



# Human Brain Organoid Transplantation: Testing the Foundations of Animal Research Ethics

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**Abstract** Alongside *in vitro* studies, researchers are increasingly exploring the transplantation of human brain organoids (HBOs) into non-human animals to study brain development, disease, and repair. This paper focuses on ethical issues raised by such transplantation studies. In particular, it investigates the possibility that they might yield enhanced brain function in recipient animals (especially non-human primates), thereby fundamentally altering their moral status. I assess the critique, raised by major voices in the bioethics and science communities, according to which such concerns are premature and misleading. I identify the assumptions underlying this skeptical critique, and mention some objections against them, followed by some possible replies. I proceed to argue that the skeptical position is ultimately implausible, because it presupposes an unreasonably high standard of full moral status. My argument appeals to David DeGrazia's idea of a "borderline person", and to the need for consistency with existing animal research regulations. I outline the practical implications of my view for the conduct of studies that might result in the development of full moral status in a transplanted animal. I also discuss some of the ethical implications of animal enhancement (particularly of rodents) below

the threshold associated with full moral status. I conclude that far from being premature, further debate on these issues is urgently needed to help clarify the prospects that a neural chimera might attain full moral status in the foreseeable future, and the level of quality of life required to make it acceptable to knowingly create such a being via HBO transplantation.

**Keywords** Animal ethics · Enhancement · Human-animal chimeras · Moral status · Neural organoids · Personhood

## Introduction: Human Brain Organoids and their Transplantation into Non-Human Animals

Human brain organoids (HBOs) are small 3D structures, made of neural tissue, that mimic various parts of the human brain. Alongside studies of HBOs done *in vitro*, which are increasingly viewed as a promising new approach to study different aspects of human brain development and disease, researchers have already started transplanting HBOs into the brains of non-human animals, both to try and achieve greater maturation and complexity than allowed by *in vitro* organoids (thanks to vascularization and sensory input), and to study new methods of brain repair [1–3]. Existing studies have already demonstrated that HBOs transplanted into animal brains can keep developing for many more months than *in vitro* organoids [3]. Animals that have so far been the recipients

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of HBO transplants include mice and rats, but also monkeys. These animals can be categorized as a new form of neural chimera. The potential benefits cited for such transplantation studies include helping us better understand the mechanisms behind neurological diseases, including neurodegenerative disorders like Alzheimer's Disease [4].

Beyond the development of new disease models, several recent transplantation studies highlight the exciting, although at present still hypothetical future prospect of using HBOs to help repair the brain following injury or disease. Kitahara and colleagues thus transplanted HBOs at different developmental stages into the cerebral cortex of mice and cynomolgus monkeys, to advance the search for a cell-based therapy for brain injury and stroke [5]. Jgamadze and colleagues transplanted HBOs into rats with an injured visual cortex, and demonstrated that they could successfully integrate with the rats' visual system, thus supporting the use of such procedures as a strategy to restore cortical function [6].

Finally, researchers using HBO transplantation to study Alzheimer's Disease also anticipate that their work could eventually lead to "personalized organoid transplants" to replace diseased or injured brain tissue [7, p. 24].

This paper focuses on ethical issues raised by HBO transplantation into non-human animals. In particular, it considers the prospect that such studies might lead to an enhancement of brain function in recipient animals, in ways that would significantly alter their moral status. My analysis proceeds as follows. Section 2 lays out the relevant concerns, distinguishing the notions of "enhancement" and "humanization". Section 3 describes the critique, raised by major voices in the science and bioethics communities like the International Society for Stem Cell Research (ISSCR) and Insoo Hyun (the lead author of an article published by members of the ISSCR Task Force subcommittee responsible for the ISSCR 2021 guidelines on stem cell research [8]), according to which such concerns about alterations of moral status in neural chimeras are premature and misleading. Section 4 undertakes to identify the assumptions underlying this skeptical critique, and describes some objections that have been levelled at them, followed by some possible replies. Section 5 argues that while those replies do have some force, the skeptical position is nevertheless implausible, because it

presupposes an unreasonably high standard of full moral status. My argument appeals to David DeGrazia's idea of a "borderline person", and to the need for consistency with existing animal research regulations. Section 6 outlines the practical implications of my view for the conduct of studies that might result in the development of full moral status in a transplanted animal. Finally, Section 7 concludes by highlighting the urgent need for further debate to help clarify the pre-requisites of full moral status, the prospects that a neural chimera might meet them in the foreseeable future, and the level of quality of life required to make it acceptable to knowingly create such a being via HBO transplantation.

### Ethical Concerns about Humanization and Animal Enhancement

One important ethical concern raised by HBO transplantation (and shared with other forms of neural chimeras created via postnatal intervention) relates to the possibility that the insertion of human neurons into the brain of a non-human animal, especially a non-human primate, might bring about changes in its cognitive function that would make it more similar to a "normal" human being. This possibility is sometimes referred to as the "humanization" of the transplanted animal [1, 2]. More specifically, scholars like Insoo Hyun have drawn a distinction between "biological" and "moral" humanization [9]. The central idea behind this distinction is that while both biological and moral humanization refer to the acquisition by an animal of human-like characteristics, only the latter involves ethically significant varieties of such acquisition, varieties that mark a crucial increase in the ethical status of the humanized animal.<sup>1</sup> One implication

<sup>1</sup> Some might define biological humanization more narrowly, as specifically involving the introduction of human cells (rather than human-like features more generally) into a non-human animal. As long as *moral* humanization is understood in terms of proximity to human functioning, however, without further presupposing that such proximity must result from the transfer of human cells, this point does not make a difference to my analysis. At the same time, wider construal of the notion of moral humanization is also possible, according to which any kind process that makes an animal more "human" in an ethically significant manner counts as moral humanization, regardless of whether or not it alters the animal's moral status. For example, one might hold that it is wrong to create human-looking chimeras because of the "unnaturalness" of such enti-

of this idea is that biological humanization leads to moral humanization once it crosses a certain threshold (an issue to be discussed further in what follows).

