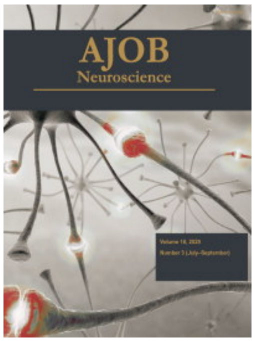

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Consciousness and Human Brain Organoids: A Conceptual Mapping of Ethical and Philosophical Literature

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ABSTRACT
Human brain organoids (HBOs) are three-dimensional structures derived from human pluripotent stem cells that model aspects of fetal brain development. As HBO models grow more complex, ethical concerns arise, particularly around the potential for consciousness. Defining and detecting consciousness in HBOs remains unresolved, with existing theories offering conflicting predictions. This systematic review examines how consciousness is conceptualized in the ethical and philosophical literature concerning HBOs. We selected peer-reviewed publications written in English from 2013 onward that directly address consciousness regarding HBOs. After screening 51 sources, 24 were analysed in themes: Consciousness Terminology, Biological Limitations, Theories of Consciousness, Detecting Consciousness, Comparisons with Conscious Entities, and Special Entities. Uncertainty about consciousness in general complicates the conversation around HBOs. Clear communication is essential to avoid misconceptions, and future research may benefit from focusing on organoid intelligence as a more tractable concept.

KEYWORDS
Consciousness; ethics; human brain organoids; philosophy; review

INTRODUCTION

Human induced pluripotent stem cells (hiPSCs) and embryonic stem cells (ESCs) have revolutionized cell biological research because they allow the use of human-derived materials to model a variety of cell types and their defects (Bai 2020). In addition, they can generate more complex multicellular systems called organoids. Organoids are self-patterning three-dimensional (3D) multicellular in vitro structures that can recapitulate certain aspects of the complex structure and function of a human tissue (Zhao et al. 2022). Many types of organoids exist, such as liver, cardiac, and blood vessel organoids. However, one particular type has gained increased attention in recent years, namely, human brain organoids (HBOs). HBOs can be described as "self-organizing structures that recapitulate the neurodevelopmental scheme to generate 3D tissue architectures that mimic various features of the developing fetal brain pertaining to cellular composition and tissue structure" (Lancaster and Knoblich 2014; Lancaster et al. 2013). These properties make HBOs valuable tools for studying neurological development and related diseases. However, the advancement of HBO research also raises pressing ethical questions. One of them, according to some discussions, is whether HBOs could develop a form of consciousness. The bioethics community needs further clarification and consensus about this topic, as advancements in HBO research may bring us closer to needing to addressing these complex questions. As research progresses, advancements in technology and methodology potentially increase the likelihood of cognitive development and raising new ethical challenges (Barnhart and Dierickx 2023).

One of the most significant challenges in consciousness research is the lack of widely accepted procedure for determining whether an entity is conscious; this issue extends beyond HBOs, to all organisms and systems under investigation (Niikawa et al. 2022). However, there have been prior studies about this issue specific to HBOs (Bayne, Seth, and Massimini 2020; Hyun, Scharf-Deering, and Lunshof 2020; Koplin and Savulescu 2019; Lavazza and Massimini 2018b; Niikawa et al. 2022; Sawai et al.

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2019). Neural correlates of consciousness (NCC), defined as "the minimal biophysical or neural mechanisms sufficient to produce conscious experience," remain a central focus of study (Jeziorski et al. 2023). However, debates persist regarding how to define and detect consciousness, as existing theories and methods often yield conflicting predications. For example, while irregular low-amplitude electroencephalography (EEG) patterns in the 20–70 Hz range and gamma synchrony are strongly associated with consciousness in humans, it is unclear whether such indicators can be applied to HBOs (Ankeny and Wolvetang 2021; Jeziorski et al. 2023). Moreover, parts of the cortex and thalamus are known to play a dominant role in the emergence of thought, experiences, and memories (Jeziorski et al. 2023). There are many existing theories of consciousness that make testable predictions about these NCC, but they provide differing predictions regarding the presence of consciousness. Furthermore, there is no consensus on how to define consciousness, as signals for detecting (un)consciousness in living adults do not necessarily translate to HBOs (Koch et al. 2016).

Because of this uncertainty, shifting the focus from whether brain organoids have consciousness to what concepts of consciousness can be considered in HBOs would be more tractable (Niikawa et al. 2022). However, there is currently a lack of an overview of the concepts of consciousness that could be present in HBOs. Therefore, the goal of this systematic review is to survey the existing peer-reviewed ethical and philosophical literature on HBOs to provide an overview of the various definitions, theories, and frameworks of consciousness as they relate to HBOs.

METHODOLOGY

The methodology of this review models the work from Strech and Sofaer for conducting a systematic review of reasons, which "take into account the specific conceptual and practical challenges of empirical bioethics" (Strech and Sofaer 2012), while preserving the systematicity associated with traditional reviews (Rahimzadeh, Knoppers, and Bartlett 2020). Their model integrates the systematic approach of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reviews (Page et al. 2021), but adapts it to the specific needs of normative and ethical literature (Strech and Sofaer 2012).

Search Strategy

For this review, we queried four different databases: PhilPapers, PubMed, Web of Science, and Google Scholar. The search string was developed in PubMed by author AVG in collaboration with KD and AJB. We searched for articles containing terms related to brain organoids, consciousness, and philosophy using keywords that were adjusted for each database. For PubMed, the following Boolean search string was inserted to gather all relevant data: ("Cerebral organoid*" [tw] OR " brain organoid*"[tw]) AND ("Consciousness"[Mesh] OR "mind" [tw] OR "conscious*" [tw] OR "aware*"[tw] OR "respons*" [tw] OR "sentien*" [tw]) AND ("Philosophy" [Mesh] OR "philosoph*"[tw]). For the other databases, the following Boolean search string was used: ("Cerebral organoid*" OR "brain organoid*") AND ("mind" OR "conscious*" OR "aware*" OR "respons*" OR "sentien*") AND ("philosoph*"). The results were collected into the bibliography software package Zotero.

Study Selection

After removal of duplicates, AVG screened all articles by title and abstract, and a second reviewer, AJB, independently screened some articles based on our eligibility criteria to find potentially relevant sources. Screening conflicts were resolved through discussion with the second author (AJB), and when necessary, a third author (KD) was consulted. Screening of the full text followed the same method and procedure as the screening of titles and abstracts. Finally, we also searched the reference lists of included articles to identify other articles (snowballing method). Updates for new potential publications continued from the databases until 15 March 2024.

