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Why bother using non-human primate models of cognitive disorders in translational research?

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ABSTRACT

Although everyone would agree that successful translation of therapeutic candidates for central nervous disorders should involve non-human primate (nhp) models of cognitive disorders, we are left with the paucity of publications reporting either the target validation or the actual preclinical testing in heuristic nhp models. In this review, we discuss the importance of nhps in translational research, highlighting the advances in technological/methodological approaches for 'bridging the gap' between preclinical and clinical experiments. In this process, we acknowledge that nhps remain a vital tool for the investigation of complex cognitive functions, given their resemblance to humans in aspects of behaviour, anatomy and physiology. The recent improvements made for a suitable nhp model in cognitive research, including new surrogates of disease and application of innovative methodological approaches, are continuous strides for reaching efficient translation for human benefit. This will ultimately aid the development of innovative treatments against the current and future threat of neurological and psychiatric disorders to the global population.

1. Introduction

The importance of brain disease research extends from a focus on individual patient health to global impact on social and economic status (DiLuca & Olesen, 2014; Olesen & Leonardi, 2003). A comprehensive report for 2010 estimated that the annual cost of neurological and psychiatry disorders in Europe, for 30 countries with over 500 million in population, was 798 billion Euros (€) (Gustavsson et al., 2011; Olesen, Gustavsson, Svensson, Wittchen, & Jonsson, 2012). These data, based on direct and other related healthcare costs and patient production losses in Europe, showed that mood disorders and dementia are the causes of greatest economic burden, with an annual amount of 113.4 and 105.5 billion € (Olesen et al., 2012), respectively. On the global scale, these estimates are substantially higher, with a reported 422 billion US dollars spent on the care of Alzheimer's disease (AD) patients in 2009 alone (Wimo, Winblad, & Jonsson, 2010). Combined with an increased life expectancy of the global population, the incidence of brain diseases are likely to rise, keeping them as major current and future public health concerns (DiLuca & Olesen, 2014).

In the challenge of overcoming the imminent threat of neurological and psychiatry disorders to health and economy (DiLuca & Olesen, 2014; Olesen & Leonardi, 2003), it is well understood that novel research encompassing state-of-the-art techniques are required, with a setup that mediates the effective translation of preclinical research to clinical application through strengthening collaborative networks from 'bench to bedside'. While this has been emphasised in a previous European summit of CNS drug research (Nutt & Goodwin, 2011) and supported by funding schemes setup by the European Commission (Rose, 2014), it is of critical importance that within preclinical research, methodological approaches, including the use of animal models, experimental measures and designs, are refined and strictly orientated in the process of reaching clinical use. Here, we discuss the importance of relevant animal models in translational research, particularly the use non-human primates (nhps), for neurological and psychiatric disorders and the latest methodological approaches utilised for effective transition into clinical applications.

2. Animal models

Animal models of neurological and psychiatric diseases are utilised for understanding the pathophysiology and investigating the brain–behaviour relationship that cannot be studied in humans

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(Fisch, 2007; van der Staay, 2006), making them appropriate tools for testing treatments prior to clinical trials (Berton, Hahn, & Thase, 2012; Button et al., 2013; Markou, Chiamulera, Geyer, Tricklebank, & Steckler, 2009; Matthews, 2008; Nestler & Hyman, 2010; Sabbagh, Kinney, & Cummings, 2013). Although it is widely accepted that no model can fully mimic the entire human condition, particularly for psychiatric disorders due to their complex nature, the most suitable animal models available have allowed researchers to control external parameters that may impact behaviour. This has allowed for causal relationships between distinct factors and behavioural phenotypes to be established (Deussing, 2006; Matthews, Christmas, Swan, & Sorrell, 2005; Overall, 2000; van der Staay, 2006).

The choice of animal model in translational research should not only fulfil the needs of the experimental design *i.e.* reproducibility, inter- and intra-observer reliability (Janssen, 1964), but also meet a clear external validity criteria for addressing hypotheses that are orientated in the process of achieving a clinical endpoint/outcome (van der Worp & Macleod, 2011). To support this, it is important to reiterate the three main validity criteria for animal models, (i) face (ii) construct and (iii) predictive (Belzung & Lemoine, 2011; Nestler & Hyman, 2010; Schmidt, 2011; Willner, 1984) that are key for determining a suitable methodological approach for basic experimental designs. The first, (i) face validity, is met when certain phenomenological similarities are found between the animal model and the disorder, which could be of anatomical, biochemical, neuropathological or behavioural nature. Modelling cognitive impairments are commonly based on face validity. An example of this is the use of transgenic mice in AD. Similar to the disorder, these animals demonstrate spatial memory impairments associated with pathophysiological symptoms, such as aggregation of amyloid plaques (Chen et al., 2000; Hsiao et al., 1996) or neurofibrillary tangles (Ramsden et al., 2005; Santacruz et al., 2005) or both (Billings, Oddo, Green, McGaugh, & LaFerla, 2005; Oddo et al., 2003). The second criterion is known as (ii) construct validity and is based on theoretical rationale. This is when etiological factors of the human disorder induce a similar pathophysiological state in the animal. However, the design of an appropriate construct model is often complicated for the reason of complex disease etiology. Genetic defects are commonly combined with numerous environmental factors that may trigger the disease onset, making it rare to know the full etiology of a neurological disease. The exception is when the disease is caused by a single dominant mutation, such as in Huntington's disease (Punnett, 1908). The third criterion is referred to as (iii) predictive validity, whereby measurable treatment effects are found in both the animal model and the human disorder. A prime example of this is the development of deep brain stimulation (DBS) for treatment of motor symptoms in Parkinson's disease (PD) patients (Limousin et al., 1998), following initial studies in the 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)-treated nhps (Benazzouz, Gross, Feger, Boraud, & Bioulac, 1993).

