Moral Permissibility of Transplantation of Human Brain Organoids into Animals

8

Insoo Hyun

8.1 Introduction

This chapter considers the moral permissibility of transplanting human brain organoids into laboratory animals. In secular ethics, an activity is morally permissible if it is neither morally obligatory nor morally forbidden. To be morally permissible is to be a matter of individual choice—to do or not to do, with no moral obligation one way or another. For the matter at hand, which involves a research technique aimed at the advancement of human brain organoid research and disease modeling in laboratory animals, the moral grounds for permissible choice lie at the intersection of two ethically sensitive areas of science. Understandably, given the ethical heat already present around both human brain organoid research and human-to-animal interspecies chimera research, people's thinking about the permissibility of transplanting human brain organoids into the brains of laboratory animals is liable to be murky, at least initially.

We can turn down the heat and increase the light at the juncture of organoid and chimera research if we consider separately what makes brain organoids and chimeras each so ethically sensitive and then consider whether the combination of these two scientific pursuits raises any additional ethical concerns that must be addressed in a new way.

I. Hyun (✉)
Department of Bioethics, Case Western Reserve University, School of Medicine, Cleveland, OH, USA

Center for Bioethics, Harvard Medical School, Boston, MA, USA
e-mail: insoo.hyun@case.edu; insoo_hyun@hms.harvard.edu

H.-G. Dederer, D. Hamburger (eds.), *Brain Organoids in Research and Therapy*, Advances in Neuroethics, https://doi.org/10.1007/978-3-030-97641-5_8

8.2 Ethical Sensitivities Surrounding Brain Organoids and Chimeras

Unlike other human organoids generated in the lab, such as gut organoids or liver organoids, brain organoids are of special ethical concern because the human brain itself is so intimately tied to people's subjective sense of personal identity. One might say that the natural human brain is distinct from other organs because of its role in supporting persons' experiences, memories, agency, creativity, and all those other mental properties that make human lives distinctive. The brain can easily be viewed as the seat of an individual's subjective sense of identity, so much so that a sudden and severe brain injury might cast doubt on whether the "same person" will survive, even as the body otherwise remains intact. Irreversible damage to other organs, even if it results in the need for a whole organ transplant, does not raise the same type of concerns about the continuity of a person's identity.

Furthermore, the brain itself is central for the possibility of personhood in Western philosophy. That is to say, human beings are classified as *persons* due to their capacity for rational agency. According to one popular version of the concept of rational agency—what contemporary philosophers call personal autonomy—an individual's rational agency consists in his or her ability to act thoughtfully on those motivations, appetites, or desires that he or she approves of having on a higher cognitive level of self-reflection.[1] To put the point another way, an autonomous person acts deliberately in accordance with his or her own values.[2] Certainly, neither personhood nor autonomy would be possible without the complex cognitive functions supported by the brain, the sum of which makes having distinctively human lives possible and gives human existence its felt coherence. John Locke once wrote that a person is "a thinking intelligent being, that has reason and reflection, and can consider itself as itself, the same thinking thing, in different times and places."[3]

It may be argued, therefore, that the moral significance of the brain derives from its role in supporting personhood, rational agency, personal identity, and personal interactions, all of which are crucial for grounding our everyday judgments of moral approbation and blame. In light of these important philosophical connections, it is easy to see why people may be much more concerned about human brain organoids than other types of organoid models. If the natural human brain is morally significant, then some might reason that organoid models of the human brain could also be morally significant, especially if they are capable of exhibiting or supporting the types of cognitive human traits mentioned above. Even if it is extremely unlikely or impossible for human brain organoids in a dish to ever exhibit agency on the level of personal autonomy in humans with intact brains, which would require the ability to interact with the world and each other, concern over the possible emergence of some basic level of humanlike "consciousness" might suffice to motivate a cautious approach to human brain organoid research.

[1] Dworkin (1970) and Frankfurt (1971).

[2] Hyun (2001).

[3] Locke (1694/1975), 2.27.9.

