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# Using Animals to Study Human Neuroses and Psychoses: Practices and Problems

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*Introduction*

Rodents (notably rats and mice) are much utilised in research directed towards improving our knowledge of human mental disorders and developing treatments for these conditions (*Brain and Marrow,* 1998). There is no doubt that mental health is a serious issue (conditions influencing an estimated 40% of the population within their lifetimes) but the use of animals in such programmes has special problems. Behavioural attributes are much more nebulous and heterogeneous than, for example, infectious agents, physiological variables and toxicity studies (where animals have played an important role in benefiting human health). Many individuals are concerned about the extent to which essentially human phenomena (like anxiety and anger) can be genuinely 'modelled' in animals, 'divorced' as they are, from the human condition. Indeed, many of the overt written attacks on the appropriateness of using animals in research, focus upon studies designed to find drugs to ameliorate mental disease.

This account attempts to provide a brief review of the situations in which laboratory rodents are used to model human mental disease, commenting on their successes and pitfalls. The use of laboratory rodents as 'models' for human neuroses and psychoses at least admits the probability that such animals can be subject to 'distress' or 'fear'. Clearly, 'welfare' is a fine balance between environmental enrichment and 'stress', a process which must take into account species, sex and strain differences of animals. The view has also been repeatedly expressed (e.g., *Brain,* 1992) that chronic pain or distress is more problematic than acute experiences - yet these are precisely the conditions that have characterised many of the 'models' of human neuroses and psychoses employing laboratory rodents.

It is intended that this review will also investigate some of the central conceptual issues such as; What is the nature of mental health? Can such attributes be studied in animals? and Are there any special ethical issues involved in creating situations in which the behaviour of animals is deliberately impaired? These are often omitted to the detriment of understanding and contribute towards a naive assumption of the direct translatability of animal models to the human condition.

*Characteristics of useful models*

*Willner* (1984) has described the procedures he sees as important for validating animal models of psychiatric disorders. *Predictive validity* (in that the drug actions in the model should largely correspond with those that work in the clinic), *face validity* (in that the model and the disorder should have similar 'diagnostic' characteristics) and *construct validity* (a convincing theoretical rationale) are all desirable for the model to be truly useful.

The usefulness of an animal model to psychiatric disorder research depends upon the use to which it is put. A model does not have to mimic exactly the human disorder in order to screen drugs of potential therapeutic importance. It is sufficient that the effects of drugs on the behavioural changes parallel their effectiveness in the clinical condition. The other major use is to help elucidate the neural substrate which underlies the disorder. This aspect of a model's usefulness (predictive validity at the mechanistic level) necessitates the model having a high degree of construct validity.

*Rodent models of anxiety*

*Brain et al.* (1991) reviewed some of the then recent developments in models of anxiety that employed laboratory rodents. It seems that the newer models (based on realistic situations where

'anxiety' might reasonably be implicated) offer improved predictive power.

Anxiety has been generally 'deduced' clinically by the verbal reports of patients. Because of the personal and unverifiable nature of this condition, suitable animal models have been difficult to design. However, animals respond with anxiety-like behaviour in a variety of situations and a number of recent attempts have been made to devise tests in rodents for anxiolytic drugs based on predator-prey interactions or exposure of individuals to dominant conspecifics (e.g., *Blanchard & Blanchard*, 1990; *Blanchard et al.*, 1990). Such models appear useful in investigations of the biochemistry of anxiety and in determining the mechanisms of actions of anxiolytic drugs. As noted earlier, pharmacology is currently the most common way of validating a proposed animal test of anxiety. *Vellucci* (1989) suggested that the necessary requirements of animal models of anxiety include:

A. The animal *must* be sensitive to clinically effective anxiolytics in a dose-dependent manner;

B. The *relative* potencies of different anxiolytic agents should be similar to those seen clinically; and

C. The tests should distinguish the effects of anxiolytic from non-anxiolytic drugs.

An enormous number of rodent models for anxiety have been investigated. They include the *open field* which involves placing a rodent in an unfamiliar area in which ambulation is assessed by "cutting" photocell beams or visually with respect to lines drawn on the floor. As the rodent crosses each beam or line, a score of one unit of exploratory activity is recorded. Fully automated, computer-assisted videotape systems distinguishing between areas traversed adjacent to walls or those more internal (indicative of reduced 'anxiety') are now common. The experimenter also often counts the number of faecal boluses deposited as increased defecation is indicative of increased anxiety or "emotionality". The ambulation score (especially of internal areas) is generally increased in such tests by anxiolytics.

