Brain diseases—including neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease, psychiatric disorders such as schizophrenia and depression, developmental disorders such as autism spectrum disorder and attention-deficit/hyperactivity disorder, brain cancers, and the effects of traumatic injury—cause tremendous amounts of suffering and death. As many as 30 percent of people experience a neurological or psychiatric disorder during their lifetimes. Together, brain diseases are the leading cause of morbidity worldwide, and psychiatric diseases incur costs of more than $200 billion annually in the United States and up to $2.5 trillion globally.

Treatments for these diseases are often completely lacking or partially effective, partly because of the practical and ethical difficulties of studying the human brain. Our brains contain nearly 100 billion neurons interconnected by trillions of connections in intricate circuits that can hold vast amounts of information. Such complexity presents formidable challenges for brain researchers, and tools for studying the brain are limited.

A particular difficulty in studying the brain is the lack of good model systems for brain research. Animal models used to study brain structure and function have been indispensable, but the brains of experimental animals have key molecular, cellular, and structural differences from human brains. This helps explain why disease treatments that have shown promise in animal models are often ineffective in humans.

Several new experimental models that use human neural cells provide powerful ways to understand normal and abnormal brain development. In particular, human neural organoids, the transplantation of human stem cells into nonhuman animal brains (sometimes called xenografts), and neural chimeras all promise a much deeper understanding of the human brain and new treatments for brain diseases.

As research models, human neural organoids, cell transplants, and chimeras are already yielding important insights into the functioning of the human brain and human brain disorders. However, as they become larger, more complex, and (in the case of transplants) more integrated into the brains of nonhuman animals, they raise difficult ethical questions. Could human brain organoids acquire aspects of consciousness or feel pain? Could animals containing transplanted human brain cells have capacities substantially different from those typical of their species? Do chimeras violate the distinction between humans and other animals that is deeply embedded in many cultures? Could experimental animals develop characteristics commonly thought of as human?
The report *The Emerging Field of Human Neural Organoids, Transplants, and Chimeras: Science, Ethics, and Governance* by the Committee on Ethical, Legal, and Regulatory Issues Associated with Neural Chimeras and Organoids, an ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine’s Committee on Science, Technology, and Law, reviews the status of this research, considers its benefits and risks, examines associated ethical issues, and discusses what oversight mechanisms might be appropriate in this area. The following text summarizes important findings from the committee’s report.

**THE SCIENCE OF HUMAN NEURAL ORGANOIDS, TRANSPLANTS, AND CHIMERAS**

Over the past few decades, neuroscientists have greatly advanced understanding of how neurons develop, function, form complex circuits, and underlie at least some simple behaviors, to the point that it is now possible to begin using this knowledge to tackle human disease mechanisms and design effective therapies. However, making this leap is difficult largely because of practical, ethical, and legal limitations to studying the human brain. Noninvasive techniques such as functional MRI (magnetic resonance imaging) or EEG (electroencephalography) provide insight into the functioning brain, but they are limited in spatial resolution, physiological information, and the types of experimental manipulations that are possible. Investigating the cellular and molecular bases of brain function requires access to brain tissue, which is difficult to obtain and generally limited to samples removed during surgery or postmortem. To address the need for novel methods of assessing the function and dysfunction of the human brain, researchers have developed new models in recent years, including human neural organoids, cell transplants, and chimeras.

Human neural organoids are three-dimensional aggregates of human neural cells grown in the laboratory from stem cells (See Figure 1). They exhibit some developmental, cellular, and molecular features of fetal human brains. Stem cells can be prepared from skin biopsies of neurotypical individuals or patients with specific brain disorders and used to generate organoids. In some cases, organoids generated from patient stem cells reproduce molecular features of human disease, and can therefore be used to analyze disease mechanisms or perform initial tests of potential therapies. Current neural organoids are small—no more than 4 millimeters in diameter—and are limited in complexity and maturity, though researchers are working to overcome these limitations.

Human neural transplants are generated by transplanting human cells into the brains of nonhuman organisms (See Figure 2). Such transplants have been performed and studied for decades, but the more recent use of stem cells for transplantation enables the study of human brain cells in the context of a whole, behaving
organism. Neural transplants into humans already have been tested in clinical trials as potential therapies for neurodegenerative diseases such as Parkinson's disease. Transplantation of human neural cells into nonhuman animals can provide essential preclinical data for designing these and other therapies.

Human neural chimeras are a special case of transplants. To generate a chimera, stem cells are injected into a nonhuman host very early in embryonic development (See Figure 3). They then intermingle with the host cells that form the brain, populating it from the earliest stage. To date, chimeras that develop to fetal stages or later have only been generated using rodent stem cells put into rodent hosts. However, research in this area is advancing rapidly, and it is possible that chimeras could eventually be generated from human cells injected into the early embryos of a nonhuman primate.

