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Review article

Aligning physiology with psychology: Translational neuroscience in neuropsychiatric drug discovery

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ABSTRACT

This review presents an overview of some of the pre-clinical and clinical issues that have contributed to the failures of potential novel neuropsychiatric drugs, which have prompted a re-examination of the role of animal models of neuropsychiatric disorders. Advances both in basic neuroscience and technology have driven the development of animal models of aspects of neuropsychiatric disorders. Genetics and environmental factors have been the primary contributors to the development of new animal models. Neuroimaging has contributed to the search for biomarkers by which neuropsychiatric disorders may be identified and differentiated, its progression monitored and that the effects of therapy assessed. Parallel to these theoretical and practical advancements have been the changes in the diagnosis and classification of neuropsychiatric disorders from DSM-4 to DSM-5, and emergence of the NIH initiatives such as MATRICS; CNTRICS and RDoC. These latter changes are shifting our concepts of neuropsychiatric disorders away from phenomenology to their biology and thus aligning physiology with psychology.

Contents

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"...psychiatry has a diagnostic and classification system that is not based on aetiology, neurobiology, epidemiology, genetics, or response to medications, but rather on a constellation of signs and symptoms. The Diagnostic and Statistical Manual (DSM-IV) is based on clusters of symptoms and characteristics of clinical course that do not necessarily describe homogeneous disorders, but rather reflect final common pathways of different pathophysiological processes involving genetic and environmental contributors."[1]

"...the 1960 and 70's was also a period that saw the development of non-mechanistic based models of depression, that is, models that were not dependent upon the induction of specific neurochemical alterations reversible by specific pharmacological manipulations. Consequently, model development concentrated on the replication of some of the changes in behaviour thought to be core to the disorder."[2]

1. Introduction and background

A fundamental problem hampering the development of novel chemical entities as efficacious therapeutics for the treatment of psychiatric disorders is that these disorders are defined by abnormal behaviour, and therapeutic efficacy is ultimately judged by changes in these behaviours. For example, present EMA (European Medicines Agency) guidelines for the evaluation of drug candidates, for depression, generalised anxiety and schizophrenia require assessment by rating scales [(e.g., Hamilton Rating Scale of Depression (European Medicines, 2013); Hamilton anxiety rating scale (European Medicines, 2005); Positive and Negative Symptom Scale (European Medicines, 2012)]. In addition, clinical global assessments may be used as secondary endpoints in determining the potential clinical efficiency of a drug candidate.

While neurological disorders are closely and causally related to neurological abnormalities, they too have psychiatric-like behavioural sequelae that characterise the disorder, and which may also be prodromal (Lyketsos et al., 2008). These behavioural abnormalities compound the pain and suffering of the affected, and determine the outcome of therapy. For example, Parkinson's is commonly associated with co-morbid depression, anxiety, and apathy, as well as cognitive psychosis (Cooney and Stacy, 2016; Holden et al., 2016). Neuropsychiatric symptoms are common in Alzheimer's disease (Spalletta et al., 2010), and treated pharmacologically with variable results (Wang et al., 2015a). Impairments in cognition are common across neuropsychiatric disorders, (Henry et al., 2016) and are severe unmet medical needs (Millan et al., 2012). Moreover, as with psychiatric disorders, cognitive impairments and change are also assessed psychometrically (Schneider, 2008).

Although changes in cognitive processes such as memory, attention, vigilance can be measured objectively, mostly through computerised test batteries [see for example, (Di Rosa et al., 2014; Gur et al., 2017; Harvey and Keefe, 2015; Smith et al., 2013)], interview-based methods and psychometric scales still form the mainstay of clinical assessment of cognitive impairments in neuropsychiatric disorders (Durand et al., 2015; European Medicines, 2008; Harvey and Keefe, 2015; Henry et al., 2016; Schneider, 2008). Psychometric scales and computerised assessment instruments measure different aspects of cognition and mood, which may be loosely related to each other [cf, (Smith et al., 2013)], prompting initiatives to improve the objectivity and reliability of standard clinical assessment scales through automating their presentation and scoring [cf, (Kobak et al., 2009; O'Halloran et al., 2011)].

On the other hand, animal models of neuropsychiatric disorders have been traditionally defined in terms of changes in behaviour [cf., (Hånell and Marklund, 2014; McArthur and Borsini, 2006; Willner, 1991a)]. As it is difficult, if not otherwise impossible to recapitulate all aspects of neuropsychiatric disorders, animal models are limited in the range of symptoms that they attempt to reflect, and, depending on the procedures used to induce pathological behaviours, tap into circumscribed presumed physiological mechanisms underlying those behaviours. Animal models are composed of procedures used to induce abnormal psychiatric-like behaviours in an otherwise healthy and "normal" animal (Geyer and Markou, 2002; McArthur and Borsini, 2006), the results of which are again measured by not only behaviourally, but also by physiological procedures such as biochemical (Muller et al., 2016), electrophysiological (Braff and Geyer, 1990), genetic (Gould and Manji, 2004), neurological (Beal, 2001), or imaging procedures (King et al., 2005).

This relationship between behavioural changes in animal models of neuropsychiatric disorders and underlying physiological mechanisms is the strength of animal models to investigate and elucidate normal and pathological behaviour, and gives substance to psychological constructs (Markou et al., 2008). Nevertheless, while animal models are fundamental to the understanding of behaviour from a physiological and psychological perspective (McArthur, 2010b), these results, are at best considered useful to progress a compound into clinical development within the biopharmaceutical industry, but are usually considered irrelevant by clinical investigators evaluating the potential efficacy of drug candidates in clinical trials (Lasagna, 1999; Littman and Williams, 2005; McArthur, 2010a).

There is considerable concern over the failures during Phase II–III clinical testing of potential novel CNS drugs (Gribkoff and Kaczmarek, 2016; Kesselheim et al., 2015; Kola and Landis, 2004; Paul et al., 2010; Riordan and Cutler, 2011). This has led to the nearly wholesale retreat of large Pharma from further investment in these therapeutic areas (Kaitin and Milne, 2011; Nutt and Attridge, 2014; Skripka-Serry, 2013). This disengagement is associated with a growing scepticism of the predictive value of animal models of neuropsychiatric disorders and clinical efficacy (Littman and Williams,

[1] Husseini Manji Page 189, In: Agid, Y., Buzsaki, G., Diamond, D.M., Frackowiak, R., Giedd, J., Girault, J.-A., Grace, A., Lambert, J.J., Manji, H., Mayberg, H., Popoli, M., Prochiantz, A., Richter-Levin, G., Somogyi, P., Spedding, M., Svenningsson, P., Weinberger, D., 2007. How can drug discovery for psychiatric disorders be improved? Nat. Rev. Drug. Discov. 6, 189–201.

[2] McArthur, R., Borsini, F., 2006. Animal models of depression in drug discovery: a historical perspective. Pharmacology, biochemistry, and behaviour 84, 436–452.