Selection Criteria

Studies were included based on the following criteria: The main focus is on exploring the meaning of consciousness for brain organoids; the publication is peer-reviewed and written in English; and the publication is published after 2013, since Lancaster et al. developed the first method for generating brain organoids from hiPSCs in 2013. All study designs were considered for inclusion.

Data Extraction and Synthesis

Direct quotes that are considered to contribute to the meaning of consciousness for HBOs are extracted from the text. These quotes were called "concept mentions" (CMs), instead of reason mentions (RMs) used in the method of Sofaer and Stretch, as the main focus of our study was on defining concepts of consciousness for HBOs and not only on normative argumentation. These CMs are indicators of frequency, measuring how often a particular definition, theory, or framework of consciousness occurs in the literature. Therefore, CMs should not be taken as indicators of moral weight or significance regarding a particular position. Similar CMs were inductively grouped into broader categories, called topics, followed by inductive categorization into themes. Further data regarding the characteristics of the publications and authors were also collected.

RESULTS

In total, 24 studies met our inclusion criteria. A PRISMA flow diagram for the selection process is provided in Figure 1. An overview of the studies can be found in Table 1.

We identified 356 CMs, which we grouped under 47 topics. The most prominent results are presented in six themes: Consciousness Terminology, Biological Limitations, Theories of Consciousness, Detecting Consciousness, Comparisons with Conscious Entities, and Special Entities. Some themes were further broken down into subthemes organized as depicted in Figure 2. Given the extensive nature of the topics found, we focus on describing the topics that are comprised of more in-depth concepts rather than a few passing mentions or concerns. Within each theme and subtheme, we specifically report on the discussions and findings from publications included in this systematic review. All citations within these reported results are from included and analyzed publications.

Theories of Consciousness

Theories of Consciousness is the most discussed of the six themes in the literature, with a CM total of 127. It comprises different theories of consciousness and how we should approach these theories when applying them to HBOs. Within this theme, 13 different theories can be identified, with the Integrated Information Theory (IIT) being the most frequently discussed theory of consciousness. Theories with a CM total of

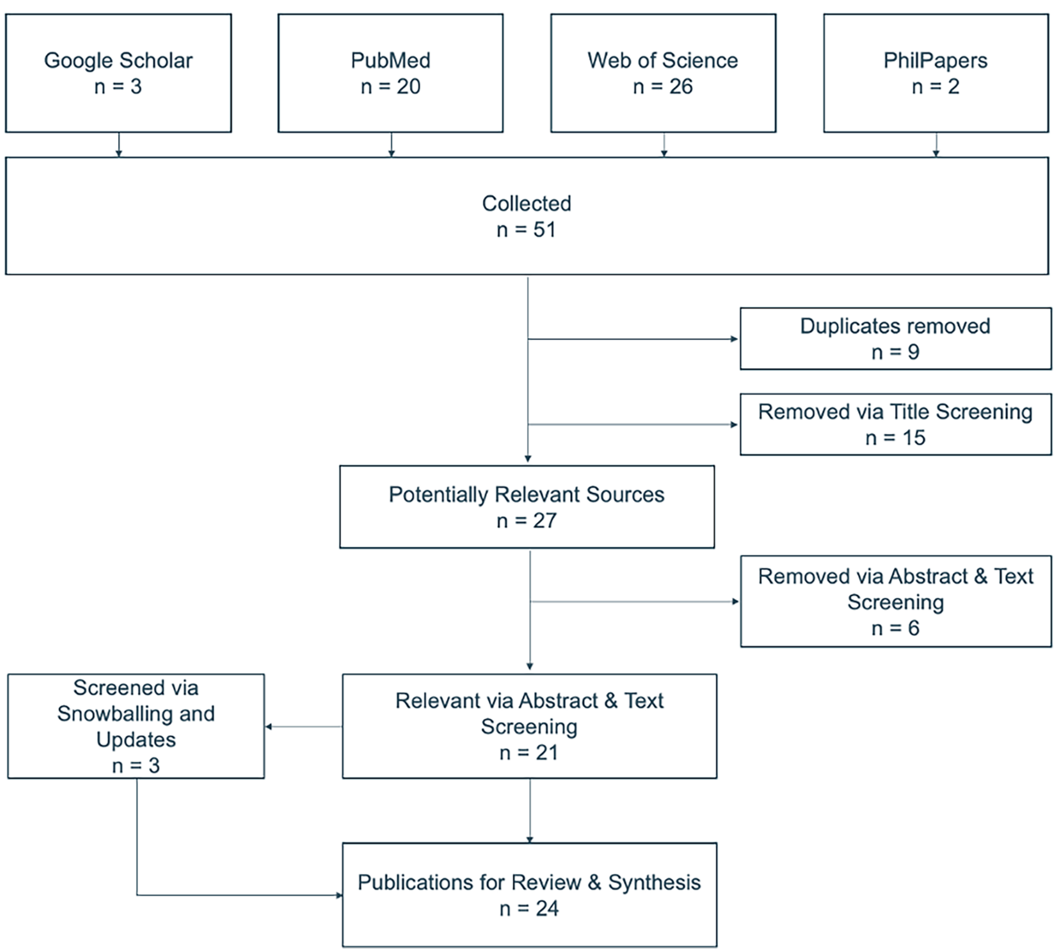

Figure 1. A PRISMA flow diagram depicting the selection process for sources used for analysis in this review.

Table 1. Overview of the theories of consciousness mentioned in the selected publications with an CM total of more than two.

