OPINION ARTICLE

The welfare of brain organoids [version 1; peer review: awaiting peer review]

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Abstract

One of the most urgent challenges arising in bioethics has been the ethical assessment of the use of brain organoids, largely because of the possibility of sentience and the potential that if they can feel, then they might suffer. But while there is a growing literature on the possibility of sentience in brain organoids and why we should take a precautionary approach towards them, there is very little guidance on what it would mean to protect their welfare. In this paper, we address this omission by exploring the question of what the welfare of an organoid might be like, and how we could scientifically assess this question. As we will show, these are difficult questions to answer, given the current lack of empirical data on many of the important features of brain organoids, but we will provide some principled empirically-informed speculation on possible answers, as well as suggestions for future research directions.

Keywords

brain organoids, sentience, consciousness, welfare, ethics

This article is included in the The Ethics of Brain Organoids collection.

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Introduction

Over the last decade, the use of brain organoids (sometimes also called cerebral organoids, or neural organoids) has become one of the fastest growing debates within the bioethical literature (Birch & Browning, 2021; Greely, 2021; Koplin & Savulescu, 2019; Lavazza & Massimini, 2018; Sawai *et al.,* 2019; Zilio & Lavazza, 2023). Brain organoids are 3D biological cultures that have been grown artificially in a lab (*in vitro*) from human or animal tissue to serve as a research model. Their purpose is to further our scientific understanding of the brain (Lancaster *et al.*, 2013) and there is a lot of funding supporting their use in research to find cures and treatments for pathologies such as Alzheimer's disease (Chang *et al.*, 2020; Gerakis & Hetz, 2019). While animal models have served as useful model systems for the study of human diseases, they do not have the molecular and genetic specificity of human brain organoids, which has made it hard to judge whether legitimate inferences can be made to the human case (Gerakis & Hetz, 2019).

However, despite their scientific usefulness, human brain organoids have raised an ethical worry that due to their intentional similarity to the human brain, they might be sentient. Sentience refers to the capacity for individual subjective experience, such that there is something that it is like to be that individual; sometimes also called phenomenal consciousness (Browning & Birch, 2022). With the ever-growing recognition of the sentience of species even very evolutionarily distant from us (e.g., Birch *et al.*, 2021b; Crump *et al.*, 2022; Gibbons *et al.*, 2022), it is clear that brain organoids - even those grown from non-human tissue - have the potential for sentience. Sentience is now a common basis for legislative and ethical protection (Browning & Veit, 2022) and is also commonly considered a basis for being a welfare subject. Although there are many different accounts of welfare (Veit & Browning, 2021), almost all of these include reference to subjective experiences with a positive or negative valence. Therefore, if brain organoids were sentient, they would be welfare subjects and we should take their welfare into account.

But while there has been a lot of recent discussion about how we might settle the question of whether brain organoids are conscious, and their moral status if they are (Birch & Browning, 2021; Greely, 2021; Koplin & Savulescu, 2019; Veit & Browning, 2023), very little attention has been given to the question of what sort of welfare protections would be appropriate. Here, we are not focussing on the question of whether brain organoids are sentient, or what would count as evidence of sentience. Instead, we want to use this paper to investigate the question of what their welfare could be like if it turns out that they are indeed sentient. What would make the life of a brain organoid go well or poorly? And how could we improve their welfare? As we will show, these questions are difficult to answer given the current lack of empirical data on many of the important features of brain organoids, but we will provide some principled, empirically-constrained speculation on possible answers, as well as suggestions for future research directions.

What do brain organoids feel?

As we have mentioned there is good reason to think that brain organoids may eventually be sentient. In this paper, we will be discussing the welfare of any current or future brain organoids that have been deemed plausible contenders for sentience, even if the question of their sentience is not settled. As one of us has previously argued: "We should not allow our uncertainty about their sentience to block the adoption of proportionate measures to safeguard their welfare" (Birch & Browning, 2021, p.56). Once an entity is recognised as sentient (or potentially sentient) and thus worthy of protection, this then raises the question of what protections should look like. What sort of measures are needed to safeguard the welfare of brain organoids? Protections for any individual should be relevant to their interests, and in this paper, we will investigate the question of what interests brain organoids might have, and - importantly - how we would know.

