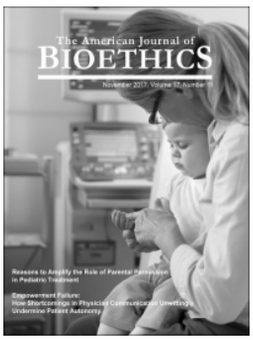

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Suzanne Metselaar, Jeroen Geurts & Gerben Meynen

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Responding to Human Brain Surrogates Research: The Value of Empirical Ethics

Suzanne Metselaar[a], Jeroen Geurts[a], and Gerben Meynen[b,c]

[a]Amsterdam University Medical Centers; [b]VU University Amsterdam; [c]Utrecht University

Greely (2021) argues that surrogates for living human brains *in vivo* might be of tremendous benefit to understanding human brain function—and eventually to curing devastating brain diseases—without the practical and ethical trouble of using human brains. However, Greely rightfully raises concerns that "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" (34). At what point do they become sufficiently like us to deserve such respect?

As possibilities for creating and using surrogates for living human brains steadily increase, Greely calls for an ethical response. We agree that such a response is necessary. Among other things, it should include rethinking concepts such as "personhood," "death" and "consciousness" in the light of human brain surrogates, as well as making distinctions such as between the ethical status of "regular" biomaterials and biomaterials that involve human brain cells, between surrogates based on organic elements versus artificial neural networks *in silico,* and between the human brain as a functioning whole versus parts of the brain. Furthermore, the social significance and social impact of using brain surrogates in research should be studied. On this basis, a normative framework can be established.

We also agree with Greely that an interdisciplinary approach is needed to accomplish this, including an integration of philosophical, ethical, legal, social science and neuroscience perspectives. This requires a collaboration of experts from these fields. As Greely argues, "combined forces from many disciplines will be crucial to answering, or at least clarifying […] some of the ethical issues raised." In addition, the importance of involving the public is acknowledged by Greely. He argues that, although "thoughtful, expert consideration of the issues raised by these technologies is necessary," it is not sufficient; as science is part of society, society needs to be involved as well. Experts should therefore "help the public understand the research and its implications, in order to encourage educated and reasoned decisions, whatever direction those decisions ultimately go." Greely mentions public education, public participation in discussions, and efforts to understand public concerns as activities that should follow upon the experts' normative orientation on the subject.

However, we maintain that the focus should not only be on informing or educating the public, so as to enable society to make the right decisions. Rather, people's moral perspectives about using brain surrogates should inform and contribute to the ethical response *itself*. Methods to integrate people's ethical views and attitudes into normative analysis have been developed—and are widely used—in *empirical ethics* (Davies, Ives, and Dunn 2015). Before elaborating on what an empirical ethics approach could look like in this case, let us consider some reasons why "lay" people's views about human brain surrogates research should inform an ethical response.

First of all, the public's normative perspective is relevant to be taken from the outset because brain surrogates will continue to have a place *in society*, i.e. they will be "living" among us. This is not only the case in a general or abstract way; some individuals

CONTACT Suzanne Metselaar s.metselaar1@amsterdamumc.nl Amsterdam University Medical Centers, Ethics, Law & Humanities, Amsterdam, The Netherlands.

will have a more or less direct and specific relationship to these surrogates. For instance, they might be working with them. Other people are or will become stakeholders because they are dealing—as patients, family members, caregivers, etc.—with the brain diseases the research using human brain surrogates focuses on, such as early-onset Alzheimer's. Yet others will have to make decisions about allocating (public or private) funds to research involving human brain surrogates. Taking into account their moral perspectives in articulating an ethical response is essential to do justice to what is important to them, and might offer valuable perspectives and values to reflection and analysis (Feudtner et al. 2014).

Second, taking along society's perspective in establishing an ethical response might prevent a situation where society's perspective is at odds with that of the experts who worked on an ethical response. As Greely argues, "societies may reach conclusions that researchers or expert groups disagree with, but […] each society […] ultimately has the power to decide what research can and cannot be done" (42). Of course, there may be good reasons for such a disagreement. However, it can also result from the fact that researchers are not sufficiently aware of the public's actual fears, concerns and hopes, and, consequently, make the wrong assumptions about people's values regarding research using human brain surrogates. In addition, certain aspects of human surrogates and their use in research that might be interesting to the public, might be less so for experts, and therefore be overlooked.

