New biological entities and their status

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Organoid technology: ethical challenges and responsible use

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Organoid revolution and ethics / All going well?

Human Organoids (HBOs) can be considered a more acceptable form of experimentation than that on human fetuses, animals and voluntary human adults.

No living being is destroyed, damaged or put at risk in tests involving organoids, and their level of scientific reliability might soon be equivalent to that of traditional methods. So, there is no efficiency loss to the detriment of the ill awaiting a cure.

Also, organoids can be cheaper— both in terms of material and working hours— than other forms of experimentation, and their use may make resources available for other relevant uses in the biomedical field.

But we need to be careful in celebrating (from an ethical standpoint)

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Extrinsic and intrinsic ethical issues

In organoid technology different biotechnological developments converge, among which fields that are subject to ongoing ethical debate, the first one being the use of stem cells from embryos (neither extrinsic nor intrinsic)

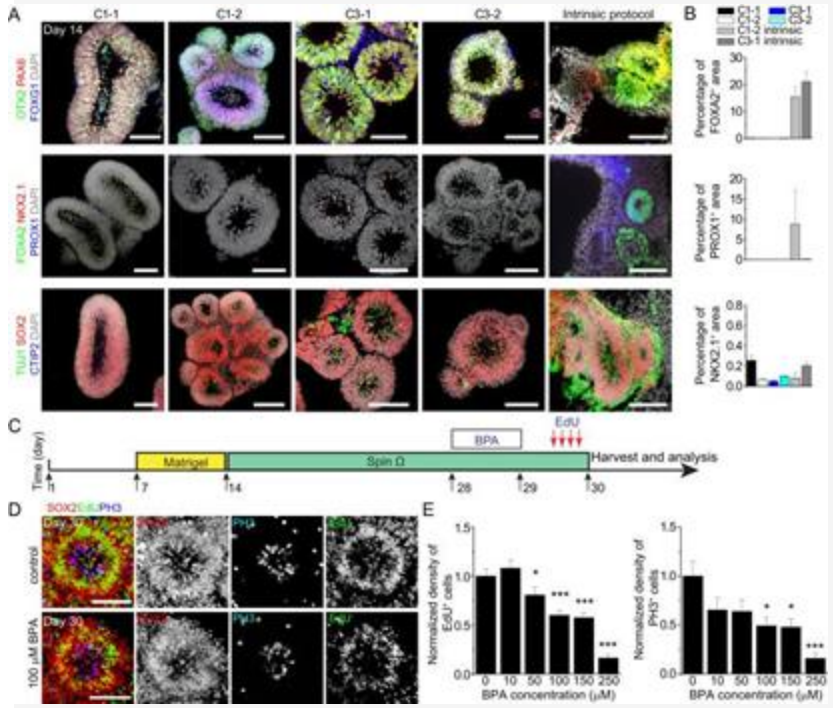
Types of issues	Potential Solutions	Remaining Concerns
Kinds of Donors	Patients /Healthy adults	Embryonic stem cells?
Informed Consent	Different types of consent	What's the best one?
Privacy of Genetic Information	Usual protection	Apt for organoids?
Intellectual Property	No patent for organoids	Is that right? (Now patentable)
Earnings distribution	No monetary reward	Gains only for profit companies?

THE PROBLEM WITH BRAIN ORGANOID SENTIENCE

"The dilemma? When we avoid unethical research by making living models of human brains, we may make our models so good that they themselves deserve some of the kinds of ethical and legal respect that have hindered brain research in human beings. If it looks like a human brain and acts like a human brain, at what point do we have to treat it like a human brain — or a human being?"

"Human Brain Surrogates Research: The Onrushing Ethical Dilemma" Greely, 2021

Human brain organoids: the main ethical concern / 1



A (controversial) study has shown for the first time that brain organoids generated by induced pluripotent stem cells **can develop periodic and regular oscillatory electrical activity that resembles the EEG patterns of premature newborns.**

This means that 10-month-old HBOs, even in the absence of external or subcortical inputs, **can develop according to a specific genetic program typical of all humans.**

The most surprising aspect: an expert software trained with the EEG data of preterm infants was able to evaluate with a good approximation the age of cerebral organoids based on their electrical activity (Trujillo et al., 2019).

