



Beyond consciousness: Ethical, legal, and social issues in human brain organoid research and application

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ABSTRACT

This study aims to provide a comprehensive review of the ethical, legal and social issues in human brain organoid research, with a view to different types of research and applications: *in vitro* research, transplantation into non-human animals, and biocomputing. Despite the academic and societal attention on the possibility that human brain organoids may be conscious, we have identified diverse issues in human brain organoid research and applications. To guide the complex terrain of human brain organoid research and applications, a multidisciplinary approach that integrates ethical, legal, and social perspectives is essential.

1. Introduction

Human brain organoids (HBOs) are three-dimensional brain tissues cultured from human stem cells. These organoids mimic the developmental trajectories, cellular composition, neural circuits, and anatomical structures of the *in vivo* human brain (Seto and Eiraku, 2019). HBOs are produced using two primary types of stem cells: pluripotent stem cells (PSCs), including embryonic stem cells (ESCs) from blastocysts and induced pluripotent stem cells (iPSCs) from somatic cells, or tissue stem cells (TSCs). The first HBOs developed from PSCs appeared in 2008 (Eiraku et al., 2008) and were named 'cerebral organoids' in 2013 (Lancaster et al., 2013). HBOs from TSCs, termed 'foetal brain organoids' (FeBOs), were first reported in 2024 (Hendriks et al., 2024).

There are various types of HBOs. While some HBOs are "unguided", meaning they differentiate autonomously and recapitulate multiple regions of the brain (Lancaster et al., 2013), many studies create region-specific HBOs by guiding their developments with necessary

signals at each stage (Qian et al., 2018). Region-specific HBOs can further be assembled with other subtypes of organoids to create "assembloids" (Kanton and Paşca, 2022). Some create assembloids by fusing multiple region-specific HBOs (Bagley et al., 2017; Birey et al., 2017; Xiang et al., 2017), while others fuse HBOs with organoids of other organs, such as muscle or retina (Andersen et al., 2020; Fligor et al., 2021). While a single HBO or assembloid is typically created from materials of a single donor, some HBOs are created from the cells of multiple donors (Antón-Bolaños et al., 2024). Finally, many studies are creating disease models by deriving HBOs from iPSCs of donors with certain neurological diseases, including microcephaly, Alzheimer's disease, or Timothy syndrome (Eichmüller and Knoblich, 2022).

A key challenge in HBO research is circumventing the structural immaturity of organoids, particularly the lack of vasculature, sensory feedback, and functional neural circuits (Seto and Eiraku, 2019). Assembloids provide a potential solution to these limitations. Another approach is to transplant HBOs into host animals to facilitate oxygen and

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nutrient delivery, and accelerate waste removal. Efforts are also underway to develop HBOs with vascular structures (Sato et al., 2023).

Developmental biologists, regenerative medicine experts contemplating human transplantation, and engineers who interface HBOs with computational systems are contributing to the field.

Since 2018, HBO transplantation into host animals has become a pioneering approach. The first intervention involved integrating HBOs into a mouse cerebrum to assess organoid viability (Mansour et al., 2018). The HBOs maintained their viability, underwent vascularisation, and exhibited significant axonal growth. Another study showed that HBO transplantation into the mouse brain leads to superior survival and differentiation outcomes compared with transplanted neural progenitors (Daviaud et al., 2018). By 2020, transplantation had been extended to cynomolgus monkeys, demonstrating axonal extension in harmony with the host brain structures (Kitahara et al., 2020). More recently, the optogenetic activation of transplanted organoids modified reward-seeking behaviour in host rats, showing behavioural-level integration with the rat brain (Revah et al., 2022). Transplantation of HBOs has the potential to restore impaired neurological function in host animals, including motor function in rats (Wang et al., 2020), learning and short-term memory in mice (Bao et al., 2021), and the damaged visual cortex of adult rats (Jgamadze et al., 2023).

An advance in HBO research would be its intersection with biocomputing, integrating cultured human neurons and computational systems. Kagan et al. (2022) developed a system using neural cells derived from human iPSCs connecting to a computer via microelectrode arrays. This system, called *DishBrain*, could play a simplified version of the computer game *Pong*, learning to optimise ball return through feedback. *DishBrain* is a type of system called ‘Synthetic biological intelligence’ (SBI), which combines biological and silicon components to achieve intelligent behaviour (Kagan et al., 2023a). SBI systems are expected to outperform traditional silicon-based computing in terms of efficiency while consuming less energy (Smirnova et al., 2023). Given the significant energy demands of current artificial intelligence (AI) technologies (Strubell et al., 2019), SBI technology has the potential to mitigate energy consumption (Kagan et al., 2023a).

Smirnova et al. (2023) have introduced a similar concept of ‘Organoid intelligence’ (OI), which can be regarded as a subset of SBI, as it specifically assumes HBOs as the biological components to create intelligent systems.¹ As we understand it, OI still lacks proof of concept. *DishBrain* is not an OI system, as it does not use organoids, but rather neurons without tissue organisation. However, the realisation of OI is expected soon. Advances in microelectrode arrays, which are suitable for monitoring activity within organoids, are progressing rapidly. A recent study demonstrates that a system incorporating HBOs can identify individual voices among multiple speakers (Cai et al., 2023). Most recently, a Swiss company is developing bio-processors that incorporate sixteen HBOs (Jordan et al., 2024). Therefore, it is beneficial to include the discussion about SBI that *DishBrain* has sparked in this paper to consider the normative issues of the near-future application of HBOs in OI technology.

With rapid advancements in HBO research and its intersection with biocomputing, ethical discourse has intensified. This scrutiny and media attention highlight the complexity of navigating scientific progress and ethical considerations (Ide et al., 2021; de Jongh et al., 2022; Presley et al., 2022). Ethical concerns in HBO research have primarily revolved around the possibility of organoids developing consciousness, and the ethical implications of enhancing chimeric animals with HBO. However, recent scientific development is broadening these concerns. Ethical examination of HBO research has proliferated in academic journals,

¹ In fact, the precise meanings of the term “SBI” and “OI” are not completely clear, partly due to the ambiguity of “intelligence” (see Section 4–2). In the relevant passages in this paper, we will tentatively use “SBI” out of respect for the terminology of the developers’ of *DishBrain*.

highlighting various challenges and underscoring the need for continued exploration (Ding et al., 2022). The ethical dimensions associated with HBO research intersect with broader societal and legal concerns, necessitating a nuanced discussion for each domain.

This study comprehensively identifies the ethical, legal, and social issues (ELSI) associated with HBO research and its applications, based on the current discourse. The novelty of this work lies in offering the first extensive review of the diverse debates across three areas of HBO research: *in vitro* research, transplantation, and applications in biocomputing (Sawai et al., 2022; Ishida and Sawai, 2024). We distinguish ethical and social issues as those intrinsic to research processes and those arising from the intersection of established knowledge with societal contexts (Douglas and Savulescu, 2010).

