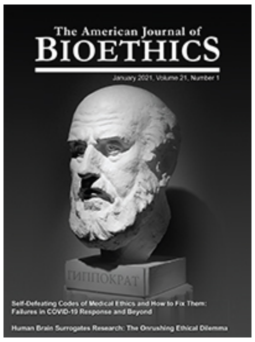

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Brain Surrogates—Empty or Full Makes the Difference

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In his Target Article, Greely examines brain surrogates and the ethical dilemma they pose:

> … 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 … . (Greely 2021, 34)

The dilemma arises, according to Greely, because "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?" (34).

It is a legitimate question, but "if" is the critical term here, which makes the dilemma conditional upon brain-likeness, as an observable and measurable phenotype. Achieving the brain-likeness of "looks like and acts like"—which suggests in this case a fully functioning human whole-brain replica—is remote. Moreover, brain-likeness inherently differs between types of brain surrogates, and to many types of surrogates it will never apply. Sliced human organoids floating in medium in a culture dish may have astonishing functional output, but that is not "acting like a brain" and such organoids do not at all look like a brain or invoke such associations (Giandomenico 2019). Yet such surrogates may turn out to be highly informative for the study of human nervous system disorders.

To place the dilemma in context, we must also take a critical look at the brain as an organ and why it is special, as that may explain why models—surrogates—of the brain are treated differently from other bioengineered organ models.

The question arises at what point the protection afforded to human research participants would apply to surrogates of any kind.

Would there be an intrinsic organ-specific dilemma if we engineer a human organ surrogate, true-to-life and fully functioning as a liver, kidney or pancreas? Is anyone concerned about "looks like and acts like" a real human organ? The most "looks like and acts like" bioengineered human organs, namely human organs grown in animals, as e.g. a truly human pancreas in a pig, raise concerns about animal welfare or the creation of an animal-human hybrid, rather than concerns about the perfect organ replica as such (Yue 2020).

So, what are the reasons that we perceive disturbing issues with—human—brain surrogates? Here it seems that the better the function, the bigger the problems. With other organ replicas, the perception is rather the opposite: a true-to-life functioning organ may better justify the moral cost that was incurred in the process leading to this outcome.

As Greely points out, human beings deserve ethical and legal respect—and, whether justifiable or not, humans are typically regarded to be at the top of the list of morally considerable beings.

Why is this relevant for human brain surrogates? If the moral status—or at least the moral considerability—is grounded in the specific properties of the human brain, does that confer such considerability automatically to surrogates or replicas?

The brain, or rather the nervous system, is identified as the biological substrate of capabilities like the experience of "pleasure and pain," the somewhat antiquated expression for a feature that is since centuries deemed to confer moral considerability. The experience of "pleasure and pain" is intricately related to the even more nebulous phenomenon of "consciousness." So far, no consistent and coherent definition of consciousness exists. There are many different context-dependent definitions. Consciousness, or the loss or regaining of consciousness, as referred to by the anesthesiologist or intensivist who through a BIS-score can measure the level of cortical activity (Jung 2013), is very different from consciousness as discussed in the multitude of theories about the "problem of

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consciousness" in philosophy, of which Van Gulick provides an extensive overview (Van Gulick 2018). Neuroscientists add their many different views on the topic (Koch 2019).

In other words, "consciousness" is too ill-defined to be useful as a benchmark in determining the brain-likeness of brain surrogates. I suggest to use another feature instead, namely *memory*, as something that is specific for nervous systems and for which there is biological evidence, the mechanism of it can be rationally explained, and it is measurable. In a nutshell: neural systems can encode sensory input in so-called "engrams" at the level of neurons and synapses. Engrams are considered the basic units of memory. This means that memories have a biological (biophysical and biochemical) neural substrate (Josselyn and Tonegawa 2020). In laboratory experiments, it was demonstrated that in the intact live animal retrievable memories can even be artificially formed without sensory perception through direct optogenetic stimulation of brain areas (Vetere 2019).