Moral humanization is also frequently tied to the acquisition of “uniquely human” mental characteristics [8, 9]. This last condition, however, may not be particularly plausible. Indeed, why should the ethical significance of a mental feature depend on whether that feature is uniquely possessed by one particular species (i.e. humans), rather than shared by different species? It would for instance seem absurd to suggest that the property of personhood can only be ethically significant if it is uniquely human, and that it would cease to count as such if we could establish the existence of non-human persons – whether great apes, cognitively enhanced animals, intelligent extraterrestrials, or highly advanced AI.

Alongside concerns about humanization, a related worry refers to the possibility of ending up enhancing brain function in the transplanted animals, in ways that could substantially alter their ethical status. Chen and colleagues suggest that this framing is more helpful than a focus on moral humanization, partly because the enhanced traits that might be conferred by HBO transplantation need not be uniquely human, and partly due to the need to consider the welfare of chimeric animals even if their cognitive capacities do not match those of humans [1, p. 466]. The difference between concerns about moral humanization and about animal enhancement need not be immediately obvious, as there is clearly some overlap between the two. Nevertheless, this overlap is only partial. To illustrate this, we can imagine someone holding the view that the conferral of a more human-like appearance on a human-animal chimera increases its moral status. Their justification might perhaps be grounded in the belief that a human-like appearance is among the properties that supposedly confer unique moral status or “dignity” on human beings, or in the concern that treating a human-looking chimera the way mice, for instance, are used in biomedical research, could

set a dangerous precedent, threatening to dull our sense of empathy for our fellow humans. The conferral of a human-like appearance would then be treated as a form of moral humanization. I do not claim that this is a particularly persuasive view (I do not believe it is), yet it seems at least intelligible, and crucially, those who might hypothetically endorse it would not thereby be asserting that any functional enhancement of the chimeric animal must have taken place.

Conversely, the enhancement of an animal’s brain function from a HBO transplant could arguably lead to biological but not moral humanization: for example, if the animal were to develop faster reaction times, without simultaneously acquiring any relevant higher-order cognitive capacities. Finally, we may note that even though most, if not all, realistic enhancements of brain function in a transplanted animal may well involve some form of humanization, this is nevertheless not a conceptual necessity. We can at least conceive of cases in which a brain enhancement bestows a new capacity on the animal that ordinary humans lack, or enhances some existing capacity (say, working memory) to superhuman levels,<sup>2</sup> making the animal less rather than more similar to humans in that regard.

In light of this, it does not seem that either the notion of moral humanization, or that of brain enhancement, can capture all of the possible concerns associated with the other one. It is therefore wise not to conflate them with each other. That said, for reasons I shall clarify in the coming sections, I do agree with Chen and colleagues that a focus on the prospect of brain enhancement, and particularly cognitive enhancement, of transplanted animals is a more constructive approach, even though the concept of moral humanization is also likely to apply to any cases that might occur in the foreseeable future.<sup>3</sup>

<sup>2</sup> Some researchers have claimed to have found evidence that young chimpanzees could already outperform human adults at certain memory tasks: [10].

<sup>3</sup> A reviewer notes that animal enhancement of potential ethical significance could occur even from the transplantation of brain organoids made of non-human cells; say, cells derived from great apes. I agree that this does seem possible in principle, given that, as we shall see, I believe the great apes deserve to be granted the sort of protections against use in harmful research associated with full moral status. My main reason for focusing my discussion on the transplantation of specifically human brain organoids is that, to my knowledge at least, scientists have so far not really considered the idea of transplanting

Footnote 1 (continued)

ties, in which case doing so would represent a form of moral humanization on the wider definition just given, even though the implications, if any, for the animal’s moral status would be unclear. In this paper, I shall rely on my narrower construal of the notion, which is more useful for the purposes of my discussion.

To try and capture at least some of the insights behind the biological-moral humanization contrast, we can distinguish between the following two kinds of brain enhancement in neural chimeras, including recipients of transplanted HBOs:

- a) Enhancements that arguably cross an ethically relevant threshold in functioning, thereby substantially altering the animal's moral status;
- b) Enhancements that do not have that effect, although they might still be ethically relevant, for instance through their impact on the animal's needs or well-being.

A paradigm example of enhancement in the first category would involve the conferral of new cognitive abilities on an animal grafted with a HBO, such as self-awareness or a theory of mind, abilities that are commonly viewed as making a significant difference to a being's moral status, conferring upon it what I will call "full" moral status – and entitling it to strong protections against involuntary, harmful use in biomedical research. Full moral status stands in contrast to the partial moral status currently granted to sentient animals used in biomedical research: while the scientific community accepts that it is ethically obligated to care for these animals' welfare, it nevertheless deems its acceptable to impose some degree of discomfort on them, and sometimes to sacrifice them, for scientific purposes that are judged significant enough. An example of the second category might for instance involve an improvement in the animal's hearing ability that would make it more sensitive to outside noise, and thereby more likely to suffer discomfort in standard research environments, necessitating

special measures to avoid unpleasant stimuli. This paper will focus on enhancements of the first type.