2. Ethical issues

2.1. Moral status of HBOs

The moral status of HBOs stands out among the ethical concerns. An entity with moral status must be treated in a specific way (Warren, 2002). The strength of these obligations depends on the degree of moral status and their nature is determined by the features grounding this status. This review focuses on the features most relevant to HBO research, which we categorise into consciousness, advanced cognitive capacities, agency, and other grounds.

2.1.1. Consciousness

The potential for HBOs to attain consciousness is a critical ethical issue (de Jongh et al., 2022). This involves two main questions. Is it possible for HBOs to gain consciousness and, if possible, what kind? And what is the value and moral significance of consciousness in HBOs?

As noted earlier, there are many different types of HBOs. Addressing the types of HBOs that may manifest consciousness involves examining the neural basis of consciousness. Different theories have highlighted various neural regions that are critical for consciousness, such as the upper brainstem, posterior parietal cortex, and pre-frontal cortex (Baars, 1993; Dehaene, 2014; Solms, 2018; Brown et al., 2019; Cleeremans et al., 2020; Mashour et al., 2020). The chosen theoretical framework influences predictions about the potential for HBO consciousness. For example, Birch (2023) emphasises the possibility of brainstem organoids possessing consciousness, whereas integrated information theory (IIT) highlights neural networks with recurrent connections and may ascribe a primitive form of consciousness to existing HBOs that demonstrate synchronised firing patterns (Lavazza and Massimini, 2018; Niikawa et al., 2022).

Contrastingly, many theories of consciousness emphasize embodiment and sensorimotor interaction with the world and thus deny consciousness in current *in vitro* HBOs (Croxford and Bayne, 2024). However, there may be varied predictions regarding the consciousness of more advanced HBOs in the future even within this mainstream perspective. To make specific predictions, comprehensive systematic studies of the interplay between consciousness theories and the development of future HBOs are imperative (Boyd and Lipshitz, 2024; Bayne et al. (2024)).²

Recent debates surrounding theories of consciousness, termed the ‘consciousness wars’ (Lenharo, 2024), highlight the difficulty of establishing scientific certainties about HBO consciousness. Still, many theories suggest that current *in vitro* HBOs are unlikely to be conscious, a

² Further, as HBOs structurally diverge from human and animal brains, they may possess a form of consciousness alien to our current understanding (Gaillard and Botbol-Baum, 2022; Diner, 2023). This is particularly likely to occur in assembloids, in which multiple region-specific HBOs are selectively fused. The possibility of alien forms of consciousness poses significant challenges for existing theories of consciousness.

Table 1
Summary of Key Findings from Interviews and Public Surveys on Brain Organoid Research (HBO: Human brain organoid).

Authors & Year	Participants	Method	Key Findings	Ethical Concerns Highlighted	Recommendations
Haselager et al. (2020)	26 patients or laymen	Semi-structured interview	Overall support for HBO research given informed consent and good governance	Moral value of HBOs, consciousness, relationship to the cell donor, international biobanks, commercialization, chimera research	Anticipatory discussions, transparent communication, patient involvement, ethical oversight
Bollinger et al. (2021)	60 patients or parents of pediatric patients	Semi-structured interview	Broad support for organoid research in medical science, drug development, and personalized treatments	Sensitivity of brain and gonadal organoids, consciousness, ethical implications, consent	Ethical oversight, good intentions, robust consent
Ravn et al. (2023)	51 participants in workshop	Deliberative workshop	Support for organoid technologies with robust governance and ethical oversight	Commercialization, healthcare access, cerebral organoids, privacy, data management	Continuous evaluation of guidelines, transparent communication
MacDuffie et al. (2023)	67 adult donors or parents of child donors	Semi-structured interview	Enthusiasm for HBO research, preference over animal models or fetal tissue	Informed consent, donor engagement, updates on research progress	Regular donor engagement strategies, e.g., newsletters
Lavazza and Chinaia (2023)	21 HBO researchers	In-depth semi-structured interview	Skepticism about HBOs developing consciousness, need for ethical scrutiny	Public communication, terminology, informed consent	Balanced dialogue between scientists and ethicists
Tanibe et al. (2024)	610 general public	Survey	Slightly more negative attitudes towards human-animal chimeric brain research	Humanization of animals, crossing human-animal boundaries, unnaturalness	Careful communication, policy design

view supported by most HBO researchers (International Society for Stem Cell Research, 2021; Hyun et al., 2022; Paşca et al., 2022). This consensus can be used for informed decision-making on HBO consciousness amid uncertainties.

The methodology to evaluate consciousness in HBOs presents a separate challenge even assuming a particular theory of consciousness is validated. HBOs' lack of sensory inputs and outputs precludes standard behavioral experiments. While interfacing HBOs with artificial systems might be a solution, it requires further technological advancements. Techniques like the Perturbational Complexity Index are proposed for HBO evaluation (Lavazza and Massimini, 2018), but are impractical due to difficulties with transcranial magnetic stimulation to HBOs (Sawai et al., 2022). Some researchers suggest using structural analogies to the human brain, which manifests consciousness (Koplin and Savulescu, 2019; Niikawa et al., 2022), but this may not account for the profound structural differences between HBOs and the human brain (Bayne et al., 2020; Diner, 2023). Also, it is difficult to make inferences about the emergence of consciousness in assembloids based on our knowledge of the normal human development process.

Although current discussions on HBO consciousness focus on *in vitro* models, advancements in animal transplantation and SBI technologies could change this. Grafted HBOs may mature and develop enhanced computational capacities and sensory-motor connections within the animal host, potentially leading to consciousness (Koplin and Savulescu, 2019; Lavazza, 2020; Koplin et al., 2021; Sawai et al., 2022). However, it remains unclear whether such HBOs would constitute independent subjects of consciousness (Kataoka et al., 2023d). The potential of HBOs to achieve consciousness through SBI technology has also been suggested (Savulescu et al., 2022; Kinderlerer, 2023; Hartung et al., 2023; Milford et al., 2023). A challenge to this possibility is that HBOs in SBI technology are anticipated to remain small in size. The integration of multiple SBIs may enhance their computational capabilities for consciousness, but it requires further technological advancements (Kataoka et al., 2024b).³

Next, we consider the moral significance of consciousness.

³ The discourse on the potential consciousness of SBI systems reflects that of AI consciousness (Metzinger, 2021). Ethical considerations in HBO research and AI technology share common ground (Hyun et al., 2020). Still, SBI technology could address scepticism about consciousness emerging from inorganic materials (Kataoka et al., 2024b).

