalta (ed.), URL = <https://plato.stanford.edu/archives/spr2018/entries/grounds-moral-status/>; Federico Zuolo, *Il problema dello status morale*, 13 APHEX, <http://www.aphex.it/index.php?Temi=557D03012202740321040705777327>.

“wronged”<sup>45</sup>, where being wronged is to be understood in the broadest sense. And the attribution of a certain moral status generally depends on the possession of a certain morally relevant characteristic. If, therefore, we believe that an HCO that proves to have even just the slightest sentience should be a candidate for the recognition of some protection or moral status, we would probably have to follow this formal scheme to reach a solid, though probably not unanimous, conclusion:

- A. To obtain a moral status, it is generally necessary to have some kind of subjective interest, and that is typically to have some kind of subjective experience.
- B. In addition, to obtain a moral status, it is necessary (B1) to possess a certain morally relevant characteristic; or (B2) to be part of a relationship of similarity or biological belonging; or (B3) to be inserted in a network of significant and appropriate relationships (such as recognition, care and respect)—these are the main theories of justification of the attribution of the moral status to an entity.
- C. After having attributed a moral status to an entity not hitherto considered from this point of view, it is necessary to clarify the moral hierarchy in which this entity is placed, what kind of rights it acquires, and what obligations other moral agents have towards it. This must be done, however, bearing in mind that (C1) obtaining a moral status does not in itself imply ownership of specific rights and does not impose specific obligations on other moral agents; and (C2) a moral status can be analytically broken down into (i) a purely evaluative function, which attributes an intrinsic value to the entity in question, and (ii) into a prescriptive function, for which this intrinsic value requires a certain treatment on part of moral agents.

The starting point (A) is therefore sentience: the minimal ability to experience sensations, which can be considered a minimal or basic degree of consciousness, if one believes that consciousness is a property that comes in degrees. For a human cerebral organoid to be attributed a moral status, it should therefore exhibit a minimal or basic form of consciousness. We are developing a moral argument here, but we cannot ignore the epistemological and empirical aspects of ascertaining the possible sentience of an HCO. In this sense, different criteria can be used, always keeping in mind that a human cerebral organoid cannot communicate or give external signals of its condition.

The first criterion that has been proposed concerns a specific theory of consciousness, which is one of the most influential theories in today’s debate. The Integrated Information Theory (IIT) posits two phenomenic axioms that give rise to postulates on the properties of brain mechanisms that support consciousness<sup>46</sup>. The axioms are (i) conscious experience is informative (each conscious experience differs in its specific

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45 Jaworska, Tannenbaum, *supra* note 43.

46 Christof Koch, Marcello Massimini, Melanie Boly, Giulio Tononi, *Neural correlates of consciousness: progress and problems*, 17 NAT. REV. NEUROSCI. 307 (2016); Giulio Tononi, Melanie Boly, Marcello Massimini, Christof Koch, *Integrated Information Theory: From Consciousness to Its Physical Substrate*, 17 NAT. REV. NEUROSCI. 450 (2016); Giulio Tononi, Christof Koch, *The Neural Correlates of Consciousness An Update*, 1124 ANN. NY. ACAD. SCI. 239 (2008); Giulio Tononi, Christof Koch, *Consciousness: Here, There and Everywhere?*, 370

ways from countless other possible experiences); (ii) conscious experience is integrated (every conscious experience cannot be divided into parts). It follows that a system has a subjective experience to the extent that it is capable of integrating information.

This capacity depends on an optimal balance between differentiation (information) and unity (integration), a nontrivial condition for a physical system. On the contrary, at the first sight, it would seem like these two properties are extremely difficult to reconcile. The IIT proposes a theoretical measure (PHI) and empirical metrics to quantify the ability of a system to integrate information.

Based on these aspects of consciousness, an objective measure has been proposed that is a proxy for the presence of consciousness in a living being. The perturbational complexity index (PCI) is a parameter inspired by the main postulate of IIT, namely that consciousness is based on the joint presence of integration and differentiation in the brain. The calculation of the PCI locally involves perturbing the cerebral cortex by transcranial magnetic stimulation (TMS) and measuring the complexity of the electrical response in the rest of the brain by EEG.

