

## Lost in Translation: Gaps in Reasoning for Primate Stroke<sup>1</sup>

Degeling C & Johnson J. (2009)

Sughrue and colleagues' target article "Bioethical considerations in translational research: Primate stroke" (2009) are to be commended for seeking to address a large gap in current bioethical discourse. The ethics of experimentation on nonhuman animals seems to have fallen between the cracks of the recent debates between clinical and research practitioners, ethicists and regulators. While happy to see that other parties acknowledge that this question is poorly dealt with and the issue remains far from closed, we have identified a number of problems with the argument contained in the article. In the first instance, the authors fail to clarify the sense in which they understand nonhuman animals as models for humans. Secondly, they ignore an important ethical argument, which bears directly on the case of stroke research put by philosophers whose views they otherwise apparently commend. And finally, throughout the article they conflate epistemological and ethical justifications for research without adequately justifying the assumptions that underpin either position. The following commentary will outline each of these criticisms, before offering suggestions as to how they may be met.

Despite the existence of an extensive literature on the fundamental problems of extrapolating from research in animals to humans, Sughrue and colleagues (2009) appear to see model shortcomings as primarily a methodological issue. Four possible explanations are given for the clinical ineffectiveness in humans of 49 of 50 agents shown to have benefit in animal models. The first three relate to disparities in the timing of interventions, and the size and design in both animal-based and clinical trials. The final explanation offered for failed extrapolations from bench-top to bedside is that rodent models "do not fully represent important clinical and biological realities of human stroke" (Sughrue et al. 2009, 3). Sughrue and colleagues (2009) then make the assertion that "non-human primate brains seem better suited to accurately predict the potential for a drug to protect ischemic tissue in the human brain" (3). Simply put, their argument is that nonhuman primates might be more successful models for this type of research because the central nervous system of rats, rabbits and mice—unlike that of monkeys—are not sufficiently homologous to that of human beings. On this basis the authors claim that primate-based research should prove to be more experimentally productive, and hence clinically predictive than current models and methods.

Research into model-based science has led philosophers and experimentalists alike to be wary of pre-emptive claims about the predictive abilities of animal models (LaFollette et al. 1993; Perel et al. 2007). In most modeling activities, the strictness of the criteria for resemblance relations between the model and target system often complicates the move from model-based representation to

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model-based predictions. A concise summary of the core epistemological issue for biomedicine is provided by the authors of a handbook for animal-based science who note:

*It is not possible to give reliable general rules for the validity of extrapolation from one species to another. This has to be assessed individually for each experiment and can often only be verified after first trials in the target species* (Hau et al. 2003, 6).

This means that despite their greater homology, there is no evidence to suggest that induced cerebrovascular events in primate models will produce accurate predictions about spontaneous disease in the target species (humans) until clinical trials on patients are undertaken. As recently demonstrated by the TGN 1412 trial (a compound which was tested on a primate model before phase I trials resulting in significant harms to human participants) it is only with the benefit of hindsight that we can know the relevant and ‘correct’ animal studies to employ.

Sughrue and colleagues (2009) then tackle the thorny issue of the ethical justification of this type of research by offering a weak synthesis of the broadest deontological and utilitarian positions, conferring nonhuman animals limited ‘rights’ to have an ‘interest’ in avoiding harms like pain and death. What is absent from this discussion however, is any engagement with what has become known as the ‘argument from marginal cases’. Although David DeGrazia, Ray Frey, and Peter Singer are correctly represented as claiming that normal humans have greater interest in avoiding death than other animals, Sughrue and colleagues (2009) fail to disclose these ethicists’ entire arguments. In their more fully articulated position each of these moral philosophers has argued that experimentation on incapacitated humans—such as encephalitic infants, brain dead adults and other so-called ‘marginal cases’—may be less morally problematic than experimentation on healthy animals.

Sughrue and colleagues (2009) then seek to defend the expansion of primate-based research by attempting to demonstrate that there is likely to be a qualitative difference between the interior lives of human and non-human primates. Their argument rests on the claim that most of the suffering which results from minor strokes—whether spontaneous or surgically induced—is “due to the delayed intellectual and psychological reaction” (3) to the resulting incapacitation. Catastrophic strokes, in both humans and nonhuman animals, are portrayed as being distinct because they cause little to no pain or suffering. The un-stated assumption is that monkeys undergoing procedures that cause any form of stroke do not experience pain or suffering because by our measure, they do not possess similar intelligence or a capacity for abstract thought. And yet beyond the mutual recognition of sentience on which all human and nonhuman animal relationships depend, a fundamental divide separates us from the interiority, or self-reflexive inwardness of animal lives (Descola 2006). The philosopher Steve Sapontzis (1987, 219–220) has argued, because we have no access to animal experiences of existence, we have no reliable way to measure the relative quality or value of their subjective selves.

In setting ethical calculations on a utilitarian scale and regarding the experimentation under investigation justifiable, Sughrue and colleagues (2009) have not properly weighed the burdens and benefits involved. It is far from clear that the experimental subjects will suffer no relevant and significant harms and that accounting for the primate’s presumed cognitive and emotional capacities, and inability to predict their fate—suffering an induced stroke—adequately reflect their interests. Nor is it clear that given the problems of homology and the evident incapacitation of the

most needy patient population, that expanding the use of imperfect and inherently fallible animal models should be preferred when there are description-based and clinically focused epistemic strategies for overcoming human pathologies (Marincola, 2007). Nor is there any guarantee that a clinical benefit will follow for patients from these experiments, which would justify any harm to experimental subjects. Scientific research is a haphazard epistemic practice with intended and unintended outcomes. Although Sughrue and colleagues (2009) make the point, the authors appear unaware of the full implications of hinging the ethics of experimentation so significantly around therapeutic advance, noting that “stroke experiments that take care to anticipate the specific needs of these animals are not unethical if they lead to the development of useful therapeutics for humans” (3). The ‘if’ in this statement is not insignificant. While we agree that animal-based research can lead to medical breakthroughs, beyond the need to conform to United States Food and Drug Administration regulations, there seems to be little justification for subjecting healthy animals to bench-to-bedside experimentation when ethically and epistemologically superior strategies such as research based around the afflicted patient population can be undertaken.

Throughout the article, Sughrue and colleagues (2009) seem unwittingly to run together epistemological and ethical arguments. This is most obvious when they make the astonishing claim that by building an ethical bridge which generates popular consensus on experimentation, they will “by extension, [have] success in curing disease”(3), i.e., that somehow solving ethical problems will validate their models and result in scientific advance. This simply does not follow.

It is our opinion that Sughrue and colleagues (2009), at a minimum, should: clarify how they are appealing to animal models and acknowledge the predictive. limitations of claims made from homology (they already cite in their article a list of past methodological shortcomings and failed translations, the import of this could simply be drawn to the reader's attention); recognize the full implications of the ethical arguments they are appealing to for cases of stroke; and finally try to carefully separate the epistemologically based arguments from ethical ones, and if they believe the former are crucial to the latter, then make an explicit argument to that effect.

## References

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