Lessons from Frankenstein 200 years on: brain organoids, chimaeras and other 'monsters'

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ABSTRACT

Mary Shelley's *Frankenstein* has captured the public imagination ever since it was first published over 200 years ago. While the narrative reflected 19th-century anxieties about the emerging scientific revolution, it also suggested some clear moral lessons that remain relevant today. In a sense, *Frankenstein* was a work of bioethics written a century and a half before the discipline came to exist. This paper revisits the lessons of *Frankenstein* regarding the creation and manipulation of life in the light of recent developments in stem cell and neurobiological research. It argues that these lessons are becoming more relevant than ever.

> [T]he nameless being given life by Frankenstein's or Mary Shelley's arts and machineries is neither ghost nor fairy; science fictional he may be; stuff and nonsense he is not. He is a creature of fantasy, archetypal, deathless. Once raised he will not sleep again, for his pain will not let him sleep, the unanswered moral questions that woke with him will not let him rest in peace.[1]

Mary Shelley wrote *Frankenstein* in 1818. The European enlightenment was in full swing, but the scientific revolution was just emerging. Luigi Galvani (1737–1798) had recently demonstrated the action of electricity on dissected animals, while his nephew Giovanni Aldini (1762–1834) had used electricity to 'animate' human corpses. The technology was applied before the ethics was considered, but to be fair, the discipline of bioethics would not emerge for another century and a half. It fell to writers like Shelley to create narratives that could help society think through the moral implications of scientific advances.

The world has changed greatly since Mary Shelley set out to write her Gothic horror story. It has become possible to manipulate life in ways that are both subtle and profound. We now have bioethics, but scientific advancement regularly outpaces our ability to think through the implications. Nowhere is this clearer than in current neurobiological research.

FRANKENSTEIN

Frankenstein describes the life of Victor Frankenstein, a young scientist, who creates a humanoid 'monster'. (It has slipped into common misunderstanding that the monster is called 'Frankenstein'; the monster, however, remains nameless throughout the story.)

Frankenstein grew up in Geneva. While his early life seemed idyllic, he was deeply affected by his mother's untimely death. In Geneva, Frankenstein educated himself from the outdated works of alchemists and natural philosophers. On moving to university at Ingolstadt, Frankenstein's study was redirected to modern chemistry—an emerging science at which he excelled. Frankenstein, however, was consumed by a passion to do something great, and embarked on a mission to find the elixir of life. He doubtless hoped to save others from death, even as his mother had succumbed to hers.

Frankenstein worked alone for 2 years, to the point of physical and mental exhaustion, assembling body parts into human form. On bringing the creature to life, Frankenstein, horrified, hides in his bedchamber. He eventually wakes to find the creature reaching out to him. Frankenstein again recoils, this time to flee his apartment.

Physically, the creature appears monstrous. But as Mary Shelley depicts him, he is sensitive, articulate and (at least initially) inclined towards kindness. The creature reaches out for human contact repeatedly over the course of his existence but is rejected each time. Blaming Frankenstein for his misery, the creature systematically kills Frankenstein's loved ones. Frankenstein laments the situation, but he expresses no sense of remorse for his actions and denies any responsibilities towards his creation. Eventually driven mad with fear and anger, Frankenstein pursues his 'monster' across Europe and onto the Arctic sea ice, where Frankenstein ultimately perishes. Having completed his revenge, the creature—who has come to view himself as monstrous and his life as worthless—pledges to immolate himself on a funeral pyre.

NEW 'MONSTERS' AT THE CUTTING EDGE OF SCIENCE

Like Frankenstein, modern scientists are creating and manipulating life in unprecedented ways. The spectre of Frankenstein's monster lurks throughout public discussions of these scientific advances. For example, some columnists worry that scientists creating brain organoids have 'gone full Frankenstein on us'[2], while *National Geographic's* coverage of BrainEx—a system to restore circulation and oxygen to 'dead' brains—also cites the Frankenstein narrative.[3] Given the tenor of these discussions, we think it is worth clarifying the moral lessons *Frankenstein* holds for these areas of research.

Brain organoids

Stem cells have been used to generate human brain organoids—three-dimensional cellular structures that can resemble miniature human brains. Many believe that consciousness could theoretically be

realised in a brain organoid. This possibility raises difficult technical questions about how consciousness could be detected, and equally difficult moral questions about the degree of moral consideration that conscious brain organoids would deserve.[4–6]

Most discussions of organoid ethics assume that consciousness is not yet a live issue. Current brain organoids are only a few millimetres in size, contain only a tiny fraction of the cells of an adult human brain and cannot interact with their environment.[5] However, despite these limitations, some neuroscientists worry that some existing organoid models might already have attained consciousness.[7] At the same time, scientists are continually working to improve organoid models. As the limitations of current models are overcome, it will become increasingly reasonable to worry that brain organoids are developing a mind of their own.