Consciousness of HBOs does not necessarily require a ban or strict regulation of HBO research. The moral significance of consciousness varies with its nature.⁴ Sentient beings capable of consciousness with value, such as pleasure or pain, undoubtedly possess a distinct moral status. However, the moral significance of consciousness devoid of such value, or of rudimentary forms of consciousness as posited by the IIT for current HBOs, remains ambiguous (Niikawa, 2018; Shepherd, 2018). To date, ethical literature on HBOs has focused mainly on sentience and rarely discussed rudimentary forms of consciousness, which it is natural to believe HBOs can most easily realize. Therefore, it is imperative to further examine whether and to what extent this type of consciousness has moral significance.⁵

Alignment with ethical norms for animal experimentation principles would be reasonable if advanced HBOs demonstrated sentience (Koplin and Savulescu, 2019; Birch and Browning, 2021; McKeown, 2023). In principle, HBO research could be ethically acceptable if its purpose is scientifically valid and it adheres to ethical principles analogous to those applied in animal studies, notably the 3R principles of 'refinement', 'reduction', and 'replacement', or more enriched principles (Beauchamp and DeGrazia, 2020). However, the application of these ethical tenets in HBO research presents challenges (Kataoka et al., 2024a). The principle of 'refinement', which requires reducing suffering as much as possible, is difficult to apply to HBO research unless the welfare of sentient HBOs can be measured, though some methods are proposed (Browning and Veit, 2023). While the concepts of 'reduction' and 'replacement' are more straightforward, HBOs are believed to mitigate and supplement the use of laboratory animals (Farahany et al., 2018), if not completely

⁴ Below, we will focus on the distinction between consciousness with value (such as pleasure and pain) and consciousness without it. The reason for this distinction is simply that the existing ethical literature is generally based on it. There are other well-known distinctions regarding the various forms of consciousness (e.g., arousal-awareness), and how they relate to HBO ethics could be an ethically important topic in the future.

⁵ Some ethicists argue that consciousness without pleasure or pain (e.g., purely visual or auditory experience) has no moral significance (Shepherd, 2018). According to this view, even if HBOs were to attain such consciousness, no additional ethical constraints on research applications would be required. However, this view may be somewhat counterintuitive, especially if one believe that, however primitive, the consciousness of HBOs has special moral significance due to the fact that HBOs belong to the species of *Homo sapiens* (see Sections 2–1–4).

replaceable (Homberg et al., 2021). Therefore, establishing a principled approach to balancing the scientific necessity and ethical concerns of various research methods is imperative.

In the ongoing debate surrounding theories of consciousness, scenarios may emerge in which the consciousness (particularly sentience) of advanced HBOs remains uncertain. To avoid this uncertainty, a precautionary approach has been proposed (Koplin and Savulescu, 2019; Birch and Browning, 2021; Niikawa et al., 2022; Milford et al., 2023). It posits that the HBO should be treated as if it were conscious in instances where there is a reasonable basis (though not absolute certainty) to believe that the HBO possesses consciousness and where the ethical repercussions of mistakenly presuming the absence of consciousness are more severe than those of erroneously attributing consciousness to it. Although ethically prudent, a comparison of these two assumptions is complex. Misattributing consciousness to HBOs could impose restrictions on research and adversely affect long-term human welfare (Żuradzki, 2021). Thus, applying a precautionary approach requires a structured framework that thoroughly examines a broad spectrum of ethical consequences. Furthermore, due to its nature, the precautionary approach cannot completely eliminate the possibility of false negatives. While such “gray zones” are unavoidable in many ethically important areas, such as the emergence of moral status or the beginning of human life, it is morally important to reduce them as much as possible. Thus, it would also be morally important to reduce the uncertainty of consciousness of HBOs by developing and constantly refining methods of evaluating consciousness, without becoming complacent with the precautionary approach.

In summary, while the potential consciousness of HBOs is significant, it may not be the most immediate ethical concern regarding HBOs. The priority is to examine how advances in consciousness science may impact HBO research and develop an ethical framework for future research aligned with existing human and animal experimentation guidelines.

2.1.2. Advanced cognitive capacities

Advanced cognitive capacities, including thinking, self-awareness, or the ability to communicate with others (Cordeiro-Rodrigues and Ewuoso, 2021), can serve as grounds for moral status. However, it is highly doubtful whether *in vitro* HBOs can acquire these capacities because they do not interact with the environment (Koplin and Savulescu, 2019). Animal transplants and SBI technology allow HBOs to interact with the outside world but with the same limitations noted above. In the case of animal transplants, HBOs that are integrated with the animal brain to the point of being able to receive inputs and outputs are likely to be part of the animal brain and no longer cognitively capable entities on their own; in the case of SBI, there would be computational capacity limitations. Therefore, HBOs are unlikely to somehow develop advanced cognitive abilities in the foreseeable future.

2.1.3. Agency

Developments in SBI technology have made agency-based moral status more relevant to HBO research (Jowitt, 2023b). Shepherd (2023) argues that if an SBI system engages in activities that contribute to its own welfare, it would have some moral status (i.e. there would be a moral obligation not to prevent such activities).⁶ Importantly, an objectivist understanding of welfare goes beyond conscious experiences to include desire satisfaction, fulfilment of needs, development of capacities, achievement, knowledge acquisition, and establishing caring relationships, such as friendship, if these are possible.

To develop this approach, we should separate matters of fact and value. Even if an SBI system has agency, it might not ground moral status

⁶ Note that this obligation is not absolute. Rather, just as in the case of animal experimentation, some ethical framework would be needed to justify research and development by paying due consideration to the welfare of SBI systems.

(Kataoka and Sawai, 2023; Ishida and Sawai, 2024). For example, DishBrain may possess ‘knowledge’ about the location of virtual balls and ‘achieve’ hitting them back. Clearly, however, such ‘knowledge’ and ‘achievement’ are qualitatively different from typical human knowledge or achievement, and thus unlikely to have the same prudential value and moral significance as human knowledge and achievement. This has become an issue in AI systems. For example, Kieval (2024) distinguishes between whether AI systems can achieve things, and whether they are capable of *valuable* achievements. The same applies to SBI systems.

2.1.4. Other grounds

The grounds for moral status may extend beyond an entity’s capacity. For example, some argue that mere affiliation of HBOs with *Homo sapiens* could be the basis for their moral status (Hostiuc et al., 2019; Zilio and Lavazza, 2023). This point also complicates the issue of consciousness. Even if they are qualitatively similar, it may not be ethically impermissible to treat animal consciousness and the “human” consciousness of HBOs differently. This kind of view is often criticized as “speciesism”, but it is certainly popular and is also widely seen in stem cell research in general (Koplin, 2024). Regardless of the view’s intrinsic plausibility, public policy on HBOs may thus need to take it into account if it is to be sensitive to public attitudes. If the species *Homo sapiens* is to be considered ethically privileged, then it would be inappropriate to compare HBO research to animal experimentation (as suggested so far), and far stricter regulations on research may be necessary.⁷ Similar issues could also arise for animals with grafted HBOs and SBI systems (Siminiuc et al., 2023), which are partially composed of human tissues. In particular, the possibility of speciesism in treating SBI introduces a novel ethical dilemma that transcends the boundaries of the traditional AI ethics (Kataoka et al., 2024b).