Authors	Title of publication	Date of publication	Integrated information theory	Global neuronal workspace theory	Representational theories	Higher order theories	Temporo-spatial theory
Ankeny and Wolvetang	Testing the Correlates of Consciousness in Brain Organoids: How Do We Know and What Do We Do?	2021	×	×	×	×	×
Astobiza	Rebutting the Ethical Considerations Regarding Consciousness in Human Cerebral Organoids: Challenging the Premature Assumptions	2023	×	×	×	×	×
Croxford and Bayne	The Case Against Organoid Consciousness	2024	✓	×	×	×	×
Gaillard	Global Versus Local Theories of Consciousness and the Consciousness Assessment Issue in Brain Organoids	2024	✓	✓	×	×	×
Hartung et al.	Brain organoids and organoid intelligence from ethical, legal, and social points of view	2023	✓	×	×	×	×
Jeziorski et al.	Brain organoids, consciousness, ethics and moral status	2022	✓	✓	×	×	×
Kagan et al.	Neurons Embodied in a Virtual World: Evidence for Organoid Ethics?	2022	✓	×	×	×	×
Koplin and Savulescu	Moral Limits of Brain Organoid Research	2019	×	×	×	×	×
Kreitmair	Consciousness and the Ethics of Human Brain Organoid Research	2023	✓	✓	×	✓	×
Lavazza	"Consciousnessoids": clues and insights from human cerebral organoids for the study of consciousness	2021a	✓	✓	×	✓	✓
Lavazza	Human cerebral organoids and consciousness: A double-edged sword	2020	✓	✓	×	×	✓
Lavazza	Potential ethical problems with human cerebral organoids: Consciousness and moral status of future brains in a dish	2021b	✓	×	×	×	×
Lavazza and Massimini	Cerebral organoids: Ethical issues and consciousness assessment	2018	✓	×	✓	×	×
Lavazza and Massimini	Cerebral organoids and consciousness: How far are we willing to go?	2018	✓	×	×	×	×
Lavazza and Pizzetti	Human cerebral organoids as a new legal and ethical challenge	2020	✓	×	×	×	×
Lavazza and Reichlin	Human Brain Organoids: Why There Can Be Moral Concerns If They Grow Up in the Lab and Are Transplanted or Destroyed	2023	×	×	✓	×	×
Lavazza and Zilio	Consciousness in a Rotor? Science and Ethics of Potentially Conscious Human Cerebral Organoids	2023	✓	✓	×	×	✓
Milford et al.	Playing Brains: The Ethical Challenges Posed by Silicon Sentience and Hybrid Intelligence in DishBrain	2023	×	×	×	×	×
Montoya and Montoya	What Is It like to Be a Brain Organoid? Phenomenal Consciousness in a Biological Neural Network	2023	✓	✓	×	✓	×
Niikawa et al.	Human Brain Organoids and Consciousness	2022	✓	×	×	×	×
Owen et al.	Theoretical Neurobiology of Consciousness Applied to Human Cerebral Organoids	2023	✓	✓	×	×	×
Sawai et al.	Mapping the Ethical Issues of Brain Organoid Research and Application	2022	✓	×	×	×	×
Sawai et al.	The Ethics of Cerebral Organoid Research: Being Conscious of Consciousness	2019	×	×	×	×	×
Shepherd	Ethical (and epistemological) issues regarding consciousness in cerebral organoids	2018	×	×	×	×	×

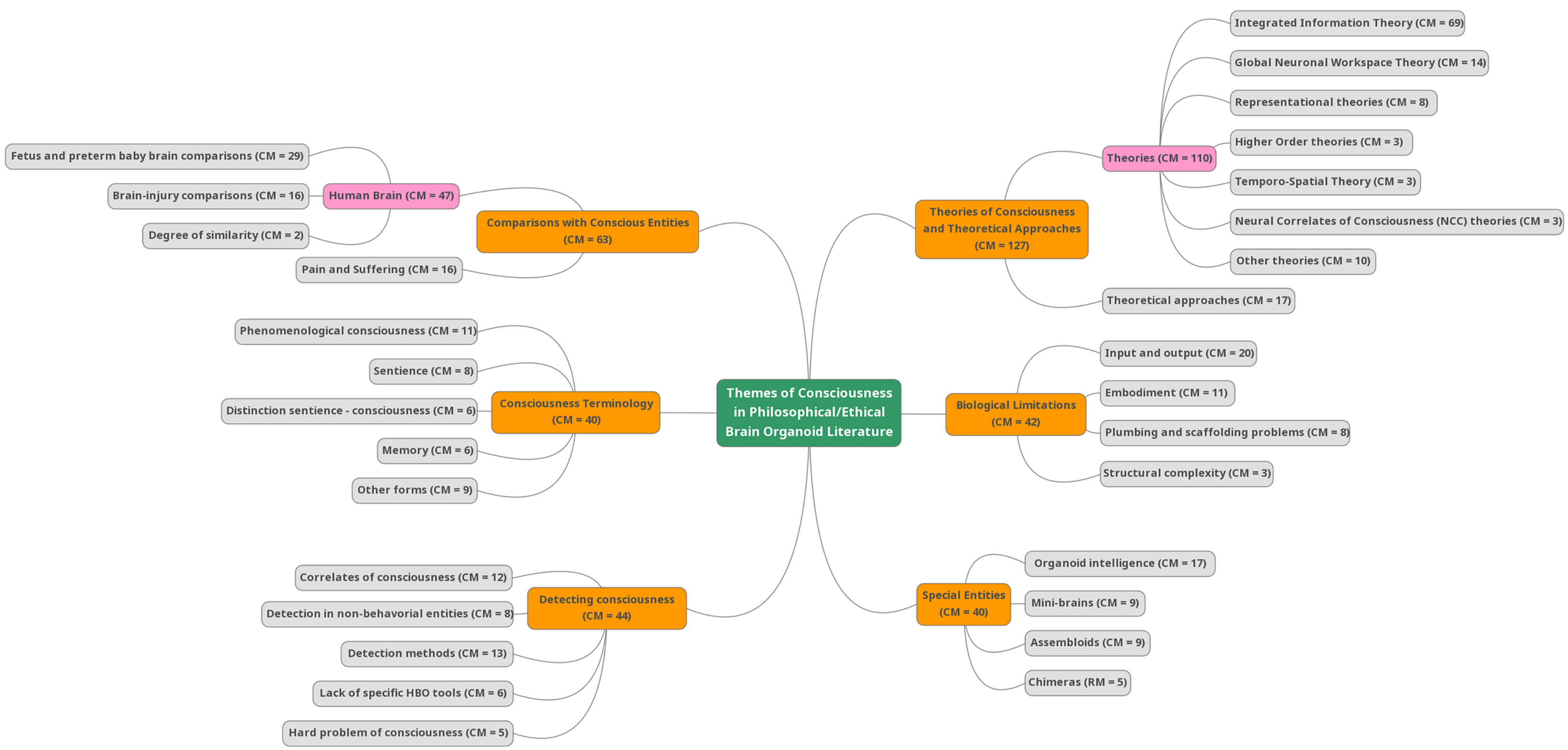

Figure 2. A tree diagram on the results of themes of consciousness found in philosophical/ethical brain organoid literature. The six themes branch off from the starting center node. Each of these themes then branches into subthemes or topics.

more than two are presented in Table 1. We observed that 10 publications discuss more than one theory, while seven publications discuss only IIT, and seven publications do not discuss any of the theories with a CM total of more than two.

Integrated Information Theory (IIT)

Integrated Information Theory (IIT), with a CM of 33 in total, emphasizes that the nature of consciousness is phenomenal consciousness (Owen et al. 2024). The predicted structure for consciousness would be a “maximally irreducible cause–effect structure” that represents the integrated information associated with consciousness (Gaillard 2024; Niikawa et al. 2022; Owen et al. 2024). This structure would be located in the posterior cerebral cortex in a “hot zone” where neurons are sufficiently structured for reciprocal projections (Owen et al. 2024).