A similar concern underlies people's apprehensions about human-to-animal chimera research, in particular the possibility of acute neurological chimerism in laboratory animals generated through the transfer of human stem cells or their direct neuronal derivatives. Here the chief worry appears to be less about whether chimeric animals could gain "consciousness" in the form of conscious access to sensory stimulation, or wakefulness, vigilance, focal attention, or sentience. Host animal species such as laboratory rodents already possess all of these mental capacities without the addition of human neural cells. Rather, the ethical concern with both neurological chimeras and human brain organoids is that organoids maintained in a dish (in vitro) or human-to-animal chimeras could somehow gain the morally significant characteristic of humanlike consciousness in the form of *subjective self-awareness*: i.e., conscious awareness of oneself as a temporally extended being with experiences, beliefs, and interests, all of which can be mentally reflected upon by oneself.

Is an ethical concern about the emergence of humanlike consciousness a realistic one for either chimeras or brain organoids? Would the transfer of brain organoids into animal models heighten the concerns around neurological chimerism that already exist in the stem cell field? To answer these questions we must first consider (a) what science has revealed about the possibilities of human stem cell-based chimera research (and thus what can be said of its moral permissibility in general) and (b) whether human brain organoids can support ethical concerns about the emergence of humanlike consciousness through their developmental capacity in vitro and/or upon transplantation into laboratory animals' brains—that is, within the context of brain organoid-generated chimeric animals.

8.3 The Promises and Limitations of Chimera Research

In ancient Greek mythology the Chimera was a monster composed of three different animals—a lion's head, a goat's body, and a serpent's tail. In contemporary biomedical science, research chimeras are entities that contain functionally integrated populations of cells from at least two zygotes of the same or different species. Experimental chimeras composed of cells from two individuals, particularly in the mouse, are used in everyday biomedical research for generating transgenic animals. More recently, advances in the generation of chimera-competent pluripotent stem cells and interspecies chimera research are opening new paths for applications of chimeras for basic biology and regenerative medicine. Generating human-to-animal chimeras using reprogrammed patient cells called induced pluripotent stem cells (iPS cells) might create an in vivo setting to study human disease and to generate transplantable human organs inside livestock animals.

Generally speaking, chimera research is not new. It pre-dates the advent of human pluripotent stem cell research. In biomedical research, the transfer of human somatic cells into animal hosts has become commonplace over the past several decades, in large part because of the scientific advantages it offers over non-chimeric animal research. Non-chimeric laboratory animals (typically rodents) are generated

to mimic human diseases via selective breeding, genetic engineering, or by physical or chemical means, after which they are used to assess the effectiveness of new drug interventions and other novel therapies. However, these purpose-built laboratory animals usually do not closely replicate human biology. For this reason, non-chimeric animal models of human disease do not always provide the surest means to aid the development of new therapeutic protocols.

To overcome these limitations, human-to-animal chimera research aims to introduce localized human cellular and biological characteristics into laboratory animals. Animal models of human disease composed specifically of localized human tissues of investigational interest can be studied for their human-specific biological processes without experimentation on human subjects during very early stages of translational research.[4] In essence, the overarching purpose of human-to-animal chimera research is to *biologically humanize* research animals in order to study human processes without using living human subjects.

Stem cell scientists join this ongoing scientific tradition of chimera research in several ways. In basic stem cell research, human-to-animal chimera experiments can illuminate on how human stem cells and their derivatives behave in a living organism and integrate into complex organ systems. In translational stem cell research, chimera experiments take place when multipotent human stem cells or the derivatives of human pluripotent stem cells are transferred into laboratory animals to assess the safety and efficacy of new stem cell-based interventions. In fact, the United States Food and Drug Administration (FDA) recommends preclinical proof-of-principle studies using at least two different animal models for all stem cell-based biological product developments.[5] Therefore, human-to-animal chimera research is a pathway for stem cell research toward clinical applications in humans. Whether for basic or for translational stem cell research, chimeric animals can be utilized to help broaden our understanding of stem cell behavior beyond the confines of the culture dish, but before stem cells are studied in humans. Assuming all animal research standards are ethically upheld in the process, it is the long-range goal of expanding knowledge and promoting clinical translation that makes stem cell-based chimera research morally permissible today.

For some observers, the scientific and social value of human-to-animal chimera research might not be enough to justify it. Specifically, some may worry that, in the process of biologically humanizing animals, scientists may inadvertently humanize animals in a *moral* sense. In pursuing stem cell-based human-to-animal chimera research, a fear is that researchers might end up creating new creatures with full or near human moral status sufficient to make experimenting on them ethically problematic.[6] A strong version of this fear might correspond to the emergence of "rational agency" of the type implied by a theory of moral personhood discussed in Sect. 8.2. A weaker version might require only that the chimeric animal exhibits some new, yet-to-be explained humanlike cognitive capability. On either interpretation,

[4] Behringer (2007).