The human brain has great sociocultural value because it is seen as a source of the self. Thus, it is argued that HBOs have ‘symbolic value’ which may ground their moral status by virtue of their resemblance to the brain (van Till and Bunnik, 2023; van Till et al., 2023).⁸ Relatedly, within AI ethics, some propose grounding the moral status of AI systems based on whether we *perceive* them as conscious, not on whether they *are* conscious, which is difficult to determine (Gunkel, 2019). The same approach can be applied to HBOs and SBI systems.⁹ The idea of focusing on human attitudes toward HBOs is underdeveloped, as are empirical investigations of such attitudes (see Section 4), and this area is worth exploring.

Yokoro (2023) argues that future HBOs could be human individuals, which could ground their moral status. This conclusion is based on the claim that the human brain, in isolation, could be a human individual, and that human individuals can constitute a moral community. Nevertheless, even if the human brain alone could be considered a human individual, it is not clear whether a HBO could also be a human individual, as it is a very different entity from the human brain. To be considered human individuals, HBOs might need the capacity to integrate vital functions or mental capacities, including consciousness (Kataoka et al., 2023c). If future advancements enable the production of HBOs as human individuals, it would raise two profound ethical concerns. The first pertains to the permissibility of creating human individuals devoid of a body (Kataoka and Sawai, 2023). The second concerns the potential equivalence of producing HBOs to human reproductive cloning (Kataoka et al., 2023c).

⁷ For a comparison of the moral status of research animals and HBOs, see Koplin, (2024).

⁸ However, the idea of moral status grounded in symbolic value can be criticised as reducible to considering relevant interests and rights (Bortolotti and Harris, 2006).

⁹ If people have a clearly wrong perception of the mental properties of HBOs, it will cause certain problems that are different from moral status. See Sections 2–4 and 4–1.

2.2. Neural chimeras

2.2.1. Animal welfare

One of the most pressing ethical issues in human-animal chimera research is animal welfare (Hyun, 2015), and this is also true for HBO-grafted animals, a type of neural chimera. To transplant a HBO, a surgical cavity must be created in an animal; immediately after transplantation, the animal's original brain is compressed by the HBO. Performing transplants to restore brain function requires animals to have artificially damaged brains.

Currently, HBO transplantation in animals is subject to regulations on animal experimentation. However, such regulations may not always effectively protect animal welfare. In recent years, ethical discussions on animal experimentation have called for stricter treatment of animals than the traditional 3R principles. Proposed alternative principles include the absence of alternative methods, an expected large contribution to human welfare, elimination of unnecessary suffering, respect for animals' basic needs, and setting an upper limit of harm (Beauchamp and DeGrazia, 2020). A study analysing two cases of HBO animal transplants from this enriched perspective concludes that these cases might not be morally acceptable (Barnhart and Dierickx, 2023).

2.2.2. Enhancement

Concerns have been raised that HBO transplantation would enhance the capacity of the host animal, and thus increase its moral status (Munsie et al., 2017; Farahany et al., 2018; Chen et al., 2019a, 2019b; Koplin and Savulescu, 2019; Sawai et al., 2019, 2022; Blue et al., 2020; Hyun et al., 2020; Lavazza, 2020; Greely, 2021; Hyun, 2022; Bassil and Horstkötter, 2023; Boyd, 2023; 2024). Importantly, this issue should not be considered in isolation from animal welfare concerns. While the problem of enhancement in chimeric animals is often conceived as 'humanisation', 'human-like' capacity becomes an ethical concern because it would greatly expand the range of relevant interests of animals, elevating their moral status. However, such an expansion of interest can occur even when the enhancement of capacity is not 'humanlike'. For this and other reasons, Koplin (2021) discourages the use of the term 'humanisation', and Chen et al. (2019b) recommend 'brain enhancement'. Indeed, there is some reason to believe that it is infeasible for an animal implanted with HBOs to acquire 'human-like' capacities, such as self-consciousness, especially if it is a rodent, owing to physical constraints (Chen et al., 2019b).

The primary question related to enhancement by HBO transplants is more specific: which capacities are enhanced and by how much? To date, Dong et al. (2021) provide the only cases in which HBOs seem to have enhanced the capacity of animals. This study observed an increase in the fear response of mice implanted with HBOs in the medial pre-frontal cortex. Although the exact mechanism remains unknown, this could be viewed as related to the emotional enhancement of the animals. These mice may be more vulnerable to harm than normal mice and thus, may deserve stronger protection. Relatedly, the enhancement of learning and memory may also lead to increased vulnerability to harm during fear conditioning (Harary et al., 2023). This indicates that cognitive enhancement can have moral significance without leading to 'human-like' advanced cognitive abilities. Since the transplantation of human neural progenitor cells has been shown to improve learning ability and object-location memory in mice (Han et al., 2013), it is plausible that the same could also occur in the near future in HBO transplantation, thus calling for immediate caution. The enhancement of sensory capacities is also plausible, which can raise concerns regarding increased pain experiences (Harary et al., 2023). Some are concerned about increased vulnerability to stress in rats and mice implanted with HBOs (Bassil and Horstkötter, 2023).

Animal welfare should be considered from the perspective of experiences other than pain. For example, if chimeric animals have the capacity of mental time travel, they might be able to behave more deliberately by anticipating the future, thereby broadening their

interests (Harary et al., 2023). Increased empathy may enhance an animal's social needs (Harary et al., 2023), which could provide a reason for further protection based on the ethical principle that the basic needs of laboratory animals should be met (Beauchamp and DeGrazia, 2020). Since the basic needs of animals include appropriate exercise, the enhancement of motor capacities can also have implications for moral status (Kataoka et al., 2023d).

Thus, there are a variety of capacities whose enhancements could lead to the elevation of the moral status of chimeric animals, and their moral significance should be further examined. For this purpose, more detailed assessments of chimeric animals' physiology and behaviour is required (Kataoka et al., 2023d). Importantly, keeping chimeric animals in an enriched environment would allow both determination of their capacities and improvement of their welfare (Boyd, 2023).