### **Animal Enhancement through HBO Transplantation: A Premature Concern?**

Ethicists and scientists have recently started discussing the possibility of cognitively enhancing (or morally humanizing) non-human animals, presumably inadvertently, via HBO transplantation [1, 2, 7, 11]. As previously mentioned, this is one aspect of the broader ethical debate on the creation of neural chimeras with enhanced brain function. Nevertheless, prominent members of the scientific community, as well as some bioethicists, have countered that having such a discussion at the present time is premature and misleading. On the topic of HBOs and human-animal chimeras, for instance, the 2021 guidelines laid out by the ISSCR caution that "any statements implying human cognitive abilities, human consciousness or self-awareness, as well as phrases or graphical representations suggesting human-like cognitive abilities risks misleading the public and sowing doubts about the legitimate nature of such research" [12, 12]

The ISSCR's emphasis on "human" cognitive capacities is notable, and as we will now see, may help explain the dismissal of concerns about altering the ethical status of chimeric animals in the 2021 guidelines. This interpretation is supported by the aforementioned article published separately by members of the ISSCR Task Force subcommittee that drafted those guidelines. The article criticizes the relevant concerns for assuming moral humanization, which it characterizes as involving the development of "unique human-like" capacities, when in fact, the authors argue, only biological humanization will follow from HBO transplantation, or any other ways of creating neural chimeras, for the foreseeable future [8, p. 4]. We have already seen that including such an assumption about unique capacities in one's definition of moral humanization seemed undesirable, but we can leave that point aside. The main reason given by the article's authors for rejecting moral humanization as a relevant prospect is that the human-like mental abilities in question, which include self-consciousness, will not develop, even in a normal human brain, in the absence of appropriate social and nurturing conditions of child-rearing, which transplanted

Footnote 3 (continued)

organoids made of cells from other species. This is presumably because the use of human cells is more conducive to the goals currently pursued by researchers, such as a better understanding of human brain development and dysfunction, as well as identifying new ways of repairing the damaged brain. Still, if the transplantation of non-human organoids were to be pursued in the future, it may well raise some of the very same ethical issues addressed here. It is also interesting to note that, somewhat paradoxically, the use of human cells may not be strictly needed for moral humanization, since even the introduction of non-human cells could in principle bring an animal closer to a "human-like" level of cognitive functioning.

animals would not be expected to find themselves in [*ibid.*].<sup>4</sup> Furthermore, Hyun, the lead author on that paper, had already presented an argument along those lines in previous work, in which he also clarified that, on his view, self-consciousness requires having propositional beliefs and a capacity for recursive thinking,<sup>5</sup> properties tied to the use of language. On Hyun's view, then, self-consciousness is therefore likely another human prerogative [13].

One can certainly agree with those critics that we should not misrepresent the current state of HBO research, or make wildly unrealistic predictions about future developments (although where to draw the line of "realism" is itself a contested matter, given the inherently uncertain nature of such predictions). Among other things, the integration of human cells into the brain of a postnatal animal still presents important challenges [9]. My aim here is not to propose a specific timeline for future brain enhancements in animals transplanted with HBOs, as a substitute for that presupposed by the critics, but I nevertheless do wish to challenge the foundation of the critics' skeptical predictions. I will argue that, *contra* the ISCCR guidelines, it is not premature to discuss these possibilities today already. On the contrary, doing so is a pressing matter, because if we are to rigorously estimate how remote those possibilities might be, we need to settle on a plausible threshold for cognitive development in animals that may undergo postnatal enhancement, a task which I contend has yet to be successfully completed.<sup>6</sup>

<sup>4</sup> The authors also mention that biological factors will limit the degree of humanization in neural chimeras. In the case of HBO transplantation, the skull size of the recipient animal would be one such factor.

<sup>5</sup> That is, the ability to "think about thinking", which as Hyun depicts it involves entertaining propositional attitudes about other propositional attitudes.

<sup>6</sup> Neural chimeras might also get created through the introduction of human cells into an animal embryo, leading to an adult animal with higher cognitive capacities than would otherwise have emerged, which might be described as a form of prenatal enhancement. The present analysis focuses on the possibility of postnatal enhancement, and on the associated issue of alterations in the ethical status of a postnatal animal.

### What Cognitive Threshold? Objections to the Appeal to "Human Self-Consciousness" and Possible Responses

One key part of the case for skepticism about the relevance, for the foreseeable future, of alterations of moral status in animals transplanted with HBOs, thus seems to be the high threshold set by the skeptics for such alterations to occur. According to them, the procedure should enhance the animal's brain function to the point of producing higher-order cognitive capacities, such as self-consciousness and theory of mind, of the kind exhibited by normal human adults. For the reasons just outlined, this is indeed not a realistic prospect. Nevertheless, in the following two sections, I will consider (and ultimately endorse) the criticism that the skeptics' proposed threshold is overly demanding, and that it can derive undue plausibility from talk of "humanization" or "human-like" mental characteristics.

Recent years have thus seen many countries introduce legislation restricting the use of great apes (chimpanzees, gorillas, orang-utans and bonobos) in invasive biomedical research. For instance, in 2015, the U.S. National Institutes of Health (NIH) followed in the footsteps of Australia, the European Union, and Japan in banning or severely limiting experiments on chimpanzees [14, 15*ibid.*].

