ETHICS

Moral Issues of Human–Non-Human Primate Neural Grafting

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If human neural stem cells were implanted into the brains of other primates what might this do to the mind of the recipient? Could such grafting teach us anything of value for treatment of neurological injury and disease? Could we change the capacities of the engrafted animal in a way that leads us to reexamine its moral status? These questions have gained significance since publication of research involving grafting human neural stem cells into the brains of fetal monkeys (*1*). In 2004, we formed a multidisciplinary working group; two plenary meetings over 12 months provide the basis for this Policy Forum.

Some group members have serious ethical concerns over *any* use of nonhuman primates in invasive research. However, we set aside broader controversies to focus on ethical challenges specific to human–to–nonhuman primate (H-NHP) neural grafting. We did not take votes or seek consensus on all the questions raised.

There is considerable controversy (reflected within our group) over the likely value of interspecies stem cell work for progress toward therapies (*2*). We cannot graft human neural stem cells into human beings solely for experimental purposes, even if they will lead to human therapies. Group members arguing for the value of research on human cells in NHPs pointed out that, because the aim is to learn about human neural stem cells, it makes most sense to use human lines. The fact that available NHP lines are few and poorly characterized (*3*) is an additional reason to use human lines. Another consideration is the need to assess candidate human cell lines for viability, potential to differentiate, and safety with regard to such possibilities as tumor formation. NHPs may be appropriate for in vivo screening.

Skeptics argued that differences between humans and NHPs could render results uninterpretable and that the preferred path for many questions is to study NHP neural stem cells in NHPs. Assessments of the scientific merit of the research must form and develop along with the field itself.

We unanimously rejected ethical objections grounded on unnaturalness or crossing species boundaries (*4*). Whether it is possible to draw a meaningful distinction between the natural and the unnatural is a matter of dispute. However, stipulating that research is "unnatural" says nothing about its ethics. Much of modern medical practice involves tools, materials, and behaviors that cannot be found in nature but are not unethical as a consequence

Another concern is that H-NHP neural grafting is wrong because it transgresses species boundaries (*5*). However, as the recent National Academy report notes (*6*), the notion that there are fixed species boundaries is not well supported in science or philosophy. Moreover, human–nonhuman chimerism has already occurred through xenografting. For example, the safety and efficacy of engrafting fetal pig cells has been studied in people with Parkinson's disease and Huntington's disease without moral objection. Indeed, some have suggested that porcine sources may be less morally contentious than the use of human fetal tissue (*7*). Merely because something has been done does not prove it right. However, we, like the National Academy, see "no new ethical or regulatory issues regarding chimeras themselves" [(*6*), p. 33].

The central challenge is whether introducing human cells into NHP brains raises questions about moral status. A variety of reasons have been given for according different moral standing to humans and NHPs. In the Abrahamic traditions, humans are set apart by God as morally special and are given stewardship over other forms of life (Genesis 1:26–28). For Kantians, human capacities for rationality and autonomy demand that we be treated as ends in ourselves (*8*). Mill finds, in the richness of human mental life, an especially fecund source of utility (*9*). Singer, although strongly defending equal consideration of nonhuman interests, argues that self-awareness affects the ethically allowable treatment of a creature by changing the kinds of interests it can have (*10*).

Many of the most plausible and widely accepted candidates for determining moral status involve mental capacities such as the ability to feel pleasure and pain, language, rationality, and richness of relationships. To the extent that a NHP attains those capacities, that creature must be held in correspondingly high moral standing. There are those, including Singer and some of our working group, who believe that we already overestimate differences in relevant mental capacities, and thus of moral status, between humans and NHPs. But the issue here is the extent to which human/NHP neural grafting might change capacities in a way that changes moral status.

Although we cannot assess altered capacities by experiencing an animal's mental life from within, we can assess its performance on cognitive tasks and observe its behavior. Establishing whether and in what ways engrafted animals undergo cognitive or behavioral changes requires an understanding of what the normal range is for a particular NHP species. Unfortunately, our understanding of NHP cognitive capacities is patchy, data are tricky to gather and difficult to interpret [(*11*); see supplementary material]. Thus, even if we observe what appear to be more humanlike capacities in an engrafted animal, we may be unable either to establish whether the capacities are outside of the normal range for that species, or to interpret the moral meaning of observed changes.

One conceivable result of H-NHP neural grafting is that the resulting creature will develop humanlike cognitive capacities relevant to moral status. H-NHP neural grafting may not be unique in having the potential to alter the capacities of NHPs. Chimps reared with humans behave in a more humanlike way than chimps reared by chimps (*12*). Transfer between species of predispositions

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relating to auditory perception was found after transplantation of already formed portions of brain tissue (*13*). Introduction of human neural progenitor cells into developing mouse brains resulted in widespread incorporation of human neural progenitor cells; but behavioral alterations were not reported (*14*). Although such results are not reasons to think it likely, one unanimous conclusion of our group is that we are unable to rule out the possibility of effects on cognition of the sort that matter to moral status.