2.3. Towards clinical trials

Here, we briefly address future clinical trials of HBO transplantation in the human brain. As HBOs can replicate the human brain architecture, they are considered suitable for repairing highly structured brain regions, such as the cerebral cortex and hippocampus (Chen et al., 2019b; Blue et al., 2020). However, this will and should not be realized in the near future. There are many associated risks, including immune reactions, oncogenic transformation, and seizures, to prevent which further technical advances are required (Chen et al., 2019a; Harris et al., 2023). Only one study transplanting HBOs into non-human primates has been carried out (Kitahara et al., 2020), and data more directly relevant to humans is almost completely lacking. Note that even clinical trials of stem cell therapy for patients with Parkinson's disease are still underway (Takahashi, 2020).

Past examples of neural transplants provide an opportunity to learn about ethical concerns other than efficacy and safety. In the 1980s, transplantation of embryonic or foetal cells for Parkinson's disease began, although its clinical efficacy is now regarded as limited (Freud et al., 2001; Olanow et al., 2003). While a major ethical concern for such research was cell procurement (Turner and Kearney, 1993), this can be avoided with iPSC-derived HBOs. However, other ethical concerns could still be applied to HBO transplants. One example is possible psychological changes in patients (Sawai et al., 2022; Harris et al., 2023). This concern was not addressed in earlier neural transplantation attempts, because assessments of transplantation effects focused only on features directly related to the disease, such as motor functions (McRae et al., 2003). Thus, future clinical trials of HBO transplants into the human brain should conduct post-operative evaluation from various perspectives, including psychological changes.¹⁰

2.4. Consent

The creation of HBOs requires cell donations from citizens. Therefore, obtaining consent from donors is of great ethical importance. It entails multiple issues, of which many are common to other human biological materials. However, moral sensitivity and its implications for appropriate methods of consent are particularly pertinent to HBO research. It is often argued that for morally sensitive research, materials obtained by broad consent should not be utilised, as they would fail to sufficiently respect the moral views of donors, and this can apply to HBO research as well (Boers and Bredenoord, 2018; Farahany et al., 2018; Greely, 2020; Kataoka et al., 2024a). Empirical research has consistently shown that citizens regard HBOs as morally salient (Bollinger et al., 2021; Haselager et al., 2020; Ravn et al., 2023). This trend may be even stronger for creating a single HBO derived from cells of multiple donors. Instead of broad consent, a preferable method would be project-specific

¹⁰ Nevertheless, concerns about psychological changes should not be over-inflated, as in the case of deep brain stimulation (Gilbert et al., 2021).

informed consent (Kataoka et al., 2024a), or a ‘consent for governance’ model, in which the conditions regulating the use of the donated cells are agreed upon by the cell donors (Boers and Bredenoord, 2018).

Relatedly, privacy protection is important in HBO research. In particular, when creating HBOs from patient-derived iPSCs, personal information about neurological disorders—which are prone to stigma—must be strictly protected (Boers et al., 2019). Similarly, ethical guidelines are needed for the handling of incidental findings in the production of HBOs (Boers et al., 2019; Hyun et al., 2020; Smirnova et al., 2023). In addition, empirical research shows that some citizens are concerned that thoughts or memories of the cell donor can be leaked from HBOs (Haselager et al., 2020; Evans, 2024). As this concern lacks scientific basis, clear and straightforward scientific communication is strongly needed to dispel such misconceptions among the public (Kataoka et al., 2024d).

For FeBOs, consent issues have become more complex (Sawai and Kataoka, 2024). Given the challenges in obtaining informed consent for foetal tissue collection in general (Barker et al., 2022), FeBO research requires a more careful approach than that for the existing HBO research using PSCs. In particular, the empirical finding that some people would feel a personal connection toward HBOs derived from their cells (Bollinger et al., 2021) highlights the importance of a nuanced understanding of donors’ feelings towards FeBOs (Sawai and Kataoka, 2024).

Importantly, moral sensitivity can be multiplied by how HBOs are used. Many citizens are known to be morally sensitive to human-animal chimera research.¹¹ In addition, many people would strongly resist SBI technology integrating cultured human neural cells into computers (Lavazza and Reichlin, 2023). For such uses, detailed consent procedures with enriched information and opportunities for deliberation are essential (Kataoka et al., 2023d, 2024b; Kagan et al., 2023a).

If uncertainty about HBO consciousness increases in the future, it may become more difficult to obtain informed consent. Some argue that if the uncertainty is too high, the consent obtained might not be sufficiently ‘informed’, even if the HBO research details are provided to the donor (Greely, 2021; Mollaki, 2021).¹² Further, even if the donor accepts the uncertainty and agrees to donate cells, this does not diminish the inherent uncertainty regarding HBO consciousness and moral status. Respect for the donor’s wishes should not be used to mask the moral uncertainty of the research itself (Kataoka et al., 2024a).

3. Legal issues

3.1. Governance

HBO research involves human subjects, stem cell research, and animal research (when transplanted) and thus is subject to related laws and regulations (Hyun et al., 2020). As of August 2024, no country had enacted specific governance frameworks exclusively for HBO research.

The consensus among the guidelines and reports is that while the current governance frameworks adequately cover the existing scope of HBO research, it may necessitate enhanced oversight when HBOs evolve toward greater complexity. The 2021 Guidelines by the International Society for Stem Cell Research (ISSCR) categorise current HBO research as Category 1 A, defined as ‘research determined to be exempt from a specialised scientific and ethics oversight process’ (International Society for Stem Cell Research, 2021). Nonetheless, these guidelines anticipate potential challenges from the long-term culture and integration of multiple organoids. The report of the U.S. National Academies of Science, Engineering, and Medicine (NASEM) also states that current

¹¹ For neural chimeras by transplantation, see Haselager et al. (2020) and Tanibe et al. (2024). For those by blastocyst-complementation, see Crane et al. (2020).

¹² By contrast, others argue that accepting high uncertainty is a part of the right to self-determination of the donor (Deuring, 2022).

oversight measures should be deemed sufficient until HBO research reaches a threshold of significant complexity (National Academies of Sciences, Engineering, and Medicine, 2021). A similar perspective was shared by the German Academy of Sciences (Pichl et al., 2023), highlighting a broad agreement on the trajectory of regulatory needs in HBO research.

Certainly, the increasing complexity of HBOs is a critical factor in future regulatory considerations. However, as discussed in Section 2, ethical concerns in HBO research are not solely due to HBOs’ complexity. Future regulations should address a broader spectrum of issues. As the ethical issues identified above are provisional and may change with scientific progress, a dynamic assessment framework for regulation needs to be explored, like those developed for environmental issues (Kano and Hayashi, 2021).

Further, achieving international harmonisation in the governance of HBO research is essential (Voeneky, 2022; Lee and Sawai, 2023; Savulescu and Sawai, 2023). International Human Rights Law, particularly freedom of scientific research and human dignity, provides a potential legal basis for global action (Voeneky, 2022). Another relevant treaty is the Cartagena Protocol on Biosafety. How these legal regimes interact with HBO research merits a deeper global discussion. With its Constitutional mandate to promote health, the World Health Organization can play a pivotal role in facilitating policy harmonisation (Lee and Sawai, 2023). Additionally, HBO-specific declarations could incentivise a harmonised regulatory mechanism if there is global consensus on the standards and guidelines addressing the ethical dimensions of HBO research (Voeneky, 2022).

