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GREY MATTERS

Miniature Human Brains: An Ethical Analysis

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I began to think myself in Lilliput. – Jonathan Swift[1]

Abstract

The recent creation of human cerebral organoids resembling miniature brains has opened a new chapter in neuroethics. Ethical analysis of this innovative biotechnology begins with a comparative examination of the biological constitution of brain-like entities, followed by consideration of the moral status of isolated brains, the potential benefits to medical science in the prevention and treatment of neurologic disease, and potential health risks of neural transplantation. Whereas these experiments touch on philosophically fascinating questions about what it would mean to have brains without bodies, thankfully such morally disturbing prospects remain beyond the reach of neuroscience for the foreseeable future.

Introduction

Regenerative medicine's most intriguing aspiration is to coax pluripotent stem cells into assembling into functional organs to replace failing organs in patients.[2] Realization of that prospect, which some have called the "Holy Grail" of medical science,[3,4] could profoundly transform the face of medicine, if not also how we think of the human body.

The tissue least amenable to engineering from cell culture to fully functioning organ may be neural tissue, as the brain is by far the most intricate and complex of human organs,[5] which is why a paper recently published in *Nature* is noteworthy. Madeline Lancaster, who is the Marie Curie postdoctoral fellow in the laboratory of Juergen Knoblich in Vienna, in collaboration with colleagues in Austria and the U.K., has successfully induced human pluripotent stem cells to aggregate into self-organizing three-dimensional tissues resembling miniature brains.[6] The neural aggregates grew to pea-sized (4 mm diameter) globules and, bathed in a nutrient mixture, could be maintained for several months in a spinning bioreactor.

What They Are

When examined under the microscope, the cellular architecture of the Viennese entities was found to recapitulate the developing human brain. Continuous neuroepithelia surrounding a fluid-filled cavity formed complex, heterogeneous, rudimentary brain structures morphologically reminiscent of the cerebral cortex, choroid plexus, and retina.[6] So novel are these brain-like neural aggregates that the researchers invented a new term – cerebral organoids – to describe them accurately.

Cultured cerebral organoids afford a useful *in vitro* model in which to study the early development of the human brain under controlled laboratory conditions. They could be used to study human species-specific aspects of embryological neurodevelopment that are unavailable in mouse or other animal models. Studies of cerebral organoid growth might, for example, identify the particular profiles of gene expression and epigenetic influences that direct the initial stages of neuronal migration in their mysterious trajectory toward forming the mature human brain.

Cerebral organoids could also be used as reductionistic models to study disease-specific neurodevelopmental disorders, such as autism spectrum disorder, epilepsy, trisomy 21, fragile X syndrome, familial dysautonomia, and nutritional and toxic causes of neurodevelopmental delay. Until now much of our current understanding about developmental neurobiology has relied on postmortem brain tissues. The knowledge gained from studying more accessible sources of organized brain tissue might lead to new ways to prevent and treat these devastating disorders.

Cerebral organoids could even be used to study patient-specific neurodevelopmental disorders, advancing neuroscience a step closer to individualized medicine.[7] Lancaster and colleagues demonstrated this by growing cerebral organoids from stem cells derived from an individual patient with a genetic form of microcephaly. In the patient-derived organoids they found that the neural tissues were smaller with premature neuronal differentiation.[6] Their findings surpassed what it had been possible to learn through animal models.

Further practical value of cerebral organoids may lie in their potential usefulness as an organic substrate on which to conduct tests of the pharmacologic effects and toxicities of new drugs that interact with neural tissue. Several decades ago, the development of cultured human cell lines represented a seminal advance in biotechnology that led, for example, to the development of vaccines for polio. Cerebral organoids represent a further refinement in tissue culture biotechnology that promises to bring within reach the ability to evaluate early neurodevelopment in the context of specific diseases or under the influence of neurotropic drugs.[8]

Currently, the cost of bringing a new drug to market in the United States is estimated at between $1.3 and $1.8 billion.[9-11] Some of this cost comes from preliminary drug studies to assess biologic effects and toxicity on neural tissue. If data that is currently obtainable only through animal models could be furnished by conducting studies on cerebral organoids, which would be a paradigm shift in drug development, then it might become possible to lower the cost of testing new drugs and also to decrease the time needed to conduct the research required to gain approval by the Food and Drug Administration. Human cerebral tissue may also have biological advantages over nonhuman animal tissue, since currently 92 out of every 100 drugs that successfully pass animal trials subsequently fail human trials.[12]

In these ways cerebral organoid biotechnology may have the potential to enlarge the repertoire of available neurological drugs and vaccines, decrease the cost to society of new drug development, and bring new drug discoveries to the bedside sooner.

