Current Topics in Behavioral Neurosciences 19

Grace Lee
Judy Illes
Frauke Ohl *Editors*

Ethical Issues in Behavioral Neuroscience

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Grace Lee · Judy Illes · Frauke Ohl
Editors

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Editors
Grace Lee
Judy Illes
Faculty of Medicine
National Core for Neuroethics
University of British Columbia
Vancouver, BC
Canada

Frauke Ohl
Faculty of Veterinary Medicine
University Utrecht
Utrecht
The Netherlands

Co-editor of Part I
Franck Meijboom
Ethics Institute
University Utrecht
Utrecht
The Netherlands

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Preface

We are pleased to present this volume on ethical aspects of studying behavior in psychiatric and neurological disorders as part of the *Current Topics in Behavioral Neurosciences* (CTBN) series. We have brought together a collection of chapters that provides both critical reviews of current advances in the field and key analyses of related ethics issues. The volume aims to bridge disciplines of neurobiology and psychology to provide a contemporary overview of the literature relevant to understanding neurobehavior and how ethics informs and reflects on neurobehavioral research. There is dual emphasis on ethical challenges in experimental approaches and in clinical research involving human participants. In essence, the central theme is one of Neuroethics, the field formalized in 2002 that is dedicated to interlocking the excitement of advances in basic neuroscience and clinical neurology with human values and the diversity of our societies.

With the range of topics covered, we hope that the volume will appeal to CTBN's readership of all behavioral neuroscientists, animal science researchers, clinical scientists, allied health professionals, applied ethicists, and to scholars in the social sciences alike. We also deeply hope that as neuroscience has an impact on and visibility in the daily lives of people in both resourced and under-resourced parts of the world, the volume will serve as a useful resource for early career scientists and scholars who must actively evaluate their research through an ethics lens today more than ever before.

This book has been a collaborative international effort from start to finish. Professor Frauke Ohl had primary responsibility for the first six chapters of the volume on the ethics of using animal subjects for neurobehavioral research, and was assisted by Dr. Franck Meijboom. Postdoctoral Fellow Grace Lee and Professor Judy Illes took the lead on the ten chapters that engage readers in a discourse on ethical issues for neurobehavioral research using human subjects, with a chapter linking pre-clinical and clinical research.

We gratefully acknowledge the support of all who generously fund the research and knowledge translation activities of both our organizations. At the University of Utrecht in the Netherlands, Drs. Ohl and Meijboom thank the Dutch Ministry of Public Health, the Dutch Ministry of Economic Affairs, Neuroscience and

Cognition Utrecht, and the Netherlands Organization for Scientific Research (NWO) provided direct or indirect support to this work. At the National Core for Neuroethics at the University of British Columbia in Canada, Drs. Lee and Illes thank The Canadian Institutes of Health Research, the National Institutes of Health Research, the Canadian Foundation for Knowledge Innovation, the British Columbia Knowledge Development Fund, GenomeBC, GenomeCanada, the Vancouver Foundation, the Stem Cell Network, NeuroDevNet, Inc., the Vancouver Coastal Health Research Institute, the Foundation for Ethics and Technology, the Dana Foundation, and the North Growth Foundation.

We are grateful to CTBN Editors Mark Geyer, Bart Ellenbroek, and Charles Marsden for the opportunity to create this volume and Susanne Dathe at Springer, for engagement in bringing the final product to you.

Vancouver — Grace Lee
Judy Illes
Utrecht — Frauke Ohl

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Part I
Experimental Animal Research

Ethical Issues Associated with the Use of Animal Experimentation in Behavioral Neuroscience Research

Frauke Ohl and Franck Meijboom

Abstract This chapter briefly explores whether there are distinct characteristics in the field of Behavioral Neuroscience that demand specific ethical reflection. We argue that although the ethical issues in animal-based Behavioral Neuroscience are not necessarily distinct from those in other research disciplines using animal experimentation, this field of endeavor makes a number of specific, ethically relevant, questions more explicit and, as a result, may expose to discussion a series of ethical issues that have relevance beyond this field of science. We suggest that innovative research, by its very definition, demands out-of-the-box thinking. At the same time, standardization of animal models and test procedures for the sake of comparability across experiments inhibits the potential and willingness to leave well-established tracks of thinking, and leaves us wondering how open minded research is and whether it is the researcher's established perspective that drives the research rather than the research that drives the researcher's perspective. The chapter finishes by introducing subsequent chapters of this book volume on Ethical Issues in Behavioral Neuroscience.

Keywords Animal behavior · Translational value · Animal ethics · Animal model

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F. Ohl (✉) · F. Meijboom
Department Animals in Science & Society, Faculty of Veterinary Medicine, University Utrecht, Yalelaan 2, PO Box 80.166, 3508 TD Utrecht, The Netherlands
e-mail: f.ohl@uu.nl

F. Meijboom
Ethics Institute, Utrecht University, Utrecht, The Netherlands

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1 Reasons for Reflection?

The first part of this book on Ethics in Behavioral Neuroscience explores the question of whether it is worthwhile, or even necessary, to reflect specifically on animal experimentation in Behavioral Neurosciences in extension of more general considerations on Animal Ethics in the broader sense. Are there distinct characteristics in this field of research that demand specific ethical reflection?

Of course, there is an obligation to reflect on the use of animals as models in Behavioral Neuroscience. But, research on animals has already triggered considerable attention during the last decades, exploring whether it may be justifiable to use animals for experiments at all and, if so, how to weigh the costs of such use against its benefits (e.g. Singer 1975; Van Zutphen et al. 1993; Brom 2002; Nuffield 2005) and these same questions hold for other areas of research and are not unique to the field of Behavioral Neuroscience.