New methods of cultivation of cerebral organoids have allowed to generate diverse nerve tracts with functional output (Giandomenico et al., 2019). **Cerebral organoids have proved capable of inducing movement, although not yet a purpose-oriented kind of movement.**

Human brain organoids: the main ethical concern / 2

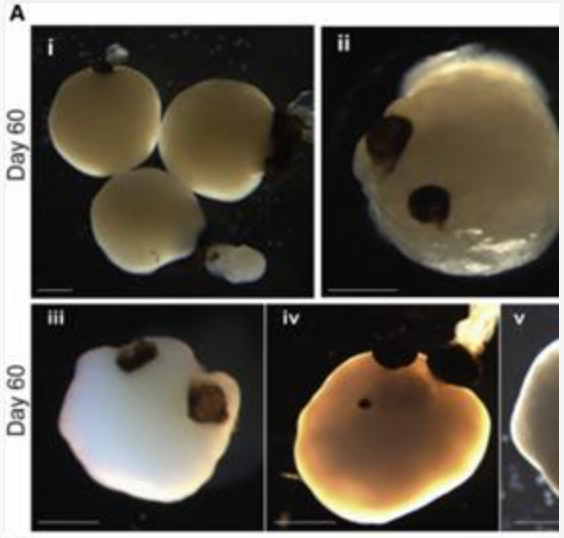


Image: Gabriel et al., 2021

HBOs also show the differentiation of photoreceptor-like cells endowed with proteins for light responsiveness. These photosensitive cells 'can respond to non-invasive, light-based sensory stimulation' (Quadrato et al., 2017). Recently, optic vesicle-containing brain organoids (OVB) have been grown (Gabriel et al., 2021).

These steps forward indicate that it is possible to transmit afferent stimulations to brain organoids.

In another study (Sakaguchi et al., 2019), researchers have managed to visualize in cortical spheroids synchronized and non-synchronized activities in networks and connections between individual neurons. Cells were capable of organizing themselves into clusters and form networks with other nearby clusters. **The manifestation of a synchronized neural activity can be the basis for various relevant brain functions.**

The main ethical concern / 3 – Scientists' view

General themes, domains, and sub-domains	Frequency
On consciousness and moral status	
Consciousness	
Skepticism about consciousness emerging in HBOs today	General
Skepticism about consciousness emerging in HBOs in the future	Variant
Repercussions on the usage of HCOs if consciousness is detected	Typical
Consciousness in HBOs would be similar to that of flies or grasshoppers	Uncommon
Moral status	
There is no ethically relevant difference between HBOs and other tissue products	Typical
There is an ethically relevant difference between HBOs and other tissue products	Variant
Human/non-human chimeras	
Chimeras are no different compared to other animals without HCOs grafts	General
Personal ethical concerns	
No personal ethical concern	Typical

[Lavazza and Chinaia, 2023]

Sentience and consciousness

1. Subjective experience is a general category, within which consciousness can be isolated as a more circumscribed phenomenon.
I take sentience to be the minimum degree at which a living entity can feel something.
I take consciousness to be the phenomenal (higher) level at which an entity can be self-aware as well.
(Some scholars use these terms in other ways)

2. Some scholars hypothesize that these emotions are experienced in a certain way only thanks to the sophisticated processing typical of the nervous system of mammals.

3. But it is not implausible to suppose that a living being can feel pain and experience lack of air even without having an inner model of the world or of itself (Godfrey-Smith, 2018).

Consciousness, moral status, and value

There are two questions about the presence of consciousness in HCOs and their possible moral status.

The first is an ontological and ethical one. It concerns how to identify what consciousness is and what characteristics attribute moral status to an entity.

The second is an epistemic one. It concerns how consciousness can be found and evaluated and the characteristics that allow moral status to be given.

In the case of cerebral organoids, moral status is linked to the presence of forms of sentience/consciousness, so that the identification of the characteristics capable of motivating the attribution of moral status derives from the presence of evidence of consciousness.

SENTIENCE IN BRAIN ORGANOIDS?

- Brain organoids do not (yet) display **behavioral outputs**
- **Proposal**: let's look at the **neural correlates of consciousness** (NCCs)
- **Problem**: different theories account for **different NCCs**

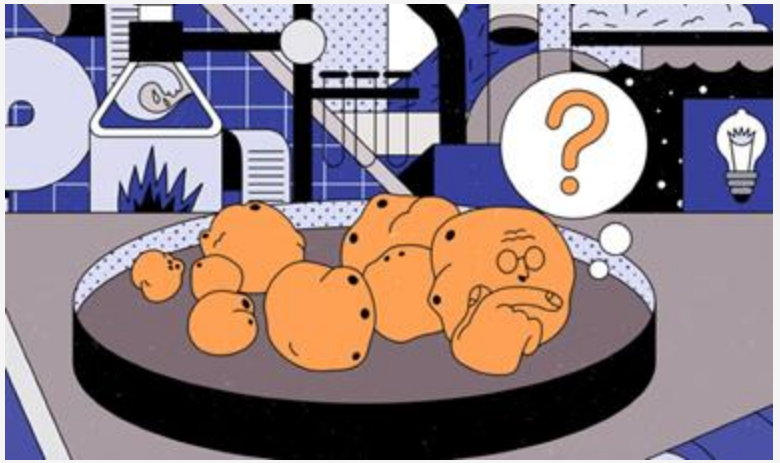


Image from: Reardon, 2020

THEORIES OF CONSCIOUSNESS and BRAIN ORGANOIDS

- Different theories provide a different account of consciousness and possible NCCs

