CAPTIVATING BEHAVIOUR: MOUSE MODELS, EXPERIMENTAL GENETICS AND REDUCTIONIST RETURNS IN THE NEUROSCIENCES

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Introduction

In December 2007, the behaviour of a genetically altered mouse, apparently expressing no fear of cats, was demonstrated in the media. The fearless mouse, generated at the laboratories of Professor Kobayakawa at the University of Tokyo, was created through a genetic mutation which shut down receptors in the mouse olfactory bulb – the part of the brain that processes information about smell – so the animal no longer reacted to the scent of its natural predator. The press appeal of the story was amplified by the release of a short video, posted widely on the internet[1]. The video, shot in a nondescript room, shows a black mouse nonchalantly approaching a tabby cat, walking underneath the larger animal and nuzzling it; it is apparently undaunted as it moves rapidly and repeatedly between the cat's front paws. The mouse's creator describes the experiment, and its meaning for him, in the accompanying *Guardian* article: '"The mice approached the cat, even snuggled up to it and played with it", Kobayakawa said. "The discovery that fear is genetically determined and not learned after birth is very interesting, and goes against what was previously thought"' (McCurry 2007). We are told his conclusions from this

[1]See for example, http://www.guardian.co.uk/science/video/2007/dec/12/mouse, accessed 21/04/2009.

experiment: confirming suspicions about the relationship between scent and fear, and suggesting the natural tendency for mice to fear cats is genetically determined. Kobayakawa's hopes for the application of this research in neuroscience are reported in *The Telegraph*: 'We think it has the power to clarify many unrevealed principles of the brain, those which generate emotions and behaviours in mammals' (Highfield 2007); mammals, of course, including humans.

This is just one example of the well-rehearsed scientific press release in which a genetically altered mouse demonstrates the potential genetic components of a relevant human behaviour. Since the 1920s, the mouse has played a critical role in understanding animal and human genetics (Rader 2004; de Chadarevian 2006). This prominence has grown with the development of transgenic mice from the 1980s, the on-going focus on genetics in understanding human disease, the mapping of mouse and human genomes and the expansion of national and regional centres for archiving and distributing genetically altered mice (Grimm 2006, Shostak 2007). Since the late 1990s, the growing availability of genetically altered strains, developed to exhibit certain behaviours, means the genetically altered mouse is taking over from the more assertive and archetypal 'lab rat' in the search for better models of human behaviours.

Many of these developments are similarly reported in the media. Recent news stories reveal mice who are abnormally aggressive, which might be used to understand criminality; mice portraying symptoms of schizophrenia, to understand and treat this mental illness; mice prone to overeating, to treat obesity, and mice who fidget, to understand weight maintenance; there are mice who are depressed and mice who are anxious, which may help understand this spectrum of the human condition; and there are

forgetful mice, which may yield insights into Alzheimer's disease. Some animals have gained popular names as well as media coverage: the so-called 'mighty mouse' or supermouse, who was bred to aid understanding of the PEPCK-C enzyme, but whose ability to run many miles without tiring, eat substantial amounts without weight gain, and have more sex and at older ages was greeted with admiration and some envy by media commentators. The announcement of such animals suggests the ability of scientists to understand and manipulate natural behaviour is being radically transformed. Yet these media reports of scientific experimentation are yet to be followed by news of clinical application. In fact, they often lack substantive detail. The complex interactions between animal strain, physical environment, genetic modification, experimental design, drug intervention and laboratory handling that influence behaviour are not introduced.

These complexities can be illustrated by going back to the video of the fearless mouse. The relationship between genetics and behaviour is open to alternative interpretations if attention shifts from the laboratory mouse to the bemused, but submissive cat, which patiently shifts position as the mouse moves around its body. The cat is not genetically altered. Rather the article suggests the video features Mochikko-chan, a domestic pet, belonging to one of the research team. The cat was chosen as especially docile and unlikely to end this uncharacteristic encounter between species. With this additional information, the meaning of the video becomes more ambiguous. The mouse has no need to fear this unusually compliant cat: perhaps this cat's behaviour is the less natural. The causality of animal behaviour is opened up from this focus on genetics. The genetic modification of the mouse is foregrounded, but the reason the cat is so quiescent is not explained in the video. We accept pets can be handled, neutered, well-fed and otherwise habituated so they do not readily express what might be seen as natural hunting instincts.

Yet corresponding questions about whether laboratory mice may be similarly accustomed through breeding, husbandry and conditioning to express particular behaviours, and indeed what is natural behaviour for a laboratory animal, are not addressed.