Human-animal neurological chimaeras

It may soon become possible to generate human organs inside of human-animal chimaeras using a new technique: interspecies blastocyst complementation.[8] The resulting creatures would be composed primarily of animal cells, with some human cells found throughout its tissues; however, some specifically targeted organs could be entirely human.

There are two ways in which such research raises moral status concerns. First: it is possible that interspecies blastocyst complementation could accidentally 'humanise' animal brains. Even if researchers are aiming to create (for example) a human-pigchimaera with a human pancreas, it is possible that some human cells might end up contributing to the chimaeric animal's brain. This raises the question of whether scientists should proceed with such research, or if they should first be required to perfect mechanisms to prevent this possibility.[9 10]

Second: interspecies blastocyst complementation could be used to intentionally create human-animal chimaeras with humanised brains, such as human-mouse or even human-monkey brain chimaeras. These chimaeric animals could yield valuable new insights into human brain development and neurodegenerative disorders.[11] However, 'humanizing' animals' brains could potentially affect these animals' mental lives—and thereby affect our moral obligations to them.

Transgenic animals with humanised brains

Genetic modification can likewise be used to 'humanize' animal brains. Indeed, such research is already underway. Scientists from China's Kunming Institute of Zoology recently created transgenic macaque monkeys with genes associated with human brain development. These transgenic monkeys displayed better short-term memory and reaction time than their wild-type counterparts.[12] This kind of research raises difficult questions about our moral obligations to transgenic animals that develop sophisticated cognitive abilities. We need to ask whether transgenic monkeys could develop cognitive capacities that increase their moral status beyond their wild-type counterparts, or potentially even confer moral status on a par with normal humans.

'Revived' animal brains

One area of research has a particularly intimate connection to the Frankenstein narrative: the partial 'revival' of slaughtered animals' brains. Researchers have recently restored some molecular and cellular processes to the disembodied brains of pigs (which had been slaughtered 4 hours earlier).[13] While the research did not restore the kind of organised electrical activity associated with consciousness, it might become possible to do so as the technology improves. We may soon need to work out our moral obligations to nonhuman animals not just while they are living, but also after they have been killed.[14]

Artificial embryos

Scientists have recently discovered how to create 'artificial embryos'—which can appear remarkably similar to normal human embryos—out of human pluripotent stem cells. This raises difficult questions about whether—or how—existing limits to embryo research should be extended to these embryo-like structures.[15 16] Although not an example of neurobiological research per se, this research raises related questions about artificial embryos' moral status.

REGULATORY CONSIDERATIONS

Victor Frankenstein chose to conduct his work in private. Although researchers at the cutting edge of science are subject to regulatory oversight, many of the earlier areas of research are not adequately covered by existing regulatory frameworks. For example, research with brain organoids is currently regulated according to mechanisms designed for non-sentient human tissues—which fail to address the possible moral status of the organoids themselves.[5] Existing guidelines for human-animal chimaera research do not explicitly consider the possibility that humanising animals' brains could increase their moral status.[17] Welfare protections afforded to research animals do not neatly extend to the revived brains of slaughtered animals, even if consciousness were to be restored.[14] And artificial embryos fall within the gaps of some (but not all) jurisdictions' regulation of embryo research.[16] Although much of this research would presumably receive some form of ethics committee oversight, there is a risk that ethics committees might not anticipate some of the novel ethical issues raised by these cutting-edge areas of research.

MORAL STATUS OF MANIPULATED ORGANISMS

In bioethical debates, *Frankenstein* is usually evoked as a warning against interfering with the natural order or 'playing God'.[18] This is perhaps unsurprising, since many film adaptations of *Frankenstein* are quite explicitly framed as a cautionary tale against human hubris. However, as Stephen Jay Gould[19] and others[20 21] have pointed out, these are the wrong lessons to draw from the story. Frankenstein made his most serious moral error not when he decided to pursue his scientific breakthrough (one which might, after all, have helped save lives), but when he failed to consider his moral obligations to the creature he created.

Frankenstein's 'monster' could experience acute emotional suffering. It could read, it had a clear interest in continuing its life, it wished for meaningful social connections and sought self-actualisation. The creature even displayed some degree of moral agency; in conversation with others, it accepted personal responsibility for the deaths it caused. Presumably, then, the 'monster' had at least some degree of moral status—which is to say, he was the kind of being to which we have moral obligations. Frankenstein refused to recognise *any* duties towards his creation, including even the modest duties we currently extend towards nonhuman research animals; Frankenstein denied his creature a name, shelter, healthcare, citizenship or relationships with other creatures of its kind. In so doing, Frankenstein wronged his creation.