  - Integrated Information Theory (IIT)
  - Global Neuronal Workspace Theory (GNWT)
  - Temporo-spatial Theory of Consciousness (TSTC)
  - Embodied Theory (ET)

Zilio & Lavazza, 2023

THEORIES OF CONSCIOUSNESS and BRAIN ORGANOIDS

Integrated Information Theory	Brain organoids could generate **complex, non-stereotypical integrated information** through recurrent networks (without the need for external stimuli and a relationship with the environment).	
Global Neuronal Workspace Theory	Brain organoids would need **long distance connectivity** and sufficient **anatomical variability** to broadcast information (which can difficult in tiny HBOs, but viable in bigger ones).	
Temporo-spatial Theory	Need to **access to the environment** to develop a structure that can organize the stimuli in a temporal and spatial fashion.	
Embodied Theory	Need for a **body (absent)** → possible solution: connecting HBOs with artificial environments or engrafting them into animals. **(Zilio & Lavazza, 2023)**	

A hot (theoretical) debate on organoid consciousness

- Nikawa et al. (2022) propose a precautionary principle that assumes HBOs have consciousness.
- Croxford and Bayne (2024): Disembodied neural organoids are unlikely to be conscious due to their lack of sensorimotor interaction and representational capacities.
- Gaillard (2024): the need for a broader theoretical perspective, including local theories like Zeki's microconsciousness.
- Kosik (2024): HBOs not conscious yet but potentially conscious as they gain internal processing systems through statistical learning and closed-loop algorithms.
- Levy 2024: moral considerability only grounded in fuctional properties.

WHY IS SENTIENCE / CONSCIOUSNESS IMPORTANT?

- Sentience/consciousness are deemed relevant for the attribution of moral status - *"moral status-qua-consciousness"* (Kreitmeier, 2023)

- Proposal of a precautionary principle (Birch & Browning, 2021)

- Repercussions in research

Consciousness: what it is and how to identify it (a proposal)

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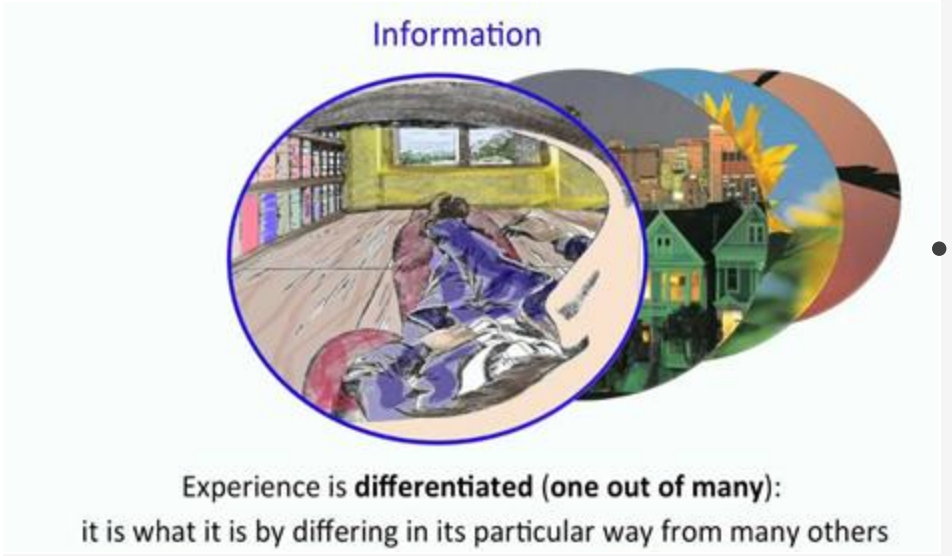

- The **theory of integrated information** (G. Tononi, M. Massimini, C. Koch) posits two phenomenic axioms that give rise to postulates on the properties of brain mechanisms that support consciousness.
- The axioms are: (i) **conscious experience is informative** (each conscious experience differs in its specific ways from countless other possible experiences); (ii) **conscious experience is integrated** (every conscious experience cannot be divided into parts). It follows that a system has subjective experience to the extent that it is capable of integrating information.

2

- This capacity depends on an **optimal balance between differentiation (information) and unity (integration)**, a non-trivial condition for a physical system. On the contrary, at first sight, it would seem that these two properties are extremely difficult to reconcile.