More recently however, Neuroethics has emerged as a distinct field of applied ethics within the philosophy of neuroscience (Stefansson 2007; Illes and Sahakian 2011). Neuroethics deals with a wide range of questions related both to the ethical implications of practical experimentation in neuroscience and the application of the results of such neuroscientific research as well as, in turn, the consequences of neuroscience for ethics (cf. Roskies 2002; Buller 2014). In practice however, it appears that, to date, these discussions have mainly focused on humans—as for example, discussions on the moral rights and wrongs of the enhancement of brain function, or questions related to the concept of free will and moral agency. Thus, although Behavioral Neuroscience does raise specific ethical questions in relation to experimental animal research, the attention of neuroethicists has not, at least to this point, been specifically concerned with this wider context of the ethics of animal experimentation in neuroscience.

Yet there are very specific issues which are raised by the use of animal experiments in this particular area of neuroscience; it is because of those specific aspects, which lie in the interactions between the fields of animal ethics and neuroethics, that we consider it relevant to dedicate a section of the book to the ethical issues of animal-based research in Behavioral Neuroscience. Alongside the more basic questions of animal ethics, a research field that is often dependent on modeling distinct mental capacities and behavioral responses in animals, may have specific implications on considerations on the moral status of animals. Thus, the very criteria that lead us to judge some animal a valid research model in Behavioral Neuroscience are pretty much the same as we would use to grant animals moral consideration for their own sake, which inevitably leads to some conflict in terms of the acceptability of their use for experiments.

Therefore, we argue that although the ethical issues in animal-based Behavioral Neuroscience are not necessarily distinct from those in other research disciplines using animal experimentation, this field of endeavor makes a number of specific, ethically relevant, questions more explicit and, as a result, may expose to discussion a series of ethical issues that have relevance beyond this field of science.

In addition to the conflict which may result from the fact that the most valid animal models may also be those which we might consider, from those same characteristics, as having the highest claim to be worthy of specific moral consideration, other questions may, for example, be related to the predictive power of specific animal models and the degree to which results gained on those models may be truly translated to other systems or species (including humans) (Rollin and Rollin 2014). How should we deal with uncertainties regarding the predictive and construct validity of given (animal) models (cf. Geyer and Markou 1995)? How much research is needed before it is justified to move from work on animals to take the step into (pre)clinical trials? And finally: how can we balance the potential benefit of using animal models that might have higher mental capacities (thus enhancing possible translational value to humans) against the cost that such higher mental capacities may imply greater suffering as the result of experimental manipulations?

This chapter briefly introduces ethical questions raising from animal-based Behavioral Neuroscience, each of which will be developed in more detail in the subsequent chapters of this section.

2 The Moral Status of Animals as a Start of Ethical Concerns About Their Use in Experiments

The use of animals in experimental research in general has raised many concerns over the years. While perhaps earliest concerns about experimentation involving live animals arose in the UK in the nineteenth century (Franco 2013), debate about the moral status of animals is not restricted to Europe, but is nowadays of concern in many countries including the US, Australia and Asian countries (cf. Bovenkerk 2012; Linzey 2014; Nuffield Council 2005). The origin of these discussions lies in the recognition of animals as moral subjects toward which we can have moral duties (Warren 1997). A significant number of ethicists concede that animals have some moral value that is independent of their use by humans. However, there is a diversity of arguments that underlie the recognition of this moral standing of animals. Some start in the recognition of animals as living beings that have a good of their own. This is based on the idea that animals develop, maintain their life, and can adapt successfully to their environment. As a consequence, they have inherent worth as animals (Taylor 1986). Others argue for the moral considerability of animals by virtue of their being able to feel (e.g. Rollin 2011)

It is beyond the scope of this chapter fully to elaborate on the diversity of views that have characterized the debate in the past few decades (Callicott 1980; Carruthers 1992; DeGrazia 1996; Midgley 1983; Korsgaard 2005; Nussbaum 2006; Regan 2004; Rollin 1981; Rowlands 2002; Singer 1995)—and these arguments are rehearsed in greater detail in later by Bovenkerk and Kaldewaij (this volume) and Vieira de Castro and Olsson (this volume). However, both within the field of animal

ethics and in formal regulations on the use of animals in research there is a consensus that we have valid and sufficient reasons to consider animals as legitimate objects of our moral concern (cf. De Cock Buning et al. 2009 ; EU 2010).

In a nutshell, such recognition implies that animals should be taken into account in our moral reasoning for their own sake. In animal research the health and welfare of animals is of course taken into account, because compromise of either state may frustrate the research or influence the results in some way. However, speaking about animals as moral subjects implies a further step: if animals are acknowledged to be worthy of consideration and significant entities in their own right, we have direct moral reasons to ensure that our actions take account of their interests as well as our own. How this consideration can be translated into practice is not always immediately clear. Some argue that, as a consequence, any type of animal research is unacceptable (Regan 2004). Others stress that there are also legitimate ethical positions that aim to take the interests or value of animals seriously, yet do not exclude the option that using animals for research can morally be justified (cf. Rollin and Kessel 1990; and see Rollin, this volume; Vieira de Castro and Olsson, this volume). This implies that, on the one hand, using animals is not something that is to be rejected by principle; on the other hand, although animals continue to be used, such use demands a careful consideration.

Frequently, such consideration is based on an analysis of the comparative costs (i.e., harm to individual animals) and benefits (see again Vieira de Castro and Olsson, this volume). Determining the moral justification of animal research in terms of such cost–benefit analysis, in effect gives particular emphasis to two central questions: does the expected result of the experiment or project outweigh the potential suffering of the animals; and is the experiment being performed in the best possible way with regard to the principles of Replacement, Reduction and Refinement (Russel and Burch 1959). Such an evaluation process implies that the ethical justification of animal experiments demands that there shall be specific benefits as a result of any experiment that are considered important enough to outweigh the costs for the animal. In general, the benefit of using animals in experiments is argued in terms of its contribution towards reduction of suffering in humans as an immediate or ultimate aim. This holds equally for experimental animal research in Behavioral Neuroscience.