The IIT is based on five phenomenological axioms about the nature of consciousness, which state that subjective experience is intrinsic, specific, unitary or integrated, definite, and structured (Gaillard 2024). Five postulates about the nature of the physical substrate of consciousness (PSC) are inferred from these axioms (Lavazza and Massimini 2018b). An example of a postulate is that “for a conscious state to be integrated, each part of the system must be connected with the rest of the system through causal interactions” (Gaillard 2024).

The idea is that the level of consciousness is associated with the amount of integrated information (Gaillard 2024; Owen et al. 2024). To quantify the ability of a system to integrate information, the IIT proposes both a theoretical measure (Φ) and empirical metrics (A. Lavazza 2021b). Here, Φ is the amount of causally effective integrated information available to a system, and maximum of Φ indicates consciousness (Montoya and Montoya 2023; Owen et al. 2024). Since the IIT holds that a nonzero value for Φ implies that a system is conscious, the IIT has no minimum threshold for the determination of consciousness as integrated information (Montoya and Montoya 2023). As a consequence, even bacteria, photodiodes, transistors, minerals, and atoms could be minimally conscious in some way, depending on whether they can be interpreted as systems that generate integrated information (Niikawa et al. 2022; Zilio and Lavazza 2023).

An example of a frequently discussed empirical metric of IIT is the Perturbational Complexity Index (PCI), which is inspired by the main postulate of IIT and measures the internal complexity of brain networks (Lavazza 2021a; Lavazza and Massimini 2018b). To calculate the PCI, the cerebral cortex is locally perturbed via transcranial magnetic stimulation (TMS), and the complexity of the electrical response of the rest of the brain is measured via electroencephalography (EEG) (Ankeny and Wolvetang 2021; Croxford and Bayne 2024; Gaillard 2024; Jeziorski et al. 2023; Kreitmair 2023; Lavazza 2020, 2021a, 2021b; Lavazza and Massimini 2018a, 2018b; Lavazza and Pizzetti 2020; Milford, Shaw, and Starke 2023; Owen et al. 2024; Sawai et al. 2022). Research indicates that the PCI reliably distinguishes between different levels of consciousness in patients who are wakeful, asleep, or under anesthesia, as well as those emerging from a coma or regaining a minimal level of consciousness (Lavazza and Massimini 2018a, 2018b; Milford, Shaw, and Starke 2023).

The IIT is the only theory that allows HBOs to be conscious, as it proposes measures that are independent of sensory processing, motor behavior, and connection with the environment (Lavazza and Massimini 2018a).

Global Neuronal Workspace Theory (GNWT)

Global Neuronal Workspace Theory (GNWT) with 14 CMs emphasizes that the nature of consciousness is access consciousness (Owen et al. 2024). The predicted structure for consciousness would be a workspace in the cerebral cortex, consisting of a network of long-range cortical neurons, that stores information and makes it globally available to all specialized systems throughout the brain, including memory, attention, and perception (Kreitmair 2023; Montoya and Montoya 2023; Owen et al. 2024). A state is conscious if and only if it is present in the global neuronal workspace (Kreitmair 2023; Owen et al. 2024).

Like IIT, GNWT states that consciousness can exist in the absence of interaction with the environment (Lavazza 2020; Zilio and Lavazza 2023). Consequently, for an HBO, developing a global workspace that receives and stores information and specialized systems that deliver the information might be sufficient (Owen et al. 2024). This means that if an HBO grows in such a way as to resemble long-range patterns of cortico-cortical interactions and sufficient functional and anatomical differentiation, it could acquire an initial form of consciousness (Zilio and Lavazza 2023). However, current HBOs are only a few millimeters, which means that these centimeter-long connections cannot be present (Lavazza 2020).

Representational Theories

Representational Theories with a CM of eight and discussed by two authors comprise a wide range of theories having a shared commitment to a "representationalist" conception of consciousness (Croxford and Bayne 2024). They state that consciousness depends on the degree of sophistication of representational capacities (Niikawa et al. 2022). Representational theories can be divided into first-order and higher order representational theories. While first-order and higher order representationalists disagree about the kind of representational structure that is required for consciousness, they agree about what is called the "representationalist constraint," namely, that only representational systems are candidates for being conscious (Croxford and Bayne 2024).

Our brain seems to develop in such way that it first gains first-order conceptions of consciousness, followed by higher order conceptions of consciousness (Niikawa et al. 2022). If an HBO's neural structure only matches that of a human brain in the first order, it could only be conscious according to the first-order representational theory. However, borderline cases may arise when there is uncertainty about the first-order representational capacity of an HBO, posing challenges for both types of theories in determining consciousness (Niikawa et al. 2022). Moreover, it appears unlikely that in vitro HBOs qualify as representational systems in the absence of a body (Croxford and Bayne 2024).

Higher Order Theories (HOT)

Higher Order Theories (HOT) of consciousness, with a CM of 3, argue that a state is conscious only if one can represent oneself as being in that state (Kreitmair 2023). Consciousness would require activity in the prefrontal cortex, but it is not clear what information activity in the prefrontal cortex would provide about the specific content of experience (Kreitmair 2023). Given that the focus lies on self-awareness and higher order thought, it will probably not predict the occurrence of consciousness in an HBO (Montoya and Montoya 2023).

Temporo-Spatial Theory (TTC)

The Temporo-Spatial Theory (TTC) presupposes the integration of sensory stimuli as basic element of human consciousness and has a CM total of 3 (Lavazza 2021a). The focus is not on an entity's consciousness developed from its own dynamic spatiotemporal structure, but on how it matches with the surrounding spatiotemporal structure (Zilio and Lavazza 2023). In this way, an HBO would be capable of developing this structure only in the presence of a spatiotemporal context, provided by the rest of the body and the environment (Lavazza 2020; Zilio and Lavazza 2023).

IIT, GNWT, HOT, and TTC are mentioned as examples of Neural Correlates of Consciousness (NCC) theories in the selected publications, which make testable predictions about the minimal biophysical or neural mechanisms sufficient to produce conscious experience, known as NCC, based on the idea that consciousness may arise only from specific areas of the brain (Jeziorski et al. 2023; Lavazza 2021a; Montoya and Montoya 2023; Zilio and Lavazza 2023).