These questions begin to take on an importance, which exceeds analysis of this short video, when they are put into wider context. Behavioural neuroscience is one of the fastest growing and potentially lucrative areas of biomedical research. There are many who have the potential to gain from innovative treatments for anxiety, depression and other affective disorders, which are some of the most widespread health problems in the West. Yet, as researchers themselves suggest 'psychiatry has proven to be among the least penetrable clinical disciplines for the development of satisfactory *in vivo* model systems for evaluating novel treatment approaches' (Cryan & Holmes 2005: 775). Nevertheless, the development of genetically altered animal models of affective disorders remains a focus for much of this research. The market for such drugs is expanding rapidly as the West ages and the mental health needs in the rest of the world become more like that of the West. The potential rewards are also high as treatment for these conditions is on-going, rather than one-off. Thus, these media reports not only reflect scientific research, but also contemporary social concerns and promissory pharmaceutical futures. The presentation and circulation of these genetically altered animals become part of what Dumit (2004) calls the production of 'surplus health'; the turning of everyone into patients or consumers-in-waiting, who can be put on drugs for life (cited in Sunder Rajan 2006; see also Lakoff 2005). It is not only the nature of animal behaviour being transformed, but also our understandings of human nature and our definitions of what is normal and what is treatable.

This chapter looks at the relationship between human and animal behaviour, as they are enmeshed in and emerge from the contemporary behavioural neurosciences. This is an area of both scientific investigation and philosophical speculation. It raises questions about the nature of behaviour, which I introduce in the next section, exploring how media framing of these scientific discourses tends to reinscribe older dualities between nature and nurture. It also raises questions about how to challenge these dualities, which I explore theoretically, through work drawing on early ethology as a prelude to more relational accounts of animals and their environment, and empirically, through tracing the complex interplay of animal and human agencies within the experimental spaces of the behavioural neurosciences. Through reference to the work of Uexküll and others, social scientists have sought new ways of addressing questions around animal and human behaviour. This provocation has been of considerable interest in anthropology (Ingold 2000), geography (Thrift 2005) and cultural studies (Broglio 2008), leading to suggestions of an ethological turn in social theory (Lorimer 2008). This is not a singular theoretical encounter and it is sometimes a contradictory impulse, at times both challenging humanism and confirming anthropocentrism. Yet the work of Uexküll, as taken up by Heidegger and Agamben, has become a key engagement for the thinking about the animal question (Elden 2006). Here I take Agamben's 2004 work *The Open* – an ontological genealogy of the articulations and divisions between humans and animals – as provocation of where to look in tracing the transaction of capacities between animals and humans in behavioural genetics. The empirical account which follows traces divergent meanings of mouse behaviour as they emerge from the practices of scientists studying in different spaces, laboratories and paradigms, reflecting on the points of connection and disruption between them. In so doing, it introduces the role of these genetically altered animals in stabilizing relations around particular trajectories of drug development, whilst also offering points at which it

might be possible to think, or behave, otherwise. Concluding, I return to the philosophical analysis offered by Agamben, finding his attention to the ontologies and topologies of the biosciences productive, but seeing little that adds to our understanding of animal, as opposed to human, nature. Instead, preliminary observations from the boundaries of ethology and anthropology suggest how we might add forms of life and understandings of nature to the experimental practices of the behavioural neurosciences.

Nature, behaviour and captivation

I start with reflections on the concept of nature in the context of behavioural genetics and the neurosciences. Nature retains a powerful place within political debates about biotechnology (Davies 2006, Hansen 2006), with concepts of nature conversely used to encapsulate what is morally troubling about new developments or designate what is merely an extension of existing practices in the genetic modification of plants, animals and humans. Nature is mobilized in the contexts of health, as both fact and value, in the classification of natural and abnormal states (Canguilhem, 1991). Further, behavioural genetics returns us to freighted and enduring arguments about the contributions of nature and nurture to the development of particular patterns of behaviour. The continued use of arguments about nature and nurture engender frustration from scientists. As Keller remarks, the debate is felt to be long resolved: ‘everything is a mixture of both, and it is all very complicated. Why then do we not save our energies for more legitimate, and more fruitful, areas of scientific inquiry?’ (Keller 2008: 118). It is this query I want to address first. For, as Keller suggests, ideas about nature as separate from nurture endure in the

models, metaphors, drugs and devices used in experimental practices and scientific claims, particularly in the study of behavioural genetics.

To elaborate, ideas about nature appears in at least three distinct ways in the above encounter between the cat and the genetically altered mouse; broadly mapping onto Raymond Williams' three-fold classification of ideas of nature as 1) the essence of something, 2) nature as universal – relating to the physical world in general – or 3) as that which is unaltered by human intervention (Williams 1983). First, there is the idea of nature as essence, character or kind. The meaning of the video depends on our understanding of the specific nature of different species, minimally of mouse as prey and cat as predator. This nature is given by the animal's *telos*, or alternatively its evolutionary history. It is based in biology, but it is also plural and differentiated, such that the nature of a mouse, the nature of a cat and the nature of a human are distinct.

Yet, for the altered mouse to become a meaningful analogue for human behaviour, a second sense of nature has to be enacted, a sense encapsulated in ideas about the laws of nature. It is the assumption of similarities between species, subject to universal laws of nature, which allow analogues to be drawn between species. These are the regularities of nature, which are seen to be everywhere and always the same (Daston 2002: 375; though see Waterton, this volume, on the precarious standardization of universal nature). Nature here is reduced to what can be shared between species and what can be held as universal, whether in clinical contexts or the behavioural genetics laboratory. The ability to transact between the two, and so use animal experimentation to reduce human suffering, is the utilitarian basis of animal experimentation in the first place. The legal status of

animal bodies within laboratory spaces are reworked around this clinical translation (Asdal 2008).