What They Are Not

In his book *That Hideous Strength*, C. S. Lewis describes the intuitive revulsion one might feel when confronting a living, thinking, human brain, severed from its body and kept alive unnaturally through technological means:

> I thought I saw a face floating in front of me… there didn't seem to be anything above the eyes. Not at first. But as I got used to the light, I got a horrible shock. I thought the face was a mask tied on to a balloon thing. But it wasn't, exactly… What it really was, was a head (the rest of a head) which had had the top part of the skull taken off and then… then… as if something inside had boiled over. A great big mass which bulged out from inside what was left of the skull… You could see it twitch. Even in my fright I remember thinking, "Oh kill it, kill it. Put it out of its pain."[13]

Contrary to sensationalist media depictions of "test tube brains,"[14-16] cerebral organoids are not actual brains. In an accompanying editorial, Oliver Brüstle points out that "the realization of a 'brain in a dish' remains out of reach," because the organoids lack the full spatial organization of the human brain as well as a circulatory system to allow further growth and development.[17]

At only 4 mm in diameter, their volume is one thousandth that of a mouse brain and one millionth that of an adult human brain. There is, of course, no formula for converting the number of neurons present to the depth and quality of thoughts that a sufficient number of neurons in their natural milieu might generate. No one knows how many neurons it would take for a distinctively human thought to emerge.[18] Notwithstanding this uncertainty and the empirical problem of even detecting such a thought, it is interesting to note that a cerebral organoid is approximately ten times the size of the brain of a honey bee.[19] Honey bee cognition, while limited, is not trivial; it comprises the capacity to interpret visual and social cues, navigate its home geography, assess distance and direction. Bees can also evaluate the plausibility of potential food sources, which biologists regard as a rudimentary form of imagination.[20] The honey bee brain, however, is designed for honey bee activities, such as buzzing around a hive, whereas a human cerebral organoid that aggregates transiently within a spinning bioreactor has no innate purposeful composition relevant to its environment and no bodily correlate.

In an age of ever intensifying microelectronic computational power that, in some respects, rivals human intelligence, cognitive criteria alone, though important, seem to be increasingly inadequate for defining human beings or understanding what about them is unique. Essential also are the meaning of embodiment and ontological status as a member of the human species.

A normal human brain develops, not in isolation, but within and as part of an integrated body. A body is not an inert structural container for the thinking brain, but rather is a sensitive interface through which the brain perceives and interacts with its environment. The body is also a conduit for intentional movement and creative expression. Hypothetically, if it were possible for a brain to be grown to a mature size in isolation, without a body, such a brain would not be, nor could it become, a person. Persons as embodied beings inhabit the world in a likeness that is shared by others while also being individually unique.

Cerebral organoids are not detached brains, since at no time in their development are they ever joined to bodies to relay sensory information from the environment, which

may be a necessary precondition for a brain capable of thinking thoughts that correspond to external reality. Absent a body or any peripheral sensory information from vision, hearing, or touch, a cerebral organoid would have no means of developing an awareness of its surroundings or even its own existence, let alone that of others.

In regard to ontological status, the embryoid bodies that formed cerebral organoids in the report by Lancaster and colleagues from the beginning lacked the capacity to develop into a human fetus, child, or adult. The induced human pluripotent stem (iPS) cells from which they were grown, which were derived from skin fibroblasts, also lacked such capacity. However, the researchers conducted parallel experiments using human embryonic stem cells (H9, WiCell), which were originally derived from human embryos at the Technion-Israel Institute for Technology. For those who consider it morally wrong intentionally to destroy nascent human life for the purpose of embryonic stem cell procurement,[21,22] the use of stem cells lines derived from those embryos raises difficult questions of moral complicity with the prior taking of innocent human life.[23]

These ethical concerns are alleviated by the researchers' finding that "cerebral organoids could be reproducibly generated with similar overall morphology and complexity from both human embryonic stem (ES) cells and iPS cells."[6] Therefore, this research supports the conclusion that it is not necessary to destroy human embryonic life to obtain useful cerebral organoids.