In response, Hyun counters that this lower standard for self-consciousness and personhood is not persuasive, first by pointing to studies suggesting that only a minority of chimpanzees successfully pass Gordon Gallup's traditional "mirror test" for self-awareness. In a 1999 article, Swartz and colleagues thus reported that out of 163 chimpanzees tested in different studies, only 73 demonstrated mirror self-recognition [16].<sup>7</sup> Secondly, even if a much larger percentage of chimpanzees (and other non-human animals) were to pass the mirror test, Hyun might still dispute that this constituted sound evidence of self-awareness, given that passing the test still does not demonstrate linguistic ability, and the "propositionally grounded beliefs" it makes possible, and which he, as we have seen, takes to be a condition of self-awareness [13, p. 145].

Hyun's stringent requirements for self-awareness, and therefore personhood, have already elicited

<sup>7</sup> Hyun cites this very data in [13], p. 145.



criticism. Julian Koplin, for instance, points out that if personhood as understood by Hyun is taken to be a precondition of full moral status, of the kind needed to rule out the use of a being in harmful, invasive biomedical research,<sup>8</sup> it seems to follow that it would be ethically acceptable to conduct such research not only on chimpanzees and other great apes, but also on human infants, and on “feral” children (or other neglected children) who missed out on elementary human socialization and, as a result, did not learn any language; indeed, such humans fail to meet Hyun’s conditions for self-awareness and personhood [17]. Worse, Hyun’s view might even make it permissible to deliberately engineer such children by depriving them of the conditions required for language acquisition, with a view to using them in research [*ibid.*].

Such implications would certainly seem damning for Hyun’s view. One possible way of defending the view’s core tenets against Koplin’s objection would be to slightly amend it, by clarifying that only the *potential* to master language and recursive thinking, rather than their actual enjoyment, is required for self-awareness. This would allow Hyun to count “normal” human infants as persons, while also, on his own account at least, keeping out both the great apes and neural chimeras at a comparable level of cognitive function. Hyun thus claims that efforts at training chimpanzees and other great apes to learn a language, in particular American Sign Language, have failed to produce convincing results [13]. Other experts, however, would dispute this verdict [18]. In any case, this first possible move runs into a number of difficulties: for one thing, it would require granting self-awareness and personhood to human embryos and fetuses, with restrictive implications for the ethics of abortion and embryo research that many may find undesirable. For another thing, it remains unclear that this move can include feral children, or at least *all* of them, into the realm of persons. Indeed, while such children may initially have had the potential to develop language and recursive thinking, this potential arguably

atrophies, and in some cases is completely lost, following the end of the so-called “critical period” for language at puberty. While some limited degree of language learning may still be possible after that point in some cases [19], in other cases it likely will not be. Feral children who end up in this latter group, together with humans with intellectual disabilities severe enough to undermine language acquisition, will not count as persons even on this less demanding version of Hyun’s view.

Perhaps a stronger response on Hyun’s behalf would be to simply accept that the human beings in question are not entitled to strong protections against use in invasive research in virtue of being persons – while adding that such protections can nevertheless still be justified in those cases on *different* grounds. Several possible justifications might be offered here, and I shall only discuss three salient candidates. First, one might argue that all human beings, regardless of their level of cognitive sophistication, deserve to be granted the kind of protections associated with personhood, simply in virtue of their being human. Humans, some might say, are a certain “kind” of being whose “nature” includes the characteristics constitutive of personhood, even if these characteristics may occasionally be missing in some individual humans [20]. This is probably the weakest of the candidate justifications I will consider here, as it is open to the charges of “speciesism” (arbitrarily treating membership in a particular species as ethically relevant, [21]), and of fallacious reasoning: indeed, if most but not all members of a group G have property X, it does not seem plausible to treat *all* members of G as having X, even those who lack it, simply on the grounds that they are members of G.<sup>9</sup>

Secondly, and somewhat more plausibly, one might point to the serious negative social consequences that could be expected to follow if harmful research on such “marginal humans” [22] were ever to be allowed: many people would feel outraged, leading to potentially violent reactions (sometimes directed at scientists believed to be involved in such

<sup>8</sup> Here, by “harmful research”, I mean research that foreseeably imposes significant harm on research subjects, without any compensating benefits for them; not improperly conducted research that results in unsafe medicines being put on the market, or research that is otherwise harmful to society as a whole (because it is aimed at developing highly destructive weapons, or reinforces certain harmful stereotypes, etc.).

<sup>9</sup> Suppose for example that most current members of Perry’s family have passed the bar exam, but Perry himself has not. It would not make sense for Perry to argue that he still deserves to be allowed to practice law despite his lack of qualifications, because he belongs to the “kind” of family that has passed the bar exam.

experiments), as well as to a general loss of trust in researchers among the general public, and political action to outlaw such experiments and withhold funding from biomedical research, causing it to slow down rather than pick up speed. This in turn leads us to a third possible rationale for protecting marginal humans, namely respect for the idea of democratic governance of science, and therefore for the public's deeply held attitudes towards scientific research. Most people, it might be argued, strongly believe that all humans deserve the same strong protections against being used in harmful scientific experiments, in part because they find it easier to imaginatively place themselves in the position of an infant or marginal human, than in the position of a non-human animal [23, 24].<sup>10</sup> By contrast, there is no similarly strong public opposition to the use of non-human animals in research, and people seem much more open to input from experts as to where the line should be drawn in that context.<sup>11</sup> As a result, the argument goes, scientists should align their research practices with those public attitudes, regardless of whether they personally regard them as speciesist, or otherwise irrational.