The basic idea is that the PCI is low if the interactions between neuronal elements are reduced (loss of integration), because the response induced by TMS is limited in space. The PCI is low even if many connected areas react to the perturbation, but they do so in a stereotyped way (with a loss of differentiation), because in this case the response is wide but not complex. The PCI should only reach high values if the initial disturbance is transmitted to a large network of neuronal elements that react in a differentiated way. As such, the PCI is independent of sensory processing, executive function or motor behavior. For this reason, with specific technologies, it could also be applied to human cerebral organoids<sup>47</sup>.

Another criterion concerns the cerebral correlates of phenomenal experience. There are currently some hypotheses about what areas of the brain are necessary for the

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PHILOS. T. ROY. SOC. B., 20140167 (2015). Giulio Tononi, Olaf Sporns, *Measuring Information Integration*, 4 BMC NEUROSCI. 31 (2003).

47 A reviewer suggested a parallelism between cerebral organoids and artificial intelligence. The suggestion is interesting and in fact IIT allows one to establish a substantial difference between a human brain, capable of giving life to conscious experience, and a computer (see also note 43). As explained by Christoph Koch (*THE FEELING OF LIFE ITSELF: WHY CONSCIOUSNESS IS WIDESPREAD BUT CAN'T BE COMPUTED* [2019]), "intelligence is about doing while experience is about being" (p. 141). Specifically, "the larger the computer, the more obvious its lack of integration owing to its sparse connectivity compared to brains, the lack of internal fan-in and fan-out, its modularity and its serial design" (p. 148). The point is that "two systems can be functionally equivalent, they can compute the same input-output function, but they don't share the same intrinsic cause-effect form" (Ib.). In this sense, a nonsentient machine seems NOT to have a moral status comparable to that of an entity capable of experience. This does not preclude treating nonsentient entities with respect or attributing value to them, whether contingent or absolute, instrumental or intrinsic. For example, an extraordinarily powerful computer capable of implementing an evolved form of artificial intelligence could be the only way to find a vaccine for an unknown and aggressive virus, or it could produce performances capable of arousing emotions just like the unrepeatable masterpieces of art (think of Leonardo's *Mona Lisa*). There would probably be moral disagreement about the priority to be given to the protection of such a machine over sentient entities such as an HCO in an advanced stage of development or a fetus, but also an adult human being. A consequentialist ethical perspective would assess the likely effects of any choice in this respect, while a Kantian deontological approach such as that set out in this paper would give priority to sentient entities capable of experience (and moral autonomy), considered valuable in themselves and not subordinate to others.

appearance of consciousness<sup>48</sup>. In our case, applying an inductive criterion, the presence of these areas in a developed and active form could be considered a proxy for the onset of consciousness in HCOs, despite their lack of a direct exchange with the external environment. Indicators and criteria concerning functional aspects have recently been listed to discern the presence of consciousness in animals and intelligent machines<sup>49</sup>, but they are difficult to test in cerebral organoids<sup>50</sup>.

It is also necessary to make a further specification so that the consolidated analytical-conceptual and empirical process of attributing moral status to a living being can be made suitable for the case of human brain organoids. In general, for most of the cases dealt with in the moral field, it is not in dispute whether the living being in question is sentient. In these cases, it makes sense that the characteristic (B1) by which the being can be granted a moral status is phenomenal consciousness, that is, the unique and specific ability of every individual to have conscious experiences, such that no one else can have those same experiences. From this condition, one can deduce the inviolable dignity of that living being (see below).

For human cerebral organoids, however, the minimal ability to experience sensations (A) cannot be taken for granted: on the contrary, the initial presumption is the exact opposite, since HCOs are one-fifth of an inch across, have some millions of neurons instead of billions, and only few cell types out of 100,000. Therefore, firstly it must be shown that HCOs are potential candidates for a moral status and, once this condition (A) has been ascertained, it is then possible to proceed to identify possible criteria that make them eligible for a moral status. In the case of organoids, one of the criteria—(B1)—may be the presence of a certain degree of consciousness, probably higher—although to be quantified, with all the difficulties involved—than the minimum degree that is the precondition (A) for obtaining a moral status.

According to (B), to obtain a moral status, it is necessary (B1) to possess a certain morally relevant characteristic or (B2) to be part of a relationship of similarity or biological belonging. According to (B1), it is plausible to think that if a human cerebral organoid developed at least some form of consciousness (sentience), it would have a dignity that we do not acknowledge in inanimate objects. Here we are following Kriegel's argument<sup>51</sup>. Dignity can be considered not to be a primary and essential attribute, in the sense that there is no explanation why it is attached to some entities but not others. In fact, it seems legitimate to believe that things have specific empirical properties underlying their dignity, which may be nonevaluative genetic, psychological, or other empirical properties. In general, we believe that we have obligations towards people and not towards rocks, and this must have to do with the factual differences between people and rocks.

