COMMENTARY

Research Ethics in Conscious Subjects: Old Questions, New Contexts

Gidon Felsen

A recent study demonstrated a method capable of partially restoring functioning in the brain of a pig that had been dead for several hours.[1] One of the many descriptions of this study in the popular press noted that the investigators "did not want to take a chance that the brains might regain consciousness," and that a plan was in place to stop the experiment "had the team seen electrical activity suggesting actual consciousness."[2] While many readers — practicing neuroscientists in particular — may have found this concern absurd, the question of how to think about research protections for conscious subjects has profoundly influenced guidelines for research in human and animal subjects[3] and has recently been considered in a surprisingly wide variety of novel contexts. An instructive example is provided by Koplin and Savulescu, who propose well-grounded ethical guidelines for research in the rapidly developing field of brain organoids.

Organoids are organ-like three-dimensional structures developed *in vitro* from pluripotent stem cells that are suitable for addressing many questions about biological function.[5] Several variants of brain organoids have been developed that are increasingly being used to study normal and disordered brain function.[6] Brain organoid research shares the classical bioethical issues of organoid research more generally (e.g., respect for tissue donors), but must also take into account the potential capability for organoids to have some capacity for consciousness. To be clear, there is no more concern about consciousness in current brain organoid models than in *ex vivo* brain slices, which have been used in research for decades.[7] As with the post-mortem pig brain experiments, such concerns may seem preposterous. Further, given the potential for clinical benefit, there is widespread agreement that discontinuing brain organoid research would be unethical.[8] Nevertheless, as the field develops brain organoids increasingly similar to actual brains (which serve as better experimental models), it is worth considering, now, the possibility that future brain organoids could possess some degree of consciousness.

Conscious beings are thought to have their own interests, raising Kantian ethical questions about their use as a means to an end.[9] In the research setting, these questions have been addressed by developing principles and guidelines for ethically performing experiments with conscious subjects. For example, animal research has long-been guided by "the Three Rs" — Reduce, Refine and Replace[10] — and human subjects research is grounded in informed consent.[11] Koplin and Savulescu build on this work by proposing guidelines for brain organoid research based on modern principles for ethical animal research.[12] However, in this and other emerging fields, the ethics of research with potentially conscious subjects continues to be debated.

For example, there is increasing appreciation that some behaviorally nonresponsive patients may actually possess some degree of consciousness,[13] and research with these patients is critical for understanding minimally conscious states, making accurate prognoses, and ultimately developing clinical treatments.[14] Using functional magnetic resonance imaging as a proxy for neural activity, it is possible for these patients to provide yes or no answers in response to carefully crafted questions.[15] In principle, such an approach could be

Gidon Felsen, Ph.D., *is affiliated with the Department of Physiology and Biophysics, University of Colorado School of Medicine, USA and the Center for Bioethics and Humanities, University of Colorado Anschutz Medical Campus, USA.*

The Journal of Law, Medicine & Ethics, 47 (2019): 768-770. © 2019 The Author(s)
DOI: 10.1177/1073110519897790

used to obtain informed consent to participate in research (as well as other important information, such as treatment preferences). But given the limitations of asking yes-or-no questions and the reliability of interpreting patients' responses,[16] research guidelines specific to minimally conscious patients must be developed.[17] This effort parallels the more general questions that the field has been addressing about the ethical treatment of patients that may possess more consciousness than previously appreciated.[18]

Similar concerns about consciousness and research ethics have even begun to emerge in non-biological systems like large-scale *in silico* neural models. The idea, which gained currency in cognitive science several decades ago,[19] is that, as these models increase in complexity and better reflect brain functioning, it is not unreasonable to think that consciousness may (somehow) emerge in them, just as it (somehow) emerges in biological brains of sufficient complexity.[20] It therefore behooves us to ask, now, whether we need guidelines for ethical research with these simulations.[21] Indeed, this concern is highlighted by one of the key questions recently posed by an international working group examining neuroscience research ethics: "What are the requisite or minimum features of engineered neural circuitry required to generate a concern about moral significance?"[22] As was the case for minimally conscious patients, these research ethics questions parallel the more general concerns about ethical behavior toward sufficiently complex engineered systems.[23]

An interesting question is whether a coherent set of guidelines for research on conscious subjects could be developed that would apply across these disparate contexts. Currently, a clear obstacle to this effort is our fundamental lack of understanding of consciousness and its physical substrates,[24] and therefore which features of it should drive ethical concern. While this is an active area of research[25] that may produce a framework for characterizing consciousness across systems,[26] consciousness is a notoriously "hard problem"[27] that may resist generalization across contexts. Koplin and Savulescu's approach of developing context-specific guidelines therefore remains practical.

However, our current knowledge gap about consciousness does not preclude adapting existing research guidelines across contexts, where appropriate. Koplin and Savulescu adeptly recognize the similarities between the ethical issues associated with animal and brain organoid research and apply the well-developed framework for the former to the latter. Just as important, they avoid the simplistic trap of equating potential consciousness in brain organoids with "personhood" and therefore correctly decide against applying principles from human research ethics. Thus, beyond developing well-grounded ethical guidelines for brain organoid research, Koplin and Savulescu provide a valuable template for adapting existing ethical guidelines to research with potentially conscious subjects in other emerging fields.

Similar concerns about consciousness and research ethics have even begun to emerge in non-biological systems like large-scale in silico neural models. The idea, which gained currency in cognitive science several decades ago, is that, as these models increase in complexity and better reflect brain functioning, it is not unreasonable to think that consciousness may (somehow) emerge in them, just as it (somehow) emerges in biological brains of sufficient complexity.