Hence, researchers should not merely educate people about the ethical aspects of using human brain surrogates so as to prepare them for democratic decision-making; they should *learn from* people and should integrate what they deem, for instance, beneficial, harmful, and justified in establishing a normative framework. An empirical ethics approach provides this possibility, as it allows stakeholders to be directly involved in the creation of an ethical response.

Empirical ethics is a general term for "methodologies that seek to use empirical data about stakeholder values, attitudes, beliefs and experiences to inform normative ethical theorizing" (Davies, Ives, and Dunn 2015). It departs from the assumption that exploring stakeholder attitudes, beliefs and experiences informs and enhances ethical analysis itself, as it makes ethicists—and other experts—more contextually aware, more grounded in the realities of lived experience, and provides better, more workable solutions for ethical problems (Leget and Borry 2010).

In general, empirical ethics emphasizes cooperation between ethicists, biomedical scientists and social scientists in integrating moral theory and empirical data derived from stakeholder consultation to reach normative conclusions with respect to a specific practice (Hartman et al. 2004). Some empirical ethics methodologies also encourage involving members of society, or specific stakeholders, in the *interpretation* of the data and in reaching conclusions. These methodologies envisage reflection on a bioethical issue as a joint moral learning process in which including those affected by the issue at hand is key. In order to establish such involvement and inclusion, both the empirical research process and the process of reaching normative conclusions can be organized in a *dialogical* way (Metselaar, Meynen, and Widdershoven, Meynen, and Denys 2017; Widdershoven, Meynen, and Denys 2015). This means that empirical and ethical elements of the research process are integrated through dialogue, in which the ethicist acts as a facilitator, stimulating interaction and reflection among, and taking part in the deliberation with, participants in practice (Widdershoven, Abma, and Molewijk 2009).

Following this approach, in the case of finding an ethical response to using human brain surrogates in research, we may not only gather information *about* stakeholders, but perform our research *together* with them (citizens, patients and their family members, policy makers, etc.). For instance, dialogue sessions could be organized in various places with members of the public in various compositions. These joint reflections may serve as a solid basis for an ethical response of a team of experts and stakeholders from society together. Clearly, what will be relevant given the complex technologies involved and the rapid developments in the field are methods that educate respondents such that they can meaningfully participate in these dialogues. It is also important that the researchers report their findings in an open and non-judgmental way to the participants. Obviously, all of this requires specific expertise about how empirical ethics studies should be conducted. Fortunately, because of much research on empirical ethics in recent years, such expertise is now in place, even though our knowledge is still evolving (Wangmo and Provoost 2017).

Thus, although we generally agree with the recommendations made by Greely, we feel that the question of how to deal with the use of human brain surrogates in research is one—among many bioethical questions—in which the value of an empirical ethics approach should not be overlooked.

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Human Brain Surrogates: Models or Distortions?

Monika Piotrowska

University at Albany State University of New York

Although neurological disease and mental illness can cause terrible human suffering, strategies for researching their causes and cures are not obvious. Invasive brain research on actual human beings is clearly not an option for ethical reasons. As a result, neuroscientists have been inspired to model living human brains outside of living human beings. Hank Greely refers to such research subjects as "human brain surrogates" and divides them into four categories: (1) genetically edited non-human animals, (2) human/non-human brain chimeras, (3) human neural organoids, and (4) living *ex vivo* human brain tissues. In his target article, Greely argues that the creation of human brain surrogates is pushing us toward the following problem:

> 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? (Greely 2021, 34)

This is an important question that may one day require serious deliberation, but that day is not on the visible horizon. At least, it is not on the horizon with respect to categories one and two from above, namely, (1) genetically edited non-human animals and (2) human/non-human brain chimeras. Largely, this is due to difficulties in assessing "how whole, living, integrated brains function inside living non-human animals when changes have been made that might tell us something about humans" (Greely 2021, 36). I want to offer two arguments to explain this difficulty, which will also serve to explain why Greely's worry is misplaced. First, I will argue that the nonhuman bodies of host models produce distortions in representing the functional mechanisms used to produce human behavior. And second, I will argue that changing host model phenotypes results in behavioral changes that are difficult to interpret.

CONTACT Monika Piotrowska mpiotrowska@albany.edu University at Albany State University of New York, Albany, NY, 12222-0100, USA.