Focusing on memory instead of consciousness changes the question from "does a brain surrogate possess consciousness?" and "should we try to engineer consciousness into brain surrogates?," to "does this particular brain surrogate possess the neurobiological features necessary for extant memory?" and "should we attempt to endow an engineered brain surrogate with memories?" These questions allow for a more rational approach of the issue of brain-likeness and may help to dismantle the dilemma of ethically acceptable research.

Not all brain surrogates are equal candidates for moral consideration and some may be at a par with other human cell and tissue cultures to which it is difficult to ascribe moral relevance. I contend that it is not shape or size—and ultimately not even species—that makes the difference, but that what matters is the *content*. There are "*full*" and "*empty*" brain surrogates.

I will zoom in on two types of brain surrogates to illustrate this point, (1) human neural organoids, and (2) living *ex vivo* human brain tissues.

First, human neural organoids. Human neural organoids are derived from human stem cells, that are often derived from human skin fibroblasts. They are induced to develop into neurons and other types of brain cells. Once formed, the cells of the neural organoids differentiate and develop further. As Greely notes, one can expose these organoids to input, e.g. to optical stimuli, to which the neurons react by firing. But, that is what neurons typically do. And while the apparatus for memory formation is there, in the form of neurons and synapses, there is no processed perception to encode as retrievable memory engrams. Note that the experiments with "artificially induced" memory were performed in live animals that demonstrated retrievable memory even if not based on "natural" sensory perception. Differences in behavior (=output) were observed after the establishment of the artificial memory.

Human cerebral organoids, that are without extant memory and sensory input (or: do the cells sense the mechanoforces of the medium they are being grown in?) are thus very far from the human brain-likeness that would lead to dilemmas as to their ethically (and legally) acceptable treatment. I regard these neural organoids as "empty" human brain surrogates.

Secondly, living *ex vivo* animal brain tissue as human brain surrogate. I refer to the published experiments by Sestan (Vrselja 2019) on restoring circulation and some functions in whole *animal* brains post mortem, or maybe one should say *trans mortem*. Under normal circumstances the tissue would be regarded as dead—irreversibly so, typical for "dead" as we know it—but the experiment shows that death can be partial, even for the cells and tissues of the central nervous system that are known to be the most vulnerable to interruption of the circulation (Younger 2019). In this situation we have whole brains that are at least partially functioning. These whole brains are "full." In contrast to neural organoids that started neural development from scratch, without any sensory organs or experiences, the living *ex vivo* or *trans mortem* brains are filled with engrams, the encoded memories of all of the creature's life. In these experiments the brains were only partially functioning (and, moreover, brain function dampening drugs were used) it is not clear if the engrams were functional, that is, if memories were internally active and could have been externally retrieved. The isolated brains had no intact in- or output systems.

Back to the dilemma predicated upon brain-likeness and its implications for moral considerability and the ethical treatment of research "subjects." I do not see any rational or otherwise compelling reasons to confer the minimally required degree of human brain-likeness to brain surrogates of the type of iPSC-derived neural organoids. These surrogates know no past and imagine no future, they are "empty." This is different with whole brains, and the encoded past may under artificial conditions be retained for some time post mortem. With living *ex vivo* animal brain surrogates the minimal requirement is the application of all measures for the care of animals used in research.

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Scientific and Ethical Uncertainties in Brain Organoid Research

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Hank Greely's (2021) target article, "Human Brain Surrogates Research: The Onrushing Ethical Dilemma" reviews the manifold scientific and ethical questions surrounding models of human brains used in research (or "brain surrogates"). We are particularly struck by two of Greely's points. First, he emphasizes the deep uncertainties surrounding whether future brain organoids might possess some form of rudimentary consciousness (Greely 2021). Second, he issues a call to come to grips with these uncertainties, in particular:

> [Ethicists] need to engage deeply with the neuroscience researchers in order to keep current with what is possible, what is almost possible, and what is becoming plausible. Science divorced from

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