Even once we recognise an individual as sentient, this unfortunately doesn't tell us much about what their experience is like. There are different dimensions along which consciousness can vary (Birch *et al.*, 2020; Veit, 2022c; Veit, forthcoming) and of particular interest in the case of welfare are the range of different positively and negatively valenced states (or *affects*) that the individual can experience (Browning, 2022; Browning & Veit, 2020b). Affects are varied and can include a range of states such as hunger, fear, pain, joy, comfort, tiredness, frustration, and pleasure, all of which can contribute to or detract from welfare. So, when thinking about the possible welfare states of a sentient individual, it helps to have a sense of which affects they might be likely to experience so we can know what sorts of things will be good or bad for them. If we think about ensuring welfare as providing living conditions relevant to an individual's interests, then which affects they can experience will determine what sorts of interests they have.

To begin with, the most basic question is whether they can experience any positively or negatively valenced conscious states. Without these, even if the organoid has some form of conscious awareness, it is not of the type that would typically be connected with welfare concern - it cannot be harmed or benefited. Some researchers have discussed the possibility that evaluative and sensory experience could come apart in some animals (see Godfrey-Smith, 2020; Veit, 2022b), which could also be relevant to the case of brain organoids. The weight of evidence for consciousness in an organoid may reach the threshold for sensory experience, without crossing the threshold for evaluative experience. In this case we may not wish to give them moral status due to their inability to experience positive or negative states. Thus, over and above determining whether a brain organoid is sentient, we would also need to determine whether it has valenced experience. There are a few lines of evidence that could be taken as suggestive of this capacity: presence of neural structures or pathways responsible for valenced experience in human brains, ability to learn, and presence of relevant neurotransmitters.

Although current brain organoids are relatively simple, we can assume that by the time they are regarded as sentient, they are likely to be more complex. At that time, we can look for the presence of neural structures and pathways that are responsible for valenced experience in humans. For instance, human brains contain a 'pleasure' system that activates across a range of qualitatively different positive experiences (Berridge & Kringelbach, 2015). If these pathways were lacking in brain organoids, we could assume that the organoids do not have the capacity for valenced (evaluative) experience. Although these valenced processes are almost certainly multiply realisable, i.e., instantiated with different forms of neural organisation in different types of organisms (Brown & Key, 2021; Browning & Veit, 2020a; Michel, 2019), we think it is plausible to assume that in human brain organoids, the pathways would need to be sufficiently similar to those in normal human brains. Thus far, neural organoids have not reached anything like the complex organisation of the human brain, which makes it very questionable that they currently possess these brain mechanisms. Nevertheless, as their case for sentience is becoming stronger and scientists are getting closer to creating miniature *in vitro* brains, it is becoming conceivable that we will be able to find these pathways in future.

A second line of evidence is whether the organoid is capable of learning through reward and punishment. Although it is an open question regarding what types of learning are necessarily connected with conscious experience (Birch *et al.,* 2021a; Grossberg, 1999; Ginsburg & Jablonka, 2019; Godfrey-Smith, 2021), once it is given that a brain organoid has been plausibly identified as sentient, we could assume that if it is also has the capacity to learn then it can be inferred to have valenced experiences that accompany reward and punishment.

Finally, we could look for the presence of neurotransmitters associated with valenced experience, such as dopamine and serotonin (Dayan & Huys, 2009; Kringelbach & Berridge, 2009). Although the presence of these neurotransmitters may not be sufficient to attribute valenced experience, as they can play multiple signalling roles within the brain (Jonnakuty & Gragnoli, 2008; Money & Stanwood, 2013), their absence would certainly make it likely that valenced experience is lacking. Current brain organoids have already shown the ability to form midbrain dopamine progenitors (Florenzano *et al.*, 2021) and thus we should pay special attention to research using organoids like these.