The majority of such experiments is aimed, if sometimes indirectly, at gaining knowledge about the executive function of the brain. Most commonly, it is the dysfunctioning of particular processes that is of especial interest, because some specific dysfunction of the CNS underlies a variety of disorders that can have a severe impact on (human) quality of life. Since many ethical frameworks stress that we have a duty to take action in the face of human suffering, there is a moral imperative to perform some form of research in this field. Having accepted such duty to care for the health and wellbeing of humans, however, there is no automatic logical presumption that animals have to be used or that use of animals is automatically justified. Therefore, an important aspect of the ethical justification of animal experimentation is discussion both of the need to use animals at all *and* on the relevance of animal models in research (to ensure that animals used genuinely

do provide appropriate models for human systems or disorders, rather than simply mimicking symptoms but in an unrelated way). We should, therefore, take a closer look at the validity of the animal models used in this field of research, and their relevance for transference of results to other systems and species.

3 Relevance of Animal Models?

The actual relevance of animal models for a distinct field of research is difficult to assess. One may get some impression of the current [quantitative] importance of animal models in experimental Behavioral Neuroscience by way of a literature research, although, of course, there is virtually no way to assess whether the use of particular animal models employed, has indeed resulted in relevant output. Given such reservations, however, it appears from a rough and explorative online screening for recent literature, that of the 7,500 original research articles that have been published on this topic during the last 5 years (PubMed 2009–2013), more than 40 % of the papers at least make some reference to animal models. More specifically, PubMed reports the following number of articles published in the last 5 years when searching with the key-phrase "behavioral neuroscience" together with [….]:

[humans]: 2400
[either humans or other animals and (computer modeling)]: 56
[either humans or other animals and (in vitro)]: 190
[other animals]: 3665

While such numbers cannot tell us anything about the actual contribution of animal studies to developments, and valid advances, within this field of research, such an overview suggests that studies in humans and animals each contribute almost equally to the overall publication output in neurobehavioral research. Given all the recent technical developments and the range of opportunities now available to perform non-invasive experiments in humans, as well as to model neural processes in vitro, it seems somewhat intriguing that animal-based experiments continue to play such a big role in Behavioral Neuroscience. For this to remain true, the results gained from animal experiments in Behavioral Neuroscience are obviously assessed, at least by the researchers themselves, or the wider research community, as of importance—perhaps because they are thought to contribute as much to the development of the research field as do studies in humans, or perhaps for other reasons. It may, for example, be that animal experiments are considered more ethically acceptable than pre-clinical studies in humans; it is also possible that research, or at least the publication of research, constrains itself by following distinct traditions, such as demanding the validation of novel findings by comparing them to already published animal models and test procedures.

One significant question arising from the continued extensive use of animals is embedded in the broader debate on the possibility of replacement of animal

experiments, the first of the 3R-principles (Russel and Burch 1959). Although, the search for animal-free methods is complex in any research field (Doktorova et al. 2012; Hendriksen 2009; Huggins 2003; Manciocco et al. 2009; Penza et al. 2009), in Behavioral Neuroscience in particular, the modeling of complex systems such as executive processes of the brain or the central nervous system (CNS) may indeed limit the possibility of finding alternatives and may thus demand use of animal models; at least at present, available in vitro methods, and computer models seem unable to display the complexity of CNS-generated, behavioral-cognitive processes. It may be of note, however, that the declared goal of one of the current EU flagship programs (the Human Brain Project) is: "to build a completely new ICT infrastructure for neuroscience, and for brain-related research in medicine and computing, catalyzing a global collaborative effort to understand the human brain and its diseases and ultimately to emulate its computational capabilities."[1]

While waiting for the results of such initiatives, the use of methods that avoid the use of live animals is still quite limited. But even if we do accept the need to base parts of research in Behavioral Neuroscience on the use of animals, some ethically relevant questions remain to be considered. And first among these questions, as above, is: what it is that animals are supposed to model and are we choosing the correct models?

If we look in more detail at the specific areas of animal experimentation, a literature search using the term "animal model" in combination with some general topics reveals that use of animal models in many cases is related to research into a variety of human-specific, mental disorders. Such a literature scan, again performed on articles listed by PubMed and over the same time period, picks out the following number of publications with the combined keywords [animal model] and […]:

[stress]: 13561
[alzheimer]: 2568
[depression]: 2918
[schizophrenia]: 1464
[anxiety]: 2340
[mood disorder]: 982
[hyperactivity]: 924
[addiction]: 868
[post traumatic stress disorder]: 247
[eating disorder]: 219

This simple screening results in the identification of more than 25,000 articles on this (artificial) selection of human mental states/disorders. [For comparison: a search on [animal model] and [cancer] delivers 20,304 hits]. Without going too far in interpreting such a crude literature search, we may feel confident enough to suggest that animal models are still considered important in investigating human mental states and/or functions; indeed this use of animal models in exploration of

[1] see https://www.humanbrainproject.eu/.

human mental function comprises the majority of those animal studies uncovered in our initial literature review.

From any consideration of the ethics of animal experimentation, such extensive usage of animals begs the question as to whether the obvious importance of animal models genuinely translates into actual useful and relevant output, since the assumption that animals are relevant models can be seen as a pivotal argument in the moral justification of animal use (Rollin and Rollin 2014). A realistic assessment of the benefits and, thus, actual relevance of animal studies is however, more or less impossible to do in practical terms (as explored in more detail in this volume by Viera de Castro and Olsson). Yet the very assumption that the animals chosen as models *are* valid and, thus, relevant models for human mental problems (such as distinct cognitive and emotional capacities) may indicate that these animals share with us morally relevant characteristics that may make them (more) worthwhile protecting, promoting additional concerns about their use in experimental treatments.

Given the need in Behavioral Neuroscience to model complex systems, and perhaps even integrate executive processes, such as learning and social behavior, it may be argued that the best choice for an animal model is the use of animals with 'higher' cognitive capacities, such as primates or dogs. However, as we have noted already, the scientific argument that these animals serve as relevant models because of the greater physiological or behavioral similarity to humans, as compared to other species like fruitflies or mice for example, is often the basis of public concerns because of exactly these same characteristics. As a result, experiments on primates and dogs often raise stronger societal resistance than experiments on rodents or fish (Hagen et al. 2012). In practice this complicates the discussion on the choice for the best possible animal model for a distinct experiment, as in fact the choice of the 'best possible' animal model becomes an interplay between value and scientific judgments.