48 Todd E. Feinberg, Jon Mallatt. *The Nature of Primary Consciousness. A New Synthesis*, 43 CONSCIOUS. COGN. 113 (2016).

49 Cyriel Pennartz, Michele Farisco, Kathinka Evers, *Indicators and Criteria of Consciousness in Animals and Intelligent Machines: An Inside-Out Approach*, 13 FRONT. SYST. NEUROSCI. (2019).

50 Cf. Matthew Owen, Mihretu P. Guta, *Physically Sufficient Neural Mechanisms of Consciousness*, 13 FRONT. SYST. NEUROSCI. (2019).

51 Uriah Kriegel, *Dignity and the Phenomenology of Recognition-Respect*, in John J. Drummond and Sonia Rinofner-Kreidl (eds.), *EMOTIONAL EXPERIENCE: ETHICAL AND SOCIAL SIGNIFICANCE* (2017); Uriah Kriegel, *The Value of Consciousness*, 79 ANALYSIS 503 (2019).



Kriegel argues that the basis of dignity is exactly phenomenal consciousness. In his words, “to describe someone as having dignity is to ascribe to her a certain inviolability; and such inviolability attaches to conscious creatures precisely in virtue of the fact that the conscious experiences of each conscious creature can only be experienced by them. I can know about your sadness, and through empathy I may even experience a token sadness type-identical to your token sadness; but I cannot feel your token sadness. On the emerging view, an entity exacts respect and merits treatment as an end just if it is a phenomenally conscious creature”<sup>52</sup>.

One could argue that HCOs do not and will not have the phenomenal complexity that comes with sadness. But Kriegel himself specifies that the ‘phenomenally grounded dignity’ approach “entails that we have duties towards not only human beings but all conscious beings, including nonhuman conscious animals: these animals ought to be treated as ends, quite independently of the hedonic quality of their lives”<sup>53</sup>. Therefore, ‘phenomenally grounded dignity’ could also be attributed to HCOs that manifest a minimal degree of phenomenal consciousness.

However, if we introduce a gradation of value with respect to the level of consciousness possessed by the entity under consideration, this affects the attribution of moral status. A basic awareness is not enough to confer a full moral status according to Hyun<sup>54</sup>, for whom full moral status is conferred to human self-consciousness, understood as a kind of higher order mental awareness of one’s own mental experiences. And this type of higher order mental awareness requires language in the form in which human beings developed it.

Another objection to phenomenally grounded dignity may be that often a Kantian perspective is adopted according to which dignity is linked to the ability of rational beings to set ends and goals. But, Kriegel replies, can an unconscious automaton be a rational end-setting being? If it cannot, then it seems that the rational end-setting status implies consciousness. If it can, instead, we must consider that we have no particular reason to treat an unconscious automaton as an end and not as a means. A domestic robot may soon be able to set its own goals in all of its activities, but we would probably not treat it as a person, because it lacks consciousness. And so we are back to phenomenally grounded dignity<sup>55</sup>.

In accordance with criterion (B1), i.e. the idea that the allocation of moral status depends solely on the morally relevant characteristics possessed by an entity, the idea that sentience or a minimal form of consciousness can confer moral status on HCOs falls within the so-called moral individualism. According to the latter, the mere ability to experience pleasure and pain is considered a morally relevant quality, for example by Singer<sup>56</sup>, although more complex cognitive abilities, self-awareness, rationality and moral autonomy are considered by other authors as preferable characteristics to indicate full moral status.

The strength of approaches to moral status that fall within moral individualism lies in the fact that they are generally consistent with current scientific knowledge, because

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52 Kriegel 2019, *supra* note 43.

53 *Ib.*

54 Insoo Hyun, *BIOETHICS AND THE FUTURE OF STEM CELL RESEARCH* (2013).

55 Kriegel, *supra* note 43.

56 Peter Singer, *PRACTICAL ETHICS* (1993).

they are based on the entities' possession of natural properties or properties that can be traced back to natural properties, which can be ascertained by objective means. From a conceptual point of view, moral individualism offers an impartial view. The justification of the attribution of moral status is in fact conducted by first identifying the morally relevant characteristics (sentience, rationality, and autonomy), independently of the subjects carrying these characteristics (human beings, nonhuman animals, chimeras, and human cerebral organoids) and then by defining the circle of subjects endowed with these characteristics.