[5] Halme and Kessler (2006).

[6] Streiffer (2005).

this concern goes beyond some people's more general objections to animal research. Indeed, for many, this is a separate concern—namely that chimera research may be ethically undesirable even if one accepts that animal research is ethically permissible in other biomedical areas. This difference in attitude could be based on the belief that stem cell-based chimerism has the potential to radically humanize the biology of laboratory animals, depending on the type and number of human stem cells transplanted, the species and developmental stage of the host animal, and the anatomical location of the animal host where the human stem cells are transferred. When human stem cells are transplanted into a postnatal animal, it is unlikely these cells will integrate significantly into the animal's existing biological structures. But if human stem cells are introduced into an embryonic or fetal animal host that is then gestated, then the percentage of differentiating human cells and the degree of human physiological integration in the developing chimeric animal may turn out to be high, especially if there is less evolutionary distance between humans and the animal species used. The worry therefore is that, in the process of biologically humanizing a research animal, scientists may end up also morally humanizing the resulting chimera, especially if there is acute chimerism of the central nervous system.

Is the potential for acute neurological chimerism a real possibility? A recent comprehensive literature review of human–animal neurological chimera experiments suggests we are scientifically far from realizing this fear.[7] This review analyzed 150 peer-reviewed scientific publications involving the transfer of human stem cells or their direct derivatives into the central nervous systems of mice, rats, and nonhuman primates. None of these studies showed any evidence that the resulting chimeric animals gained altered cognitive or behavioral traits that would make them more "humanlike." Indeed, few of these studies which involved the transfer of human cells into diseased or injured animal models restored the resulting chimeras' cognitive or motor functions to the same level of healthy control animals.

Perhaps the limited chimerism evidenced in these studies could be explained in part by the short time periods in which the chimeric embryos and fetuses were allowed to develop and by the differences in developmental timing between human and nonhuman cells. Regardless of the specific reason, an important qualification to consider is that researchers did not produce acute neurological chimeras despite the fact that they transferred human cells into embryonic and fetal animal hosts—one of the methodologies most feared by chimera research critics.

8.4 Chimera Successes: Transplanting Human Glial Progenitor Cells and Brain Organoids

There have been, however, two exceptional research strategies to date that have resulted in significantly higher levels of neurological chimerism than the 150 studies mentioned above. These experiments deserve closer examination here.

[7] Crane et al. (2019).

The first is the neurological chimera work of the Goldman lab at Rochester Medical Center in New York. In a widely publicized study, Goldman and colleagues reported that human glial progenitor cells (GPCs)—which are technically not stem cells, but a little more developed—can successfully integrate into the brains of neonatal immunodeficient mice, where they generate high levels of human glial progenitors and astrocytes.[8] Not only do the transplanted human cells mature in vivo to adulthood, but these cells also retain the size and unique structural complexity of human astrocytes and even appear to serve their normal functions of regulating synaptic transmission, plasticity, and learning. Indeed, the experimental outcome that drew the most public attention was the team's claim that their human glial chimeric mice outperformed control mice in four different learning tasks: auditory and contextual fear conditioning; Barnes maze; and novel object-location. Importantly, on the other hand, there was no evidence that neurological chimerization had any effect on how these chimeric mice interacted with control mice and littermates. Their "sociability" was not affected in any discernable way. This is an important point we shall return to shortly.

Goldman's human glial-chimeras provoke intriguing questions about the role of human GPCs in cognition. Do human glia influence neural network function in a species-specific manner? Since human astrocytes possess greater fiber complexity than those of non-primate mammals, can human glial-chimera models inform questions about the role of human-specific GPC in human cognitive evolution? As Goldman and colleagues write, the ability to generate high degrees of human glial chimerization in mice "should permit us to address these questions, by rigorously evaluating the in vivo contributions of both human astrocytes and their progenitor cells to neural network activity, and hence their respective roles in human cognition."[9]

