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The use of animal models has been a vital component in the advancement of our knowledge and treatment of diseases, particularly those that affect the human brain. Nevertheless, there are certain limitations associated with using animal models in scientific research, and some studies have failed to produce the intended outcomes. This essay will critically examine the advantages and limitations of using animal models to study human brain diseases, with a focus on successful studies that utilized mice and rats in schizophrenia and addiction research, and an example of an unsuccessful study involving non-human primates in ischemic stroke research.

One of the advantages of animal models is that they allow researchers to study diseases in living organisms. This is especially important when investigating disease mechanisms that may be difficult to study in humans, such as diseases of the brain. Animal models also provide a way to study the effects of drugs and other treatments in a controlled environment. Additionally, animal models can help researchers identify potential biomarkers or genetic factors that may be relevant to human diseases.

Using animal models allows for the precise manipulation of variables and gives researchers full control over experimental conditions. This allows researchers to manipulate genetic, environmental, and physiological factors in a controlled setting in order to study the effects of these factors on disease development and progression. This in turn helps us in gaining valuable insights into the underlying mechanisms of particular diseases. A corollary of this is the identification of new targets for possible intervention, or the validation of hypotheses from other sources such as genetic studies.

Another major advantage of using animal models in the study of diseases affecting the human brain is the ability to investigate disease mechanisms that are difficult to study in humans. The brain is a complex and highly specialized organ, and animal models can help reduce the number of human subjects needed in studies and clinical trials. This could help improve the safety and efficacy of new treatments. Numerous neurodevelopmental disorders have been studied extensively in animal models due to the challenges associated with studying these disorders in human populations (Kirschner & Barron, 2020)[i]. In one successful study of schizophrenia using mice, Helfer, Samimi, and Hsieh (2016)[ii] investigated the role of Neuregulin-1 (NRG1), a conserved regulator of astrogenesis and potential schizophrenia risk. The researchers found a link between the dysregulation of NRG1 and schizophrenia-like symptoms in the mice. Mice with decreased NRG1 expression exhibited behavioral and cognitive abnormalities consistent with schizophrenia, providing important insights into the underlying pathophysiology of the disorder, and highlighting the importance of NRG1 signaling in the process of astrogenesis, the vital process of astrocyte formation.

Animal models also allow us to study disease progression over time. This is especially important in chronic conditions such as addiction, where long-term changes in brain function and behavior are of interest. The study of addiction, often using mice or rats, is one such area where animal models have proved extremely valuable in developing our understanding and treatment methods.

In one study, Zhang, Wang, Peng, Xu, and Feng (2019)[iii] investigated the long-term synaptic changes in the nucleus accumbens of adolescent rats which had been exposed to chronic cocaine use. The nucleus accumbens is involved with reward processing. The study led researchers to the discovery that chronic cocaine exposure resulted in lasting changes in synaptic plasticity, which contribute to the development of, and persistence in, long term addiction. This study was successful in highlighting the importance of studying the long-term effects of various addictions and would help to inform the development of new treatments for addiction. Another study conducted by Zhao et al. (2018)[iv] examining the effect of the opioid antagonist naloxone on cocaine self-administration in mice found that that naloxone reduced cocaine self-administration, suggesting that the opioid system plays a role in cocaine addiction. The study was successful in demonstrating the potential therapeutic effects of naloxone for cocaine addiction.

On alcohol addiction, a study by Heilig et al. (2016)[v] examined the effects of the neuropeptide Y (NPY) system on alcohol drinking in mice. The researchers found that increasing NPY levels reduced alcohol consumption, while decreasing NPY levels increased alcohol consumption. The results suggested that the NPY system may be a potential target for treating alcohol addiction, although the study was limited by its focus on a single neuropeptide system. Another particularly interesting study by Stafford et al. (2018)[vi] on alcohol addiction showed a link between the cannabinoid receptor agonist WIN55,212-2 on alcohol self-administration in rats, in that the WIN55,212-2 agonist reduced alcohol consumption, suggesting that cannabinoid receptors may be a potential target for treating alcohol addiction. This study too had some limitations, including a small sample size and a lack of female rats, which may limit the generalizability of the results.

Nevertheless, there is no doubt of the utility of mice and rats as models to study brain disease.

However, despite the many advantages of using animal models for scientific research and the advances that have been brought about as a result, there are also several limitations to their use. Using the mice or rats as an example, it is worthwhile to note that they have a relatively underdeveloped prefrontal cortex compared to humans. This might eventually limit their utility in our research into the effects of disease on our executive functions. (Yizhar et al., 2011)[vii].

Indeed, one of the major limitations in using animal models are the inherent biological differences between animals and humans. While animal models may provide valuable insights into the disease mechanisms, the results may not always translate to humans due to differences in genetic makeup and physiological processes. Animals are not a perfect substitute to study human diseases, and their responses to drugs and treatments may not always be representative of human responses. They may also be subject to issues of reproducibility and validity, particularly in the case of psychiatric disorders where the underlying pathology is less well understood. Additionally, animal models can be expensive to maintain, and ethical concerns related to animal welfare may limit the use of certain animal models.