While it may be challenging to establish whether a sentient brain organoid has valenced experiences, still more difficult is the question of what specific affects they may experience. In the case of nonhuman animals, this can typically be investigated in part with reference to the ecological niche and evolutionary history of the species. For instance, we can ask what types of environmental stimuli it would be relevant for them to perceive, and which resources it would be beneficial for them to be motivated to obtain, given their life histories. However, this makes apparent a problem in determining the range of affects that a sentient brain organoid might experience: this individual is plausibly sufficiently decoupled from its species-typical evolutionary-ecological niche such that we can't reliably make inferences about what it might feel.

Although the brain organoids we are interested in are of human origin, this doesn't mean that we can take them to possess the range of affects and emotions that a typical human might experience. There is a strong role for environment, development, and learning, in determining the range of feelings a human will normally experience, all of which a brain organoid would be lacking. This is particularly true if we accept a constructivist view of emotions, such as that proposed by Feldman-Barrett (2017). Under this view, there are only a few basic affective states that are 'hard wired' into our brains, while most of our emotion states are constructed through sociocultural experiences and learning. At best then, under this view we might expect human brain organoids - if connected in a sufficiently similar way to human brains - to have instead only these basic affects, though it is not even yet clear exactly what these include. Other less constructivist views in the field recognize older evolutionarily core/basic affects such as those that are proposed by Panksepp – seeking, rage, fear, lust, care, panic, and play (Panksepp, 1998; Panksepp, 2005). We would take the current lack of structural complexity in brain organoids to be a reason to focus primarily on core affective states for now.

There is an extra layer of complexity arising from the fact that brain organoids are not part of a functioning body system, but rather exist in a more isolated state. This means they lack the sensory inputs and bodily outputs that are usually part of affective experience. Many affects are experiences that result from an interaction between brain and body and thus it seems unlikely that they would occur in a brain organoid. The experience of hunger, for instance, requires certain inputs from the gastrointestinal system, as well as bodily hormones and metabolites. Brain organoids – at least in most instances – lack such connections since they are typically only modelling parts of the brain and do not have any bi-directional connections to other body parts (Homberg *et al.*, 2021). This means they will not have the inputs or feedback loops necessary to trigger a range of feelings that require body systems. Additionally, many of these structures may require for their proper development recurrent inputs with feedback from other growing body systems. While this relies on an understanding of the ontogeny of affect that we don't currently possess (as evidenced by the current uncertainties about sentience in foetal development) this is certainly reason to be sceptical that brain organoids will possess many affects that are typical in normal humans, or for that matter even infants.

One way of determining which affects an organoid can experience could be through looking for the presence of the neural structures that typically underlie that affect. This is

complicated by the need to identify the structures responsible for consciously experienced affect as opposed to non-conscious brain processes. In humans, it appears that the brain pathways responsible for some of the unconscious bodily responses to fear, for instance, are not entirely identical to those responsible for conscious experience (LeDoux, 2019). Thus, possession of the former pathways does not necessarily serve as proof for conscious experience. However, it is also possible that consciously experienced affect is created through an interaction between the unconscious pathways specific to each affective system alongside more general machinery for conscious experience of certain selected processes, such as might be expected from some global workspace theories of consciousness (e.g. Baars, 2005). This is particularly plausible if we consider the role of consciously experienced affect to be to enable organisms to bring together different demands (e.g. hunger and avoidance of pain) in order to deal with trade-offs between them (Cabanac, 1992; Peters *et al.*, 2006; Veit, 2022a). In this case, any individual that is identified as a plausible sentience candidate and that also possesses the structures associated with that affect could reasonably be inferred to have conscious experience of that affect, even where that experience is perhaps not of the richer forms associated with the phenomenological complexity of human experiences such as fear. Although we don't have a full map of these in the human brain, the presence of some key structures or connective pathways could be sufficient. For instance, evidence from comparative neuroeconomics regarding the role of reward molecules such as dopamine could constitute evidence for the core role of affective structures for the brain (Levy & Glimcher, 2015; Spurrett, 2020; Veit, 2022a). If we could show that neural organoids not only have these kinds of hedonistic reward pathways, but more importantly can make use of them to learn complex associations (Browning & Birch, 2022), this could provide convincing evidence to take their capacity for welfare seriously.