One option is to treat any development of more humanlike cognitive capacities as a risk to avoid. Alternatively, it might be argued that the challenge is less to avoid a direct ethical ill and more to understand the mental capacities of engrafted animals and to treat them in a manner appropriate to their moral status. Indeed, it might even be argued that such changes constitute a potential benefit to the engrafted animal, insofar as the changes are viewed as enhancements of the sort we value for ourselves. However, these more humanlike capacities might also confer greater capacity for suffering that would add to existing concerns about the harms caused by inadequate conditions for NHPs in research.

We propose six factors that research oversight committees and other review groups should use as a starting framework. They are (i) proportion of engrafted human cells, (ii) neural development, (iii) NHP species, (iv) brain size, (v) site of integration, and (vi) brain pathology.

Though even a few engrafted cells may affect neural activity, we expect that a higher proportion of engrafted human cells relative to host cells will increase the prospect of more humanlike neural function and, thus, of more humanlike cognitive capacities. High proportions of engrafted cells are more likely to be achieved by implantation early in neural development.

We also expect that the potential for engrafted cells to have significant functional influence will be markedly greater for engraftment at very early stages of development than for engraftment into the established architecture of adult brains. Although neural progenitor cells engrafted into the neonatal primate brain disseminate widely and integrate throughout the brain (*1*), the mature primate brain tends to resist incorporation of engrafted cells (*15*).

A graft recipient's degree of relatedness to our own species may matter for several reasons. Genetics contribute to brain structure by providing the protein building blocks that shape neurons and their interconnections. Factors such as cell surface markers and the mechanisms of cellular signaling are more similar in our closer relations (*2*, *3*). Also, although the picture is complicated by lifestyle similarities that cut across phylogenetic groups, our closest relatives among NHPs tend to show greater neuroanatomic similarities to human brain structures (*16*).

Also related to recipient species is brain size. It is unlikely that the structural complexity needed for any significant degree of humanlike mental capacity can be achieved under tight size limitations. However, brain size influences the size of the developing cranium, an effect seen naturally in hydrocephalus. Thus, a fetal marmoset engrafted with human neural cells might, to some extent, develop a larger brain than is typical for the species.

The specific sites into which the human neural cells become integrated within the recipient brain is also of potential significance. Functional integration into the cerebrum, which is associated with higher brain functions, seems more likely to affect cognitive capacities than does integration into the cerebellum; although engrafted neural cells may migrate and project to disparate brain areas.

Overall, we think it unlikely that the grafting of human cells into healthy adult NHPs will result in significant changes in morally relevant mental capacities. However, in the case of NHP models of human neurological disease and injury, adult recipients of human neural cells may have extensive disruption to their neural structures that might allow greater scope for engrafted human neural cells to affect cognitive capacities. We do not consider this a strong possibility, because diseased or injured brains will be starting from an impaired state from which even a return to species' normal functional levels is unlikely. However, the therapeutic point is to reinstate lost function, and we cannot be certain that this will be the only functional result of interspecies neural grafting. Furthermore, some of the disorders likely to be of interest (such as Alzheimer's) involve higher-level cognitive capacities.

There is no simple relation between these factors and, thus, no formula for making evaluative judgments. Considering issues of moral status that go beyond the ethical challenges attending any invasive NHP work, our framework suggests that experiments of greatest concern are those in which human neural stem cells are engrafted into the developing brains of great apes and constitute a large proportion of the engrafted brain. On the basis of this concern, and on doubts about scientific merit, some of us believe that engraftment of human neural cells into great apes should not be permitted, particularly early in neural development. Others argue against outright prohibition on grounds that scientific justifications might be forthcoming as the field progresses. For example, if a useful great ape model of a neurological disease is developed, and a promising human neural stem cell line is ready for use, there might be reason to proceed with human–great ape work, rather than waiting to develop great ape lines. Our framework suggests that experiments involving engraftment into healthy adult brains of our most distant monkey relations, especially when the proportion of engrafted cells is small relative to host cells, are the least likely to raise concerns about significant cognitive effects. However, especially as we consider experiments involving implantation of relatively large numbers of human cells early in development, there is no present empirical basis on which to rule out changes that might implicate moral status, whether the engrafted NHPs are great apes or monkeys.

In view of the challenges arising from moral status, we support the National Academy's recommendation that H-NHP neural grafting experiments be subject to special review. We agree that such review should complement, not replace, current review by animal-use panels and institutional review boards. We further recommend that experiments involving H-NHP neural grafting be required, wherever possible, to look for and report changes in cognitive function. Explicit data collection on cognition and behavior will help to ensure that ethical guidelines can be developed appropriately as the field advances.

References and Notes

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