Finally, there is a third and perhaps more contested meaning of nature implied. The altered behaviour of the mouse in the video is not presented as a manifestation of its nurture; it is located in its biology, in its altered brain receptors, in its individual nature. It is innate to this animal, a manifestation of the specifically altered DNA coding for this animal's development. As Keller explains, this argument is 'specific not only to a species but to an individual, and however much it may depart from the norms of that species, it is nonetheless genetic' (Keller 2008: 122). Nature here appears as an uneasy synonym for the genetic make-up of the individual animal. Dichotomies of nature and nurture are mapped onto a duality between genes and environment, sidelining the importance of social, historical, environmental or other experiential elements to an animal's behaviour. A form of hierarchical thinking about nature in biology, which continues to position the DNA molecule as the fundamental agent, as the natural basis of behaviour, thus emerges as remarkably resilient. It may draw on obsolete notions of genes as agential, discrete and invariant, but these endure in this experimental demonstration and in the explanatory rhetoric of the press release. As Keller suggests, this nature/nurture debate owes its perpetuity in part to slips in the use of words like 'genetic' and 'environmental' by scientists themselves, 'even while acknowledging the importance of interactions between the two, it is widely assumed that the basic division provides an appropriate starting point' (Keller 2008: 122). Nowhere is this more evident than in media presentations of behavioural genetics as, above all, a continuing search for the genetic factors influencing affective capacities, in humans and animals, in experimental practice and everyday life.

This is, of course, not the only way of conceptualizing the nature of animal behaviour in relation to environment. Social scientists have recently returned to the history of biology, seeking more relational accounts of the sensing organism, located within their environment or *Umwelt*, drawing on the early ethologist Jakob Von Uexküll (1957), and the development of his ideas in the work of Heidegger, Deleuze and Agamben (Heidegger 2001, Deleuze and Guattari 1987, Agamben 2004). Motivations for this search include the desire to replace reductionist explanations of human and animal subjectivity, with accounts of interactions between organism and milieu, which stress the affective and material capacities of humans, animals and environments in relation (Lorimer 2007, Thrift 2005). Such relational accounts promise to challenge genetic determinism, decentre the grand claims of humanism and introduce attention to the varied perceptual worlds of animals. Yet in drawing on the interpretations of ethology favoured by Heidegger, some work has been criticized for retaining a particular conception of the animal as 'poor in the world', risking reintroduction of a further anthropocentrism, where the nature of animal life is defined in opposition to the human (Elden 2006, Acampora 2006). Despite cautions, these arguments are worth considering, for they offer an alternative vision of the relations between human and animal behaviour, used to diagnose the implications of the changing boundaries of animality and humanity in the context of genomics.

Agamben's account (2004) starts with now well-known arguments about the behaviour of a tick in relation to the specific elements of its environment. Working in the 1920s, Uexküll's proposes the animal's behaviour can be understood through intensities of affect – the smell of butyric acid in the sweat of a mammal, the heat of a mammal's body and the

textures of mammalian hair – all ultimately leading to nourishing blood vessels. The tick lives out a short life cycle that comprises, almost wholly, of an intimate relationship with these elements. The tick is open only to these environmental phenomena, 'captivated' (in Heidegger's terms) by events that trigger or disinhibit its specific behaviours. A relational ontology of the animal and its *Umwelt* emerges: the tick is this relationship; 'she lives only in it and for it' (Agamben 2004: 47). Heidegger develops this way of conceiving of animal being in the world (Heidegger 2001). The animal has a specific form of captivation towards elements of its environment, yet it is not conscious of this captivation. In Heidegger's formulation, the animal is caught in a relation of being openly drawn to elements in the world, yet simultaneously not exposed to the openness of being itself. As Agamben summarizes, 'the mode of being proper to the animal, which defines its relationship with the disinhibitor, is captivation. Insofar as it is essentially captivated and wholly absorbed in its own disinhibitor, the animal cannot truly act or comport itself in relation to it: it can only behave' (p52). The animal is captivated in its world. It behaves in the environment according to its instinctive imperatives: its nature. This nature does not reside singly in the animal or the environment, but in the relation between the two, so challenging genetic determinism, but also reintroducing a further division between the being of humans and animals.

For Heidegger, humans also share this propensity for captivation towards elements in the world. Yet human activity is distinct in its capacity to being open to being itself. We have, Heidegger suggests, moved away from captivation to be able to recognize and interrupt our relationship to captivation. As Agamben describes, 'the world has become open for man only through the interruption and nihilation of the living being's relationship with its disinhibitor' (Agamben 2004: 70). For Heidegger, boredom is central to human experience

and thus to his consideration of the open. ‘Dasein [the concept Heidegger uses to question what it means to be human] is simply an animal that has learned to become bored; it has awakened from its own captivation to its own captivation’ (Agamben 2004: 70). Agamben builds on Heidegger to suggest what is both discovered and subsequently excluded in this definition of the human is our own animality, our own captivation: ‘this awakening of the living being to its own being-captivated, this anxious and resolute opening to a not-open, is the human’ (Agamben 2004: 70). The human becomes human by simultaneously recognizing and excluding this animality.