How to measure consciousness (also in organoids) / 1

1 The IIT proposes a **theoretical measure (PHI)** and empirical metrics to **quantify** the ability of a system to integrate information.

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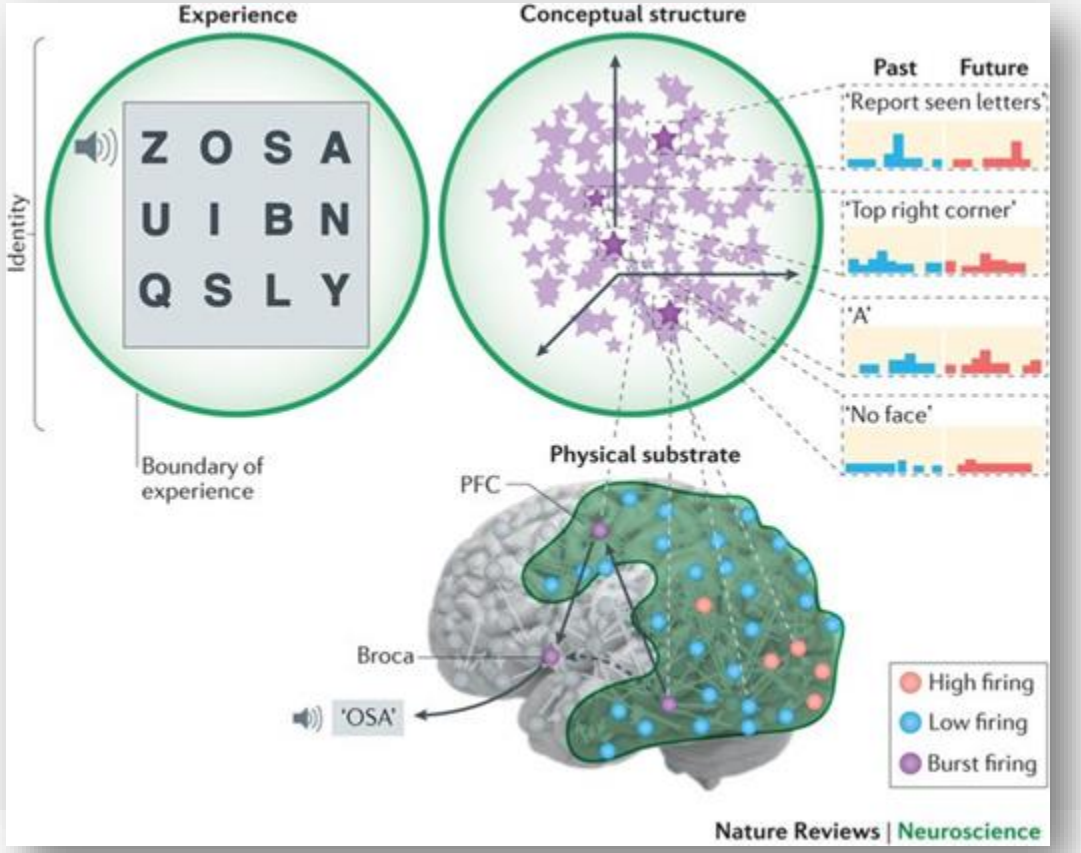
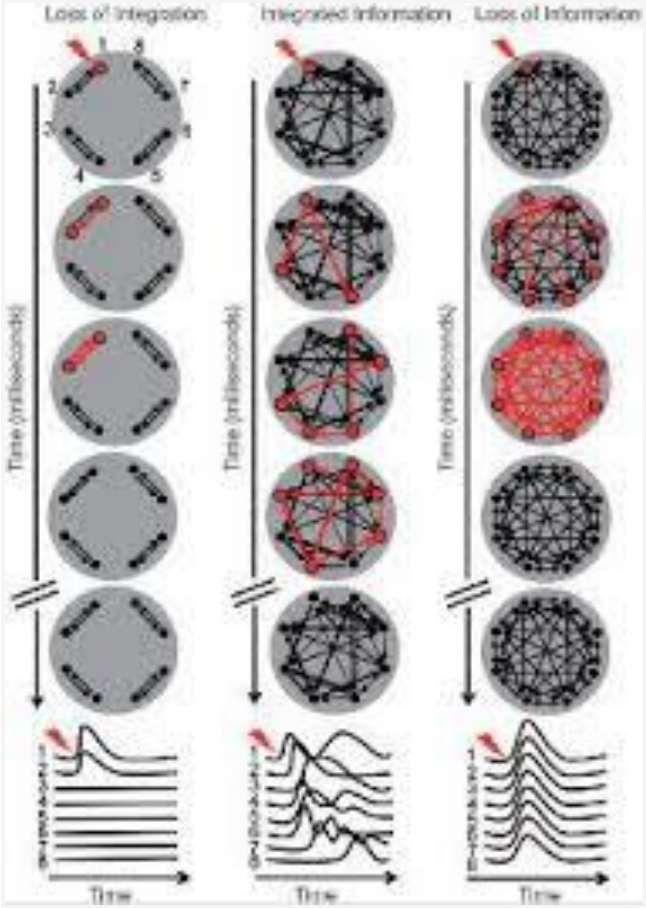