The *Two-Chambered Light-Dark Transition* takes into account the rodent's aversion to bright light. The subject is placed in an area divided into light and dark compartments and the number of transitions between the two is used as the measure of anxiety. The subject is effectively faced with conflict between a desire to explore a novel area and an aversion to bright light. Anxiolytics significantly cause a general increase in the number of transitions.

The *Elevated-Plus Maze* also involves conflict between exploration and aversion. The apparatus is elevated and consists of two open arms and two closed arms in the form of a cross. The subject is placed on an elevated open arm generating anxiety due to the mouse's aversion to elevated open spaces. Anxiolytics usually increase the relative amount of time spent in the open arms. The elevated plus maze is commonly used for assessing the anxiolytic/anxiogenic properties of drugs but the precise effects of psychoactive compounds on plus maze behaviour are much influenced by details of how the test is applied (*Hogg*, 1996). Unless a multiplicity of anxiety states exist with subtly different substrates, the sensitivity of the model to extraneous variables suggests that the test tells us little about the fundamental changes underpinning anxiety in humans. The test may also produce 'false positives' with certain categories of drug (see *Charrier et al.*, 1995).

Anxiolytic drugs decrease the *Ultrasonic Distress Calls* emitted by rodent pups separated from their mothers. Claims have been made that the BZP-agonist and 5HT antagonist-induced reductions in calls is due to the drug's sedative, muscle relaxant or hypothermic actions but *Brain et al.* (1991) have produced evidence that decreases in ultrasonic calling are simply related to these effects. The test appears at least as promising as those mentioned earlier and is also relatively simple to carry out and (being automated) does not require substantial training of the operative. In terms of studying the substrate(s) of anxiety, there is the problem that the neonate's brain is not identical to that of the adult.

*Rodent models of hostility*

A very wide range of rodent models of 'aggression' have been repeatedly employed in the laboratory (*Brain*, 1994). 'Hostility' is viewed as a tendency to react with threat or attack under inappropriate circumstances or to show "excessive" aggressiveness. Obviously value-judgements are involved in making such distinctions. The models

include:-
*Social conflict* - these (generally intraspecific encounters) involve competition for a mate, a territory, social status or food, and success in the encounter increases the animal's relative fitness (breeding potential). The conflicts often employ strategies minimising the potential for serious physical damage.
*Parental defense* - these (intra- or inter-specific encounters) protect the attacker's young, or nest sites from potentially destructive intruders.
*Self-defense* - these (inter- or intra-specific situations) involve using threat and attack to protect the actor from potential predators or attacking members of their own species. These behaviours are generally only seen if flight or escape is precluded and do not involve injury- limiting strategies.
*Infanticide* - this involves the killing of (generally) unrelated young. This strategy in males seems a method of increasing the individual's reproductive fitness whereas in females it is generally a response to 'stress' or disturbance.
*Predation* - these (inter- or intra-specific responses) involve efficient killing and they are generally followed by feeding activity.
Consequently, 'hostility', as studied with laboratory rodents, is a heterogeneous set of phenomena. Studies with inbred strains, hormonal manipulations and application of psychoactive drugs *all* strongly confirm that the threat and attack seen in the different rodent tests serve a variety of functions, namely offence, defense and predation. Having said this, the idea of 'pure' offence and defense cannot easily be supported by the data. Factors such as changing the opponent's nature, the opponent's sex or prior social experiences have profound effects on the form of the generated threat and attack. It should be further noted that many of the rodent 'models' (which are often clearly adaptive responses) do not easily represent human behaviours receiving the label 'hostility' (which are generally viewed as maladaptive or inappropriate use of threat or attack in particular situations). Indeed, animal models with greater emphasis on defense or predation might be more appropriate to studies of human hostility which can often be viewed as excessive defensiveness or an almost predator-like response with low arousal (psychopaths).