As we consider the field of psychiatric disorder research, it is apparent that reliable predictive animal models remain lacking. This may be a result of the large variation in treatment responses of patients to available treatments for psychiatric disorders, as only approximately 50% of patients respond to antidepressant therapies, making animal models difficult to characterize (Berton et al., 2012; Schmidt, 2011).

3. Important considerations of animal models in translational research

When using models, whatever the species, researchers are facing a catch-22 situation (*i.e.* unsolvable as it involves mutually conflicting or dependent conditions (Berton et al., 2012; Nestler & Hyman, 2010). Controversies regarding animal models might come from the distinct definitions of validities used by researchers (Belzung & Lemoine, 2011). But it is also likely that a good animal model requires more than the 3 validity criteria described above. The "homological validity" (involving the species and strain choices regarding the aim of the model) or the "remission validity" (*i.e.* the reversal of the pathological state by treatments should involve the same mechanisms in animals and Humans) have been suggested as well (Belzung & Lemoine, 2011). Schmidt raised the issue of sample sizes that are often too small to highlight inter-individual differences, so characteristic of the depressive population (Schmidt, 2011) and considered adding a "population validity" criterion (*i.e.* the occurrence of the pathological condition in animals should be similar to the prevalence of the disorder among Humans). Sample sizes are twice as important as they also guarantee the relevance of the results' statistical significance. Underpowered studies might lead to false negative or positive results (van der Worp et al., 2010). However, this should be balanced with the ethical legislation, such as the 3R rule (*i.e.* replacement of animal models when possible, refinement of experimental conditions and reduction of sample sizes) (Russell & Burch, 1959).

In the aim of modelling cognitive and mood disorders, researchers also face the issue of emerging the methodological gap between the preclinical and clinical fields. Diagnosis is based upon a wealth of symptoms that are often verbally reported by patients or their relatives, but may not be directly observed in the patients' daily life. Thus, translation of the observable behaviours and measurable features assessed in animal models can be somewhat limited (Fisch, 2007; Nestler & Hyman, 2010; Overall, 2000). In order to overcome such limiting factors, it remains important to utilise the model of disease that is the closest resemblance of the human condition and to develop innovative methodologies for translational research.

4. The relevance of non-human primate disease models in research

There are some obvious challenges when it comes to the use of nhps for basic and applied scientific research, such as expense and technical expertise. While this may be reflected in the relative number of monkeys used for research compared to other species like rodents (0.1% vs. 80%, respectively; (Roelfsema & Treue, 2014)), nhps remain critical for the accumulation of biomedical knowledge given that they are the closest resemblance to humans in aspects of anatomy, physiology, immunology, social behaviours, and cognitive function (Fooden, 2006; Gibbs et al., 2007; Sereno & Tootell, 2005). Indeed, major discoveries have been made in these areas of research using nhp models, which include development of rabies, smallpox and polio vaccines and the study in the pathogenesis of other infectious diseases, such as human immunodeficiency virus (Capitanio & Emborg, 2008; Chemical Heritage Foundation; Roelfsema & Treue, 2014; Thomson et al., 1998). Recent phylogenetic studies have assessed the relationship between cortical mass and the number of neuronal cells. While the neuronal density decreases uniformly with the increase of cortex neurons in most mammalian species, the primate brain shares the unique characteristic of keeping a stable neuronal density with an increased number of neurons (Herculano-Houzel, Manger, & Kaas, 2014). Using functional magnetic resonance imaging and cluster analysis, evidence has been provided for several topologically and functionally correspondent human and monkey networks in sensory-motor and attention regions, especially for the human ventral attention network (Mantini, Corbetta, Romani, Orban, & Vanduffel, 2013).

In neuroscience, the use of nhps due to similarities with humans in brain network organisations (Herculano-Houzel, 2009;

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