A problematic aspect that also involves our test on the moral status of HCOs is that of the threshold. If morally relevant characteristics are natural properties owned by individuals to varying degrees, one may ask whether the basic possession of these characteristics is enough to attribute a certain moral status or whether it is necessary to have these properties to a specific degree. In the second case, a relevant threshold should be set. Yet this may raise an objection: a theory that attributes a moral status to all beings capable of minimal sensitivity (for example, HCOs) must admit that moral status is a progressive property and that there are differences between the moral status of entities (e.g. an adult human being and an organoid) that reflect their differences in terms of basic properties.

We have seen that (B) can be formulated as a disjunction. But it is interesting to note that this stems from the fact that the debate on moral status has so far revolved essentially around the theme of its extension to other living species and only recently to human-animal chimeras. The particularity of human cerebral organoids is that they are entities with characteristics still subject to both empirical and theoretical investigation. That said, HCOs could also fall into (B2), as they biologically belong to the human species. The theories of moral status based on the species attribute value to the individuals who belong to a species, usually *Homo sapiens*.

The main line of (B2) is in fact called humanism, according to which the notion of species is not purely biological, but is rather a structurally moralized notion, inherent to our being, so much so that our preference for co-specifics is natural and not further explainable<sup>57</sup>. Furthermore, it is argued that morally relevant properties cannot have value regardless of our act of conferring value. And only human beings can create moral value<sup>58</sup> (although this in itself does not exclude that human beings may attribute value to other entities). Finally, human individuals acquire value because they are potentially able to achieve a certain genus-specific condition, which is based on a typical representative of the species. In this sense, it is in the proper and substantial nature of human beings to be endowed with full moral status, even when a specific individual lacks the abilities that give rise to a moral personality<sup>59</sup>. Obviously, this argument is used for embryos and, as we know, there is strong disagreement about its validity. It would seem even more controversial to extend it to HCOs, even if they showed a minimal level of consciousness.

The criteria used by species-based theories of moral status are the subject of strong criticism for their alleged speciesism, both for their formal circularity in the justification

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57 Mary Midgley, *ANIMALS AND WHY THEY MATTER* (1983)

58 Bernard Williams, *The Human Prejudice*, in Id., *PHILOSOPHY AS A HUMANISTIC DISCIPLINE* (2006).

59 Patrick Lee, Robert P. George, *The Nature and Basis of Human Dignity*, 21 *RATIO JURIS* 173 (2008).

of the attribution of moral status and for positive prejudice to the human species. However, given the particularity of HCOs that we have already underlined, these criticisms do not apply here, since HCOs are entities of their own kind that could fall into both (B1) and (B2). The only possible criticism to the attribution of a moral status to sentient HCOs with respect to (B2) is that related to the typical individual. A cerebral organoid cannot develop, not even potentially, into a “complete” individual, and therefore attributing a moral status to it should be based on an objective criterion (phenomenal consciousness) rather than on its species. One could, however, reply that the technical and nonnatural potential of an HCO comes with the prospect of a transplant, thanks to which it can become the brain of a person. However, head or brain transplantation does not seem feasible or desirable for various reasons<sup>60</sup>.

As for (B3), it seems plausible to affirm that a sentient HCO could not enter into any relationship, not even as the passive object of one. This instead can easily happen to an individual who has entered a persistent vegetative state, or an individual born with very serious cognitive deficits, as relatives, friends or even strangers can develop relationships of respect, care and recognition with such individuals.

Let’s move on to (C). If a moral status were attributed to an entity such as an HCO with some form of minimal conscience, it would be necessary to clarify the moral hierarchy in which it would be placed, what kind of rights it would acquire and what obligations would other moral agents have towards it with respect to the treatment to be reserved to it. In this sense, it could be said that in principle a human brain organoid with a rudimentary form of sensitivity, i.e. the ability to experience something in phenomenal sense, should have a moral status, if not full at least partial. However, for empirical reasons, whether this capacity for experience is present will probably remain uncertain for a long time.