There is a tendency to extrapolate too far when using laboratory rodents to further our understanding of human hostility. We should recognize that the studies provide valuable insight about the possibilities of particular biological, situational or experimental factors changing the propensity for threat or attack in inter-individual situations, but they tell us little about murder, rape or war.

*Rodent models of 'depression'*
Human depression is a debilitating phenomenon with major episodes lasting at least two weeks and with core symptoms of depressed mood and markedly suppressed interest and a lack of reactivity to pleasurable stimuli. Common associated symptoms include weight loss, sleeping disorders, fatigue or loss of energy, feelings of worthlessness, lessened ability to concentrate on mental tasks and repeated thoughts of death or suicide.
This common human condition has been modelled in laboratory rodents using a variety of paradigms (reviewed by *Willner*, 1984). 'Promising' paradigms included:-
*Behavioural Despair* induced in rats or mice by being forced to swim in a confined space.
*Chronic Unpredictable Stress* involves rats being subjected to a variety of different stressors including electric shocks, cold water immersion and reversal of the light/dark rhythm.
*Chronic Mild Stress (CMS)* was largely developed as a modification of the above, having the apparent advantages of removing the need for substantial stressors and concentrating on anhedonia (the loss of the effectiveness of reward) . The model was designed to induce a state of anhedonia in rodents (as measured by sucrose intake) mimicking, as closely as possible, the human condition. Anhedonia is a core symptom of depression as listed in the DSM-IV (*American Psychiatric Association*, 1994). Consequently, claims have been made that CMS can be used to determine the underlying neural mechanisms of anhedonia e.g. that in rats it is mediated by changes in dopamine D2 receptor sensitivity in the nucleus accumbens and, by implication, that anhedonia in humans reflects a homologous change in the sensitivity of accumbens dopamine receptors.
Recently, *Willner* (1997) has reviewed 10 years of experience with the CMS model and has admitted that it is not always reliable. Doubts have also

been cast on the construct validity of the CMS model e.g. *Matthews et al.* (1995) and *Reid et al* (1997) have suggested that changes in sucrose intake following the CMS regime may be more related to changes in body weight rather than anhedonia. Establishing the construct validity of animal models of human psychological states is extremely difficult. The behavioural change in the animal can often arise from a multitude of causes. Whilst there is doubt about whether the animals subjected to CMS are actually anhedonic, the claims made about the underlying mechanisms of depression derived from the model must also be in doubt even if the unreliability problem can be overcome.

*Intracranial self-stimulation (ICSS)* has been used as a rodent model of human depression, assessing as it does, the effectiveness of 'reward centres' in the brain. *Willner* (1984) argues that these tests have a strong basis in that "...depression is associated with a low frequency of positive reinforcement, particularly social reinforcement".

*Loss of Social Status.* There has been a further attempt to assess whether loss of social status in rats may also produce a valid model of human depression. Impairment of aggressive behaviour resulting from chronic stress was said to be reduced by repeated treatment with a range of antidepressive agents (*Zebrowska-Lupina et al.*, 1991). Rats exposed to CMS also appeared to behave more submissively when a conspecific intruder was introduced into their home cage (*D'Aquila et al.*, 1994). (*Willner et al.* 1995) suggested that weekly defeat by rats of the aggressive Tryon Maze Dull line decreased home cage dominance behaviour of previously stable Lister rats as well as their consumption of palatable sucrose solution. Both effects were reportedly 'normalised' by three weeks of treatment with the tricyclic antidepressant imipramine. The approach needs much more detailed evaluation before it can be seriously considered an effective model of human depression. Indeed, the construct validity of the model has recently been challenged (*Marrow and Brain*, 1998).