Where then does this leave us in our assessment of which affects brain organoids are likely to experience, and – more generally – what their interests are likely to be? As our discussion has made obvious, there are still more questions than answers on this issue. However, we think the key things to look for should be brain structures or pathways typically associated with specific affects. We can also think about the conditions of the world in which a brain organoid exists, and thus the affects that might play a role in its development and experience. As we have mentioned, the lack of connections to sensory and bodily input means that a range of experiences related to these inputs would be lacking. For instance, brain organoids - like all brain tissue - lack nociceptors and thus are unlikely to experience pain resulting from manipulations or damage to the organoids themselves. However, we cannot rule out the activation of pathways similar to pain processing pathways even in the absence of the usual sensory input - akin to the 'phantom pains' experienced by humans or other animals after the loss of a limb, for example. As discussed above, looking for activity in the usual pathways associated with these experiences could help to identify which experiences are present.

Right now, any discussion of the possible affective experiences of brain organoids is necessarily speculative. There is an insufficient understanding of how consciously experienced affects develop even within the normal development of a human brain, let alone how this would work in a brain organoid in the absence of any of the normal inputs and outputs that would shape experience. Using a precautionary approach, we could then recommend that where there is some non-negligible possibility of a brain organoid experiencing an affect (based on the development and living conditions of organoids, and the presence of associated brain structures and pathways), we should treat it as though it can have this experience (similar to the more general precautionary approach for brain organoid sentience advocated by Birch & Browning, 2021).

At the very least, this should include an investigation into whether the organoid is likely to experience *any* positively or negatively valenced states and if so, to care for its welfare accordingly. This then requires taking care not to keep it in conditions that could trigger negative affects and attempting to provide conditions that will trigger positive ones. Even if we don't have a good sense about which affects an organoid experiences, we might think in a more general sense about the conditions it finds aversive (negatively valenced experiences) and those it finds rewarding (positively valenced experiences) and strive to avoid the former and provide the latter. This then raises another difficulty, in determining which conditions these are likely to be and in assessing the welfare status of organoids, to which we will now turn.

Measuring the welfare of brain organoids

We have discussed the challenges of determining what affects a brain organoid might experience, and therefore in determining which interests it might have. We suggested that we could instead just group experiences into 'aversive' (negative) and 'rewarding' (positive). However, even with this strategy there is still a significant problem with measuring the welfare of brain organoids. This includes both determining which conditions will be aversive or rewarding for an organoid and assessing their welfare more generally. In this section we will discuss these two problems, with reference to the science of animal welfare, which has tools for answering these questions for sentient animals.

Unlike humans, animals can't tell us directly what they like or dislike, or what they are feeling, however we now have a quite advanced science in animal welfare to help find out the answers to these questions. This science focuses both on assessing the overall welfare state of animals (i.e. are they doing well or poorly) as well as identifying the conditions under which their welfare is increased or decreased. This is done through using a range of behavioural tests and physiological indicators. Although these indicators vary

in their quality or informativeness and are not yet all validated as measures of the animal's affective experience (Browning, 2023), in general the science has been quite successful at providing information about welfare states of and preferred conditions for animals. However, the methods currently used by animal welfare science rely strongly on behavioural and bodily changes that will necessarily be inapplicable to brain organoids.