Agamben’s account offers a structural connection between definitions of humanity and animality, but an asymmetry between human action and animal behaviour. However, he suggests contemporary developments in global genomics are changing this connection, seeking control over the animality of humanity. A contemporary preoccupation with understanding life and being from the perspective of the biological sciences has generated much comment from social theory (Habermas 2003, Agamben 2004). Much of this focuses on the challenge to human subjectivity raised by genetics and the neurosciences. For Agamben, humans, by seeking the control of life in this way and searching for the material basis of their own cognitive and emotional processes, are in the process of closing themselves to their own openness. This is couched in terms of humans making ‘being’ their specific disinhibitor. He suggests, the ‘bare life’ of animality has become the disinhibitor of human life and technology its medium, captivating humanity, whilst closing down reflections of the nature of this captivation, a process akin to animal captivation. In this context, Agamben suggests ‘the total humanization of the animal coincides with a total animalization of man’ (p77).

Agamben's work focuses on the production of ontologies of the human, and the spaces through which boundaries between human and the not-quite human are produced (see for example Agamben 1998). It is both a political project – tracing the ontological mechanisms responsible for producing definitions of the human, and a metaphysical one – developing a philosophical gaze that reinvests meaning into life. Yet, despite the centrality of animality to his accounts of humanity, it is largely disinterested in animals themselves. Despite his identification of an 'anthropological machine' through which humanity is created with and against animality, he has little to say about the specific technological processes in which human and animal natures are bought into being (for further discussion see Oliver 2007). Yet attention to changing patterns of captivation appears a productive analytic in the contexts of behavioural genetics, for here both patterns of animal captivation and human captivation with being are deliberately transformed. A more symmetrical account, attending not only to transformations of human nature, but also to specific animal capacities and technological interventions through which this encounter is achieved, add points from which to consider the relations between humans and animals, as well as between animals and their environment. This is the challenge as I turn to practices modelling human behaviours in the neurosciences.

Modelling human behaviour

> 'Dangle a mouse by its tail, and it will wriggle and strain to escape before eventually recognizing the hopelessness of its situation. Measure the time it takes

to abandon thoughts of helping itself, and you have one of the classic animal tests for depression' (Abbott 2007: 6).

There is an alternative measure; it is equally provisional. In the forced-swim-test, instead of taping the tail to immobilize the animal, the mouse is immersed in water, in a straight-sided glass jar, from which it cannot escape. The researcher measures the time taken for the behaviour to change from swimming, with the goal of escaping the water, to just treading water. If the mouse stops trying to escape earlier than other mice, it is interpreted as a sign of depression. The forced-swim-test (FST) was developed in the late 1970s by Roger Porsolt. It is also known as the Porsolt test or behavioural despair test (Cryan & Holmes 2005). Initially, it was assumed to model the acute trauma that might herald the onset of human depression. When the mouse gave up struggling in the water it was regarded as a sign of despair. The depressed mouse was seen to maintain behaviours that expressed forms of captivation towards safety and security, but this response is interrupted. Even if depression was not best understood as an interruption of captivation, this was how it was modelled in the laboratory mouse.

With the documentation of complex, overlapping and chronic symptoms in clinical depression this interpretation has changed (Craddock & Forty 2006; LaPorte et al 2008). Scientists now acknowledge these tests are limited analogues of human behaviour (Abbot 2007; Cryan & Holmes 2005). However, the forced-swim-test remains the most widely used test in researching the genetics and treatment of depression using laboratory animals[2]. From the 1970s, the test has acquired a powerful facticity in the

[2] For an ethnographic analysis of experimental systems in behavioural genetics see Nelson, forthcoming.

pharmacogenetic paradigm for depression research, though an intersection between diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV), the role of FDA legislation, known drug effects, established laboratory practices, and the growing use of genetically altered mice in neuropsychiatric research.

The key to the continuing validity of this model is the finding that the administration of clinically effective antidepressant treatments causes mice to engage in more active escape directed behaviours. This is particularly the case with the class of depressants known as selective serotonin reuptake inhibitors (or SSRIs). Increasing the level of serotonin available to bind to the postsynaptic receptors in mice increases the length of time these animals will struggle ineffectually to escape the water. As Abbot reflects, ‘classical animal tests for psychiatric disorders are based on responses to clinically proven drugs’ (Abbott 2007, p6). This interpretative shift is underlined by Chalouff (2007): ‘the tail suspension test or the forced swimming test are by no means animal models of depression but tests which respond to antidepressants. This difference, which may appear subtle for the non specialist, is huge in terms of consequences for the construct of adequate animal models of depression’. Even if the test is now considered a limited model for human emotional disorders, its value persists as a quick and cost effective test for the efficacy of related anti-depressant drugs.