The manipulated organisms created by scientists today also raise issues of moral status. For some of these entities—such as artificial embryos and brain organoids—we need to ask whether

(or under what conditions) they could acquire moral status. For others—such as chimaeric and transgenic animals—we need to ask whether (or under what conditions) they deserve greater moral consideration than normal research animals.

In thinking through these issues, we should begin by recognising that sentience is tightly linked with—and arguably necessary for—moral status. This is because the way we treat an entity cannot matter *to* that entity unless it has interests. If an entity lacks sentience, it presumably also lacks any stake in how it is treated; accordingly, we presumably cannot have any obligations *to* that entity.[22] Chickens, chipmunks and chimpanzees have interests, and therefore have (at least some degree of) moral status; a rock lacks interests, and probably for this reason lacks moral status altogether.

Tying moral status to sentience is admittedly controversial. For example, it is sometimes argued that certain non-conscious entities (such as early human embryos) have moral status by virtue of the kinds of beings they might become.[23] We think potentiality arguments are problematic. We are not generally required to treat entities that have the *potential* to become a different kind of entity as if they have already realised that potential. We are not, for example, required to afford acorns the same respect as old-growth oak trees.[24] However, for the purposes of this paper, we can place potentiality (and other possible bases of moral status) to one side. For now, it is enough to note that if an entity has interests, then we ought to take these interests into account when deciding how to treat it.

Having said this, we should be wary of restricting potentially beneficial research unnecessarily. Indeed, given the good that might be realised via the areas of research surveyed above, we have a moral imperative not to hamper it without good reason. Insofar as the manipulated organisms described earlier *lack* sentience, there is no obvious need to restrict their use in research (beyond how we restrict research with human and animal tissues more generally). The issue becomes more complicated if there is reasonable uncertainty about the sentience—and therefore moral status—of a manipulated organism. If there is a realistic possibility that an entity has interests, then we ought to afford it at least *some* degree of moral consideration; we would risk serious moral wrongdoing by treating it as though it were mere biological material.[25]

Some entities with moral status may deserve greater protection than others.[i] While most people believe neither humans nor mice should be harmed gratuitously, many people plausibly believe that normal human adults deserve greater moral consideration than laboratory mice. By the same token, it might matter, morally, if an advanced brain organoid develops capacities beyond bare sentience, or if a chimaeric or transgenic animal achieves greater cognitive sophistication than its wild-type counterparts. It is therefore important to consider not only whether manipulated organisms cross the threshold into acquiring moral status, but also what degree or kinds of protection they should be afforded.

How should we determine what *degree* of moral consideration to grant different kinds of manipulated organisms? This is a controversial question, and there are no clear answers. Different accounts of moral status appeal to as diverse a range of properties as cognitive sophistication, species membership, special relationships, membership in relevant communities and the strength of a being's interests.[26] While we cannot hope to offer a definitive answer here, we do think that *Frankenstein* can help narrow the range of plausible contenders.

Two key insights can be drawn from the *Frankenstein* narrative. First, we should reject the view that if we have created an entity in order to experiment on it, we do not need to extend much consideration to its interests or preferences. Frankenstein is not absolved of responsibility towards his 'monster' purely because he made it to serve his own purposes.[ii] Indeed, on many conceptualisations, Frankenstein's 'monster' was not merely a being with some degree of moral status, but moreover a full moral person. Since Frankenstein had reason to suspect his creation would achieve some degree of sentience, physical function and intelligence—and since these capacities are highly relevant to how the monster should be treated—Frankenstein should have anticipated these possibilities and developed a plan for how to respond.

This is an obvious point, but it is also an important one. It is important in part because scientists cannot always rely on existing regulations to anticipate moral issues associated with the creation of new kinds of organisms. For example, as described earlier, in some jurisdictions 'artificial' embryos are, by dint of the way they are created, exempt from restrictions to research with 'natural' embryos.[16] Similarly, under the current regulatory landscape, it is unclear whether revived animal brains would receive the protections afforded to research animals, again due to the unique way these entities have been created.[14] The basic moral point here is that it is important to consider the moral status of the entities we create, not merely how they fit within the current regulatory landscape.

The second lesson of *Frankenstein* is that we should be wary of any prejudice we feel towards beings that look and behave differently to us. Frankenstein described his creation as hideous; the creature himself concurred. Yet the creature is nonetheless portrayed as having the ability and desire to learn and relate to others. Tragically, none of the humans in the story recognise the depth of the creature's emotional life; they are too frightened and repulsed by its appearance. (The sole exception is a blind man that the creature encounters midway through the narrative.) One lesson we should draw from *Frankenstein* is that we should interrogate any knee-jerk intuitions we have about the moral status of unfamiliar kinds of beings.[iii]

In 1997, Leon Kass (in)famously argued that repugnance can be the 'emotional expression of deep wisdom'.[27] *Frankenstein* highlights the dangers of this view. The things that evoke repugnance can be, and often are, morally irrelevant. In the case of *Frankenstein*, Victor recoils from the creature's yellow skin (which 'scarcely covered the work of muscles and arteries beneath'), watery eyes ('the same colour as the dun-white sockets in which they were set') and 'shriveled complexion and straight black lips'.[28] While Frankenstein's repulsion helps explain his rejection of the creature, it does nothing to justify it. Here, and elsewhere, repugnance serves to distort moral thinking.