To begin, there is the question of what the interests of brain organoids are, i.e. which conditions they will find aversive or rewarding. In other animals, a common heuristic for determining their likely welfare requirements is to take information about the living conditions of their wild counterparts, to suggest which conditions will probably be experienced as positive or negative by the animals. This method is clearly not available for brain organoids. It does not seem plausible that the living conditions for normal humans should serve as a guide for what is likely to be in the interests of brain organoids. This means that it will be even more difficult to answer questions about brain organoid welfare than it is for animals.

One potential method for finding out what is good or bad for brain organoids is the use of neuroimaging or sampling of neurochemicals to determine what types of experiences they are having at any specific moment - in particular whether they are having experiences with positive or negative valence. As we have mentioned, there is a 'pleasure' system in the human brain that activates for different positively valenced experiences (Berridge & Kringelbach, 2015). Activation of these systems in brain organoids could reasonably be taken to indicate experience of pleasure. Presenting brain organoids with particular conditions, such as housing in different substrates, or subjecting them to different manipulations, and looking for the patterns of activation that result, could serve as a guide to whether these are positively or negatively valenced experiences. Roughly, this could tell us which conditions the organoids 'like' and which they 'dislike'. This could then help guide decisions about what is good or bad for brain organoids, or likely to increase or decrease their welfare.

The second question is how we might assess the overall state of welfare of brain organoids. Here, we suggest two possible welfare biomarkers that are currently being developed within animal welfare science and may be applicable to the case of brain organoids: telomere length, and hippocampal volume. Telomeres are present at the end of chromosomes, and shorten with each cell division, leading to many of the effects of ageing (Monaghan, 2014). Recent research has demonstrated that the rate of telomere attrition correlates with levels of stress experienced by the organism: faster rates are seen in individuals with more stressful experiences, and slower rates in those with more positive experiences and thus this could be an indicator of cumulative welfare (Bateson, 2016; Bateson & Poirier, 2019). While this has not yet been fully validated as a measure of affective experience as opposed to merely physiological stress, initial results are suggestive, showing striking correlations between telomere length and positive and negative experiences in animals (e.g. Wilbourn *et al.*, 2017). If so, similar effects could be present in brain organoids and could serve as a guide to their overall welfare. Although neurons themselves do not appear to show shortening of the telomeres, this effect is seen in glial cells (Tomita *et al.*, 2018), which are now becoming more commonly integrated in neural organoids (Dang *et al.*, 2021; Koo *et al.*, 2019). Where glial telomeres are shortening more rapidly, we could take welfare to be poorer and where they are shortening less rapidly it could be taken to be better.

Another proposed measure of cumulative welfare in animals is hippocampal volume. The hippocampus is a part of the brain associated with learning and memory, and emotional regulation. The volume of (and rate of neurogenesis in) the hippocampus has been demonstrated to correlate with the cumulative welfare experience of the subject – with higher volume correlating with positive experiences and lower volume with negative, across a range of species (Bateson & Poirier, 2019; Poirier *et al.*, 2019). Where brain organoids have a sufficiently complex structure to have hippocampi, or functionally similar structures, the volume and rate of neurogenesis in these areas could thus be used as indicators of the welfare status of the organoids. While current brain organoids have not yet reached this degree of complexity and structural organisation, hippocampal neurons have been cultivated (Todd *et al.*, 2013), and we suspect that it would at least in principle be possible to cultivate something like a miniature hippocampus that could be used in this way.

These are just two suggestions, and as research into animal welfare indicators continues, there is the potential to identify more indicators that may be applicable to brain organoids. Although many indicators rely on behaviour or whole-body physiology and will thus be unsuitable, some biomarkers - particularly those that focus on the brain - could apply to brain organoids. These indicators could then also be used to gather information on the interests or welfare needs of brain organoids. By taking baseline measures of indicators such as telomere length or hippocampal volume, then placing the organoids in different conditions and subsequently comparing the measures, we could get a sense of which conditions are positive or negative for the organoid, and by how much.

