Open Peer Commentary: "Mapping the Ethical Issues of Brain Organoid Research and Application," Sawai et al.

Title: Pursuit of perfection? On brain organoids as models

In this issue, Sawai and colleagues (2022) draw a map of the emerging field of brain organoid ethics. The constitution of this field is dependent on the concept of a brain organoid that would be considered as deserving ethical consideration. Brain organoid research in itself is a broad field and many different entities could qualify as brain organoids, from the early self-organizing neural cell cultures (Lancaster 2013) to organoids modeling this or that part of the brain, until complex physiological systems such as assembloids (Birey 2017), and we might also discuss problems raised by brain organoids made from human material, human-animal chimeras, and so on. While the target article reviews the different questions that might be raised for different kinds of entities, the diversity of entities that we group conveniently under the label brain organoid should not be underestimated.

In his *Ethics*, Spinoza (1677, IV, preface) notes that an architect knows whether the building that s/he is building is completed or not (anyone who knows the goal of the architect could also make the same judgment), and depending on whether this goal is achieved or not, the building will be said *perfect* or *imperfect*. However, because of personal history, individual preferences, or prejudice, each of us is inclined to take a specific instance or model (*exemplar*) for the unique and universal idea of the thing. "After men began to form universal ideas, and devise models of houses, buildings, towers, and the like, and to prefer some models of things to others, it came about that each one called perfect what he saw agreed with the universal idea he had formed of this kind of thing, and imperfect what he saw agreed less with the model he had conceived, even though its maker thought he had entirely finished it." According to Spinoza, this trend to focus on imperfection, deeply rooted in our psychology, is a misleading one: a house is not an imperfect tower. When dealing with something new to us, or when we do not know what its author had in mind, we tend to refer to a certain image and consider the thing in front of us as an imperfect version of this image. But it might sometimes prevent us from considering what the thing really is or could become.

Too often, brain organoids are presented as "lacking" something. This is more than a rhetoric trick. For instance, current organoids would display "incomplete recapitulation of brain structure, size, maturity, vascularization, lamination and lack of input/output systems, external stimuli, and non-neuroectodermal cells" (Sawai 2022). It is true that nervous systems *in vivo* develop as parts of organisms and make them able to perceive and/or act upon their environment, but is it still always relevant to emphasize that *in vitro* organoids lack an organism and an environment? The same holds true for the concept of consciousness. Is there is a standard state of consciousness that could serve as a template for a possible consciousness in brain organoids? You might not agree with the idea, but this is yet to a template of this kind that refer claims deflating ethical issues by saying that brain organoids are far from displaying a human state of consciousness (ISSCR 2021) or claims raising awareness by saying that brain organoids might be able to reach this stage at some point in the future. This is also to this kind of template that points the analogy with patients in persistent vegetative states and the problem of "detection of consciousness" with measurement tools (such as Integrated Information Theory, Lavazza & Massimini 2018) designed for adult, human brains. Along the same line is the often-quoted statement that

brain organoids already display the same pattern of electrical activity as premature babies or fetuses of several weeks (Trujillo 2019) and the idea that the ongoing "enhancement" of organoids in research laboratories will inevitably make them closer to typical, mature, embodied human brains.

In all these cases, brain organoids seem to be conceived as potential "miniature organs." Occasionally, the reader could feel that the main horizon of brain organoid research is to produce real human brains and that organoids are drawing the attention of bioethics because they are getting closer to this ideal. Then we should indeed ask: when will brain organoid research be able to carry them to full term? However, as Spinoza suggested, it is better to get rid of any implicit, misplaced teleology.

Brain organoid research is a rich field of inquiry, but this is not an enterprise aiming at producing miniature versions of real brains (Baertschi 2020). Brain organoids are models of development. Models in themselves are not perfect or imperfect, they are modeling a certain aspect of nature under selected conditions. What would be a perfect model, that does not lack anything—the thing in itself? Models are partial and simplified representations. In this sense, models are imperfect and we learn from them precisely because they offer a simplistic, controlled version of natural phenomena. Models are also artefacts designed to answer specific questions. Often, we gain knowledge from these epistemic tools because we can manipulate them (Baird 2004, Knuuttila 2011). Artificiality is not a defect of scientific models; it is their nature and an asset. In this sense, models are perfect if they reach their epistemic goals.

Undoubtedly, brain organoids are evolving and will evolve—we are dealing with ongoing research: laboratories all around the world are striving to produce new models for the study of brain development, disease, drug testing, and so on. Each experimental laboratory makes its own models according to its research needs. Spinoza's lessons would be the following. There is no single idea of a standard, conscious brain and a series of entities getting more or less similar to this idea that we could put on a scale to assess their potential moral status. Instead, there are as many brain organoids as there are biomedical researchers or laboratories, each with a specific target in mind. In terms of evolution as well, there are many directions in which these models are going to be developed.

For ethicists, the challenge might not be in identifying whether brain organoids will have "our" consciousness, or a degree of sentience comparable to the one of a fly or a mouse, but to stay open to all their potentialities and to what they can teach us, including on different forms of consciousness. As new artefacts, novel entities produced in the laboratory, brain organoids might have new properties. We need procedures and debates to assess these properties, but the best epistemic tools to gain knowledge on what brain organoids are and can do, are brain organoids themselves. This sounds like a circle, yet this is the best way to avoid teleology and anticipatory judgments, that is, assessing the entities of interest—organoids—without evaluating their conformity or non-conformity to an ideal. Spinoza said also that "no one has yet determined what the body can do" (1677, III, 2), against those prompt to claim that our ability to act lies in our consciousness (or free will, somewhere in the mind). Organoids are new kinds of bodies, with potential new powers. It is still a long way until we can agree on the criteria to define, identify, and detect any form of consciousness in them.

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