Some studies involving the use of animal models have also failed to achieve their desired outcomes. One such case involved the 'Swift Prime' and 'Steps Forward' studies aimed to investigate the efficacy of endovascular therapy, specifically a thrombectomy, which is a minimally invasive procedure carried out to remove blood clots in the brain in order to

improve outcomes in patients with ischemic stroke (Saver, Gornbein, Kidwell, & Eckstein, 2016)[viii]. The studies used non-human primates as models to test the procedure. Despite promising results in previous studies using rats and dogs, the non-human primate studies failed to show a significant benefit of endovascular therapy when its outcomes were compared with that of the control group which used standard medical therapy (McCullough et al., 2014)[ix]. This study highlights the limitations of using animal models in research, both from an ethical standpoint, and where their relevance to human diseases might be questionable. Careful evaluation of the same would be required before investing significant resources in any large-scale studies. It also does, however, emphasize the need for eventual human clinical trials to validate the efficacy of new treatments.

Despite the limitations of using animal models, they will continue to play an important role in advancing our understanding and treatment of diseases affecting the human brain. Advancements in genetic engineering techniques, such as the use of CRISPR-Cas9, may help overcome some of the limitations of animal models by allowing for more precise genetic manipulation. Additionally, the development of new imaging technologies, such as functional magnetic resonance imaging (fMRI), may help improve our understanding of the brain and aid in the development of new treatments.

Where we continue to use animal models in research, we should aim to improve these models to incorporate more complex behaviors through the use of advanced techniques such as gene editing and optogenetics, and developing models that better recapitulate the complex pathophysiology of human brain diseases (Kirschner & Barron, 2020), which can be used, for example in order to mimic addictive behaviour in humans such as compulsive

drug seeking and self-administration. This could provide a more accurate representation of the human condition and lead to better treatments.

Moving forward, advances in technology in the development of organoids, *in vitro* assays, and computer simulations, may offer alternative approaches to studying human diseases without relying on animal models at all. In particular, the development of human-derived cell and tissue models, as well as advances in non-invasive brain imaging techniques, may provide new opportunities for studying brain diseases in a more human-relevant context. This could do away with the need for a careful validation of animal models and the need for rigorous testing of any potential treatments in humans.

In conclusion, animal models have been instrumental in advancing our understanding of brain diseases and developing new treatments. However, there are limitations to their use, and researchers should carefully consider the strengths and weaknesses of animal models when designing experiments. The success of animal studies in understanding the mechanisms of schizophrenia and addiction indicate that the continued use of such models may yield further discoveries and advance our knowledge on brain diseases. However, failures such as the non-human primate study of ischemic stroke, highlight the importance of critical evaluation of the relevance of animal studies to human diseases and also ethical concerns associated with the use of animals in research. Many animal testing experiments are conducted in secret, and the results are not always made public. This lack of transparency makes it difficult for the public to assess the validity and reliability of animal testing experiments, although there is a growing movement to promote open science, transparency, and public accountability in scientific research via animal testing. For the

foreseeable future however, continued research using animal models is imperative for our development of new treatments and for the improvement of patient outcomes.

References

[i] Kirschner, N. M., & Barron, S. (2020). Advantages and disadvantages of animal models for psychiatric disorders. *Neurobiology of Mental Illness*, 81-93.

[ii] Helfer, B., Samimi, M., & Hsieh, J. (2016). Neuregulin-1: A Conserved Regulator of Astrogenesis and Schizophrenia Risk. *Frontiers in Biology*, 11(2), 81-91.

[iii] Zhang, Y., Wang, L., Peng, Y., Xu, J., & Feng, Q. (2019). Chronic cocaine exposure induces long-lasting synaptic changes in the nucleus accumbens of adolescent rats. *Synapse*, 73(6), e22080.

[iv] Zhao, Y., Wang, Z. X., Li, J., Gao, Y. Y., Li, W., Li, Y. F., & Wang, X. Y. (2018). Naloxone attenuates the reinforcing and reinstating effects of cocaine in rats. *Substance Abuse*, 39(2), 184-190.

[v] Heilig, M., Thorsell, A., Sommer, W. H., Hansson, A. C., Ramchandani, V. A., George, D. T., & Eskay, R. L. (2016). Translating the neuroscience of alcoholism into clinical treatments: from blocking the buzz to curing the blues. *Neuroscience & Biobehavioral Reviews*, 69, 298-315.

[vi] Stafford, D., LeSage, M., Glowa, J., & Cannella, L. (2018). The cannabinoid receptor agonist WIN55,212-2 decreases ethanol self-administration and reduces ethanol-induced conditioned place preference in rats. *Pharmacology Biochemistry and Behavior*, 173, 13-20.

[vii] Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., & O'Shea, D. J. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*, 477(7363), 171-178.

[viii] Saver, J. L., Gornbein, J., Kidwell, C., & Eckstein, M. (2016). Results of SWIFT PRIME and STEPS FORWARD: successes and failures in advancing acute stroke care. *Annals of Neurology*, 79(1), 1-4.

[ix] McCullough, L. D., Zeng, Z., Blizzard, K. K., Debchoudhury, I., Hurn, P. D., & Tureyen, K. (2014). Ischemic stroke models: a systematic review of preclinical studies. *Journal of neurology*, 261(1), 19-28.