In this context, it might be of interest to get some idea on what animal species actually are being used to investigate human mental disorders. Once again, we have used PubMed to search for all articles in PubMed which use again [animal model], but this time with [anxiety]. This search delivers 2,340 hits for publications between 2009 and 2013; repeating the same search with reference to individual species gives the following numbers of publications:

[mice or mouse]: 998 (355 on [C57BL])
[rat]: 970 (369 on [Wistar])
[primate]: 615
[fish]: 59
[dog]: 9
[rabbit]: 2

Although surely not fully representative, these findings are at least indicative of current patterns of research publication based on experiments using different animal species: first, we may note that about 25 % of publications within this specific area of research refer explicitly to primates. This high proportion undoubtedly overpresents the number of experiments actually done in primates, since the proportional

representation in publications reported here does not reflect the distribution of species reported as being used in research (reported for example by the EU in 2010 as: mice 59.3 %; rats 17.6 %; other rodents including guinea pigs and rabbits 5.2 %; ungulates 1.4 %; cats, dogs and other carnivores 0.3 %; and non-human primates 0.08 %; birds, reptiles, amphibians, and fish taken together 15.9 %; see Hagen et al. 2012). Secondly, and perhaps not surprisingly, experiments on mice and rats dominate the report on actual animal use (rats and mice combined, around 70 %) and, in this case are represented to about the same extent of (again combined) roughly 60 % of published articles.

What is interesting though is that more than a third of publications on mice refer specifically to the inbred strain C57BL, and that about the same proportion of rat studies seem to involve the Wistar strain. Further, when we look at methodologies employed in experiments, our literature screening on [animal model] with [anxiety] and now specifying [elevated plus maze, or open field, or dark light box] results in 769 hits (again about one-third of the total of 2,340 hits). Overall, there seems to be at least some indication that animal experiments in anxiety research, as merely one example, is being based to a significant extent on only a small number of test systems and primarily on experiments on one distinct mouse or rat strain, respectively.

Such considerations may be of special relevance when considering future developments in experimental Behavioral Neuroscience research. It is predicted that mood disorders in humans, as for example clinical depression, will become one of the leading causes of disability worldwide (Murray and Lopes 1997; Rodríguez et al. 2012). Such a prediction increases the drive to understand better the development and underlying mechanisms of such disorders in order to develop better prevention and treatment; this, in turn, may increase the requirement or motivation to undertake more research, in all probability based in the same way on the use of animal models. This potential development focuses further a debate on the appropriateness and validity of models currently used.

While we would not want to overstate the implications from this limited survey —a more rigorous analysis would clearly demand a much more extensive literature research—we may at least wonder whether indeed the combination of these test systems and strains is genuinely believed to deliver the best possible results in anxiety research or is simply based on tradition, conservatism and lack of exploration of alternative models—or acceptability to journals and their equally conservative referees. To us it seems important at least to raise the question as to whether animal-based research may be self-perpetuating as the result of unimaginative and conventional thinking regarding the choice of animal models and test systems used, and whether such conventional choices are truly the best possible choices in the search for innovative research findings. Gold standards surely have their use, but we should not forget that such standards are established within the frames of knowledge at their time of establishment. Scientific knowledge however develops rapidly—or so we hope—and it may be reasonable to wonder about the half-life of any gold standard, before it turns into fool's gold.

In a recent review article on the predictive value of animals models McGonigle and Ruggeri (2014) state: "For major mood disorders, such as depression and anxiety, inadequacies in the animal models have helped undermine the confidence of major pharmaceutical companies to the point that several, if not the majority have either withdrawn from this therapeutic area or significantly reduced their internal research activities." Indeed it seems of crucial importance not only to try and optimize procedures of animal-based research as such, but carefully to evaluate how appropriate is the model chosen and, in this way not only optimizing the translational value of studies in animal models, but also allowing for actual, retrospective assessment of such translational value. McGonigle and Ruggeri conclude from their review that "Comparison of models within a given therapeutic area, approaches to models and cross fertilization between therapeutic areas will do much to improve translational research. By thinking outside the box that each therapeutic area has created, improvements will be made to existing models to make these more predictive. These advances will inform both the development of new models and biomarkers that will enhance the translational relevance as well as the predictive utility of pre-clinical animal models of human disease, irrespective of therapeutic area."

4 Thinking Out-of-the-Box

Research claims to be innovative, with the exception of experiments that are being done to confirm previous findings. But innovative research, by very definition, demands out-of-the-boxthinking. At the same time standardization of animal models and test procedures for the sake of comparability across experiments inhibits the potential and willingness to leave well established tracks of thinking. Indeed, as Rob Hutter states: "…today's neuroscience research can be described as 'what happens' research versus 'how to make happen' research. One could argue that the former precedes the latter, but there are perspective issues that drive the type of questions researchers are likely to ask as well as the scope of tasks and behaviors that can be included in rigorous experimental conditions."[2] We may thus wonder how open minded research is and whether it is the researcher's established perspective that drives the research rather than the research that drives the researcher's perspective.

In search of the best possible research results in animal-based Behavioral Neuroscience and, thus, in trying to optimize the benefit of animal experiments, while at the same time minimizing the costs, any innovative perspective will be closely linked to the choice of the animal model used. Is it, for example, necessary for an animal to being able to perceive pain in order to resemble a valid animal

[2] DO.Anything; The Science of Intentional Change, posted by Rob Hutter, January 2013; http://robhutter.com/neuroscience/the-neuroscience-of-behavioral-insight/.

model for pain research? Bernard Rollin (this volume) suggests that "the modification of *telos* by way of combining genetic engineering with behavioral neuroscience as a remedy for practices that cause pain or suffering by violation of *telos* represents a whole new approach to intractable problems of animal welfare that emerge from contemporary animal use" and is supported in this by Adam Shriver (this volume) who argues "that we already have, or are extremely close to having, the capacity to dramatically reduce the amount of suffering caused in biomedical research via genetic modification of the animals used in research." The appropriate selection, or perhaps even creation of animal models thus deserves special attention in relation to options for reducing the potential for animal suffering, in relation to the improvement of animal welfare and the considerations of animal integrity (cf. Van der Staay et al. 2009). Such evaluation processes may, however, also profit from some out-of-the-box thinking and the subsequent chapters in this book are intended to stimulate such out-of-the-box thinking in animal-based Behavioral Neuroscience.