2 The **Perturbational Complexity Index (**PCI) is a parameter inspired by the main postulate of IIT, namely that consciousness is based on the joint presence of integration and differentiation in the brain.

3 **The calculation of the PCI l**ocally involves perturbing the cerebral cortex (by transcranial magnetic stimulation, TMS) and measuring the complexity of the electrical response in the rest of the brain (by EEG).

How to measure consciousness (also in organoids) / 2



1

The basic idea is that **the PCI is low if the interactions between neuronal elements are reduced** (loss of integration, L.), because the response induced by TMS is limited in space. The **PCI is low even if many connected areas react to the perturbation, but they do so in a stereotyped way** (with a loss of differentiation, R.), because in this case the response is wide but not complex.

2

The PCI should only reach high values if the initial disturbance is transmitted to a large network of neuronal elements that react in a differentiated way (C).

3

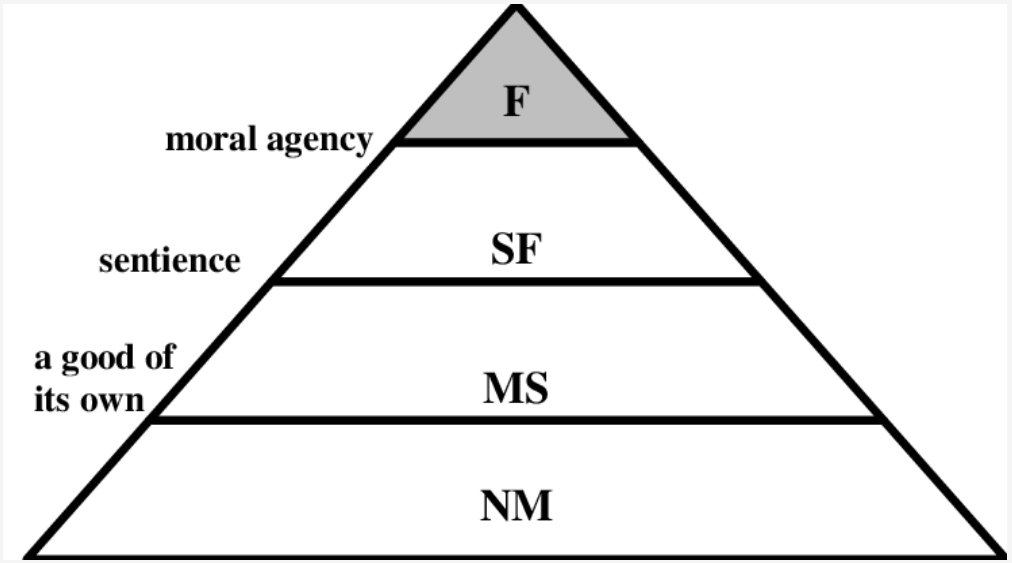
The **PCI is independent of sensory processing**, executive function or motor behavior. **For this reason, with specific technologies, it could also be applied to cerebral organoids**.

(Lavazza and Massimini, 2018)

Moral status and moral value

Moral status is a condition for which a certain entity receives consideration in the ethical sphere for being that entity and not only for its relations with other entities (Jaworska and Tannenbaum, 2018).

Moral status is not equivalent to moral value, the former being a basic condition that does not determine the degree of the latter. Moral status is attributed based on a being's intrinsic properties and, for living beings, can only be attributed to entities that have subjective interests, i.e. interests in having or not having specific subjective experiences and interests in not being harmed in a general sense.



Granting moral status

Subjective interests are linked to certain subjective experiences, so to obtain moral status it is (generally) necessary to have some form of sentience/consciousness.

Moral status can be attributed based on various justifications, the most relevant of which include having a certain relevant moral characteristic, having a biological affiliation o being similar to other entities already granted a moral status.

In the case of HCOs, the necessary premise seems to be the possession of subjective interests and, therefore, of some even minimal form of consciousness, i.e. sentience. If cerebral organoids possessed this characteristic, this would not qualify them as entities with a moral status as such: **they would probably have to reach a certain threshold of complexity.**

(Cf. Lavazza, 2021)

Moral status and value

Once an entity has been given moral status, this does not imply any necessary consequences.