These long-term research ambitions may not be so far-fetched, for another major finding of the Goldman lab was that transferred human GPCs tend to thrive in their mouse neural environments—so much so that they can developmentally outcompete their hosts' resident GPCs. By the time the chimeric mice reached adulthood, very large proportions of their forebrain glia were comprised of human cells. The remarkable competitive advantage of human GPCs was also shown in some of the Goldman lab's earlier work. Nine months after transplantation, nearly all of the mouse glial progenitors were replaced by human GPCs.[10]

This ability to generate neurologically chimeric mice containing large populations of aggressively expanding human glial cells opens up exciting new scientific possibilities. For one, this makes it feasible to explore the role glial cells might play in hereditary human neurological disorders, as the contribution of these cells to neuropsychiatric pathologies is very challenging to define.

In the case of studying childhood-onset schizophrenia, human glial chimeric mice engrafted with GPCs from patient-derived induced pluripotent stem cells were found to develop abnormal astrocytic morphology, hypomyelination, and

[8] Han et al. (2013)

[9] Goldman et al. (2015).

[10] Windrem et al. (2014).

behavioral and sleep abnormalities.[11] These results suggest again a strong causal contribution of cell-autonomous glial pathology to the development of neurological disease. The chimeric mice's behavioral abnormalities—increased anxiety, antisocial traits, and disturbed sleep—suggest it is impaired glial function itself that may be causing these abnormal patterns. Recall that in Goldman's earlier work the chimeric mice produced from healthy human GPCs exhibited none of these unusual behaviors. Goldman's healthy glial chimeric mice could learn faster, but they were not "antisocial."

As one can see from the disease modeling work of the Goldman lab, even chimeric animals that have large amounts of *disease-specific* human neural cells are not cognitively enhanced above species-typical levels, much less so to justify people's worries about "moral humanization." Instead, neurologically chimeric human disease model animals are much more likely to experience functional deficits that call into action the typical issues around animal welfare in animal research. As long as such research is scientifically justified and conducted humanely—with appropriate standards for interventional euthanasia approved by animal research committees and the veterinarian staff overseeing the work—then it should be regarded as morally permissible.

Besides the transfer of human stem cells or their direct neuronal derivatives in disaggregated form into animals, are there any scientifically justified reasons for transplanting whole human brain organoids into the brains of laboratory animals? And would such experiments raise additional ethical issues not found in current forms of disaggregated human neural cell chimeric transplantation? The answer seems to be "yes" to the first question and "no" to the second.

The first transfer of human brain organoids into the brains of laboratory animals was reported by Fred Gage's team at the Salk Institute in 2018.[12] Since brain organoids lack the vasculature, microenvironment, and neuronal circuits that exist in vivo, researchers engrafted 40 to 50-day old human brain organoids into immunodeficient mice and observed them for 0.5–8 months to see if any of these missing aspects could be established. The organoid grafts showed good integration, vascularization, and survival in their in vivo environment. Gage and colleagues further demonstrated that human brain organoids could integrate and form progressive neuronal differentiation, maturation, gliogenesis, integration of microglia, and axon growth into multiple regions of the mouse host brain. Optogenetic control of the grafts suggested that synaptic connectivity was established between the organoids and their host brains. Finally, the team assessed the spatial learning abilities of the grafted mice in comparison to ungrafted mice using the Barnes maze. There were no observed differences between the two groups, although the grafted mice did not perform as well as their controls when tested for spatial memory. There seemed to be no other observed ill effects (or any benefits) conferred to experimental mice by human brain organoid engraftment.

[11] Windrem et al. (2017).

[12] Mansour et al. (2018).

The overarching scientific rationale for this brain organoid engraftment study was to enable the eventual study of the pathogenesis of neurodevelopmental, neuropsychiatric, and neurodegenerative disorders (and perhaps preclinical drug testing) under physiological conditions of the host animal using human brain organoids derived from patient-specific iPS cells. Again, like the Goldman studies, the scientific and translational value of transplanting human brain organoids into animals should make this research methodology morally permissible, assuming that animal welfare standards for biomedical research are upheld.