*Learned Helplessness.* Many of the previously-mentioned tests were devised as modifications of this paradigm (*Seligman*, 1975) which employed exposure to inescapable and uncontrollable stress to induce a "cataleptic-like state" on which the effects of anti-depressant agents could be assessed. This model certainly generated some useful insights but it has been regarded as too extreme by some national legislative agencies.

There is considerable debate about the usefulness of rodent models in this area of research but some seem potentially useful for rapidly screening drugs. Whether they can be genuinely claimed to mimic the features of full clinical depression is much less certain. Certainly, some of the paradigms do not appear to work reliably in all laboratories, suggesting a need for fuller exploration.

Having said this, there is a more fundamental problem. If one takes out the linguistic, ideological and economic components of depression, then the transferability of animals to humans in this sphere loses much of its validity. People react to environmental stimuli in a variety of ways depending on individual choice. This can drive certain people into depression whilst others may even derive pleasure from the same circumstances. Different attitudes must at least be influenced by the environmental impacts that generate the individual. This aspect clearly cannot be modelled with animals.

*Rodent modelling of social anxiety*

Social phobia "...is a collection of fears generally linked to the presence of other people. Eating, speaking or virtually any other activity that might be carried out in the presence of others can elicit extreme anxiety" (*Davison & Neale,*1974). *Brain* (1995) examined the features of potential rodent models of this activity concluding that candidates must involve social behaviour in a social species and should not be based on hierarchical relationships. Although there are a number of potential tests where rodents show high anxiety levels (many of these feature in the section on anxiety) it is actually impossible to establish that a rat or a mouse avoids conspecifics for 'irrational' reasons. Often the responses are clearly adaptive (avoidance of a social dominant by a subordinate is an adaptive response) or, at least, interpretable in terms of neophobia. Social phobia clearly is not a condition that is likely to be amenable to modelling in rats or mice. We can deal with anxiety or avoidance but not rationality, feelings of loneliness and low self esteem.

*Final comments*

This difficulty of dealing with rationality is the feature with respect to which one can have least confidence in *all* animal models of human neuroses and psychoses, based, as they are, on apparent breakdowns of normal responding. We consequently have to be extremely careful in what we attempt to take from such studies.

Rodent models have played a pivotal role in the development of a range of specific psychoactive drugs and have improved our understanding of the roles of biological and other factors in human mental disease. Rodent studies have been essential in assessing the potential involvement of neural areas in such conditions and have also been useful in evaluating the impact of genetic and experiential effects in their genesis. Rodent models have had, however, other more fundamental benefits in, e.g., profoundly changing our appreciation of the concept of hostility. Their use reinforced the view that employing threat and attack did *not* signal that a single motivation had been implicated, they emphasized that it was unlikely that a simple physiology underpinned all expressions of this behaviour and that conflict was a dynamic phenomenon involving temporal changes in both the attacker and the attacked.

Having said this, it seems to be becoming increasingly difficult to defend the use of large numbers of rats and mice in studies of human neuroses and psychoses. One reason is clearly rooted in our greater understanding of the behavioural 'needs' of rats and mice and recognition that well-being of large numbers of such animals is chronically impaired in such models. On the cost versus benefit approach to animal utilisation, one has to be convinced about the potential benefits to humans. This surety is challenged by the plethora of different tests available - often with very different characteristics and outcomes. There needs to be a serious re-evaluation of existing paradigms.

The tendency to claim too much on the basis of rodent tests should also be resisted. The limitations of animal models of human mental conditions should be freely admitted. Wittgenstein (1953) wrote "It is sometimes said that animals do not talk because they lack the mental capacity. And this means: "they do not think and that is why they cannot talk". But, they simply do not talk. We have to be very careful when talking about the mental activity of animals (we have enough problems with humans). If animals did think, they couldn't relate it to us, so all we can say is that they don't speak. Any thought or mental state attributed to animals (even the concept "depression") is problematic. We therefore have to rethink what these kinds of sentences mean and the circumstances in which animal models are useful. For example, perhaps one should hear more about the impact of a certain hormone or drug on defensive threat rather than the compound's "anti-hostility" properties? In many cases, we should be happy to accept the predictive properties of a test in drug development without reading too much into other aspects of the model.

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