Theoretical Approaches

As there is no consensus about what standard theory of consciousness is the most promising and different theories cover different concepts of consciousness, most authors suggest that a complementary approach that considers features of different theories might be helpful in informing the neuroethical debate on HBOs (Astobiza 2023; Gaillard 2024; Niikawa et al. 2022; Owen et al. 2024; Shepherd 2018; Zilio and Lavazza 2023). Only Lavazza and Massimini (2018b) suggest that there is a need for a theory-first approach with a general theory of consciousness that attempts to explain what experience is and what type of physical systems can have it, relying on IIT as the general theory of consciousness (Lavazza and Massimini 2018b).

In response to this theory-first approach, two authors suggest moving away from any theoretical approach by focusing on processes that differentiate various states of brain activity, such as brains in coma versus brains under anesthesia (Shepherd 2018). Moreover, a constraint-based approach could be applied by considering what constraints on consciousness might suggest with respect to consciousness in HBOs (Croxford and Bayne 2024).

Comparisons with Conscious Entities

Comparisons with Conscious Entities is the second most discussed of the six themes in the literature, with a CM total of 63. Within the theme, we found two general topics of discussion, namely, comparisons with consciousness in the human brain (CM = 47) and comparisons with pain and suffering in conscious entities (CM = 16).

The Human Brain

Within the topic of the human brain, comparisons are made between HBOs and the brains of human fetuses, preterm infants, and injured brains. HBOs resemble both genetic and developmental processes of the human brain in terms of structure and electrical activity (Lavazza 2020, 2021a, 2021b; Lavazza and Pizzetti 2020; Milford, Shaw, and Starke 2023; Niikawa et al. 2022; Zilio and Lavazza 2023). Transcriptional analysis indicates that after 2.5 months, HBO cortical neurons resemble those of the midfetal brain (19–24 weeks post conception) (Lavazza 2021a, 2021b; Lavazza and Massimini 2018b; Milford, Shaw, and Starke 2023). Ten-month-old organoids exhibit oscillatory electrical activity akin to preterm infants' EEG patterns, suggesting that they can develop complex brain activity, including synaptic firing rates and various brain wave patterns (Croxford and Bayne 2024; Lavazza 2021a, 2021b; Lavazza and Pizzetti 2020; Milford, Shaw, and Starke 2023; Owen et al. 2024; Sawai et al. 2019, 2022; Zilio and Lavazza 2023). A machine-learned model confirmed no significant differences in EEG patterns between HBOs and preterm babies (Lavazza 2021a, 2021b; Lavazza and Pizzetti 2020; Owen et al. 2024). In addition to their resemblance in electrical activity, HBOs acquire structural traits of mature neurons, including dendritic spine-like structures, which form neuronal networks displaying self-organized patterns of activity (Lavazza 2020, 2021b, 2021a). Although these findings are potentially significant, some authors suggest that the findings do not strongly support consciousness in HBOs (Croxford and Bayne 2024; Jeziorski et al. 2023; Koplin and Savulescu 2019; Lavazza 2021a; Owen et al. 2024; Sawai et al. 2022; Zilio and Lavazza 2023). For example, the similarities observed may relate more to the neural functions essential for cognitive development rather than to consciousness itself (Zilio and Lavazza 2023). Additionally, the fetal brain benefits from bidirectional communication with the body, which HBOs lack (Croxford and Bayne 2024; Lavazza 2021b). Koplin and Savulescu (2019) additionally suggest that it is possible to infer whether HBOs are conscious based on their structure, particularly in relation to the threshold of consciousness development in human fetuses, which is thought to begin at approximately 20 weeks of gestational age. This raises the argument that HBOs may lack a rudimentary form of consciousness until they resemble the fetal brain at this developmental stage.

An analogy between HBOs and brain-injured patients is often made, as both are noncommunicative, unresponsive, and unable to provide behavioral or communicative indicators of consciousness (Gaillard 2024; Lavazza and Massimini 2018b; Owen et al. 2024). Consciousness in brain-injured patients has been diagnosed as "islands of consciousness" or "islands of awareness," referring to "some conscious stream whose contents cannot be conveyed through muscular output and are not modified by sensory input from the body of the outside environment" (Astobiza 2023; Croxford and Bayne 2024; Kreitmair 2023). While consciousness in HBOs in the absence of a body may be similar to these islands of consciousness, HBOs do not have a history of clear indicators of consciousness through communication and observable behavior, such as brain-injured patients (Lavazza and Reichlin 2023; Owen et al. 2024).

The question remains as to which degree of similarity is needed to make plausible inferences about the capacity of consciousness in HBOs. For example, it remains uncertain whether HBOs need to perfectly mimic the organization of the neurotypical human brain to achieve consciousness, as individuals with disorganized or structurally challenged brains can still exhibit conscious awareness (Jeziorski et al. 2023). Future research may clarify the relationship between HBOs and conscious human brains (Jeziorski et al. 2023; Owen et al. 2024; Zilio and Lavazza 2023).

Pain and Suffering

Although HBOs lack pain receptors, some authors suggest that an isolated HBO may theoretically experience pain or discomfort (Koplin and Savulescu 2019; Lavazza 2020). This claim is based on analogies with phenomena such as phantom pain, where pain is experienced in the absence of a physical body part or sensory nerve fibers (Lavazza 2020). Furthermore, unlike animals, HBOs might not suffer from the deprivation of typical behaviors but could instead experience pain and discomfort akin to that reported in patients with altered states of consciousness (Lavazza and Massimini 2018b). Additionally, authors claim that they may endure sensory deprivation, reflecting a "defective" state of consciousness regarding input reception (Koplin and Savulescu 2019; Zilio and Lavazza 2023).

Detecting Consciousness

In addition to theories of consciousness, methods to detect the potential for consciousness in HBOs are also discussed in the literature. With a CM total of 44, Detecting Consciousness is the third most discussed theme within the six themes. It mainly comprises the NCC (CM = 12), followed by some methods to detect consciousness in HBOs based on what we know about NCC (CM = 10).

Neuroscientists and philosophers have already been searching a long time for the minimal biophysical or neural mechanisms sufficient to produce conscious experiences, known as NCC (Jeziorski et al. 2023;

Kreitmair 2023). If these could be identified, inferences could be made about the presence and nature of consciousness on the basis of brain states (Kreitmair 2023). This makes it possible to predict the presence of conscious states in nonverbal and nonbehavioral entities, such as brain-injured patients and HBOs (Astobiza 2023; Kreitmair 2023; Zilio and Lavazza 2023). In this way, some features that are likely to be necessarily associated with the presence of consciousness in the human brain can be used to make hypotheses about the presence of consciousness in HBOs (Kreitmair 2023; Lavazza 2021b; Lavazza and Reichlin 2023).