[i]We leave open the question of whether this is because some beings have a greater degree of moral status than others, or whether different kinds of beings merely have different interests that warrant different kinds of consideration.

[ii]By the same token, parents are not absolved of responsibility towards their children if the pregnancy was not intentional or voluntary. It might be possible to satisfy one's obligations by (eg) putting the child up for adoption—but a parent cannot ethically vivisect the child just because they didn't intend to create it. We thank an anonymous reviewer for drawing this parallel.

[iii]Stephen Jay Gould has made a related point.[19] For Gould, Frankenstein's repulsion at his monster resembles (and is wrong for the same reason as) aversion towards seriously malformed humans. This paper aims to extend Gould's point to various kinds of manipulated organisms.

RESPECTFUL TREATMENT IN THE ABSENCE OF MORAL STATUS

Although sentience is probably necessary for moral status, we might have additional moral reasons to treat certain non-sentient entities with respect. It seems instinctively unethical to use a human skull for soccer practice, burn an irreplaceable work of art or gratuitously despoil a river. Skulls, paintings and rivers lack moral status; they do not have any direct stake in how they are treated. Even so, it seems intuitively plausible that they should be treated with respect, and that we should therefore abstain from using them in certain ways or damaging them for 'frivolous' purposes.[29]

Our reasons for treating non-sentient entities with respect are often tied up with our moral obligations to entities that *do* have moral status. How we treat human remains can matter to the family of the deceased, and how we treat a famous painting can affect whether others will be able to enjoy it. However, it is possible to think of cases where respectful treatment seems important independently of how (or whether) this respectfulness affects people (or other beings that have moral status). It seems intuitively wrong to kick a human skull down the road, even if nobody is around to see us do so and the deceased's descendants will never find out.

We suspect that many people will share these intuitions—but intuitions can be mistaken. Are there concrete moral reasons to treat non-sentient matter respectfully?

Charles Foster has enumerated one possible set of moral considerations (in this case, related to the treatment of human tissues.) These considerations include that disrespectful treatment might violate the wishes of the person who donated the tissue; that the abuse of body parts can disturb others' peace of mind; that abusing human tissues diminishes the abusers' own well-being; and that establishing rules to ensure tissue is treated respectfully will express and promote a social commitment to human flourishing.[30] Foster's concerns might extend to the manipulated organisms discussed in this paper. Scientists' treatment of these manipulated organisms might affect the interests of human tissue donors, discomfort those aware of the practice and/or erode a commitment to human flourishing. Arguably, then, we should treat these manipulated organisms *respectfully*, and use them only for important purposes—even if (in the case of artificial embryos, organoids or revived animal brains) these entities lack sentience, or (in the case of chimaeric or transgenic animals) 'humanising' the animal's brain neither bolsters its cognitive abilities nor enhances its moral status.

Victor Frankenstein evinced a clear lack of respect for the bodies he plundered from graves and charnel houses. His actions were motivated not by weighty moral purposes, but rather by his fascination with the power of 19th-century science. By contrast, current research with artificial embryos, organoids, chimaeras, transgenic animals and 'revived' pig brains is aimed squarely at medical advancement. Even so, *Frankenstein* serves as an important reminder that researchers should continue to engage with the ethical aspects of creating novel organisms, including issues of respectful treatment. This is especially true when their research falls within the gaps of existing regulations.

CONCLUSION

Mary Shelley's *Frankenstein* shows why it is important that we reflect on the scientific objectives we pursue, the materials that we use and the purposes we use them for. This lesson will only become more important as scientific advancements give us unprecedented power over the creation and manipulation of new forms of life. We have discussed *Frankenstein*'s relevance to novel entities such as brain organoids, human-animal chimaeras and revived pig brains. There are also other scientific endeavours that could benefit from the lessons of *Frankenstein*, including gene editing, human enhancement and advanced robotics.

The scientific advances described in *Frankenstein* remain squarely in the realm of science fiction. Even with 200 years of scientific progress, we are nowhere near able to build a living person from dead parts. Yet the reason why science fiction is valuable is not (or not only) because it helps us anticipate the future. Instead, science fiction is valuable because it helps us view familiar problems from new angles. In his seminal essay on creative fantasy, J.R.R. Tolkein has described this function as the 'regaining of a clear view'.[31] It is because *Frankenstein* can help us regain a clear view that it serves as an important tale for the rapidly developing science of neurobiological research.

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