The development of drugs in this area is challenging and expensive, ‘with the cost of central nervous system drug development higher than that of any other major therapeutic area’ (Cryan & Holmes 2005: 776). However, as the rapid uptake of each SSRI indicates, potential rewards are high. With its simplicity and its predictive qualities, the forced-swim-test provides a method of rapidly screening related pharmaceuticals for new anti-

depressant qualities. This approach fits well with definitions of safety and efficacy contained in US Food and Drugs Administration legislation, and the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, which since the 1960s and 1970s have shaped 'psycho-pharmaceuticals into agents with specific effects' (Lakoff 2005: 10). The forced-swim-test allows the articulation of animal, apparatus and experimenter around the known drug response. It is also a practical solution to the growing globalization of scientific research, which 'makes it safer to publish data from well-accepted tests rather than to modify them or invent new methods' (Kalueff et al 2007: 3). Through devices like the forced swim test animal behaviour is transformed into a simplified array of standardized data, which can be circulated between laboratories.

The development of genetically altered mice, identified to express traits that perform in these tests in particular ways, has further reified both the role of simple behavioural tests and a particular understanding of genetics in modelling future treatments for human depression. The genotype of the laboratory mouse can be altered in a large number of ways; if there is interest in the animal's behavioural phenotype the battery of tests on the resulting animal is likely to include the forced-swim-test[3]. Although not a search for a genetically altered model of human depression as such, this research reinforces a view of animal behaviour understood through its genetic components. The continued articulation between forced-swim-test, drug intervention and animal model allows elaboration and

[3] This can be exemplified by a paper in the journal *Neuropsychopharmacology* (Liu et al 2007). This article explores the behaviour of three groups of mice, including wild-type mice, and the heterozygotic and homozygote modifications to a particular gene linked to the transport of the neurotransmitter gamma-amino butyric acid in the brain. The bulk of the article involves discussion of two groups of graphs, histograms representing the response of the three mouse genotypes to the forced-swim-test and tail suspension test. In the first set of graphs, initial animal responses to these tests are represented; in the second, the measurements are rerecorded when treated with the known anti-depressant Prozac™. Wild type mice are apparently less 'depressed' when on Prozac™; yet the modified mice show little difference, opening up avenues of enquiry into specific molecular pathways.

refinement of the pharmaceutical interventions used to treat human depression, but this is a singular lens for studying both the meanings and mechanisms of animal and human captivation and its interruption. These 'strains of mice that show characteristic patterns of behaviour are critical for research in neurobehavioural genetics' (Crabbe 1999: 1670), yet they are also subject to ambiguities, which occasionally puncture these stabilized circulations of animal behaviour.

Challenging animal models

The interpretation of behavioural tests is open to question in a number of ways. Firstly, there are different versions of the meaning of the animal's behaviour measured by the forced-swim-test. Some critics argued the early quitters gave up useless struggling to save energy. As Tecott suggests, 'immobility may be alternatively viewed as a reasonably adaptive strategy for coping with this experimental situation' (2003: 652). When mice stop struggling to float on the water this could be seen as an appropriate response to an abnormal situation, rather than an abnormal response akin to human depression. Other researchers dispute this interpretation, suggesting when mice stop struggling they display a freezing posture, a further indication of abnormal behaviour. Again there is a rebuttal: there are many interpretations of freezing postures in mice. Perhaps more subtly, there are questions about the brain processes tested through the forced-swim-test. Critics suggest divergence between drug action during this acutely stressful episode and the chronic treatment of depression in clinical settings, speculating the drug may not operate on the same brain pathways in humans and animal models (Cryan & Holmes, 2005).

There are also a range of environmental effects, which can alter or reverse genetic effects on behaviour (Würbel 2001: 207). This was famously demonstrated to the research community through comparative research carried out when Crabbe et al (1999) tested six behaviours across three laboratories. They found significant differences in the behaviours exhibited by genetically altered strains of mice, bred to express specific identifiable behavioural traits. Despite reporting going to 'extraordinary lengths to equate test apparatus, testing protocols, and all features of animal husbandry', they still conclude, 'experiments characterizing mutants may yield results that are idiosyncratic to a particular laboratory' (Crabbe et al., 1999: 1670). These, they suggest, are due to often unknown environmental background effects. Despite attempts to standardize experimental procedures, there may be differences in the management of mouse colonies, in the past experiences of animals, subtle alterations in physical environments (such as light or ultrasound levels) and researcher attitudes, resulting in different outcomes in separate laboratories. In particular, there is the suggestion that varied human agencies, which exceed standardization, are intricately involved in the expression of these different animal behaviours.

The interaction between researcher expectations and animal behaviour is the focus of philosopher and psychologist Despret's discussion of Rosenthal's 1966 experiment on 'good' and 'bad' rats. In this Berkeley experiment, Professor Rosenthal presents two groups of experimental psychology students with two sets of rats, explaining one are inbred laboratory animals, selected to perform well in laboratory mazes, and the other are 'normal' naïve animals. Each group of rats and students performs to expectations, returning the predicted deviation in data (Rosenthal 1966); one group perform well in the maze, the others less so. Yet, we are then told, both groups of rats are from identical

albino stock; all are naïve and have no demonstrated competence with this experimental apparatus. In the relation between supervisor, students and animals the expectations of behaviour are communicated and enacted. 'The students […] put their trust in their rats, emotional trust, trust that is conveyed in gestures, in students' bodies, in all these rats that were manipulated, caressed, handled, fed and encouraged: the students succeeded in attuning their rats to their beliefs' (Despret 2004: 122).