This “gray area” also includes the debate on the moral status and the treatment to be reserved to human-animal chimeras. With regard to human-pig chimeras and their alleged cognitive abilities beyond those of regular, nonchimeric pigs created for the purpose of research or transplantation, Savulescu proposed the following argument. “In the absence of conclusive research on these questions, any such chimera should be accorded the highest moral status consistent with its likely nature (. . .) If it could plausibly have higher cognitive functions, it should be treated as if it would have them. In considering the new life forms we create we should err on the side of sympathy and generosity”<sup>61</sup>. Other authors defended the idea that if we have no certainty about some being’s moral status, we should treat it as if it had at least a partial moral status, a perspective that refers particularly to animals<sup>62</sup>.

In a similar vein, Koplín and Wilkinson have recently proposed a Moral Status Precautionary Principle (MSPP), according to which “a course of action should not

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60 Mirko Daniel Garasic, Andrea Lavazza, *Why HEAVEN Is Not About Saving Lives at All*, 8 *AJOB NEUROSCIENCE* 228 (2017).

61 Julian Savulescu, *Should a Human-Pig Chimera Be Treated as a Person?*, *AEON* (2016) <https://aeon.co/ideas/should-a-human-pig-chimera-be-treated-as-a-person>.

62 R. Harry Bradshaw, *Consciousness in Non-Human Animals: Adopting the Precautionary Principle* 5 *J. CONSCIOUS. STUD.* 108 (1998); Simon Knutsson, Christian Munthe, *A Virtue of Precaution Regarding the Moral Status of Animals with Uncertain Sentience*, 30 *J. AGRIC. ENVIRON. ETHICS* 213 (2017); Jeff Sebo, *The Moral Problem of Other Minds*, 25 *HARV. REV. PHILOS.* 51 (2018).

be pursued if there is a reasonable fear that the course of action will cause serious harm to beings of full moral status, even if there is nonconclusive evidence that the being will actually have full moral status”<sup>63</sup>.

In a crescendo of protections, once their moral status is recognized, one might think that (1) whole human brain organoids should not be created with harmful genetic alterations (which would prevent the creation of models for the study of pathologies, but the latter could be studied on organoids of specific parts of the brain, not sentient); (2) HCOs should be sedated during invasive or destructive experiments (although it is difficult to imagine the conditions causing distress to a sentient organ, and a sedated organ may be scientifically useless); (3) HCOs should be studied only observatively and preserved until their natural death; (4) HCOs should not be developed beyond a certain period of time, so as to prevent the onset of forms of sentience.

One could argue that research on HCOs could lead to the discovery of therapies or to the laboratory growth of brain parts suitable for treating severely debilitating and or even fatal neurodegenerative diseases such as Alzheimer’s. It could also be pointed out that sentient animals are being used in laboratories, albeit with increasing care for their well-being. In the case of life-saving research, if none of the protections suggested above could be granted, one could apply a principle such as that formulated by Koplin and Wilkinson, namely “Moral status non alternative principle” (MSNAP). According to it, “a course of action may be pursued if there is a reasonable fear that the course of action will cause serious harm to beings of full moral status, *only* if there is no alternative course of action that would achieve the same benefit without any risk of serious harm to beings with full moral status”<sup>64</sup>.

In fact, it is plausible to think that there would be consensus in using HCOs, even if they were minimally sentient, in research that could save individuals and prevent them from losing their autonomy and rationality. In this case, however, one may wonder what the attribution of moral status serves for if it can justify such a variable value and such a different array of moral treatments. Moral status would appear to be a mere label of moral consideration of some kind, the weight and regulatory implications of which must however be determined by the degree of morally relevant properties based on which the moral status is granted<sup>65</sup>.

Koplin and Savulescu have very recently proposed to make the use of HCOs proportionate to the importance of the research purposes or the expected benefits of the research results<sup>66</sup>. This view implies the lawfulness of using both “conscious or potentially conscious brain organoids (equivalent to 20 weeks’ *in vivo* brain development or more)” and “brain organoids with the potential to develop advanced cognitive capacities (e.g., mature brain organoids capable of interacting with the outside environment).” This framework to regulate the use of HCOs capable of developing higher consciousness and cognitive abilities is based on a consequentialist perspective that seems to make room for a limited exploitation of human cerebral organoids in exchange for great expected benefits related to biomedical research.