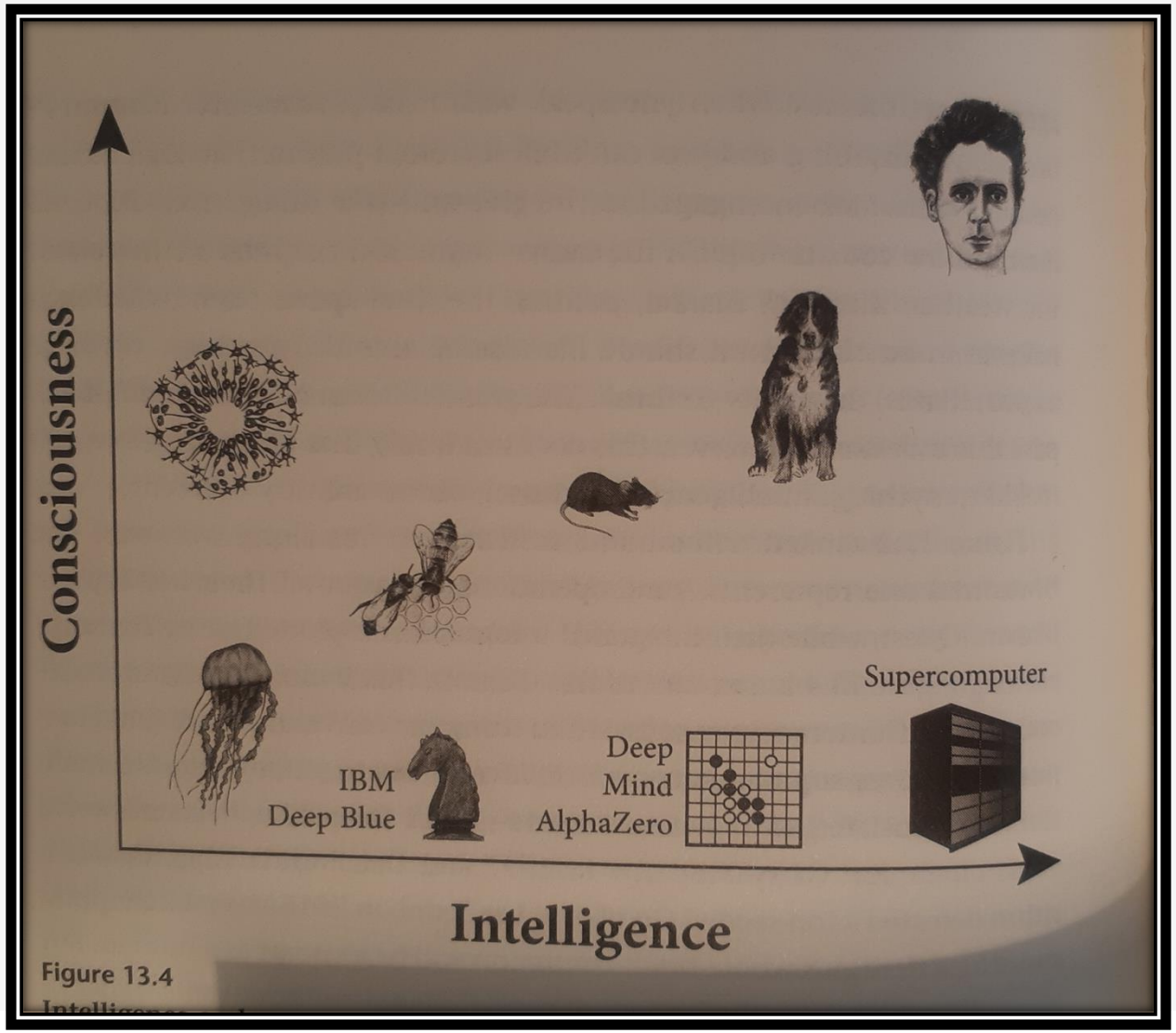
One may consider that there are different levels (threshold) of moral status, or that moral status is a continuum, based on the characteristics and complexity of the psychic life of the entity. **One must specify the moral hierarchy the entity is inserted in, what kind of rights it acquires** and what kind of obligations other moral agents have towards it.