Rosenthal had staged the experiment to seek 'the little things that affect the subjects to respond differently than they would if the experimenter had been literally an automaton' (1966: 119, cited in Despret 2004: 117). Yet, there are further questions about whether automata would be able to perform these experiments in the first place. Michael Lynch, reporting on ethnographic work in animal laboratories, suggests not. Laboratories often employ specialists who show particular abilities at 'handling animals [… revealing] an empathetic orientation to lab animals as living, holistic, creatures with needs to be attended and reactions to be monitored. […] Scientists who are 'good with animals' can sometimes obtain compliance from their subjects which otherwise would be impossible. This is particularly the case in behavioural experimentation' (Lynch 1988: 282). The bodily and empathetic engagement between humans and animals is vital to staging experiments in the first place. Despret questions Rosenthal's interpretation of the experiment as a search for confounding factors, his desire to eliminate these and define conditions under which the data would be uncontaminated. Instead, she argues, such attunement between bodies may be essential to the articulation of the animal body within a laboratory context; recognition of subjectivity a necessary currency for successful experimentation.

Such relational attributes make data from behavioural studies tricky to standardize and Crabbe et al conclude by urging caution for the attribution of behavioural effects to genetic manipulation (1999: 1672). Yet, the main response to concerns about contingency has been to invest further in standardizing protocols, environments and practices, around shared protocols and industry standards. This ignores the additional danger that 'standardization increases the risk of obtaining results that are idiosyncratic to a particular situation' (Würbel 2001: 210). The pressures to standardize around the simplest procedures and most economically efficient cage designs may make the behaviour exhibited more stable, but at the same time they may, ironically, make it less meaningful.

Enriching environments

Mice kept in the standard laboratory cages are known to exhibit what are called stereotypic behaviours, or stereotypies. These include cage biting, jumping, hanging, back flips and barbering, when the mice remove hair from themselves and each other. Stereotypies are repetitive, unvarying and apparently functionless behaviour patterns. In the literature, they are frequently linked to animal suffering, to be addressed though good animal husbandry (Mason & Rushen 2006). In this literature, stereotypies are sometimes compared to human obsessive compulsive behaviours, and the likely impacts on animal welfare imputed by the distress known to be caused to psychiatric patients by similarly repetitive behaviours. However, perhaps due to a separation between animal welfare literatures and mouse genetic researchers, they are less often considered in relation to the outcomes of behavioural tests (for an exception see Kalueff et al., 2007).

To address recognized welfare issues there are now moves towards providing cage enrichments, including nesting materials, burrowing mediums and social interaction, which discourage the development of stereotypic behaviours. The types of enrichments provided are derived from ethological studies and preference tests. A recent review by Balcombe explains, these show ‘mice value the opportunity to take cover, build nests, explore, gain social contact, and exercise some control over their social milieu, and that the inability to satisfy these needs is physically and psychologically detrimental, leading to impaired brain development and behavioural anomalies (eg stereotypies)’ (2006: 217). Through enrichment, the stresses of captivity are to be replaced with captivation: an engaged interaction between animal sensation and the material environment, reducing repetitive and destructive behaviours.

Few mice are now singly housed, except for more aggressive males and for certain experiments. Most laboratory guidelines recommend minimum cage enrichments, including nesting materials and sometimes a cardboard tube, which can be chewed, used for shelter or as platform. The US National Institute of Health facilities recently reported 90% of mice received nesting materials and 50% a cardboard tube or plastic shelter (Hutchinson et al 2005). In the UK, all units surveyed provided either nesting material or sawdust substrate, with 63% providing further enrichment items (Leach & Main 2008). Such basic items are easy to incorporate within the stacked racks of standard laboratory cages. These are typically shoe-box sized, approximately 30-40cm long, 10-15cm wide and 12-14cm high, housing around 4 individual animals. Less widely used are larger cages, complex environments offering animals a choice of association, exercise opportunities such as running wheels, devices which encourage food searching and the variation of enrichments to support novelty seeking behaviours. Even with basic

enrichments many animals continue to exhibit stereotypies. They remain extremely prevalent in certain strains – about 98% of ICR mice are thought to exhibit stereotypic behaviours (Garner & Mason 2002) – and, overall, stereotypies are estimated to afflict some 50% of all laboratory-housed mice (Mason & Latham 2004).