Bernice Bovenkerk and Frederike Kaldewaij make a start by reflecting on the tension between the need for translatability in animal models and the moral status of animals. They invite us critically to think about some justifications for the claim that human beings and more complex animals have superior moral status and argue that contemporary approaches which attribute equal moral status to all beings that are capable of conscious strivings (e.g., avoiding pain and anxiety; aiming to eat and play) are based on more plausible assumptions. They further suggest that, while there might be good reasons to assume that more complex beings would be harmed more by a specific physical or environmental intervention, it may also be possible that higher cognitive capacities result in less harm, because of a better ability to cope.

The ultimate use and validity of animal models would require to prove that indeed their use achieves its objective, that is that the results of a given animal study is a benefit that could not be gained otherwise. Ana Catarina Vieira de Castro and Anna Olsson in their chapter explore how cost-benefit analyses currently are being approached, and they conclude that specific 'costs' of animal experimentations in terms of harms inflicted on the animals, are far easier to assess that their benefits—a problem that actually may not be specific for Behavioral Neuroscience. Still, as outlined above, Behavioral Neuroscience often may affect the emotional and/or cognitive state in animals used, and such harm is difficult to counteract. Olsson and Vieira de Castro however come to the conclusion that effective cost-benefit analysis suffers from a lack of realistic ability to assess the true benefits and provocatively suggest that perhaps the benefit assessment should be discarded from any procedural ethical consideration, which, instead, should focus exclusively on the three Rs and improving animal welfare.

Paula Droege and Victoria Braithwaite continue with "a cross-disciplinary debate about the sort of framework that will best organize the growing body of data on behavior, development and anatomy of fish and other non-human animals in order to assess the capacity for consciousness." Fundamentally, considerations on how to assess consciousness in the first place remind us that a taxonomic classification of 'higher' and 'lower' species may be a poor guideline for the assessment

of a species capacity to suffer. Instead, as Droege and Braithwaite state, only "once we have a means of determining what sorts of animals feel conscious pain, we can more effectively think about ways to minimize or eliminate their suffering."

Bernard Rollin then reflects on the question why we would consider it ethically problematic or even unacceptable to eliminate an animals' capacity to suffer by means of genetic manipulation, if we do find it acceptable to cause such suffering in the first place? "In biomedical research, we do indeed inflict major pain, suffering and disease on animals. And genetic engineering seems to augment our ability to create animals to model diseases, particularly the more than 3,000 known human genetic diseases. […] Perhaps one can use the very genetic engineering which creates this dilemma to ablate consciousness in such animal models, thereby escaping a moral impasse." Underlying Rollin's considerations is the understanding that it is the individual one can wrong, not the *telos*.

In the concluding chapter, Adam Shriver explores how genetic manipulation of animals in order to reduce the animal's capacity to suffer would translate into experimental practice. What would be the benefit wnd what the costs of such manipulation? And would the elemination of the animal's capacity to suffer not be the most logical way to solve ethical dilemmas in experimental animal research?

As Bovenkerk and Kaldewaij state in their conclusions: "We have not attempted to give definitive answers here, but rather to raise some moral issues and to point out normative assumptions made in animal experimentation in general, and neurobehavioral research in particular." Indeed, ethical issues, as opposed to neurobehavioral questions, cannot be answered by way of statistical significance, but demand an ongoing and constructive discussion, to which we hope to contribute with this book.

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The Use of Animal Models in Behavioural Neuroscience Research

Bernice Bovenkerk and Frederike Kaldewaij

Abstract Animal models are used in experiments in the behavioural neurosciences that aim to contribute to the prevention and treatment of cognitive and affective disorders in human beings, such as anxiety and depression. Ironically, those animals that are likely to be the best models for psychopathology are also likely to be considered the ones that are most morally problematic to use, if it seems probable that (and if indeed they are initially selected as models because) they have experiences that are similar to human experiences that we have strong reasons to avoid causing, and indeed aim to alleviate (such as pain, anxiety or sadness). In this paper, against the background of contemporary discussions in animal ethics and the philosophy of animal minds, we discuss the views that it is morally permissible to use animals in these kinds of experiments, and that it is better to use less cognitively complex animals (such as zebrafish) than more complex animals (such as dogs). First, we criticise some justifications for the claim that human beings and more complex animals have higher moral status. We argue that contemporary approaches that attribute equal moral status to all beings that are capable of conscious strivings (e.g. avoiding pain and anxiety; aiming to eat and play) are based on more plausible assumptions. Second, we argue that it is problematic to assume that less cognitively complex animals have a lesser sensory and emotional experience than more complex beings across the board. In specific cases, there might be good reasons to assume that more complex beings would be harmed more by a specific physical or environmental intervention, but it might also be that they sometimes are harmed less because of a better ability to cope. Determining whether a specific experiment is justified is therefore a complex issue. Our aim in this chapter is to stimulate further reflection on these common

B. Bovenkerk (✉)
Philosophy Group (CPT), Wageningen University, Wageningen, The Netherlands
e-mail: bernice.bovenkerk@wur.nl

F. Kaldewaij
Research Institute for Philosophy and Religious Studies, Utrecht University, Utrecht
The Netherlands
e-mail: F.E.Kaldewaij@uu.nl

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assumptions behind the use of animal models for psychopathologies. In order to be able to draw more definite conclusions, more research will have to be done on the influence of cognitive complexity on the experience of (human and non-human) animals.