It is important to note however that, unlike the transfer of disaggregated human neuronal cells into animal models, the transplantation of human brain organoids faces two limitations not usually associated with other forms of neurological chimera research. First, given the limitations imposed by an animal's small skull size, pieces of the animal's brain have to be removed prior to transplantation to allow room for the human brain organoid. This fact alone drastically limits both the size and number of human brain organoids that can be transferred into a single animal, since removing too much brain tissue would injure the animal beyond what would be ethically acceptable for animal research and beyond what would be beneficial for the study itself (a gravely injured or dead animal holds little scientific value for furthering one's research aims). Second, human brain organoids cannot be transplanted just anywhere the researcher would like, since it would be detrimental to remove existing tissue from crucial areas of the brain necessary for the animal's survival and function. These two types of limitations further constrain how much human neural matter can actually be transferred into an animal via human brain organoids and, consequently, how much of an impact human brain organoids are likely to have on an animal's cognitive capacities.

Finally, it is worth mentioning that if, for some unexpected reason, a human brain organoid could go beyond integration, vascularization, and survival in an animal's brain to actually play a role in improving the chimeric animal's cognitive functioning, then the clinical implications of this discovery for stroke patients and other people with brain injuries would be enormous. This would be such a significant experimental result, in fact, that this discovery—that transplanted human brain organoids could rescue cognitive function in mammalian brains that have had tissue removed and engrafted with organoids—would far eclipse ethical concerns that chimeric animals in this proof-of-concept study might have experienced a cognitive gain-of-function beyond control species levels.

8.5 Going Forward: Chimera Research Oversight

Going forward, research involving the transfer of human brain organoids into laboratory animals will have to be reviewed and approved through a process of scientific and ethics oversight before it can be deemed to be ethically permissible. What would this review process look like?

Review will most likely be in accordance with the ethical standards already put into place by the International Society for Stem Cell Research (ISSCR) for stem

cell-based human-to-animal chimera research.[13] Because human brain organoids are themselves derived from human stem cells, the ISSCR standards for chimera research will be directly relevant for human brain organoid engraftment studies like the one performed by the Gage team.

According to the ISSCR, any time human stem cells or their direct derivatives are integrated into the central nervous systems of laboratory animals, stem cell specific review must take place to oversee chimera research. This review should build upon and remain consistent with animal welfare principles, but with added stem cell expertise to consider the further developmental effects on animal welfare of human-to-animal chimerism.

Past experience with genetically altered laboratory animals has shown that reasonable caution is warranted if genetic changes carry the potential to produce new behaviors and especially new defects and deficits. Best practices dictate that research involving genetically modified animals must involve the following: (1) the establishment of baseline animal data; (2) ongoing data collection during research concerning any deviation from the norms of species-typical animals; (3) the use of small pilot studies to ascertain any welfare changes in modified animals; and (4) ongoing monitoring and reporting to oversight committees authorized to decide the need for protocol changes and the withdrawal of animal subjects.

In addition to adopting these standards, researchers must also justify why a particular species of host is necessary for their experiments. For the time being, it appears that the transfer of human brain organoids into animal models can be done using rodents; thus, researchers who wish to use larger animal species will have to explain why. In principle, the use of other laboratory animal species commonly used for neurological research is potentially permissible, including nonhuman primates, except great apes and lesser apes (i.e., except chimpanzees, gorillas, orangutans, bonobos, gibbons, and siamangs). The use of great and lesser apes is excluded for two main reasons. First, it is a widespread international research restriction that apes cannot be used for invasive biomedical research. Second, the use of great and lesser apes for human organoid chimera research would not be justified as long as other "lower" NHP species that are more evolutionarily distant to humans are available and routinely used for neurological research. As long as researchers can scientifically justify why a particular host species is necessary and that there are no adequate alternatives available (which alone would restrict how often non-rodent species might reasonably be used), then the main ethical issues to consider for the moral permissibility of this research are essentially animal welfare considerations appropriate for animal research.

Some might object that this primary focus on animal welfare misses the mark when it comes to what may be most ethically worrisome about brain organoid transplantation and other forms of neurological chimerism—namely the concern that researchers might create a morally ambiguous research animal in the process. As alluded to above, I believe this concern has a tendency to run too far ahead of the actual science, and that it erroneously conflates higher degrees of *biological*

[13] Hyun et al. (2021) and ISSCR (2021).

structural humanization with greater *moral* humanization. In the strong version of this moral concern, moral humanization would involve the emergence of humanlike cognitive capacities such as higher-order intellectual processing capabilities and thought, and of self-consciousness. Such complex mental traits are not biologically assured even in infant brains that are 100% human, without the social and nurturing conditions of child-rearing over many years.[14] Since the social support and language-use conditions necessary to support human consciousness in this most robust sense are absent from the laboratory conditions within which neurological chimeras are created and maintained, the threat of conscious self-awareness does not appear to be a serious ethical challenge for biomedical research employing the transfer of human brain organoids.