3.2. Legal protection of welfare

The protection of the welfare of sentient HBOs has significant legal dimensions. Given that many countries have well-established legal frameworks for animal welfare, these could potentially be extended to provide legal safeguards for the welfare of HBOs. Legislation on animal welfare typically pursues two primary objectives: protecting animal welfare and addressing public sensitivity toward animal suffering. These objectives can, in principle, be extended to sentient HBOs (Lavazza and Pizzetti, 2020). However, the applicability of the second objective also depends on public attitudes toward HBOs. Public’s concerns about HBO suffering may be less uniform than concerns about animal suffering, especially if HBOs do not exhibit behaviours indicative of pain. This consideration is crucial for countries like Japan, where animal welfare laws is based solely on the second objective.

The feasibility of implementing legal protection of the welfare of future HBOs varies across jurisdictions. Notably, in Germany, extending welfare protection to HBOs may require a constitutional amendment (Pichl et al., 2023) because HBO production is protected under the constitutional guarantee of scientific freedom, which can only be constrained by considerations of similar constitutional concerns.

What should be considered further is whether the mere extension of animal welfare laws can guarantee adequate welfare protection for HBOs. First, there would be a wide variation in the means that can be chosen for objectives that do not harm HBOs. As in the case of laboratory animals, appropriate means should be chosen based on the nature of HBOs, which requires scientific efforts in addition to legal ones. Second, judicial remedies and administrative regulations must be guaranteed when HBO welfare is infringed. Jowitt (2023a) highlights a case in which an elephant was denied legal protection because of its legal status as property. To prevent similar issues in future HBO research, ethical considerations regarding the treatment of potentially sentient HBOs must be incorporated into legal frameworks (Jowitt, 2023a). This underscores the need to evaluate the legal status of HBOs carefully.

3.3. Legal status of HBOs

In many jurisdictions, HBOs are classified as property with no

distinct legal considerations beyond those applied to other human biological materials (Lavazza and Pizzetti, 2020; Taupitz, 2022). However, there is a growing discourse suggesting that as technology advances, HBOs might be recognised as legal persons (Jowitt, 2023a, 2023b; Kataoka et al., 2023b).

Legal personhood is categorised into two types: juridical personhood, designated for nonhuman entities such as corporations, and natural personhood, attributed to human individuals. Three reasons have been proposed to advocate HBOs' juridical personhood. The first is granting juridical personhood to HBOs to safeguard their welfare (Jowitt, 2023a, 2023b; Kataoka et al., 2023b). Indeed, animals are sometimes accorded juridical personhood for this reason (Seewer, 2021).

The second rationale for granting juridical personhood to HBOs is to reflect on societal beliefs and values. A notable example of this kind of juridical person is the Whanganui River in New Zealand, which is recognized so by reflecting indigenous perspectives that regard it as a living entity (Clark et al., 2018). This illustrates the influence of social beliefs and values on the recognition of juridical personhood (Hutchison, 2014). As discussed in Sections 2–1–3, HBOs can embody symbolic value. If this perspective is accepted in society, it could lead to the recognition of HBOs as legal persons (Kataoka et al., 2023b).

The third rationale pertains to advancements in the SBI technology. There is a vibrant debate on the legal status of AI systems, and it is evident that the evolution of SBI technology will provoke a similar discourse. If SBI systems generate text, images, music, and other output, it would raise potential legal challenges concerning intellectual property rights and the recognition of juridical personhood.¹³ Currently, no country has recognized legal personhood of AI systems for this reason (Chesterman, 2020). However, legal discussions surrounding AI are dynamic and subject to change, with significant implications for the future trajectory of SBI technology (Kataoka et al., 2024b).

Beyond the discourse on juridical personhood, the potential for the natural personhood of future HBOs is also under consideration (Kataoka et al., 2023b). Brain death is widely recognised in many countries as marking the cessation of natural personhood. From this perspective, HBOs demonstrating minimal brain activity that would not be considered brain dead may be considered natural persons (Lavazza and Pizzetti, 2020). However, a critical flaw in this argument lies in the distinction between the legal definitions that mark the termination and initiation of natural personhood (Lavazza and Pizzetti, 2020). The inception of natural personhood, that is, legal birth—the (partial) expulsion of a foetus from the mother's body—does not apply to HBOs.

The conventional definition of birth is, however, not unproblematic. While this definition precludes entities developed *in vitro* from human biological materials without embryonic development in the womb from being recognised as natural persons, this is increasingly at odds with contemporary scientific and technological advances. Technological innovations that facilitate foetal survival outside the womb are rapidly advancing. The temporary removal of foetuses for medical interventions has already introduced ambiguity regarding their natural personhood (Romanis, 2020), which is expected to escalate with the advent of artificial uterine technologies. Concurrently, the ability to engineer progressively complex entities from PSCs, including HBOs, body-on-a-chip systems (Skardal et al., 2020), and embryo models (Oldak et al., 2023)—further challenges the traditional legal interpretation of birth. This evolving landscape necessitates a reassessment of

the legal definition of birth and suggests that the natural personhood of a sufficiently advanced HBO warrants serious consideration (Kataoka et al., 2023b).¹⁴

3.4. Ownership

Traditionally, donors relinquish the ownership of their donated materials to researchers or research institutions (Boers et al., 2016). However, advances in HBO research may challenge this practice (Kataoka et al., 2024c). Empirical studies have indicated that donors often feel a profound personal connection to HBOs derived from their cells (Haselager et al., 2020; Bollinger et al., 2021). Although these sentiments do not necessarily translate into claims of ownership, they would increase the potential for future disputes. Moreover, the current practice excludes donors from any commercial gain resulting from the use of their cells in HBO research (see Sections 3–5). This situation has sparked discussions on the re-examination of current ownership conventions to allow some kinds of benefit-sharing (Boers et al., 2016; see also Sections 4–3–1). It should also be noted that these issues become even more complicated when the HBO is derived from the cells of multiple donors.

Some argue that the potential consciousness of HBOs could also raise issues for ownership (Sawai et al., 2022). However, as evidenced in the case of animals, the presence of consciousness does not inherently render an entity unownable (Holm and Lewis, 2022). However, ownership does not necessarily mean unlimited freedom to do as one pleases, just as even the owner of animals must not treat them cruelly. In order to avoid similar improper handlings of sentient HBOs, it may be necessary to legally assign the stewardship to someone other than the researchers (Farahany et al., 2018). Also, given that HBOs are of human origin, the range of permissible treatment may be more limited than in the case of animals, for the reasons given above. Finally, should the legal status of HBOs transition away from property, as suggested in Sections 3–3, ownership would naturally become subject to limitations.