Keywords Animal models · Neurobehavioural research · Moral philosophy · Philosophy of animal minds

Contents

1 Introduction

Much research in behavioural neurosciences is aimed at the prevention and cure of cognitive and affective disorders in human beings. These disorders, such as anxiety, depression, and alcohol addiction, have a severe impact on individuals' quality of life. While virtually anyone would applaud the aim of neurobehavioural science to relieve human suffering, the moral acceptability of the use of non-human animals in reaching this aim is a matter of controversy. It is significant that animal models are used precisely because we consider the use of human beings in such experiments morally impermissible. If the use of animal models is morally justified, there must be a relevant difference between human beings and the animals used in these experiments that justifies the differential treatment. Yet, if these animals are indeed good models for certain psychopathologies, it might be considered likely that they have experiences that are similar to human experiences that

we consider to have strong reasons to prevent or cure (such as anxiety or sadness). What, then, justifies the use of animal models? Also, in the practice of animal experimentation we see that it is considered preferable to use animals that are less like or further removed from human beings, e.g. rats rather than apes, and zebrafish rather than rats.[1] Is such a preference morally justified?

To determine whether the use of specific animal models is morally justified, we need, first, to determine the basis of moral status. This is an issue that is widely discussed in moral philosophy. The concept of moral status will be explained in more detail below, but roughly, it involves whether and how much a being should count in our moral considerations. We shall see that moral status is often linked to the possession of specific kinds of capacities, e.g. sentience (being able to have negative and positive physical and psychological experiences) or rationality.

Besides determining the sensory or cognitive capacities required for moral status, we need to investigate whether specific species of animals (rats, zebrafish etc.) have these capacities. This will also help us determine whether their interests differ from ours and vary between different kinds of non-human animals. If non-human animals suffer much less from the experiments performed on them than human beings suffer from the pathologies we aim to cure, this might be considered a reason to regard the use of these animal models justified. To find an answer to the question what capacities specific species of animals have, and what they can be thought to experience, we require empirical evidence on different species of animals, e.g., data on their behaviour and neurophysiological responses in certain situations. However, there is an interpretational gap between data and meaning: between test results and what they actually tell us about what certain animals can do and experience. This is why this is also an issue in what is called "philosophy of mind". Philosophy of mind studies the nature of the mind and consciousness, and its relation with the brain.

We do not intend to give an exhaustive discussion of all positions in animal ethics (or moral philosophy, more generally) and the philosophy of animal minds. These are very rich and complex fields, and we cannot fully do them justice in this chapter. We have more modest aims. First, to bring to the fore some of the more important questions that need to be considered to determine whether using animals in neurobehavioural research is morally acceptable and whether it is more justified to use certain animals than others. Second, we want to show that common assumptions about the moral status or capacities of animals that may lie in the background of the use of animal models in the behavioural neurosciences are not uncontroversial, and indeed, that there is good reason to question them.

We will argue that common defences of the view that human beings have a higher moral status than animals (or even that non-human animals lack moral status altogether) involve implausible assumptions or implications. We will present two very divergent positions in contemporary moral philosophy that nevertheless both defend attributing equal moral status to all beings that consciously strive to attain

[1] See Hagen et al. (2012) and Stafleu (1994).

goals, and point out the comparative merits of these views. Furthermore, we shall also question views that less cognitively complex animals have a somehow lesser sensory and emotional experience than more complex beings across the board (or even lack consciousness altogether). We shall argue that while there are good reasons to assume that there are differences in the way that different kinds of animals are affected by negative sensory or emotional states like pain, anxiety and depression, this does not necessarily mean that less complex animals are not seriously harmed by these states.

From the outset, it is important to note that it is extremely difficult to generalise about the cognitive and sensory capacities of animals; thus, different taxa may have widely different capacities for suffering, or for coping with any suffering which may be experienced: mammals may have totally different experiences in a given situation than fish or insects. While animal ethicists tend to talk rather loosely of animals in general, especially for the purposes of this chapter, it makes a lot of difference what type of animal we are discussing. Where appropriate, we will try to specify what group of animals we are discussing, although there remains the problem in many cases that at present, we do not have perfect knowledge about the emotional and cognitive abilities of those different animal taxa, nor do we have enough knowledge on the influence of cognitive complexity on different kinds of emotional suffering.

In our considerations below, we presuppose that all neurobehavioural experiments involve some kinds of physical and environmental interferences with animals, which are aimed at making them models of specific human psychopathologies. The question is whether specific examples of such interferences are morally problematic.

2 Moral Status

2.1 Introduction

To determine whether it is morally acceptable to use specific kinds of non-human animals in experiments in the neurobehavioural sciences, the first question that we need to answer is whether these animals have moral status. If animals have moral status, this means that we should take them into account in our moral decision-making. There are, however, different ways in which things can figure in our moral decision-making: directly or indirectly. Some people have thought that we only have *indirect* duties regarding animals. One example of such a view is that we should not treat animals cruelly only because this is likely to harden us to suffering and therefore to make it more likely that we will violate our duties to other *human* beings (e.g. Kant 2000, p. 6, 442). Also, it might be thought problematic to harm an animal, because in doing so, we harm the owner of that animal. However, the concept of moral status is generally used to signify that a being counts in its own right. If animals have moral status, we that should treat them in a certain way

(e.g. not treat them cruelly) *for their own sake*, rather than for the sake of others, say, human beings. We then do not merely have duties *regarding* animals, but also *to* them.

To determine whether animals have moral status, we need to know what is a necessary and sufficient basis for moral status to be accorded to them. We shall first critically discuss some justifications of attributing *unequal* status to human beings and the other animals, and to animals with different degrees of cognitive complexity. These are based on some general assumptions about the nature and basis of morality that we will argue involve implausible assumptions or implications. Then we shall discuss two different approaches in moral philosophy, that both advocate attributing equal status to all conscious animals. As these two authors also conclude, we will argue that it makes sense to consider moral questions from the perspective of all beings that have an evaluative perspective.