However, in the meantime we should be aware of the knowledge gap here regarding the welfare needs of brain organoids. This can lead to enaction of a precautionary suggestion previously suggested by Birch & Browning (2021): "when evaluating the harms and benefits of research on human brain surrogates, we should recognize our own ignorance regarding their welfare needs and take into account the risk of unforeseen harm that results from this ignorance" (p. 58). Until we can be sure about the welfare

requirements for brain organoids and which conditions may be harmful for them, we should be extra cautious about imposing conditions that have the potential to cause unforeseen harms.

Conclusion and further directions

If brain organoids are sentient, this means they are welfare subjects and should be protected accordingly Browning & Veit, 2023. Understanding and measuring the welfare of brain organoids poses more significant challenges than similar efforts for other organisms, however here we have suggested some potential ways forward. Firstly, we have described three ways to determine whether an animal deemed to be a candidate for consciousness should also be considered a candidate for valenced experience: the presence of structures and pathways related to valenced experience in humans, the existence of neurotransmitters/reward molecules such as dopamine and serotonin, and the ability to engage in reward-based learning. Secondly, we have argued for a need to assess which kinds of evaluative experiences neural organoids might experience, drawing on affective neuroscience to determine the minimal states of affective experience and the nervous system requirements for such experience, given that neural organoids are very unlikely to have complex mental states. Thirdly, we have provided several suggestions for how we might begin to study the welfare of neural organoids, using neuroimaging tools alongside welfare biomarkers such as hippocampal volume and telomere length.

Understanding the welfare of brain organoids can help provide guidance on what types of protections and care they should receive. Importantly, recognising the sentience of brain organoids, or a need to protect their welfare, does not automatically rule against their use in research. Rather, it requires that some conditions should be met to justify their use, in the same way as for other sentient animals. A commonly used framework to protect the welfare of animals used in research - and one that could also be usefully applied in thinking about regulating the use of sentient brain organoids - is the '3 Rs': replacement, reduction, and refinement (Russell & Burch, 1959).

Replacement refers to the replacement of sentient animals with non-sentient (or less sentient) alternatives. Indeed, one of the intentions behind the use of brain organoids is to replace, at least partially, the use of sentient animals for research. In this context then, we could look at replacing the use of sentient brain organoids with simpler, non-sentient organoids, for any application where the fully developed organoid is not required. As the cultivation of human brain organoids resembles their natural development in the growth of the human brain (Eichmüller & Knoblich, 2022), a precautionary approach to brain organoids might thus create a limit on how long we will be allowed to store them - perhaps one year - to try and avoid the point where they are likely to develop sentience. While such a cut-off might seem arbitrary at the current state of organoid research, as the probability of sentience increases this may become a useful response to avoid unnecessary harms.

Reduction refers to a reduction in the number of sentient animals (or, in this case, brain organoids) used, through careful attention to experimental design and through use of harm-benefit analysis to avoid unnecessary research. Finally, refinement refers to alteration of experimental design and housing to minimise potential harms or suffering. As we have discussed, this is a challenge for brain organoids as we don't yet know precisely what conditions will be harmful or beneficial, but this uncertainty is a reason for additional caution. Even though they are made from human tissue, with structural and functional resemblance to human brains, we think it is exceedingly unlikely that their conscious experience would resemble the complexity of a normally developed human brain. Instead, they are more likely to have a simpler range of experience, with correspondingly basic welfare needs, which may mean that conditions for their housing and use won't be excessively stringent.

To conclude, we strongly recommend further research on brain organoid welfare, as ignoring the welfare of potentially sentient individuals risks causing significant harm. The interests of brain organoids are unlikely to be complex, and their welfare protections therefore unlikely to be overly demanding, however this should not be taken as reason not to enact them. Instead, sentient brain organoids should have similar protections to any other sentient research subject, in line with their interests, to minimise their potential suffering.

Data availability

No data are associated with this article.

Author contributions

Both authors contributed to the conceptualisation and writing of this article.

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