While these latter two justifications do strike me as having some force, many will still find them unsatisfactory, or even perverse, as they implicitly acknowledge that marginal humans do not have the same ethical status as humans who are persons, and therefore that they are not entitled to protection from use in harmful biomedical research in virtue of the kind of beings they are, but rather out of deference to the preferences of "normal" humans, which might be viewed as a "shaky" foundation [26, 27], as most of us oppose the use of sentient "marginal" humans in such research, regardless of the severity of their cognitive disability. From that perspective, the case of feral children is but one aspect of the broader ethical challenge of marginal cases.

<sup>10</sup> This closer emotional connection is strengthened by the fact that real-life marginal humans are typically related to human persons via family ties, a property that has no strict equivalent in the case of non-human animals (although some beloved pets may come close to having such a status).

<sup>11</sup> True, the issue of research involving animals remains a divisive one in many countries. A 2021 Gallup poll thus found that only a slim majority (52%) of Americans regarded medical testing on animals as ethically acceptable [25].

Perhaps abolitionism is in fact the correct position to take on the ethics of animal research. Nonetheless, accepting it, at least in the current state of affairs, would have radically revisionary implications for the conduct of such research (and for our treatment of animals more generally), outlawing many practices that are currently treated as acceptable in most countries, and potentially slowing down the pace of research considerably. If we are not prepared to go down that path, Hyun might argue, then we should accept that Koplin's objections to his view are not decisive. Furthermore, we may note that if abolitionism is accepted, the whole debate about the cognitive enhancement of animals transplanted with HBOs (or of other kinds of neural chimera) becomes otiose. If sentience marks the threshold for full moral status, then no such enhancement can be expected to alter the ethical status of the (sentient) recipient animal. And in any case, if such studies were expected to present any significant risk of harm to the animal, then they should not be conducted at all.

### Remaining Problems with the Skeptics' Approach, and a Better Path Forward

Some lines of reply are therefore available to Hyun, and those who share his view, against the objections outlined above. Nevertheless, even if we accept that any non-abolitionist position on the ethics of animal research is likely to have some uncomfortable implications regarding our justifications for granting strong protections to marginal humans, the approach to full moral status favoured by Hyun and the ISSCR still seems unsatisfactory, for two main reasons. First, it does seem to set the threshold for full moral status unnecessarily high. We have seen that while Hyun takes self-awareness to require the ability to represent the world propositionally, and therefore a mastery of language, many will dispute the plausibility of that requirement – including, for instance, those who take Gallup's mirror test to be an adequate measure of self-awareness. Supporters of that test might thus argue that if an animal manifests the behavioral dispositions required to pass the mirror test, and if it is appropriate to infer the right functional states from those dispositions, then this animal should count as having a self-concept, and therefore, self-awareness [28]. Hyun

may plausibly point out that this is still not enough to qualify as having “human-like” self-awareness, because it does not demonstrate an ability for propositional and recursive thinking. Yet is it obvious that this more sophisticated form of self-awareness is required for a being to enjoy full moral status? I submit that it is not.

Importantly, this is not a mere linguistic dispute about how terms like “self-awareness” should be used, but one about the kind of capacities that make a key ethical difference. We could consistently accept that an animal lacks “self-awareness” on the grounds that it fails to meet Hyun’s conditions, and still maintain that it displays a level of cognitive sophistication sufficient to be granted full moral status. Perhaps coming “close enough” to the capacities of a normal human is sufficient for that purpose. David DeGrazia, for example, has characterized the great apes as “borderline persons” based on the sort of abilities highlighted by the authors of the *Philosophers’ Brief* (i.e. capacity for mirror self-recognition, planning, use of tools, and understanding of social hierarchies), while recognizing their lack of linguistic ability [29]. In a similar vein, other authors have suggested that while animals like chimpanzees, as well as human infants, may lack a full-fledged theory of mind due to their apparent inability to represent propositional attitudes, they may nevertheless be ascribed a “minimal” theory of mind based on “belief-like” states [30]. Some recent studies offer empirical support for at least such a claim about theory of mind in great apes [31]. DeGrazia argues that *human* borderline persons have full moral status, and on that basis, proceeds to extend that conclusion to non-human borderline persons like the great apes [29]. It seems to me that some animals transplanted with HBOs, particularly non-human primates, could potentially also attain the status of (non-human) borderline person.

I suggest that this more inclusive approach to full moral status is more appealing than one that treats normal adult humans as the standard setters. At the very least, if it is not intuitively clear to us that the latter approach is the correct one, it is arguably preferable to adopt the former as a precautionary measure. Furthermore, doing so can better match our intuitions about cases like that of feral children by extending the range of marginal humans who will qualify for full moral status, and therefore deserve protection from involvement in invasive research on intrinsic rather

than extrinsic grounds – even though it admittedly cannot extend that range to all sentient humans.