One way is to measure HBO electrical activity via multielectrode arrays since consciousness is strongly correlated with irregular low-amplitude EEG activity in the 20–70 Hz range (Ankeny and Wolvetang 2021; Koplin and Savulescu 2019; Lavazza 2021a). However, this information can provide inconclusive elements for the assessment of possible forms of consciousness (Lavazza 2021a). Moreover, the bispectral index (BIS), which combines different features of the EEG to gauge anesthetic depth in anesthetized patients, could be performed in HBOs complemented with other types of analyses (Ankeny and Wolvetang 2021; Lavazza and Pizzetti 2020). Similarly, magnetoencephalography (MEG) is proposed as a valuable method for comparing magnetic fields generated by electrical activity in HBOs and in the human brain (Ankeny and Wolvetang 2021; Lavazza and Pizzetti 2020). In addition, while it has been suggested that the level of human consciousness varies depending on the glucose metabolic levels of our brain, some unconscious organisms can also metabolize glucose (Niikawa et al. 2022). Other authors mention the importance of firing patterns and connectivity benchmarks as reliable correlates of consciousness (Lavazza 2021a; Niikawa et al. 2022). As previously described, the PCI, an important metric of IIT that combines TMS and EEG recordings, appears to be a reliable parameter for measuring consciousness and could be promising for HBOs (Ankeny and Wolvetang 2021; Croxford and Bayne 2024; Lavazza 2021a).

However, empirical indicators in the human brain do not necessarily indicate the same phenomenon in HBOs (Kreitmair 2023; Owen et al. 2024). Moreover, HBOs do not resemble fully grown human brains, on which the current models of consciousness in cognitive neuroscience are based (Gaillard 2024; Kreitmair 2023). Therefore, new methods to objectively assess the capacity for consciousness have to be developed for HBOs (Lavazza 2021b; Lavazza and Massimini 2018b; Lavazza and Pizzetti 2020). Besides explaining functional aspects of consciousness in the brain, there is also a need to understand the phenomenological dimension of conscious experience, which is considered the hard problem of consciousness (Hartung, Morales Pantoja, and Smirnova 2023; Milford, Shaw, and Starke 2023; Sawai et al. 2022).

Special Entities

Special Entities, with a CM total of 42, focuses on ideas or entities that are created using HBOs to discuss the possibility for consciousness. We identified four different topics of discussion in the literature: organoid intelligence, assembloids, mini-brains, and chimeras. Assembloids are compounds of organoids that replicate distinct brain regions or other organs (Gaillard 2024; Kreitmair 2023). The topic Organoid Intelligence has a CM of 19, dealing with different subtopics, such as DishBrain, learning, and synthetic biological intelligence. Chimeras is the least discussed with a CM of 5 and focuses specifically on cerebral chimeras to emphasize the focus on HBO transplantation.

Organoid intelligence, first introduced in 2023 by Smirnova and colleagues, is considered as a novel interdisciplinary field at the intersection of biological computing and brain–machine interface technologies, with a focus on the development of biologically inspired intelligent systems using HBOs (Hartung, Morales Pantoja, and Smirnova 2023; Lavazza and Reichlin 2023). To study organoid intelligence, new miniaturized instruments and an increase in the size of brain organoids are needed (Lavazza and Reichlin 2023). An example of a first step toward organoid intelligence is DishBrain, with a CM of 8, a system developed by Kagan and colleagues to explore the learning ability of human neuronal cultures in a dish (Hartung, Morales Pantoja, and Smirnova 2023; Milford, Shaw, and Starke 2023; Montoya and Montoya 2023). Two of the selected publications are entirely devoted to the possible emergence of consciousness in this entity (Milford, Shaw, and Starke 2023; Montoya and Montoya 2023). Referring to HBOs as "mini-brains" can be misleading, as they still lack most of the functional and anatomical characteristics found in the human brain (Lavazza and Massimini 2018b; Lavazza and Pizzetti 2020; Zilio and Lavazza 2023). A better approach might be to imagine them as miniature brain regions that mimic specific properties, rather than as whole brains (Gaillard 2024). Assembloids offer several advantages, such as overcoming HBO growth limits, enabling sensory channels, and better modeling of brain region interactions, which could result in substrates of consciousness (Lavazza 2021a; Jeziorski et al.

2023; Owen et al. 2024; Sawai et al. 2019; Zilio and Lavazza 2023). However, Gaillard (2024) argue that the critical mass of neurons and long-distance connections required for consciousness in biological settings are still out of reach of stem-cell biotechnology. Finally, studies with chimeras show that transplanted HBOs can integrate into the brain without harming the animal and may contribute to perception (Lavazza and Reichlin 2023). In the future, chimeras created by transplanting HBOs in animals may face heightened stress levels compared to standard laboratory animals due to the unique biological complexities of such integrations. Additionally, researchers expressed the possibility that the transplanted HBOs could develop conscious experiences within the host animal, raising further ethical considerations (Hartung, Morales Pantoja, and Smirnova 2023; Lavazza and Reichlin 2023; Owen et al. 2024).

Biological Limitations

This theme focuses on existing biological limitations affecting organoid maturity, size, and development affecting their capacity to generate consciousness and on efforts already being made to overcome these limitations. The main limitation for consciousness in HBOs discussed in the literature is the absence of sensory input and motor output when HBOs are created in a dish, with a CM of 20 out of 46. Second, the absence of a body is most discussed (CM = 11), followed by the so-called "plumbing and scaffolding problem" (CM = 9).

While it is still unknown whether sensory input or motor output, during development if not in adulthood, is required for the human brain to be conscious, it is argued that HBOs not receiving sensory inputs cannot have awareness, self-consciousness, phenomenal consciousness, or access consciousness (Ankeny and Wolvetang 2021; Jeziorski et al. 2023; Sawai et al. 2019). Ongoing efforts focus on establishing sensory stimuli and motor outputs for HBOs (Jeziorski et al. 2023). For example, it is already possible to create HBOs assembled with photoreceptor-like cells, making them sensitive to the input of external light stimuli, and HBOs have been connected to mouse spinal cords, resulting in HBO-induced muscle contractions (Koplin and Savulescu 2019; Kreitmair 2023; Lavazza 2020; Lavazza and Massimini 2018b; Lavazza and Pizzetti 2020; Zilio and Lavazza 2023). This finding suggests that afferent stimulation that might trigger simple sensations can be transmitted to HBOs (Lavazza 2021a, 2021b; Lavazza and Massimini 2018b; Zilio and Lavazza 2023).