ETHICAL CONCERNS

Strong moral arguments support research using neural organoids, transplants, and chimeras derived from human cells. Research using these models could produce new ways to understand and treat neurological and psychiatric disorders that cause immense suffering. However, these potential benefits are not absolute and must be weighed against other ethical considerations such as using human biological materials appropriately, ensuring animal welfare, and maintaining safety.
For existing biological materials that were collected with appropriate consent and deidentified so that donors cannot readily be linked with materials, federal regulations specify that these materials may be used in future research projects, even if most donors were not aware that their tissues would be used for neural organoid, transplant, or chimera research. Discussions are under way regarding the advantages and disadvantages of obtaining specific consent for this research of this type when collecting fresh tissue.

A key ethical concern with the use of human neural cells in animal models is that a fundamental distinction between humans and other animals could be blurred. The increasing ability to generate human–nonhuman animal chimeras and to integrate human neural cells in nonhuman animals heightens these concerns, and these concerns are likely to be even greater if nonhuman primates are used as hosts.

As research progresses, research animals could show behaviors resembling human disease symptoms that would be seen as distressing were they to occur in humans. Close observation of experimental animals can identify such behaviors, which may need to be avoided or mitigated to maintain animal welfare. Another concern is that animals may acquire behaviors atypical of their species, such as new forms of problem solving or more complex social interactions. The committee authoring the report found scant evidence that this is a realistic possibility in the foreseeable future, but surveillance of this rapidly developing research is essential.

OVERSIGHT AND REGULATION

Research on human neural organoids, transplants, and chimeras is subject to a wide range of oversight mechanisms regarding the use of human tissues and stem cells and the use and welfare of nonhuman animals. These mechanisms can address the ethical concerns raised by current and near-future research. However, some concerns will need to be reassessed as the science develops.

Unless they become significantly more complex, neural organoids will not raise issues that require additional oversight. In the foreseeable future, it is extremely unlikely that they would possess capabilities that, given current understanding, would be recognized as awareness, consciousness, emotion, or the experience of pain. From a moral perspective, neural organoids do not differ at present from other in vitro human neural tissues or cultures. However, as scientists develop significantly more complex organoids, the possible need to make this distinction should be revisited regularly.

Current oversight mechanisms can also address issues arising in transplant and chimera research now and for the immediate future. These mechanisms include institutional animal care and use committees, stem cell research oversight committees, institutional review boards, funding restrictions, and professional guidelines. Some oversight bodies might need additional expertise in evaluating the behavior of animals after transplantation of human neural cells.

Some future research—including that involving more complex human neural organoids, transplants, and chimeras and the generation of transplants and chimeras in nonhuman primates—will benefit from broader discussion of ethical and social issues than occurs today. Possibilities for additional oversight or safeguards include pilot studies followed by re-evaluation, implementation of novel measures to monitor capacities of research animals, and designation of research that should not be conducted at this time. Carrying out such discussions at the national level would enable a wide range of viewpoints and disciplinary backgrounds to be heard and considered.

PUBLIC ENGAGEMENT AND COMMUNICATION

Greater public engagement in assessing the value of emerging areas of biomedicine can help the public understand the research, identify public concerns, facilitate informed discussion, and influence science policy. However, the United States currently lacks robust mechanisms for facilitating such engagement. Because of the plurality of religious and secular views in the United States, ongoing respectful dialogues between religious and secular perspectives and among different viewpoints are important.

Terms used to describe human neural organoids, transplants, and chimeras are sometimes inaccurate, inadequately descriptive, or misleading. As one of many examples, neural organoids are sometimes referred to in the press as “mini-brains,” but in reality they model only some limited aspects of brain tissue. The use of such terms can evoke emotional responses that do not reflect the science and can be used to pull the public toward acceptance or rejection of a technology. Closer attention to nomenclature by scientists and research institutions would facilitate a more informed public debate about brain research.
THE NEED FOR CONTINUED ASSESSMENT

The brain is the organ that, more than any other, gives humans their individual identity, so there are unique sensitivities around research on brain cells and tissue. Progress in studying the brain using human neural organoids, transplants, and chimeras has been rapid. While current regulations can govern this research adequately at present and for the foreseeable near future, new regulations may be necessary as the research advances.

Committee on Ethical, Legal, and Regulatory Issues Associated with Neural Chimeras and Organoids

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For More Information... This Consensus Study Report Highlights was prepared by Steve Olson for the Committee on Science, Technology, and Law, based on the Consensus Study Report, *The Emerging Field of Human Neural Organoids, Transplants, and Chimeras: Science, Ethics, and Governance* (2021). The study was sponsored by the National Institutes of Health and The Dana Foundation. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.