The second reason to find the position of Hyun and the ISSCR inadequate is that, whether or not one is convinced by the arguments just outlined, granting the protections associated with full moral status to the great apes has, as previously mentioned, become a growing international trend in the regulation of biomedical research. Notably, Hyun and the ISSCR Task Force subcommittee do not argue against such protections – on the contrary, they endorse them in the context of research on human-animal chimeras, on the basis that they represent standard regulation in much of the world [8]. What is more, Hyun himself acknowledges being “very sympathetic” to the view that non-human primates possess a degree of moral status that warrants protection against use in invasive research. He goes on to add, however, that his discussion of self-awareness and personhood in his 2013 book is directed at “those who believe that invasive nonhuman primate research is, in principle, ethically permissible” [13, p. 133]. This, then, may explain the stringent standard for full moral status that he, and the ISSCR Task Force subcommittee in his wake, end up relying on in their assessment of neural chimera research.

Yet it is practically (if not also theoretically) inconsistent to, on the one hand, take for granted existing prohibitions on the use of great apes in invasive research, and on the other hand, set a threshold for altered moral status in neural chimeras, including animals transplanted with HBOs, that requires a substantially higher level of cognitive function than that characteristic of the great apes. Of course, animals – such as some Old World or New World monkeys – that would be the most likely to attain “great ape” level through cognitive enhancement, whether accidental or deliberate, would by hypothesis not start out at that level, so that using them in invasive research could not initially be ruled out on those grounds. Yet our concern here is with the possibility that they might acquire full moral status as a result of the intervention. Even if scientists and bioethicists were to support protections for great apes solely out of respect for public attitudes, and not based on a belief in the animals’ moral status (which apparently does not reflect Hyun’s personal view), truly respecting those attitudes would still require them, at least in places where they are prevalent, to mention to the public that



consistency with existing practices required adopting similar protections for enhanced neural chimeras at a comparable level of cognitive functioning, and to indicate when the creation of such chimeras might be a realistic possibility. This would not impede the freedom of experts who might regard stronger protections for great apes as unjustified to argue for their revocation, and against extending them to enhanced neural chimeras.

Based on considerations of intrinsic plausibility, moral caution, and consistency with existing practices, I therefore conclude that “human-like” cognitive capacities are not the proper threshold to use to assess when an animal whose cognition got enhanced as a result of HBO transplantation (or other form of postnatal enhancement) may have acquired full moral status. Instead, we should prefer a less demanding threshold, namely the one currently associated with the great apes. Further debate is required to determine what exact capacities are required to meet that threshold: for instance, should one or more capacities be viewed as both necessary and sufficient conditions? Or must a being simply have enough, although not all, of the properties which, together, constitute personhood, as DeGrazia suggests [29]? I will not attempt to resolve this complex issue here. For the purposes of the present discussion, we can say at least that while the great apes already have the capacities required to meet the relevant conditions, it is possible that other species, currently used in research, will make the cut (without the need for cognitive enhancement), depending on how we decide to set the threshold. And of course, members of additional species that do not “naturally” meet the threshold could end up doing so as a result of cognitive enhancement.

Moving to such a lower threshold does not yet demonstrate that alterations in the ethical status of any animals used in HBO transplantation studies are likely in the foreseeable future. Nevertheless, it does call into question the grounds for skepticism about such alterations that Hyun and the ISSCR have been relying on in their analysis. For instance, even though important physiological differences remain between say, Old World monkeys and chimpanzees, in terms of cranium and brain size, these differences are still clearly less significant than those between Old World monkeys and normal adult humans. Moreover, the case might be made that some Old World monkeys already meet at least some of the criteria for being

considered “borderline persons”: some researchers have thus claimed that rhesus monkeys can pass the mirror test, if they are first trained on how to use a mirror (but not trained to touch their foreheads [32]). It therefore matters that future expert assessments of the likelihood of such alterations in moral status should be rooted in this less demanding cognitive threshold.

My discussion so far has focused on possible changes in moral status following the transplantation of HBOs into non-human primates. Yet what about other non-human recipients of transplanted organoids – especially rodents, which have been the research subjects of choice in the studies conducted so far? I believe we should not rule out in advance the possibility that they, too, might at some point meet my proposed cognitive threshold. Nevertheless, this currently appears to be a less likely prospect in the case of rodents than in that of non-human primates, in light of the evidence regarding the latter’s cognitive capacities as compared with the former’s, and of the constraints imposed by physiological differences like cranium size [1]. If so, enhancements in the mental functioning of rodents transplanted with HBOs that might occur in the foreseeable future should probably not be expected to turn them into borderline persons, and to entitle them to the protections associated with full moral status. Harary and colleagues thus envisage that transplanted rodents might experience increases in functions like sensory sensitivity, motor function, some aspects of memory, and prosocial behaviour, but they judge the acquisition of “higher-level” capacities such as self-awareness to be “much less likely” [33]. (The relevance of the last two types of function to borderline personhood, however, may warrant further discussion.)

That said, even enhancements “below the threshold” could still have significant implications for the ethical treatment of animals used in such research. I will discuss such potential implications, as well as those associated with enhancements to full moral status, in the next section.

## Practical Implications

Let me now consider the practical implications of the preceding analysis for the conduct and regulation of future HBO transplantation studies. A first set of

questions concerns *accidental* and *unforeseen* cases of brain enhancement through HBO transplantation, conferring full moral status on the research animal. A second set concerns the even more speculative prospect of *foreseeably* enhancing an animal beyond the threshold as part of such a study.