Two authors argue that consciousness cannot exist divorced from a body (Croxford and Bayne 2024; Jeziorski et al. 2023). Croxford and Bayne refer to HBOs as disembodied neural organoids (DNOs), arguing that DNOs cannot be conscious at all because of the "embodiment constraint," stating that "only a brain with a history of embodiment and sensorimotor interaction with the world has a genuine chance of supporting consciousness" (Croxford and Bayne 2024). To overcome this limitation, HBOs are being connected to controllable robotic "bodies" or implanted into animal brains (Koplin and Savulescu 2019).

Moreover, most HBOs lack supporting structures, such as vascularization, leading to the "plumbing and scaffolding problem," that is, how to bring oxygen and nutrients and grow organoids beyond the current millimeter scale (Lavazza 2020; Lavazza and Massimini 2018b; Lavazza and Pizzetti 2020). HBOs with greater structural complexity may demonstrate greater cognitive and executive abilities than less complex HBOs (Zilio and Lavazza 2023). However, it is not yet known whether the lack of supporting structures compromises the capacity for consciousness (Gaillard 2024; Jeziorski et al. 2023).

Consciousness Terminology

Consciousness Terminology is the least discussed of the six themes, with a CM total of 41. It focuses on the terminology used when discussing consciousness in HBOs, and we find that phenomenological consciousness (CM = 11) and sentience (CM = 8) are the most frequently used terms.

Authors refer mostly to phenomenological consciousness when discussing consciousness (Kreitmair 2023; Sawai et al. 2019, 2022). It is considered any subjective phenomenal experience with qualitative content (Jeziorski et al. 2023; Sawai et al. 2019). It is therefore characterized by what-it's-likeness and sometimes called "qualitative consciousness" or "qualia" (Kreitmair 2023; Owen et al. 2024; Sawai et al. 2022; Shepherd 2018). For HBOs, it would involve not only the ability to react to external stimuli and/or produce internal activity, but also the ability to feel something in doing so (Zilio and Lavazza 2023). Sentience is mostly considered a minimal form of consciousness and defined as "the basic capacity to experience negative subjective states, such as physical pain and other forms of suffering, and positive subjective states, such as pleasure" (Lavazza and Massimini 2018b; Lavazza and Reichlin 2023; Sawai et al. 2019; Zilio and Lavazza 2023). It is argued that it is reasonable to think that HBOs could present a basic form of sentience rather than other types of consciousness (Zilio and Lavazza 2023). Consciousness is often used interchangeably with sentience, but some authors argue that sentience and consciousness should be distinguished because it may be imprecise and may lead to some conceptual conflations (Kagan et al. 2022; Lavazza and Reichlin 2023). Additionally, while the two are intuitively related and would typically coexist, it is possible to imagine certain situations where they exist independently (Kagan et al. 2022).

Memory (CM = 6) is mentioned as an example of phenomenological consciousness. According to the Cell Assembly Hypothesis, it is characterized by a synchronized and spontaneous neural activity that has already been discovered in cortical organoids (Lavazza 2021a; Lavazza and Pizzetti 2020; Sawai et al. 2019). Other less frequently used forms of consciousness mentioned in the literature are self-consciousness (CM = 4) and access consciousness (CM = 2) (Koplin and Savulescu 2019; Owen et al. 2024; Sawai et al. 2019). However, these two forms of consciousness are considered too complex for HBOs (Kreitmair 2023; Sawai et al. 2019). Other forms of consciousness mentioned are awareness, self-representation, creature consciousness, and state consciousness (Milford, Shaw, and Starke 2023; Niikawa et al. 2022; Owen et al. 2024).

DISCUSSION

The results described are primarily topics and arguments with more in-depth development and discussion. This section addresses less developed or important considerations regarding the debate around concepts of consciousness in HBOs by evaluating IIT and considering pragmatic implications, by examining the need for clear and concise communication, discussions dominated by particular authors, future considerations regarding organoid intelligence (OI), and the limitations of this systematic review.

IIT and Pragmatist Implications

We see that IIT is the most proposed theory in the selected literature to predict consciousness in HBOs. This is not surprising, as IIT has been considered as a leading theory of consciousness in neuroscience due to its measurable predications, such as Φ (integrated information) and the Perturbational Complexity Index (PCI). However, authors have become more cautious when applying IIT as a general theory of consciousness (Cerullo 2015; Gaillard 2024; Goddard et al. 2023; Searle 2013; Zilio 2019). Several neuroscientists and philosophers of mind express concerns about IIT's empirical testability, with some even labeling it as pseudoscience in an open letter. They argue that IIT's broad applicability to varied systems makes it immune to falsification and that "IIT requires meaningful empirical tests before being heralded as a 'leading' or 'well-established' theory" (IIT-Concerned et al. 2023). These concerns were brought to the forefront in *Nature Neuroscience*, where the original letter was formally published as "What makes a theory of consciousness unscientific?," followed by a series of responses and counterresponses (Arnold et al. 2025; Gomez-Marin and Seth 2025; Tononi et al. 2025). This controversy extends to HBOs, where IIT predicts that any entity capable of generating integrated information could be minimally conscious (Niikawa et al. 2022; Zilio and Lavazza 2023). In this way, IIT was the only theory in the reviewed literature that predicts the possibility of consciousness in HBOs, even in the absence of sensory input, motor output, or environmental interaction.

The contentious nature of IIT, along with the lack of theoretical consensus in the literature, highlights the broader epistemological dilemma of empirically measuring consciousness and conscious experience. It might thus be useful to turn, as Stoeklé et al. (2022, 110) also previously suggested, toward a more pragmatist approach to both consciousness and HBOs. Rather than seeking a single, overarching theory of consciousness, researchers could focus on developing shared vocabulary, concepts, and contextual decision-making frameworks to responsibly and carefully navigate the moral and regulatory considerations around HBO research.

What does this look like when we attempt to answer the question of what *is* consciousness? A starting point might be to take a cue from American pragmatist William James (1907) and first ask, what do we *practically mean* by consciousness? James gives an example of answering similar questions via a story about a squirrel. In James's example, a man is trying to get around a tree, and on the opposite side of the tree there is a squirrel. As the man moves around the tree, the squirrel also moves, always keeping the tree between itself and the man. The following question arises: Does the man go around the squirrel? From one perspective, the man does go around the squirrel because he completes a circular path around the tree, which also contains the squirrel. From another perspective, the man does not go around the squirrel because he never sees the back of the squirrel; the squirrel keeps turning on the tree, so the man never sees it. The dispute about whether the man goes around the squirrel can be resolved by clarifying what "going around" means in practical terms.

