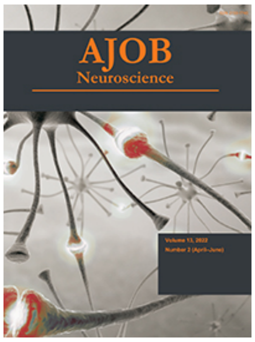

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Neurons Embodied in a Virtual World: Evidence for Organoid Ethics?

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INTRODUCTION

The development of neural organoids—three-dimensional constructs of neural tissue—resulted in significant advances in neurophysiological understandings, as well raising key ethical concerns. Sawai et al. (2022) discuss the use of these neural organoids, proposing policies to regulate this technology. The most pressing issue arises in the proposed metrics for assessing phenomenological consciousness and how they may be related to neural organoids. Secondary is their application of the precautionary principle. Our commentary seeks to position these points raised by Sawai et al. (2022) in the broader context of research, including recent evidence that lab-grown human brain cells are able to engage in enactive learning, while embodied in a virtual world through real-time closed-loop electrophysiological stimulation and recording (Kagan et al. 2021).

THE TROUBLE WITH DEFINING AND DETECTING CONSCIOUSNESS VS SENTIENCE

Foremost, it is important to distinguish between key states which organisms may possess. Sawai et al. (2022) focus their discussion on phenomenological consciousness, characterized by what-it's-likeness, which they use interchangeably with the term *sentient*. While colloquially the terms are exchangeable, it is imprecise and may lead to some conceptual conflations and to the wrong ethical conclusion. For the purpose of this commentary the term *consciousness* is used in line with phenomenological consciousness as per Sawai et al. (2022) *Sentience* on the other hand has been formally defined as "responsive to sensory impressions" (Friston, Wiese, and Hobson 2020). While the two are intuitively related and would typically coexist, it is possible to imagine states where they may present exclusively. For example, Type 1 Blindsight patients present with visual sentience—where they can receive visual information, process that information, then act upon it—while reporting no conscious experience of the stimulus. Accordingly, the definition of consciousness needs to be better defined regarding organoids and *in vitro* neuronal tissues. Such definitions need to include all aspects of consciousness to measure and determine its presence in tissues (engineered or other). Specific definitions would consider other aspects of consciousness for clearer and objective classifications, such as first-person introspective, qualitative character, phenomenal, subjectivity, perspectival, intentionality and transparency, unity and importantly, dynamic flow (Van Gulick 2021).

Sawai et al. (2022) refers to recent studies which detect complex neural activity occurring within *in vitro* cultures (Sakaguchi et al. 2019; Samarasinghe et al. 2021; Trujillo et al. 2019), presenting the argument that following the integrated information theory (IIT) (Tononi et al. 2016), this activity may be sufficient for attributing consciousness to an *in vitro* organoid. However, it must be noted that IIT proposes additional postulates, namely that changes in information integration upon exposure to the environment reflect a system's ability to match the casual structure of the world (Tononi et al. 2016). Given Sawai et al. (2022) recognize this as a limitation, it seems inconsistent that they would propose IIT as a suitable theory to confirm *in vitro* consciousness. Especially when Sawai et al. (2022) explicitly are focusing on phenomenological consciousness where, according to IIT, the

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physical substrate of consciousness must converge with phenomenology (Tononi et al. 2016), something lacking in organoids without integrated experience. While Sawai et al rightly recognize the importance of detecting consciousness in organoids—phenomenological or otherwise—the proposed method of the Perturbational Complexity Index (PCI), while useful in humans for key purposes, has substantial limitations when applied to organoids. Functionally the measure acts to quantify the interaction amongst cortical areas in response to perturbation by transcranial magnetic stimulation (TMS) through assessing normalized Lempel-Ziv complexity (Sinitsyn et al. 2020). The application of this technique on neural monolayers or single organoids would not yield results interpretable as consciousness as Sawai et al. (2022) propose, only connectivity. While some early work has started assessing 'assembloids' that may be a more relevant target of this measure, it is still vital to note that connectivity is likely a necessary but not sufficient condition of consciousness.

Indeed, the utility of the PCI in humans is established via exploiting the deterministic patterns of causal interactions among brain areas electricity via perturbation (Sinitsyn et al. 2020). Yet for that purpose it is relied upon only as a neural correlate of consciousness, not consciousness itself, phenomenological or otherwise (Figure 1). It is possible to consider that sentience alone would be a sufficient state to give rise to comparable results observed in humans with the PCI. Indeed, sentience, if taken strictly literally, has recently been observed in monolayers of cortical cells as they can respond to external signals in a goal directed manner (Kagan et al. 2021). Yet such cell cultures are far less complex than the organoids referenced and most comparable to Hydrozoa in complexity, which have seldom been proposed as capable of phenomenological consciousness. As formally sentience alone is not sufficient for consciousness; the argument that the PCI represents a proof of principle for consciousness gives rise to a premise subject to equivocation which compromises the conclusion. Therefore, there is the need to define and consider the different aspects of consciousness to classify the different types of engineered tissues and possible occurrences of conscious behaviors adequately.

APPLYING THE PRECAUTIONARY PRINCIPLE IN CONTEXT

Sawai et al. (2022) propose that the precautionary principle should be adopted given the uncertainty about whether organoids exhibit consciousness. Yet the precautionary principle does not mean that without any evidence for consciousness one should take such actions. This is especially when such evidence is unsubstantiated and the implications may be ultimately undesirable, even unethical, when considered in context.