Much resistance to further enrichment is based on practicality, economics and past practice. However, there is opposition from some researchers. Research shows mice are able to adapt, reduce or change their behaviours using environmental resources. 'Varied environments allow animals to learn how their own actions affect their environment' (Shepherdson 2001, cited in Balcombe 2006: 229). Enrichment fosters behavioural competence and enhances the animal's ability to cope with the challenges of captivity; it may also alter the outcomes of behavioural tests. For Alzheimer's research, environmental enrichments significantly alter the memory data generated from genetically altered mouse models (Jankowsky et al., 2005). From the perspective of the behavioural geneticist, cage enrichments introduce contingencies of environment and animal agency onto the genetic alternations used to produce behaviours and the precariously standardized tests used to measure them. This is sometimes couched in ethical terms: if enrichment increases variation in the data, more animals would be needed for each experiment, creating a conflict between refinement and reduction of animals used in scientific research. It also reveals, again, the persistence of hierarchical thinking in biology, in the search for genetic factors, before considering environmental configurations or the potential of animal agency. Thus, for now, the animals used to model human affective processes are those most likely to exhibit stereotypic behaviours. These produce the most widely circulated data, but perhaps the most ambiguous results, for the specific causes of stereotypic behaviours are still unknown.

This raises questions outside the paradigms of animal welfare and behavioural genetics, returning to philosophical reflections on human and animal captivation. As outlined above, boredom is central to Heidegger's conception of the human. There are also debates in laboratory animal studies about whether animals suffer boredom; many discussions of stereotypy use this term informally (Wemelsfelder 1990). Anderson, writing about human boredom, suggests it can be understood in affective terms. It 'discloses a malady in the circulation of intensity' (Anderson 2004: 744). Boredom is both in the sensing body and in the material environment (see also Anderson & Wylie forthcoming). 'Boredom emerges once a materially heterogeneous collection of bits and pieces are held together under a type of relation that embodies the paradox that "something expected does not occur"' (Anderson 2004: 750). Reworking boredom in terms of a suspension of affect, which is both of the body and the material world, suggests it is a relevant concept for both animals and humans. As in human boredom, stereotypies suggest a suspension of the circulation of affect involving both body and environment; they cannot be allocated simply to environmental effects or to abnormal animals. This is reflected in questioning within animal welfare literatures about 'the difference between normal animals in un-natural situations and animals which have themselves become profoundly abnormal? Between newly developed ARBs ['abnormal repetitive behaviour] and ingrained habits? Between different forms of brain malfunction? As yet, we have rather more hunches than we do hard data' (Mason & Rushen 2006[4]). Stereotypic behaviour exists in the frustrated movement between potential captivation and suspension of affect.

[4] On-line introduction, Mason, G & Rushen, J (2006) *Stereotypic Animal Behaviour - Fundamentals and Applications to Welfare* http://www.aps.uoguelph.ca/~gmason/StereotypicAnimalBehaviour/library.shtml, accessed 21/04/09.

It is thus possible to argue for a reversal of the patterns of captivation and boredom traced by Heidegger, to follow Agamben's arguments about the changing structural connection between humanity and animality, this time through the perspective of the animal. Here again we may find 'the total humanization of the animal coincides with a total animalization of man' (p77). It is humans who are captivated by the material search for understanding life – seeking the genetic basis of human and animal natures, agencies and capacities. It is the animal which exhibits the stereotypic behaviour of boredom or at least of frustrated attempts at captivation. The laboratory environment suspends the animals' immediate relationship with its disinihibitors – the bored animal becomes the contemporary model for understanding human nature. Human affective disorders are modelled through the animal, just as animal behaviour becomes remodelled through this interruption of affect.

This has implications for the future development of anti-depressant drugs and for theoretical arguments about changing relations between humanity and animality. For some researchers in psychiatry, this linking of animal models, explanatory metaphors and experimental design has limited innovation in the treatment of anti-depressants, for it is insensitive to therapeutics with different mechanisms of action. As one comment posted in *Nature* suggests: 'we have not had fundamentally new drugs in psychiatry, not because of the intrinsic inadequacy of all animal models, but because of the cookie-cutter nature of design strategies by big Pharma … [which] … has dictated one serotonergic and noradrenergic agent after another' (Watt 2007). He goes on: 'behavioural neuroscience has been hamstrung in its efforts to avoid anthropomorphism by the complementary danger of speciesism – we think we are more different from mammals than I believe we really are' (Watt 2007).

So does Agamben offer any way out of this scientific and philosophical quandary? Despite Agamben's interest in the exchange of properties between humans and animals, he ends *The Open* by suggesting we accept the void at the centre of our accounts of human agency and capacity. We should disconnect ourselves from the specific disinhibitor for understanding and exploiting 'being' we have found in the contemporary technosciences. Rather than seeking new forms of articulation with animality, for Agamben this means accepting a hiatus, and allowing the animal to exist outside of the sphere of being: to 'let the animal be'. As he puts it: 'to render inoperative the machine that governs our conception of man will therefore mean no longer to seek new – more effective or more authentic – articulations, but rather to show the central emptiness, the hiatus that – within man – separates man and animal, and to risk ourselves in this emptiness' (Agamben 2004: 92). This is his challenging, but pessimistic conclusion. There is little guidance on where to go next in understanding the interplay between human and animal capacities, agencies and natures as they are enacted in behavioural genetics, or indeed elsewhere. Tracing the relations between sensing bodies, material environments and genetic technologies above provides reasons for their endurance, but also offers hints at other possibilities for relating. There is more needed than a challenge to humanism. To avoid a concomitant return to anthropocentrism 'we require a multispecies and a multi-expertise way of doing/thinking worlds and ways of life' (Haraway, 2004: 308), developing accounts and experimental practices that recognize and allocate agency in creatively open ways.