This is based on the premise that obtaining a moral status **in itself** neither implies the acquisition of specific rights, nor imposes specific obligations on other moral agents. **But, in general, entities with moral status deserve special consideration.**

Consciousness, moral status, and value / 3

The dimensions of entities

Human Brain Organoid →



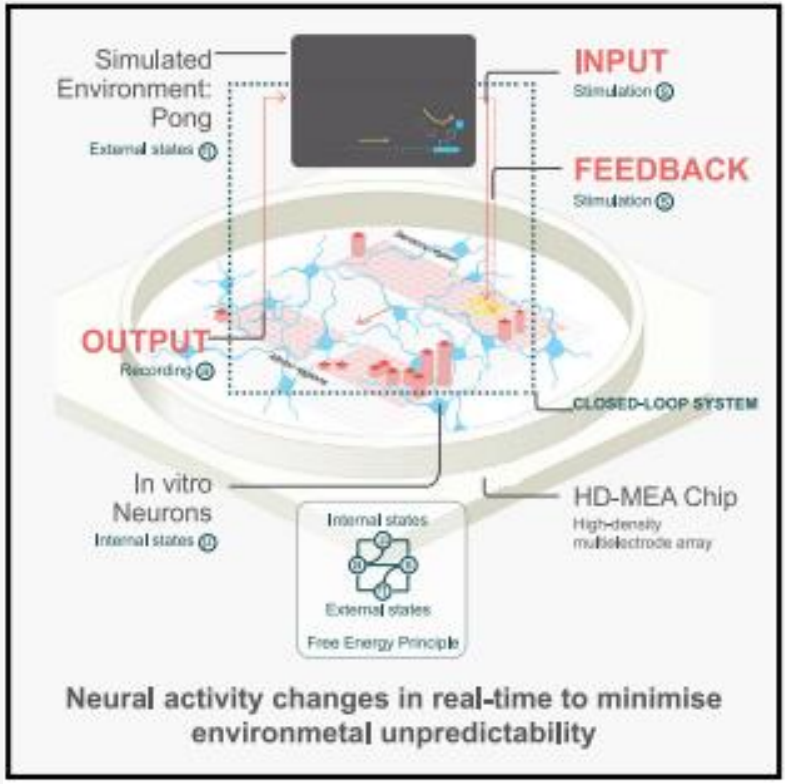
From Koch (2019)

Are sentient HCOs already with us?

1. In vitro neural networks from human or rodent origins are integrated with in silico computing via a high-density multielectrode array. Through electrophysiological stimulation and recording, cultures are embedded in a simulated game-world, mimicking the game “Pong”.

2. Applying implications from the theory of active inference via the free energy principle, we find apparent learning within five minutes of real-time gameplay not observed in control conditions (Kagan et al., 2022).

3. Sentience as being «responsive to sensory impressions» through adaptive internal processes (Friston et al., 2022)



Neural activity changes in real-time to minimise environmetal unpredictability

Chimeric research

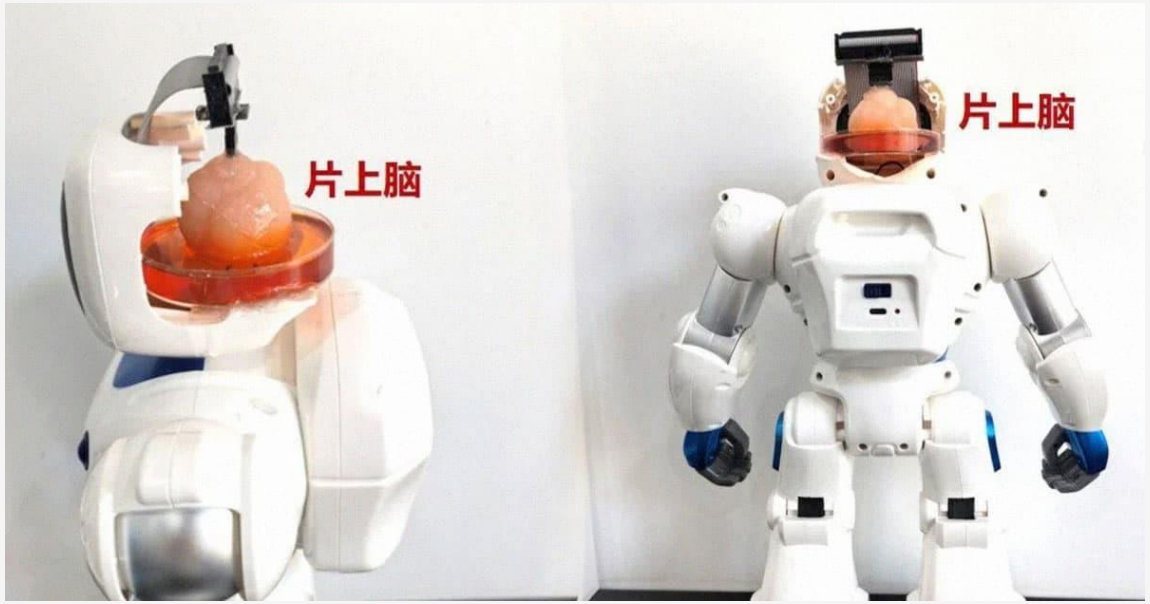
A chimera is a single organism composed of cells with distinct genotypes. Various forms or chimera research have been taking place without much ethical debate, such as transplantation of human cancers cells into mice.