3.5. Commercialisation and patents

HBOs have attracted considerable commercial interest, which can raise various issues (Hoppe et al., 2023). By 2019, 19 companies were involved in the organoid sector, with six focusing on HBOs (Choudhury et al., 2020). In the EU, regulations exist which prohibit the commercial trade of human bodies, but there are currently no legal obstacles to the commercialisation of HBOs derived from iPSCs for multiple reasons (Taupitz, 2022). When HBOs are made from iPSCs, what is obtained from the donor are blood or skin cells. The procurement is minimally invasive, and such materials are viewed as detached body parts not impinging on human dignity, and nor having a great normative importance. Additionally, there is little risk of exploitation.

Relatedly, patent eligibility of HBOs is noteworthy. Patents for HBOs have been issued in jurisdictions including the US, the EU, and Japan. Generally, HBOs are patentable because they are invented using donated tissues, unless specific exceptions apply. In the EU, Article 6(2)(c) of Directive 98/44/EC prohibits patents for the 'uses of human embryos for industrial or commercial purposes'. 'Human embryos' here have been interpreted as including ESCs and their derivatives (C34–10 *Oliver Brüstle v Greenpeace eV*, 2011), but this does not apply to iPSC-derived

¹³ The questions about the exact nature of agency of AI or SBI systems are relevant here as well (see Sections 2–1–3). Still, even if their agency is more advanced, it may still not necessarily change their legal status as property, as slaves in Roman law (Pagallo, 2013).

¹⁴ Furthermore, HBO research could challenge the current brain death criterion in the distant future. First, if it becomes possible to create living HBOs with consciousness, one could argue that the definition of natural person and death should be re-examined to include them (Greely, 2021). Second, if brain function recovery through future HBO transplantation becomes possible, it may become unclear when brain death should be diagnosed. Still, it is difficult to imagine that local transplantation of HBOs would enable recovery from a state of brain death (Farahany et al., 2018).

HBOs (Wolff, 2024). As HBO technology advances, Article 6(1) of the Directive, which excludes inventions contrary to ‘*ordre public* or morality’, could impact patentability of future HBOs with human- or animal-like capabilities (Wolff, 2024).

4. Social issues

4.1. Hype

HBOs have received considerable media attention (Ide et al., 2021), but this coverage often exaggerates HBO research (Presley et al., 2022). Inappropriately hyperbolic communication of science and technology has been known as “hype”, which can undermine public trust, mislead the audience about risks and benefits, and impede evidence-based decision-making (Intemann, 2022). Hype about HBO research has long been a concern (Munsie et al., 2017; Hostiuc et al., 2022; Kataoka et al., 2023a; Bassil, 2024). Notably, the term ‘mini-brain’ has been criticised as misleading and is now rarely used in academic contexts.

One of the most worrisome hypes about HBO research is about its therapeutic utility. This issue is common in stem cell research, where there has been a risk of disappointing patients and promoting unapproved treatments (Caulfield et al., 2016). Currently, HBOs can model only early neural development, which limits their medical application to diseases caused by early neuronal malformations. As such, HBOs have aided drug screening for microcephaly caused by the Zika virus (Zhou et al., 2017), but they are less relevant for many neurodegenerative, neurodevelopmental, and mental disorders (Kataoka et al., 2023a).

Exaggeration of ethical concerns in research is called ‘ethics hype’ (Caulfield, 2016), which is a particular issue in HBO research. Ethics hype can delay beneficial medical applications and complicate donor consent (Bassil and Horstkötter, 2023; Kataoka et al., 2023a; Schneider et al., 2024). Debate about HBOs’ potential consciousness is especially prone to ethics hype (Lavazza and Chinaia, 2024). As discussed in Sections 2–1–1, most researchers agree that HBOs will not be conscious in the near future (Hyun et al., 2022; Lavazza and Chinaia, 2023). The ISSCR advises not to portray HBOs as possessing human-like consciousness or cognitive abilities (International Society for Stem Cell Research, 2021). While the ethical implications of HBOs’ potential consciousness are important, the speculative nature of the issue must be fully emphasized, especially in the context of public communication.

4.2. Terminology challenges

Inaccurate media description of HBOs may be the result of inconsistent terminology used to name various 3D models of the human nervous system (including organoids). Proper terminology is important for scientific purposes and for the responsible communication of research. It can also lead to sound normative discussions, preventing overgeneralisation of ethical claims (Bassil and Horstkötter, 2023). To address this terminology problem, some researchers have proposed a consensus (Paşca et al., 2022). There, the use of ‘mini-brain’ is explicitly rejected and even ‘brain organoids’ is implicitly avoided in favour of ‘neural organoids’. Additionally, the term ‘chimeric animals’ is discouraged in relation to HBO transplantation into animals. However, it is still difficult to establish proper terminology balancing accuracy, convenience, and social implications. Indeed, some researchers are reluctant to dismiss ‘mini-brain’ owing to its usefulness in scientific communication (Lavazza and Chinaia, 2023).

With the advent of SBI, terminology problems have become even more complicated. In particular, Balci et al. (2023) criticise use of the terms ‘intelligence’ and ‘sentience’ to describe DishBrain as misleading. Crucially, ‘sentience’ implies moral status within bioethical parlance, and its indiscriminate use risks muddling ethical evaluation of SBI. However, the terminology used by DishBrain’s developers follows another research tradition and it is not entirely arbitrary (Kagan et al., 2023b). Here, ‘sentience’ is defined functionally in terms of the

responsiveness to sensory inputs, explicitly denying implications for subjective conscious experience (Friston et al., 2020). Interdisciplinary dialogue and public engagement are both important to bring these terminological disputes to resolution (Rommelfanger et al., 2023; Kataoka et al., 2024b).¹⁵

4.3. Distribution of responsibility: benefit-sharing and misuse

4.3.1. Benefit-sharing

HBO research has diverse applications with various potential benefits and harms to society. Deciding among whom to distribute the responsibility of these effects and how to do so are a main social challenge in HBO research.

First, on benefits, we saw above that the HBO research has given rise to a debate about benefit-sharing to cell donors. The need for benefit-sharing is further increasing with SBI technology, which is expected to have a very wide variety of potential applications (Savulescu et al., 2022; Kinderlerer, 2023; Kataoka et al., 2024b).

The best ways of benefit-sharing need to be determined according to the type of HBO research and to be socially well acceptable. For medical research, donors can be provided with preferential access to resulting medical knowledge and treatments (Boers et al., 2016). However, this situation is complicated by the emergence of SBI technology. Given the current trends in AI technology, many SBI technology applications are considered non-medical. In this case, donors could be paid for donating cells (Savulescu et al., 2022; Kinderlerer, 2023).