What They Might Become

Looking ahead to further potential applications of cerebral organoid biotechnology, the prospect of transplantation may eventually arrive. Whereas whole human brain transplantation would be neither feasible nor desirable, patients with brain or spinal cord damage from stroke, trauma, encephalitis, or focal degenerative disorders might benefit greatly from transplantation of viable neural tissue, provided that the transplanted tissue could functionally integrate with, and not disrupt, the patient's own nervous system.[24]

Imagine a spinal cord graft for Christopher Reeve for his paralyzing cervical spine injury, anterior horn cell grafts for Lou Gehrig to treat his amyotrophic lateral sclerosis, substantia nigra grafts for Michael J. Fox to treat his Parkinson disease, hippocampal grafts for Rosa Parks to treat her Alzheimer disease, or a frontal lobe graft to restore moral awareness to injured railroad foreman Phineas Gage. Such grafts, if they could be engineered, would not in all likelihood achieve full restoration of neurologic function, but they might provide the best possible regenerative treatment obtainable through medical science.

A considerable amount of research is needed before such dreams of regenerative medicine could be realized. In addition to deciphering the multitude of precise cellular conditions and chemical signals needed to induce cells to differentiate into viable neurons that can survive and functionally integrate with host neurons, a number of safety concerns should be addressed. We must be certain that cells grown in a laboratory dish and implanted into a patient will not, once established in the target tissue, continue to grow and form brain tumors. We must be certain that the implanted cells do not harbor potentially lethal latent infectious agents such as endogenous retroviruses or prion diseases – which might also be a concern for vaccines developed on cultured neural tissue. Finally, we would prefer that implanted tissue match the patient's own cellular composition closely enough

to evade immune rejection, so that the patient does not have to commit to a lifetime of expensive and potentially harmful immunosuppressive drugs.

Within the safety and ethical constraints discussed so far, this writer considers the development of cerebral organoids to be ethically permissible and its potential medical applications in general to be ethically praiseworthy.

As forethought is an indispensable aspect of ethics, there are further possibilities to ponder. Stretching the imagination toward a distant possible future, depending on how it is developed, this (as any) biotechnology might also carry the potential to spawn some troublesome ethical problems.

Currently, cerebral organoids grown to 4 mm, which appears to be the upper limit for growth in the laboratory in the absence of a circulatory system, model just the earliest stages of neurodevelopment. Subsequent stages of development, including neuronal migration, axonal and dendritic outgrowth, branching, myelination and other neural-glial interactions, synaptogenesis, synaptic pruning, and connectivity, are also of scientific and medical interest, and the development of living models of these phenomena may eventually be pursued. If it were to become possible, through, for example, an artificial circulatory system, to grow more developmentally advanced cerebral organoids with greater and greater functional capacities, where, then, should the ethical line be drawn that delimits how far along the developmental pathway such entities should be created? What would count as a morally significant boundary? Would it be brain volume, number of neurons, structural complexity, computational processing, abstract thought, language, ability to respond to threat, self-awareness, or some other measurable emerging characteristic? How might the earliest indications of such capacities in tiny organoids be detected? Do immeasurable qualities also matter?

The goal of finding better and better human disease models could translate to designing living entities that resemble ever more closely human structure and function. The more useful biological brain models were to become, it may be that the more human they would seem. Whether future versions of human cerebral organoids, monitored and connected to their environment by microelectronic interfaces – interfaces that might also function as sensory prostheses, as a kind of body, would or should be recognized as members of the human community might not always remain a question solely dealt with by science fiction. As long as morally concerned people remain interested in biomedical science, there will continue to be new and interesting questions with which to grapple.

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