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63 Julian Koplin, Dominic Wilkinson, *Moral Uncertainty and the Farming of Human-Pig Chimeras*, 45 J. MED. ETHICS 440 (2019).

64 *Id.*

65 Zuolo, *supra* note 43.

66 Julian Koplin, Julian Savulescu, *Moral Limits of Brain Organoid Research*, 47 J. LAW MED. ETHICS, 760 (2019).

Finally, one can consider the so-called indirect perspective with respect to moral status, a perspective that could find the consensus of those who do not want to engage in the procedure of attributing moral status to a new entity. This view imposes certain obligations towards specific entities, not because the entities in question have their own moral status, but because the moral entities that have relations with them have general obligations, such as, for example, not to cause unnecessary suffering or to respect everything related to the human being. In this context, it could be claimed that HCOs with a basic form of sentience might not have their own moral status, but it would still be advisable neither to create them nor, above all, to use them in destructive experiments. Obviously, from the indirect perspective, different obligations on the part of moral agents can be weighed up. And the obligation to seek treatment for serious diseases that afflict many human beings could prevail over the obligation not to cause unnecessary suffering to entities that do not have a full moral status.

To sum up, ethical reflection on HCOs is only in its infancy and the proposals put forward so far are necessarily provisional, scattered along a continuum calling for very different kinds of regulations. However, on the basis of the arguments developed here about the possible moral status of human cerebral organoids, it seems reasonable to suggest that researchers engaged in the cultivation of HCOs should try to develop or implement tools and techniques able to evaluate the presence of a degree of consciousness in human cerebral organoids themselves. Based on that potential evidence, an expanded ethical discussion should be opened in which to consider the implications of an absolute novelty such as a human brain isolated from body and environment. Our general idea is that HCOs that manifest an ability to feel pain and have subjective experiences should not be used as mere laboratory tools, whatever the possible benefits of utilizing them for research. Our position is more restrictive than most, but it's consistent with a Kantian-like deontological approach, although we are aware that without communications it will be extremely difficult to assess how conscious human cerebral organoids may be.

## CONCLUSION

Rapid progress in research on human organoids and on human cerebral organoids in particular has led to the laboratory growth of the so-called mini-brains that have *in nuce* most of the structures and functions typical of a normally developed human brain. It is therefore not implausible to think that in the not-too-distant future some HCOs may develop a rudimentary form of sentience understood as the minimal form of consciousness related to the basic experience of pleasure and pain that characterizes many animal species.

This may raise ethical and legal questions, which are indeed beginning to be the focus of reflection on the general theme of the production of human organs in a dish<sup>67</sup>. Since the broad ethical aspects of the issue have already been partially addressed<sup>68</sup>, in this article, we started by dealing with the topic, unprecedented to our knowledge, of the legal provisions that might be required regarding the production of HCOs suspected of having a rudimentary form of phenomenal consciousness.

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67 Jeremy Sugarman, Annelien Bredenoord, *Reflections on Organoid Ethics*, 24 CELL STEM CELL 849 (2019).

68 Cf. *supra* note 3

Our analysis is based on Italian law and European law as a superordinate system. This is a legislative and legal architecture comparable to that of most Western countries and that, given the potential conclusion of this analysis, has the advantage of being traditionally “conservative” in terms of bioethics. Based on the current legislation and jurisdictional rulings, it must in fact be concluded that HCOs have no right to any special legal protection, as they do not fall into any category other than that of biological material, which is subject to its own specific rules.

The second part of our analysis then focused on the possible moral status that future HCOs—sentient or potentially sentient—could obtain based on their scientific characterization and the ethical categories on which there is most consensus. The result seems to be that HCOs would have at least partial moral status. This conclusion implies the attribution of a progressive set of rights (translated into duties of the researchers who manipulate them) to such future HCOs, on the grounds that they would be sensitive entities. This is not a widely accepted conclusion, but it can be considered fully consistent with the main perspectives on the attribution of moral status and its justification.

This suggests that the legal system may also be called upon in the future to consider the evidence about the supposed phenomenal consciousness of HCOs and the consequences of attributing them a moral status of some kind. These considerations therefore call for ethical and juridical research. The recent discovery of a complex cerebral electrical activity in human cerebral organoids requires careful evaluation of the unexpected development that they exhibit<sup>69</sup>. So, further reflections ought to be elaborated in the face of the rapid progress of scientific research, its technical translation, and its clinical applications.

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69 *Supra* note 20.