2.2 Unequal Moral Status

One view of the basis of morality is the idea that it is in our mutual self-interest to accept moral constraints in our dealings with one another. It might be thought that animals do not have moral status, as we cannot make a mutually advantageous agreement with them, and expect them to uphold their side of the bargain by reciprocating (e.g. Morris 2011). However, we think that the incapacity of animals to reciprocate does not give us a sufficient basis for denying them moral status. Undoubtedly, a lot of rules in social life and much of the practice of politics centre around the idea of reciprocity, but this does not seem to cover the whole content of even human morality. After all, we take it to be wrong to exploit people who are too weak (or too far removed from us) to reciprocate or take their revenge on us. If we think morality goes beyond the confines of mutual interest through reciprocation, we need to find another basis for such duties.

Another proposal for the basis of (human) morality is social sentiment. Most humans are not only motivated to pursue their self-interest, but are at least to some degree sympathetic to others. The famous 18th century philosopher Hume based morality on sympathy. However, he noted that we have limited sympathies, and that our sympathy is greatest for those closest to us and similar to us (Hume 1978; Cohon 2010). While our sympathies are not limited to human beings,[2] it has been noted that we are generally more emotionally attached to members of our own species (Midgley 1998). Wenz (1988), suggesting a "concentric circles" model of justice: we have the strongest duties to those we are in a closest relationship with, and our duties to others become less strict with distance. We do not want to deny here that human social sentiments and capacity for sympathy may play a very large

[2] Indeed, virtue ethical accounts in animal ethics aim to base duties to animals in our sympathy for them (eg. Walker 2007).

role in morality. We do want to question the view that our basic moral duties vary with how close we feel to the other, or what relationships we have with others, especially duties not to harm others. Hume himself noted that our moral judgments on the characters of those who harm or help others do not vary along with our sympathies for those affected. He proposed that we estimate the effects of people's character from a "common point of view", which abstracts from our own self-interest but rather involves the viewpoints of everyone affected by the action (Hume 1978, T 3.3.1).[3] It might be argued that we have stronger positive duties (duties to assist) those whom we have relationships with, but it seems implausible to hold that negative duties (duties not to interfere) depend on the strength of (affective) bonds. Such a view could justify harmful treatment of those with whom one is or feels less connected, like those with a different ethnic background or those on the other side of the world.

A final way to argue for unequal moral status would be to resort to 'everyday moral judgment' which says that rational beings, such as humans, matter more than merely sentient beings, such as many animals. Balzer et al. (2000), for example, say that it fits better with our considered intuitions to assign a hierarchy of inherent moral standing to different kinds of beings. Similarly, DeGrazia (2008) argues that moral status varies with the capacities of beings, e.g. being conscious, self-aware, moral agency, language, and so on. This does appear to be the common view. However, is this view justified? We need to ask *why* exactly it matters whether a being is capable of language or is a moral agent for how we ought to treat them. Sure, it would be problematic to defend a moral theory that has no connection at all to our views about the content of morality. However, we think that a view being commensensical alone does not suffice to justify moral claims. After all, we now consider views that were once common, such as the view that slavery is morally right, as completely morally unjustified. We think we need to dig a little deeper to determine whether our everyday moral judgments are indeed justifiable.

It is important here to consider what a hierarchy of moral status actually means. It means that different creatures would all have moral standing, but would have so to a varying degree. In other words, if we need to decide how to treat two different creatures, the creature with higher moral status would automatically receive preferential treatment, regardless of the specific interest of the creatures involved in that specific dilemma. So, for example, if we must choose to hurt either a rat or a human being, even if their pain would be equally severe, we should choose to spare the human being, because her/his interests matter more *in principle*. However, this begs the question as to why this human being's interests matter more. It cannot be because she/he experiences more pain, because in this example the pain was equally severe for the rat and the human. Could it then be because the human can use

[3] Hume appears to be describing human nature; explaining what human beings do when they make moral judgments. One can question whether and why we *should* take such a common point of view. We describe a utilitarian and a Kantian argument for a similar idea in the next section.

language or is a moral agent? This raises the question why these differences would be relevant in this context. Again, more than a simple reference to common sense is necessary to explain such a position.

2.3 Equal Moral Status

So far, we have argued that three of the most common arguments for attributing unequal moral status to humans and animals are problematic. What bases could there be for attributing *equal* moral status? In this section, we will discuss the views of the prominent practical philosophers from two very different moral-philosophical backgrounds. Peter Singer is a proponent of the theory of utilitarianism, and a prominent animal ethicist. Christine Korsgaard is a Kantian philosopher, and has in recent years discussed the place of animals in her wider philosophical work. While there are important differences between them, the two authors both think that we have moral duties to others that are not dependent on reciprocity or sympathy for others and both are critical of everyday moral judgments. We will now explain how they justify moral claims.

Singer (1999) takes a basic starting point for the moral point of view to be that one should consider what ought to be done not just from the standpoint of self-interest, but from the interests of all involved. The basis of morality, in Singer's view, is the principle of equal consideration of interests: all comparable interests should be weighed equally. If interests differ, however, then this should be taken into account. For example, all people have an equal interest in mobility, but for disabled people this means getting access to facilities like a wheelchair, while for able-bodied people it doesn't. Equal consideration of interests, then, may lead to dissimilar treatment. Singer suggests that not only human beings, but also certain species of animals may have interests. Singer understands interests in terms of the satisfaction or frustration of preferences. The question then is what animals can have preferences. In Singer's view, a minimal requirement to be able to say that a being can form preferences is that the animal can have positive or negative experiences. Singer appears to regard all negative affective states as forms of suffering which they have a preference to avoid and all positive affective states as forms of joy which they have a preference to strive for. [4] If an animal can suffer negative experiences such as pain, or fear, it will have a positive motivation, a preference, to not suffer. Such animals may

[4] Note that it is our aim here to introduce the philosophical reasoning of Singer, and not to add new insights to the debate about what constitutes animal welfare. More in general, suffering could be described as 'strong, negative affective states such as severe hunger, pain, or fear' (Fraser and Duncan 1998) and can result from 'experiencing a wide range of unpleasant emotional states such as fear, boredom, pain, and hunger' (Dawkins 1990). A discussion is possible about the question whether all negative affective states in fact amount to suffering as such. After all, animals can often adapt their behaviour to short-term negative states, such as hunger or fear, in a way that is rather functional for them. Real suffering may result only from intense or prolonged exposure to negative stimuli combined with a negative stance towards such experiences.

also have preferences for positive states, unconnected simply to the avoidance of suffering, e.g. play or food or being with conspecifics.