Let us begin with accidental enhancements. First, how should we go about assessing whether an animal transplanted with a HBO has crossed that threshold? The ISSCR's call to monitor neural chimeras for any behavioural changes is well taken, and scientists could sound the alarm if they noticed something unusual in a transplanted animal. That said, to ascertain whether a key ethical line has been crossed, we would need more specific criteria. Since I have not sought to provide an exact list of conditions to be met for an animal to enjoy full moral status, arguing instead that such conditions should be established through further dialogue and consensus-building among experts, I would extend those remarks to the empirical tests we should use to assess any alterations in an animal's moral status. Nevertheless, setting the relevant threshold at the cognitive level of the great apes does suggest some possible candidates.

The most obvious one is the mirror test. No doubt, the test has received its share of criticisms, and I cannot review them all here. I will confine myself to noting that doubts about the presence of even "minimal" self-awareness (of the kind highlighted by Gordon Gallup) in chimpanzees, cannot simply be grounded in the observation that only a minority of chimpanzees have been shown to pass the test so far. Indeed, whether or not mirror self-recognition does constitute good evidence of an animal having the relevant mental capacities is something to be judged independently of how many animals might demonstrate that ability. If the answer is yes, then chimpanzees who pass the mirror test do have at least minimal self-awareness, and the failure of other chimpanzees must be explained in terms of certain individual differences in cognitive functioning, which seem to correlate strongly with age.<sup>12</sup> The test will then still leave room for concerns, but about false *negatives* rather than

false positives. For instance, perhaps more chimpanzees would pass the test if provided with training on how to use mirrors.

Other candidate tests include those designed to assess a being's understanding of false beliefs, such as the "goggles test" [31]. Several such tests could be administered in succession, whether to verify the presence of multiple relevant cognitive abilities in the animal, or to minimize the risk of false negatives, depending on how exactly we choose to identify the cognitive threshold for full moral status. We may also ask how to view members of a species who consistently fail the relevant tests, even though many if not most of their conspecifics successfully pass them. Should strong protections against use in invasive research be extended to "marginal chimpanzees", for instance, and if so, on what grounds? Are some of the considerations cited above, in relation to marginal humans, applicable here as well, or is it enough to invoke pragmatic considerations, such as the need for reasonably simple regulation (one single set of rules for each non-human species)? In any case, what is clear from the preceding remarks is that, if the acquisition of full moral status by an animal with an enhanced brain is our concern, we cannot just rest comfortably in the awareness that the animal was not exposed to the process of socialization required for the emergence of linguistic abilities.

Secondly, if an animal – again, presumably a non-human primate – turned out to pass the relevant cognitive test(s) for full moral status following transplantation with a HBO, what would be the ethical implications? The main one is clearly that in virtue of that newly found higher moral status, the animal would be entitled to greater protections against harmful treatment of the kind commonly found in biomedical research. This could create some challenges for researchers. For instance, full moral status is typically viewed as entailing a right to life. If so, it seems to follow that the life of a transplanted animal who had accidentally achieved full moral status should not be terminated, as commonly happens to monkeys used in brain research, for purposes of tissue histology, for instance [34, 35]. Rather, the neural chimera in question should be retired to an animal sanctuary [36] or other suitable setting, and should not be used in any further invasive research, even if these constraints happened to conflict with some of the original goals of the study.

<sup>12</sup> Swartz and colleagues thus suggest that the capacity for mirror self-recognition "develops in the chimpanzee during the third year of life, and is shown robustly by 5 to 6 years of age" [16, p. 290].

While these claims strike me as very plausible, it is nevertheless worth noting that they involve certain assumptions about the quality of life that the transplanted animal could be expected to enjoy following the procedure. Namely, they presume that the animal's quality of life would be "sufficiently" high, however this notion is to be exactly cashed out. Yet such a presumption might be questioned. We may for instance wonder whether an animal enhanced in this way would still be able to smoothly integrate into a community of unenhanced conspecifics in an animal sanctuary. If not, social isolation could hurt its quality of life.

Other possible harms to the animal could result from some aspects of the study itself. So far, scientists who have conducted HBO transplantation studies have thus been ensuring that the recipient animals had dysfunctional immune systems, in order to prevent rejection of the human cells grafted into their brains [37, 38]. One might worry that this kind of measure could negatively impact the well-being of transplanted animals after the studies have been conducted, making them more vulnerable to diseases, and potentially shortening their lifespan. Harm might also result from complications related to the transplant, for instance if its cells did not survive for the rest of the animal's life. The quality of life of an enhanced animal following a HBO transplantation study should therefore be carefully assessed, and steps taken to try and optimize it as much as possible. Euthanasia might be justified if the animal's life post-transplantation were to be judged bad enough, although luckily, this may not be particularly likely, even if some of the pitfalls just listed could not be avoided.

Some might contend that the standard for what constitutes a "sufficient" quality of life should be set higher in the case of *foreseeable* enhancements from HBO transplantation. The rationale for such a claim might be that the expected quality of life required to make it permissible to deliberately "create" a being with full moral status (including by cognitively enhancing an already existing being with only "partial" moral status) is higher than the level required to make it wrong to terminate that being's life *once it already exists*. For the former purpose, one might argue, a higher standard than a life "merely" worth living should be met.<sup>13</sup> The following example might be taken to provide intuitive support to such claims: many people think it is wrong for prospective parents

to deliberately give birth to a child with spina bifida if they could have avoided doing so without facing unreasonable costs, even though the lives of people with such a condition may typically be well worth living. Such a line argument is not uncontroversial, however. Not everyone will agree that prospective parents have an ethical obligation (as opposed to, say, weaker moral reasons) to take all reasonable measures to avoid having a child with spina bifida, given that a life with that condition can still be expected to be worth living. Those in that camp might also counter that the analogy with spina bifida does not support a higher quality of life standard in the case of foreseeable enhancements, because in both cases, no one can properly be said to suffer any *harm*. Just as a child with spina bifida will not be made worse off than they otherwise could have been by the fact their parents allowed them to be born with that condition, if the alternative was for a *numerically distinct* child to be born without it [40], a cognitively enhanced animal suffering from a compromised immune system may not have been brought into existence at all if that procedure had been ruled out from the start.