Just as the squirrel example requires us to clarify what "going around" means, the question of consciousness requires us to practically define what me mean by "consciousness." Are we referring to self-awareness, the ability to process information, or some other criteria? Moreover, a pragmatic approach would then have us consider the practical implications of HBOs as potentially (un)conscious. This includes how such designations might affect research practices, ethical guidelines, and societal perceptions. One could assume a degree of consciousness and consider the practical philosophical and ethical implications (Barnhart and Dierickx 2023).

Communication and Consensus Building

As the increase in organoid research has been met with great expectations from both the scientific community and the public, it is crucial to be prudent when discussing the capabilities of HBOs as there is potential for miscommunication, misinformation, and unscientific oversimplication (Bassil 2024). As mentioned before, referring to HBOs as "mini-brains" could be misleading and could create an impression that HBOs are somehow human-like or possess advanced cognitive abilities. As various literature highlights, HBOs are simplified models and still lack most of the functional and anatomical characteristics found in full human brains (Bassil 2024; Gaillard 2024; Lavazza and Chinaia 2024; Lavazza and Massimini 2018b; Lavazza and Pizzetti 2020; Zilio and Lavazza 2023). Another example previously mentioned is the resemblance of electrical activity with that of preterm babies. To study this, researchers used cortical spheroids, which are highly simplified regionalized neural organoids. However, in the study, the term "cortical organoids" is used instead of cortical spheroids, which can lead to an overestimation of organoid abilities (Trujillo et al. 2019).

Generally, then, there is a need to ensure that what is communicated about HBOs and how the communication is achieved are appropriate—to provide hope, not hype. The primary goal should be to provide well-reasoned hope, scientific understanding, and thoughtful discussion, rather than unsubstantiated hype or sensationalism. Researchers, ethicists, policymakers, and the broader public must engage in a nuanced, interdisciplinary, and inclusive dialog to build a robust consensus around the capabilities, limitations, and ethical considerations of HBOs. This is especially crucial given the inherent complexity and profound implications surrounding discussions of consciousness in these systems, which span scientific, philosophical, and societal domains that require careful deliberation and collaboration. If this fails, then there is a potential risk of creating further mistrust in organoid research, especially for medical purposes (Bassil 2024).

Discussions Dominated by Particular Authors

The discussion of consciousness in HBOs is dominated by certain authors. Lavazza was the (co-)author of eight publications, and Sawai was the author of two of the 24 publications. As such, ideas surrounding concepts of consciousness are mostly presented from their perspective influencing discussions by other authors. For example, Shepherd starts his discussion by looking at the opinions of Lavazza and Massimini, and Astobiza starts from the opinion of Zilio and Lavazza (Astobiza 2023; Shepherd 2018). We could ask why this field is dominated by these two authors only. One hypothesis could be that research concerning consciousness in HBOs is a slowly emerging field. If so, then the pace of the consciousness debate is outpaced by the speed of bench-lab science. Should it be the case that consciousness somehow does indeed become a morally silent factor for the ethics of HBOs, then the growing body of HBO science may become morally problematic and the ethical discussions would be lagging behind the pace of scientific advancement and output. Another hypothesis could be that scientists and/or ethicists argue that consciousness in HBOs is a less than relevant topic, or that there are perhaps more pressing scientific and moral matters to consider (Barnhart and Dierickx 2023). In any case, it is important that this discussion on HBO consciousness becomes more inclusive to ensure a diversity of viewpoints and to avoid overreliance on the ideas of a few authors.

Future Directions on Organoid Intelligence

A further outgrowth of HBO research is some recent experiments with organoid intelligence (OI). While OI is a relatively new emerging field, it will be promising to study concepts such as learning and memory in HBOs. Indeed, well-controlled follow-up experiments demonstrated that a closed feedback loop seems to be related to apparent learning effects (Smirnova and Hartung 2022). When considering OI, it is important to consider that intelligence corresponds with the ability to perform simple computer functions, not human-level cognition and intelligence (Smirnova and Hartung 2022).

More importantly, we see this line of research as a future direction for philosophical and neuroscientific conversations surrounding concepts of both consciousness and intelligence. With OI and other forms of biocomputing on the horizon, there may be a shift from studying natural organic intelligence and consciousness (as in the human brain or animal brain) to studying synthetic intelligence. These technological advancements prompt us to reevaluate how we define and conceptualize consciousness and intelligence, and to potentially consider the ethical implications that may arise as these emerging technologies challenge traditional understandings.

A key question for the field is whether intelligence, as framed within a computational paradigm, is a more workable concept than consciousness for studying HBOs. Intelligence, when defined as measurable capabilities such as problem-solving, learning, and memory, offers a more concrete and empirically grounded approach. This contrasts with the complex, philosophical, and often elusive nature of consciousness, which lacks universally accepted definitions and measurable markers. By focusing research efforts on the manifestations of intelligence in HBOs, rather than trying to assess their level of consciousness directly, scientists may be able to make more tangible progress in characterizing the emergent properties and functional capabilities of these simplified brain models. This could, in turn, inform our broader understanding of the relationship between intelligence and consciousness, and of how these concepts may be embodied in both natural and synthetic neural systems. Ultimately, a deeper exploration of intelligence in HBOs may serve as a valuable steppingstone toward unraveling the mysteries of consciousness in these and other biological neural networks.

Limitations

A limitation of this review could be that the search for sources is conducted only in English. It may be possible that others have written on concepts of consciousness in HBOs in other languages and are thus not captured in our search. Another limitation of this review is that we focused only on in-depth explanations, according to our inclusion criteria. While we searched various databases to include both scientific and philosophical articles, our emphasis was on how concepts are examined within philosophy, particularly with regard to normative aspects. Given that this review follows a conceptual methodology, modeled on the approach proposed by Strech and Sofaer, it does not involve formal assessment of empirical bias. However, we acknowledge that the process of identifying, interpreting, and categorizing concepts involves an inherent degree of subjectivity. This includes decisions about which conceptual distinctions are significant, how different usages are grouped or contrasted, and how context influences conceptual framing. Additionally, the scope of included literature may shape the visibility of certain conceptual interpretations over others. Finally, the methodology of literature assessment cannot provide any measurement of moral weight or significance to the concepts provided, only the frequency at which these concepts appear in the literature.

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Aileen Van Gyseghem: conceptualization, formal analysis, investigation, methodology, visualization, writing—original draft preparation, writing—review and editing; **Andrew J. Barnhart and Kris Dierickx**: conceptualization, funding acquisition, methodology, supervision, visualization, validation, writing—review and editing. All authors read and approved the final article.

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article or its supplementary materials.

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