8.6 Concluding Thoughts

The incremental ethical approach outlined above for chimera research attempts to avoid giving undue influence to unsupported, imagined possibilities and strives to be grounded in observable animal behaviors and reasonable inferences. A concern over the possible emergence of humanlike consciousness seems to motivate a cautious approach to advancing human brain organoid and neurological chimera research. However, I wish to conclude by acknowledging that humanlike consciousness—that which forms the very basis of the moral life of humans—can only be realized in normally functioning human brains starting from infancy within nurturing social environments and through the acquisition of language that would enable one to have reflective beliefs about one's own beliefs and experiences.

Perhaps ultimately people's concerns around human brain organoid and chimera research reflect a broader unease about interfering with the natural (and implicitly normative) order of the world. However, such a "natural law" framework—broadly speaking—for determining moral right and wrong is not an easy fit for modern scientific pursuits such as those being considered in this chapter. In order for natural law to provide guidance for research, many, if not most, scientific techniques would have to be abandoned. According to the implicit norms of the natural law tradition, scientists must only passively observe and record the "natural order" of the world; they must never disrupt this order during their act of observation. However, organoid and chimera research—like most other forms of biomedical research and technological advancement—violates this observation constraint. For example, in the process of studying the full potential of human stem cells, researchers must cultivate or form new biological entities (e.g., bioengineered organoids or chimeric animals) that do not have direct natural analogues in the developed human body or in the animal kingdom. The "unnatural" is an anathema for the natural law tradition in ethics. But all branches of the modern biological sciences must proceed through the performance of unnatural acts.

[14] Hyun (2016).

Secular ethics, such as the research ethics framework sketched out in the chapter on chimera research, at least allows for the possibility that unnatural acts may be ethically permissible. If unnatural acts are an ineliminable part of modern science and biomedical research, then research ethics must provide room for the performance of unnatural acts. Ultimately, the important distinction for research ethics is not between the *natural* and the *unnatural*; rather, it is between the *ethically* unnatural and the *unethically* unnatural. The transfer of human brain organoids into animal models is an ethically unnatural act, but it is ethically permissible according to secular ethics.

References

Behringer R (2007) Human-animal chimeras in biomedical research. Cell Stem Cell 1:259–262
Crane A et al (2019) Concise review: human-animal neurological chimeras: humanized animals or human cells in an animal? Stem Cells 37:444–452
Dworkin G (1970) Acting freely. Noûs 4:367–383
Frankfurt H (1971) Freedom of the will and the concept of a person. J Philos 68:5–20
Goldman SA, Nedergaard M, Windrem MS (2015) Modeling cognition and disease using human glial chimeric mice. Glia 63:1483–1493
Halme DG, Kessler DA (2006) FDA regulation of stem-cell-based therapies. NEJM 355:1730–1735
Han X et al (2013) Forebrain engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice. Cell Stem Cell 12:342–353
Hyun I (2001) Authentic values and individual autonomy. J Value Inq 35:195–208
Hyun I (2016) Illusory fears must not stifle chimaera research. Nature 537:281
Hyun I et al (2021) ISSCR guidelines for the transfer of human pluripotent stem cells and their direct derivatives into animal hosts. Stem Cell Rep 16:1409–1415
ISSCR (2021) Guidelines for stem cell research and clinical translation. https://www.isscr.org. Accessed 1 March 2021
Locke J (1694/1975) An essay concerning human understanding. Clarendon Press, Oxford
Mansour AA et al (2018) An in vivo model of functional and vascularized human brain organoids. Nat Biotechnol 36:432–441
Streiffer R (2005) At the edge of humanity: human stem cells, chimeras, and moral status. KIEJ 15:347–370
Windrem MS et al (2014) A competitive advantage by neonatally engrafted human glial progenitors yields mice whose brains are chimeric for human glia. J Neurosci 34:16153–16161
Windrem MS et al (2017) Human iPSC glial mouse chimeras reveal glial contributions to schizophrenia. Cell Stem Cell 21:195–208