Conclusions

In seeking to recuperate from Agamben's final point of separation, I return one final time to the genetically altered mouse and the unusually compliant cat. To this image, we can now add the intermediary agencies enabling this experimental encounter and reflect on its ambiguities and exclusions anew. It is a strangely choreographed encounter of beings, unnatural even, yet it is one through which other possibilities of affective learning may emerge, which are more open than either the explanations of genetic determinism or the ethological interpretations of Heidegger suggest. The mouse may learn there are dangers from close interactions with cats; even the animals with an altered sense of smell froze when the cat meowed. The cat retains the potential to discover the consequences of playing with a costly research animal. As *The Telegraph* reports, 'even the cowardly cats would eventually begin to stare, then raise a paw, a sign they were about to pounce, at which point the researchers whisked them away from their valiant GM mice' (Highfield 2007). This demonstrated lack of fear does not have a single author either in the animal's altered nature or in its environment – it emerges from the genetic manipulation, the prior sensual experiences of the mouse, the quiescence of the cat and its removal by researchers. The outcome of this encounter is not fixed, there is an essential openness to these interspecies associations (Morris 2005, see also Latour 2004, Lestel et al 2006). The project of articulating a multispecies and multi-expertise way of doing neuroscience, which is responsible to the worlds and ways of life of animals and humans is beyond the scope of this chapter, but a few starting points can be identified.

First, it requires a shift in our practices for questioning nature; a shift from demonstrating reductionist accounts to creating experiments that *add* to the world and our understanding of it (Latour 2004). Despret suggests a difference between what is being made available and what is being rendered docile in the context of the laboratory encounter (Despret

2004: 123). She identifies a ‘contrast between the scientist who relies on the availability of both the apparatus and the animal, and a scientist who requires docility (this scientist being himself docile to the perceived prerequisites of science)’ (Despret 2004: 124). Despret calls the first caretaker, the second judge. The articulations of behavioural neuroscience traced above have tended to be reductive, requiring the docility of animal agency to known drug effects and simple behavioural tests. This is extended in the videoed encounter, the cat made docile by researchers, whisked away if the prelude of a raised paw hints at a more active engagement from this element of the mouse’s ‘environment’. Yet, the use of animal models can be additive and animals more active in these experimental encounters. Holistic approaches to studying mouse behaviour in their home environments, monitoring movements in space and time, recording the licks, foraging behaviour, and social interactions of their daily lives are less common, but may be more revealing. Enhancing animals’ capacities can produce experiments which are more sensitive to test effects. Acting as caretaker, rather than judge, researchers breeding populations of mice in species-typical societies in naturalistic environments have enabled the detection of deficits in transgenic mice not recognized in conventional tests (Vyssotski et al 2002, cited in Balcombe 2006: 230, see also Cryan & Holmes 2005).

Second, it suggests a shift in our thinking about nature in the biosciences, to a view of nature as phenomenal, rather than reduction of phenomena to nature. The relational encounters which constitute this experiment suggest a multiplicity of becomings; the powers of one body enhanced or diminished only in relation to the changing capacities of another (Deleuze & Guattari 1987). There is a blurring of the boundaries that define these bodies and the agencies that set them in motion: between natural behaviour and laboratory artefact; between the properties of DNA and drugs; between gene and

environment all the way down. There is growing awareness of this complexity and multiplicity in much laboratory science. The *Nature* article for this research contains more modest queries about the way odour information activation within distinct areas of the olfactory bulb is interpreted by the brain (Kobayakawa et al 2007). The complex web of agents is expanded to encompass odour information, receptor characterization, brain function and learning. Here, we find hints of the heterogeneity of phenomenal nature, replacing the gene paradigm enduring in media presentations of genetic determinism and the impoverished understandings of animal being in the world inherited from the Heidegger.

Yet these determinist accounts of species behaviour still persist in media presentation. The final addition to the videoed images is the person operating the camera, posting the images to the web, adding but also extracting from, this dance of beings. Researchers may find alternative ways of expressing the public meaning of this encounter for conceptualising relations between genes and environment, if we still want to use those words; though perhaps here there is most resistance to alternative framings. Even as scientists recognize the limitations of the gene paradigm, Keller suggests the biotechnology industry requires this division between nature and nurture to sustain its expansionist claims (Keller 2008). The 'diagnostic liquidity' (Lakoff 2005) underpinning pharmaceutical development is transacted here by the exchange between known drug effects, specific measures of behaviour and genetically altered mouse models. This embodies, and links, limited models of animal behaviour and human affective disorders. Meaning and validity are sidelined; rapid circulation and persuasive demonstration is central. The video is perhaps, finally, a fitting metaphor. This cat and mouse game is fixed. The cat will never win. Akin to the never-ending pursuit for the 'true nature' of behaviour,

the mouse provides an opportunity for a captivating dance, but will remain always just out of reach.

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