But we might wonder whether it is ethically appropriate to use *in vitro* structures of human origin in chimeric research, especially when this may 'enhance' or 'humanize" a non-human animal. It happens when we introduce human early-stage organoids into the brain of animals. Enhancing means an augmentation of some functions; humanizing means providing a non-human animal with human characteristics.

A relevant concern seems to be that in chimera research we can (inadvertently or on purpose) biologically or morally enhance and humanize a non-human animal. Biologically ***means introducing different cells;*** morally ***means providing them with new higher cognitive functions capable of conferring a diverse moral status (Erler, 2024)***

Robots controlled by human brain organoids?

As the “South China Morning Post” reported July 1, 2024, researchers from Tianjin University and the Southern University of Science and Technology hooked the brain tissue to a neural interface, allowing it to pass on instructions to the humanoid robot body.



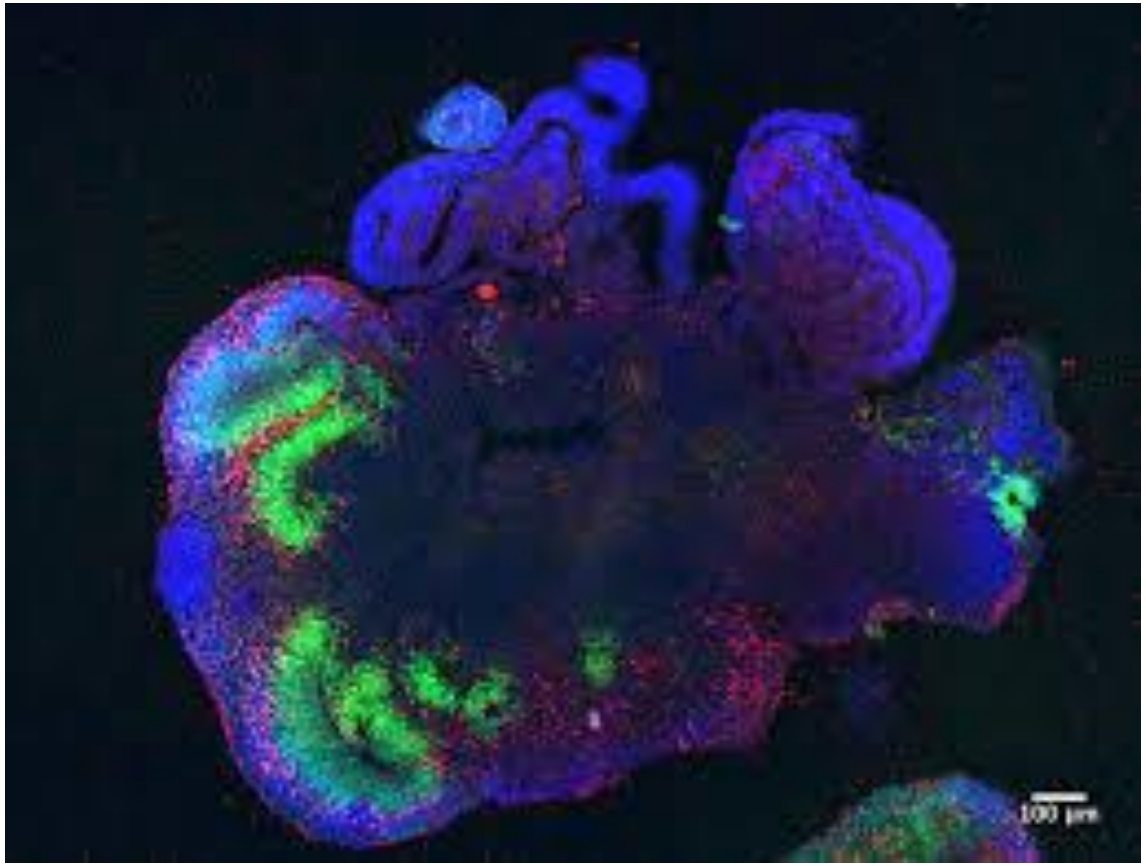
According to a statement by the researchers, the brainy robot is the "world’s first open-source brain-on-chip intelligent complex information interaction system."

To conclude: more questions than answers

What should we do if cerebral organoids presented a glimmer of consciousness in the form of integrated information?

Will we be able to use brain organoids to try to unravel the mystery of consciousness?

Ultimately, do we need new and special rules for the creation and use of human cerebral organoids?



Thank you for your attention

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