Singer is a utilitarian, and that means that he thinks that in determining the right thing to do, we ought to compare, aggregate and maximise the interests of everyone involved. Thus, for example, in choosing whether to help someone with her homework, or bring someone with a serious injury to the hospital, we ought to do the latter, because that is here the more important interest. Singer noticed that in practice, even when human and animal interests are considered comparable, for example when humans and animals are thought to experience the same amount of pain after a specific procedure, the human interest is generally considered more important than the animal interest. He posed critical questions about this, and popularized the term "species-ism", meant to signify discrimination on the basis of biological species, which he considers as unjustified as sexism and racism. Only when different species in fact have different interests, it is justified to treat them differently. For example, dogs cannot benefit from human education, so it would not be speciesist to deny them access to schools. He also attacked the idea that it is specific capacities of human beings that make them especially morally significant, such as rationality or their being moral agents. After all, we also think that human babies' pain matters equally to adult beings' pain, even if they are less rational than adult humans, and we accept that just as we may not harm rational humans, nor should we harm intellectually disabled humans.

As a utilitarian, Singer thinks that we should always maximise the satisfaction of the interests of everyone involved. Traditionally, this approach to morality is most contrasted with the moral views inspired by the 18th century philosopher Immanuel Kant. Kant (1785, and more recently reprinted 1998) thinks that we should not act morally for the sake of an external goal, such as self-interest or even the interests of others, but simply from respect for moral law. He sees the moral law not as legislated by an external authority, such as God, but as a law of our own reason. In acting on the moral law, human beings are autonomous (literally: self-legislating). Kant claims that the capacity of autonomy makes human beings "ends in themselves": we ought to respect them for their own sake, not only use them as means to another end (e.g. our self-interest). Kant thinks we do not have any direct moral duties to animals, as they lack the capacity of autonomy. He does think we ought not be cruel to animals, but that is because it undermines a duty to ourselves: to cultivate those capacities (e.g. sympathy) that enable us to do our moral duty (Kant 2000, p. 6, 442).

Christine Korsgaard, a prominent contemporary Kantian author, has offered an internal criticism of Kant's position.[5] Korsgaard (2011) argues that Kant was wrong in thinking we only have duties to autonomous beings. Like Kant, she takes

[5] An external criticism of this view has been given on the basis of the previously mentioned analogy with humans without rational capacities: if we do not have direct duties to animals because they are not rational, what about human beings with similar lack of rational capacity, such as babies or severely mentally challenged people? Should we only not treat them cruelly because of the implications for other beings? Such an argument (e.g. Singer 1999; also Regan 2004) points to an inconsistency in the way that we treat different kinds of beings with similar capacities.

morality to be based on a law that human beings legislate to themselves. As humans, we cannot simply go along with our impulses, but we need to have reasons for what we do. Insofar as we consider our choices rational, we must think that the objects of our choices are objectively good. Korsgaard emphasises, however, that the *content* of our reasons cannot be given by respect for autonomy itself. Rather, we find reasons in what is naturally good for us (Korsgaard 2011, p. 108). While things can be said to be good or bad for plants, only conscious animals care about their own natural good (Korsgaard 2009a, pp. 34–35).[6] Animals can act purposively, to avoid things that they dislike, and to attain things they want (Korsgaard 2009b, pp. 10–15). When we avoid pain and suffering, we act for a purpose we share with other conscious animals. But even if we value ends that other animals do not share, we still value what is good or bad for the kind of beings that we are. When we, rational beings, act for the sake of an aspect of our own good, we take something's being naturally good for us as objectively good: as a law for ourselves and others (Korsgaard 2011, pp. 107–108).

Korsgaard says that we thereby accord ourselves a certain standing: of an end in itself. Kant thought that we only have to respect ourselves as ends in ourselves insofar as we are rational, or autonomous. Korsgaard explains that Kant conflates two different conceptions of the end in itself: (1) the source of legitimate moral claims that should be recognised by all rational agents, and (2) someone who can give the force of law to his claims, or participate in moral legislation. She notes that a law can protect someone who did not participate in the making of it (2005, p. 21). In legislating a law that what is naturally good or bad for us is objectively good or bad, we confer value on our animal selves. We therefore have to accept duties to all those who have a good that they care about, even if they cannot claim respect for it. Korsgaard argues that on the basis of this reasoning, conscious animals too should be regarded as "ends in themselves" (2011, pp. 108–109). We should respect their good for the sake of the individual animals involved, and not just treat them as means for our own ends.[7]

Utilitarianism and Kantianism are usually understood as very different approaches, and some important differences will come to the fore when we apply these theories to the practise of using animal models in neurobehavioural research (in Sect. 4). Here, we want to point out what these specific variants of these

[6] Note that Korgaard is making a philosophical argument here to the effect that those animals who actually experience pain and pleasure and have positive or negative emotions care about their own good in a way that insensate beings cannot. Of course, her argument does not hold for the group of animals who do not have these experiences. To what group of animals such emotions are restricted is a question that should be answered by use of biological research together with reflection about the philosophy of animal minds.

[7] Other animal ethicists, such as Taylor (2011) or Rollin Smulewicz-Zucker (2012) have also emphasised that animals have moral status because they have a good of their own. Korsgaard's theory differs to Taylor's in the sense that in her view, animals should care about their own good in order to have moral status. She differs from Rollin in the structure of her moral theory. Korsgaard tries to show that, as rational agents, we cannot rationally avoid accepting moral duties to all conscious animals.