Firstly, neural organoids have already resulted in significant clinical, preclinical and basic research findings that have or will likely lead to important health and scientific gains (Kim, Koo, and Knoblich 2020). Secondly, organoids—especially when developed from minimally invasive, renewable sources, such as induced pluripotent stem cells—act as a solution to the desire to apply the precautionary principle to animal research, particularly in non-human primates and rodent-related work. Restrictions on the use and development of organoid technologies could impose unnecessary barriers that would prolong testing with these complex animals to achieve similar health benefits. In this manner, adopting a precautionary principle to organoids without any clear evidence of consciousness fails to recognize the existing framework of what these organoids are replacing, impacting human dignity concerns by limiting important research, and increasing the burden on animal subjects. This ties to the common implicit assumption, specifically that a collection of cells from a human source should deserve additional protection over far more complex creatures which are not human. At this stage it has been challenging to collect any definite evidence supporting the idea that human cells are more or less likely to display sentience or experience consciousness over non-human cells. While significantly more research is required, preliminary evidence shows that while neurons from a human source can significantly outperform neurons from a mouse source in a simulated task (Kagan et al. 2021), this difference was minimal and quantitative only. Moreover, to our knowledge, there has not been strong evidence of qualitative difference between various neuronal types to warrant different standards of ethical priority. Therefore, organoids should be considered relative to the complexity of similar biological organisms, at least until evidence of other criteria which may further alter the status of these tissues. The most apt comparisons to even the most complex organoids currently are those from the Arthropoda phylum, which in most countries receive little to no dedicated ethical protections (Drinkwater, Robinson, and Hart 2019). Therefore, it is critical that classifying the status of synthetic biological tissue is considered without unwarranted "human" hype.

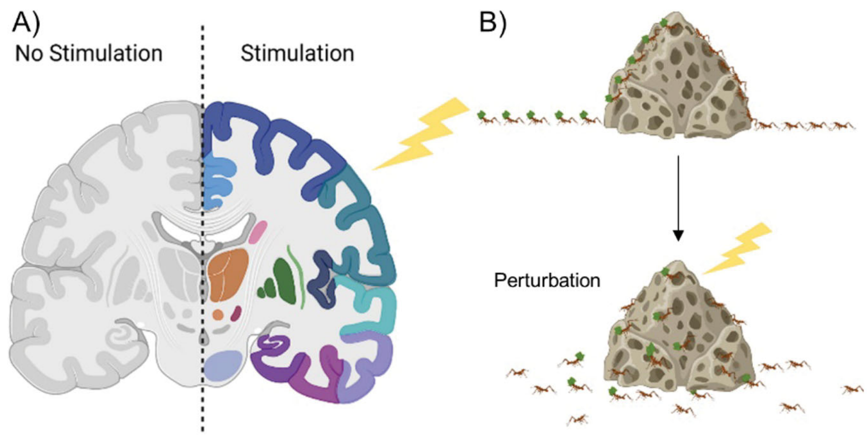

Figure 1. Simplified comparison between neurological complexity and a perturbed ant nest. (A) demonstrates how stimulation may lead to different patterns of activity in regions, where different colors represent the increase in complexity over the system, in line with the use of the PCI. However, as in (B) mathematically a comparable increase in complexity may occur looking at the order of ants before and after perturbation. This does not mean the ant nest as a collective displays phenomenological consciousness.

OUTLOOKS AND RECOMMENDATIONS

Before discussions about the ethical line between what should be "permissible and impermissible" within research on brain organoids, there is substantial work required for an objective approach driven by constructive goals. At all costs, we should avoid a slippery slope rhetoric at such an early stage of research. Foremost, there is a critical need to establish distinct terminology and clear definitions to capture the difference between various states and processes. To use these terms interchangeably may increase risks to obfuscate the range of potential states an organism may possess which ultimately may hinder any attempt at regulation. Secondly, more research should be dedicated in the establishment of more adequate techniques to evaluate consciousness levels in organoids and engineered tissues. Rather, work should be carefully considered in context of the structure and potential function of the organoid while recognizing the considerable spectrum of synthetic neural tissues. Hence it is important to create classifications and policies that categorize them accordingly. Indeed, premature restrictions of organoid research may unnecessarily impede the ability for researchers to identify where such states such as consciousness begin or stop. Being an emerging technology, it would be more appropriate to establish Best Practice Guidelines to inform researchers in conducting ethical work while enabling the exploration of the technology in an ethically guided manner. Additionally, inclusive and fair discussions around social, ethical, and legal implications of organoid research against the potential benefits and risks should accompany the technological expansion including all stakeholders. Ultimately, the use of neural organoids has swiftly given rise to important findings while creating value through minimizing harm to complex animals by providing a sustainable research model that does not experience suffering. While we agree with Sawai et al. (2022) that these ethical concerns should be carefully considered, it is critical to consider the unknown risks against known ethical potential promises that organoids can offer across multiple spheres.

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Cerebral Organoids and Biological Hybrids as New Entities in the Moral Landscape

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Sawai et al. (2022) offer a helpful map of the ethical issues of brain organoid research and application. One point that deserves further investigation is the connection of potentially sentient human cerebral organoids (HCOs) to other living and non-living entities. Firstly, it has to be assessed whether this line of research is necessary to achieve scientific advances. Providing HCOs with access to the environment is *per se* controversial; if exploring the issues of lack of vascularization and potential uses for transplantation makes understandable—from a utilitarian point of view—the engraftment of HCOs in non-human animals, the same can hardly be said for their coupling with non-living entities.

Secondly, the ontological and moral status of both potentially sentient human cerebral organoids and hybrids produced by the connection to HCOs needs to be carefully considered. Our claim is that sentient (or conscious) human cerebral organoids are living entities of a new kind, endowed with a specific moral status, and that hybrids of any type inherit from HCOs said moral status, or will have a higher one, if HCOs do not lose their key features.

PROVIDING HCOs WITH A BODY

In their review, Sawai et al. (2022) thoroughly explore the ethical controversies that might spring from the

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