4.3.2. Misuse

The potential for misuse in HBO research has not received much attention in the ELSI discourses around HBOs. In general, research on damage to the central nervous system has the potential to be misused to harm people, and there have been many examples of HBO research of this type, in which HBOs are exposed to chemicals or pathogens to assess the damage (Depla et al., 2022; Fan et al., 2022). As HBOs currently mimic brain tissue only in the early development stages, the risks associated with their misuse are considered very small. However, if research on the damage to more complex HBOs progresses, the potential for dual use could be significant (Rinaldi and Colotti, 2019; Mollaki, 2021).

Similar issues may arise with SBI. Given the extensive military use of current AI technology, it is necessary to be vigilant about the future military use of SBI technology (Mollaki, 2021). A more plausible misuse of SBI systems could come from text generation like today’s generative AI: generating discriminatory text or misinformation. The question of where the responsibility for such harmful misuse lies has been actively debated in AI ethics, but a new question in SBI is whether and how much responsibility should be placed on the cell donors (Kataoka et al., 2024b).

4.4. Public engagement

4.4.1. Why it matters

The incorporation of civic values into HBO research and applications is crucial (Boers et al., 2016, 2019; Bredenoord et al., 2017; Munsie et al., 2017; Farahany et al., 2018; Greely, 2020; Lensink et al., 2020; International Society for Stem Cell research, 2021; MacDuffie, 2022; Sawai et al., 2022; Stoeklé et al., 2022; Hartung et al., 2023). The reasons for this are manifold. In general, integrating civic values into research is supported by democratic principles (Greely, 2020, 2021) and the need to build public trust (Klingler et al., 2022). It can also

¹⁵ Some even argue against using terms like ‘learn’ or ‘play’ for DishBrain, claiming that only humans can learn or play, not the brain (van Till and Bunnik, 2024). However, this seems excessive given the varied usages of ‘learn’ in different research fields, including machine learning.

contribute to the formation of ethical policies by balancing ethical theories or principles with public opinion (Savulescu et al., 2021). More specifically to HBO research, it can identify and mitigate the moral sensitivity of the research by examining any possible discrepancy between HBO research and traditional civic values (Greely, 2020; Metselaar et al., 2021; National Academies of Sciences, Engineering, and Medicine, 2021; Boyd and Sugarman, 2022; Stoeklé et al., 2022). It also helps eliminate misconceptions and unfounded fears (Boers et al., 2016; Munsie et al., 2017; Mollaki, 2021; MacDuffie, 2022; de Jongh et al., 2022). Importantly, public concern about HBOs may differ from that of experts, including ethicists (Evans, 2022; Zuk et al., 2022). Further, it can avoid using donated cells against donor values (Boers and Brede-noord, 2018; Farahany et al., 2018; Greely, 2020). Donors' views on the need for benefit-sharing should also be considered as pointed out above (Boers et al., 2016, 2019; Lensink et al., 2020).

4.4.2. Interviews and surveys

There are many different objectives and methods of public engagement, and it is important to choose them appropriately (Scheufele et al., 2021). For HBO research, more deliberative and active participation is considered to be ideal (Metselaar et al., 2021; Mollaki, 2021; Sharma et al., 2021; Boyd and Sugarman, 2022; Klingler et al., 2022). Still, interviews or surveys can be a useful initial step (Greely, 2021; National Academies of Sciences, Engineering, and Medicine, 2021; de Jongh et al., 2022).

To our knowledge, there are four empirical studies that focus on citizens' attitudes toward HBOs (Haselager et al., 2020; Bollinger et al., 2021; Ravn et al., 2023; MacDuffie et al., 2023). Additionally, a study examining expert attitudes toward HBOs (Lavazza and Chinaia, 2023) and a psychological study of public attitudes toward neural chimeras created by transplantation of human neural cells (not limited to HBOs, strictly speaking) (Tanibe et al., 2024) also deserve attention here (Table 1).¹⁶

The results of interviews and public surveys collectively underscore broad support for HBO research provided it is conducted with robust ethical oversight and transparency. Patients, parents, and donors recognise the potential of organoids to advance medical science, while emphasising the need for informed consent and continuous engagement. The importance of patient and public involvement in fostering trust and ensuring responsible innovation has become a recurring theme across studies. Ethical issues remain pivotal in public discourse, and clear communication alongside updated guidelines are essential to align societal expectations with the capabilities of organoid technologies.

5. Conclusion

Research on HBOs has made significant strides in mimicking the developmental processes, cellular composition, and neural structures of the human brain. These advancements have propelled scientific understanding; however, they also present ethical, legal, and social challenges. As HBO research continues to intersect with fields such as biocomputing, addressing these issues has become increasingly important.

So far, a primary ethical concern about HBOs has been their potential to develop consciousness (de Jongh et al., 2022). Still, HBOs are unlikely to attain consciousness in the near future. This review rather highlighted the existence of various other ethical issues in HBO research besides consciousness. Developing ethical frameworks that can adapt to these new insights is crucial to balance scientific exploration with ethical responsibility.

Currently, the existing laws and regulations provide a foundational

framework for HBO research. However, as HBOs grow in complexity, enhanced oversight and international harmonisation of governance structures are needed. While we could find various legal issues in this review, legal considerations of HBO research are considerably less formidable than ethical discussions (Kataoka et al., 2024c), and further investigation is urgently needed.

The social impact of HBO research is multifaceted. Appropriate representation of HBO research both among professionals and to society is important to forestall many social issues as well as to strengthen public trust and to facilitate informed decision-making. Further empirical examination of public attitudes and more deliberative public participation are vital to bridge the gap between scientific progress and societal values.

Overall, a multidisciplinary approach that integrates ethical, legal, and social perspectives is essential to navigate the complex terrain of HBO research. This study outlines a framework to address immediate and foreseeable challenges, advocating for proactive and adaptive governance. As HBO technology advances, continuous dialogue between scientists, ethicists, legal experts, and the public will be indispensable for guiding responsible innovation.

CRediT authorship contribution statement

Masanori Kataoka: Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Julian Savulescu:** Writing – review & editing, Funding acquisition. **Tsutomu Sawai:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization. **Takuya Nii-kawa:** Writing – review & editing, Writing – original draft, Funding acquisition. **Naoya Nagaishi:** Writing – review & editing. **Tsung-Ling Lee:** Writing – review & editing. **Alexandre Erler:** Writing – review & editing.

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Data Availability

No data was used for the research described in the article.

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¹⁶ In da Silva et al. (2024), some expert opinions on HBO research are found as well. In the final stages of writing, we noticed Evans (2024), in which many interesting results on the public's view of HBOs are reported.

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