Note

The author has no conflicts to disclose.

References

1. Z. Vrselja, S.G. Daniele, J. Silbereis, et al., "Restoration of Brain Circulation and Cellular Functions Hours Post-Mortem," *Nature* 568 no. 7752 (2019): 336-343.
2. G. Kolata, "'Partly Alive': Scientists Revive Cells in Brains From Dead Pigs," *The New York Times*, April 17, 2019, *available at* <https://www.nytimes.com/2019/04/17/science/brain-dead-pigs.html> (last visited November 18, 2019).
3. *Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects* (1964), *available at* <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> (last visited November 18, 2019); The Animal Welfare Act Public Law 89-544 Act of August 24, 1966, *available at* <https://www.nal.usda.gov/awic/animal-welfare-act-public-law-89-544-act-august-24-1966> (last visited November 18, 2019); *The Belmont Report* (1979), *available at* <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html> (last visited November 18, 2019).

The Journal of Law, Medicine & Ethics, 47 (2019): 768-770. © 2019 The Author(s)

https://doi.org/10.1177/1073110519897790 Published online by Cambridge University Press

4. J.J. Koplin and J. Savulescu, "Moral Limits of Brain Organoid Research," *Journal of Law, Medicine & Ethics* 47, no. 4 (2019): 760-767.
5. M. Simian and M.J. Bissell, "Organoids: A Historical Perspective of Thinking in Three Dimensions," *The Journal of Cell Biology* 216, no. 1 (2017): 31–40.
6. E. Di Lullo and A.R. Kriegstein, "The Use of Brain Organoids to Investigate Neural Development and Disease," *Nature Reviews Neuroscience* 18, no. 10 (2017): 573–584.
7. N. A. Farahany, H.T. Greely, S. Hyman, C. Koch, C. Grady, S.P. Paşca, N. Sestan, et al. "The Ethics of Experimenting with Human Brain Tissue," *Nature* 556, no. 7702 (2018): 429-432.
8. Farahany, *supra* note 7; Koplin, *supra* note 4.
9. I. Kant, *Groundwork for the Metaphysics of Moralsi* (1785).
10. W.M.S. Russell and R. L. Burch, *The Principles of Humane Experimental Technique* (London: Methuen, 1959).
11. R.R. Faden and T. L. Beauchamp, *A History and Theory of Informed Consent* (Oxford University Press, 1986).
12. T. L. Beauchamp and D. DeGrazia, *Principles of Animal Research Ethics* (Oxford University Press, 2019).
13. A.M. Owen, et al. "Detecting Awareness in the Vegetative State," *Science* 313, no. 5792 (2006): 1402–1402.
14. D. Fernández-Espejo and A.M. Owen, "Detecting Awareness after Severe Brain Injury," *Nature Reviews Neuroscience* 14, no. 11 (2013): 801–809.
15. M.M. Monti et al., "Willful Modulation of Brain Activity in Disorders of Consciousness," *NEJM* 362 (2010): 579-589.
16. A. Peterson et al., "Assessing Decision-Making Capacity in the Behaviorally Nonresponsive Patient With Residual Covert Awareness," *AJOB Neuroscience* 4, no. 4 (2013): 3–14.
17. J.J. Fins, J. Illes, J. L. Bernat, J. Hirsch, S. Laureys, and E. Murphy, "Neuroimaging and Disorders of Consciousness: Envisioning an Ethical Research Agenda," *The American Journal of Bioethics* 8, no. 9 (2008): 3–12; C. Weijer et al., "Ethics of Neuroimaging after Serious Brain Injury," *BMC Medical Ethics* 15 (2014).
18. J.J. Fins, "Neuroethics and Disorders of Consciousness: Discerning Brain States in Clinical Practice and Research," *AMA Journal of Ethics* 18, no. 12 (2016): 1182–1191.
19. D. R. Hofstadter and D.C. Dennett, *The Mind's I: Fantasies And Reflections On Self & Soul* (New York: Basic Books, 1981).
20. S. Dehaene, H. Lau, and S. Kouider, "What Is Consciousness, and Could Machines Have It?" *Science* 358, no. 6362 (2017): 486–492.
21. T.D. Bancroft, "Ethical Aspects of Computational Neuroscience," *Neuroethics* 6, no. 2 (2013): 415–418.
22. J. Amadio et al., "Neuroethics Questions to Guide Ethical Research in the International Brain Initiatives," *Neuron* 100, no. 1 (2018): 19–36.
23. D. J. Gunkel, *Robot Rights* (MIT Press, 2018).
24. Dehaene, *supra* note 20.
25. S. Dehaene, L. Charles, J.-R. King, and S. Marti, "Toward a Computational Theory of Conscious Processing," *Current Opinion in Neurobiology* 25 (2014): 76–84; G. Tononi, M. Boly, M. Massimini, and C. Koch, "Integrated Information Theory: From Consciousness to Its Physical Substrate," *Nature Reviews Neuroscience* 17, no. 7 (2016): 450–461.
26. A. Lavazza and M. Massimini, "Cerebral Organoids: Ethical Issues and Consciousness Assessment," *Journal of Medical Ethics* 44, no. 9 (2018): 606–610.
27. D.J. Chalmers, "Facing up to the Problem of Consciousness," *Journal of Consciousness Studies* 2, no. 3 (1995): 200-219.

The Journal of Law, Medicine & Ethics, 47 (2019): 768-770. © 2019 The Author(s)