In light of such philosophical controversies, what exactly counts as the correct standard of "sufficient" quality of life to create a neural chimera with full moral status is a difficult question that needs to be clarified through further debate. Additionally, related questions also need to be resolved, having to do for instance with the best way of measuring an animal's quality of life. The ethical status of some relevant cases, however, is already clear enough. If the nature of the study would require terminating the animal's life after the procedure, the study should not be carried out, as it would either foreseeably violate the enhanced animal's right to life (assuming its life would be worth living), or represent a case of "wrongful life" (if its life, no matter how short, would be so bad as to be worse than death). Once a standard of minimally acceptable quality of life has been agreed upon, we can then use it to evaluate other

<sup>13</sup> David Benatar draws a related distinction between "a life worth continuing" and "a life worth bringing about" [39]. His distinction, however, revolves around *prudential* considerations, whereas I am concerned with our *ethical* obligations towards borderline persons whose lives we might either extend or create.

cases involving less severe expected consequences for the animal.

The provisional outcome of this discussion, which very much demands to be continued, is that it need not be wrong *in principle* to foreseeably create an animal with full moral status via HBO transplantation. If the animal's life were protected, and if we could expect its quality of life following the intervention to meet whatever threshold we had settled upon, then the study in question might be ethically permissible (provided that it met other relevant constraints, such as compelling scientific rationale, and so on). However, in light of the concerns just outlined, there is reason to doubt that HBO transplantation studies would be likely to meet those conditions in the foreseeable future. Even if we think that the acquisition of full moral status is itself a boon to the animal, as some have suggested [41], it is not very plausible to think this could outweigh the burdens imposed on the transplanted animal. If that is correct, a reasonable policy would be for researchers to refrain from proceeding with any such studies if they took an enhancement of the animal to full moral status to be a real possibility – at least as long as it couldn't be convincingly established that the enhanced animal would enjoy a “sufficient” quality of life.

As for cases of enhancement remaining below the threshold linked to full moral status, which I have argued will be most plausible with regards to rodents for the foreseeable future, they may not make it fundamentally wrong to create such animals with the expectation of terminating their lives. Nevertheless, there need not be a very sharp line between such cases and those involving enhancement above the threshold, as research on animals that do not count as borderline persons should still be subject to appropriate ethical constraints, and as such constraints could sometimes be stringent enough to rule out a proposed study. Consider for instance the promising framework for animal research ethics recently proposed by David DeGrazia and Tom Beauchamp, based on six principles meant to improve upon the traditional “three Rs” [42]. While this framework does not endow research animals with a right to life, it nevertheless includes a “Principle of Upper Limits to Harm”, according to which “animal subjects must not be caused to endure severe suffering for a lengthy period of time” (p. 313). Assuming, as Harary and colleagues have suggested, that some enhancements – of memory for instance

– could cause rodents to experience increased suffering, it is at least conceivable that knowingly producing such enhancements might violate DeGrazia and Beauchamp's principle of upper limits to harm, which would justify a prohibition on studies that would have such an outcome.<sup>14</sup>

## Conclusion

The prospect of cognitively enhancing non-human animals through interventions like HBO transplantation has recently garnered increasing attention from ethicists. At the same time, concerns that such enhancements might lead to an alteration in the ethical status of those animals have been denounced as premature and misleading by major authorities in the science and bioethics communities. I have argued that while we should certainly pay careful attention to what scientists are telling us about the current and foreseeable state of the science, this skeptical critique is nevertheless unwarranted, because it presupposes an indefensibly high threshold for full moral status. For such concerns about altered moral status to be valid, I have submitted that a lower threshold is sufficient, involving not full but only partial humanization, or what we might call, somewhat less elegantly, “chimpanzification”.

While making the case for this lower threshold on grounds of intrinsic plausibility, moral caution, and consistency with existing practices, I have not sought to provide a definitive answer regarding its exact nature. Rather, I have suggested that further debate is needed to help clarify this matter, as well as other, related ones. These include how realistic the prospect of crossing that threshold might be in future HBO transplantation studies, as compared with full humanization; what counts as a “sufficient” quality of life for a neural chimera with full moral status, and whether this represents a higher standard than that relevant to a life worth continuing for such a being. Attention should also be paid to potential cognitive

<sup>14</sup> The implications of such an ethical framework for cases of HBO transplantation, and other potential forms of animal enhancement, will clearly depend on the specific impact of a given enhancement on the animal. As suggested previously, in some cases, adjustments to the animal's environment to minimize any discomfort might be sufficient.

enhancements that would fall short of full moral status, even though they have not been my main focus here. Far from being premature, discussion of those issues is highly timely if we wish to ensure that such animal studies are conducted in a responsible manner in the years to come.

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**Conflict of Interest** The author declares that he has no conflict of interest relevant to this article, and that no funding was received in association with it.

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