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Publication Date

2020-09-01

DOI

10.1016/j.neubiorev.2020.07.008

Peer reviewed

Neuroscience and Biobehavioral Reviews 116 (2020) 452–453

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Commentary

Lost in translation: At the crossroads of face validity and translational utility of behavioral assays in animal models for the development of therapeutics

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Translational endpoints, including behavioral outcomes in animal model systems, are essential for studying mechanisms of neurodevelopmental, neuropsychiatric, and neurodegenerative disorders. As such, these endpoints are necessary for driving the development of effective therapeutic treatment strategies. Yet, often overlooked is that not all behavioral tests and phenotypes studied in the laboratory in animal models are robust, reliable, reproducible, nor optimal for enabling translational application to the clinic. In clinical trials, there has been an overwhelming and persistently high rate of failure for novel therapeutic compounds to meet efficacy endpoints for behavioral constructs/outcomes (e.g., depression, cognition), enabled by supporting behavioral data generated in animal models. So what went wrong? This question challenges the field to take an honest look at recognizing the limited value of some behavioral paradigms utilized for determining the translating potential of novel therapeutics; and to seek improved, innovative strategies and outcome measures.

Translational assays should encompass functional outcomes and measures that can be assessed in both humans and animals. Indeed, there are obvious methodological differences and challenges inherent to testing animals and humans, such as the use of language for instructions and verbal-based assessments in humans. Thus it seems imperative that a rodent or non-human primate task designed as an analogue of a human task should consider the translational validity carefully. In this context, some assays currently utilized to phenotype animals have historically claimed validity, but their relevance and translational value remain unclear. For example, humans do not bury marbles, nor are they suspended by their feet, or forced to swim in clinical trials to assess improvements in affective symptoms in patients. Clinical trials for therapeutic agents seeking to improve cognitive impairments in patients do not use fear conditioning nor require the patient to undergo physical stressors or physically navigate mazes. That is not to say such assays in animal models have no value, but rather that *an observed behavioral trait manifested in an animal paradigm may not necessarily capture the behavioral construct impacted in human disease; at least not enough to make claims regarding the putative clinical efficacy of a new therapeutic compound*. Nearly every drug candidate that failed in the clinic with cognitive endpoints was supported by positive preclinical data demonstrating its ability to improve cognitive impairment using some of these traditional behavioral assays (e.g., fear conditioning, water maze, novel object recognition) that have been in practice since their inception in the latter half of the last century. Despite these data demonstrating the false positive nature of these assays for predicting clinical efficacy, researchers persist. In response to the growing numbers of these false positive studies, funding agencies have stated a need to deprioritize behavioral outcomes in animals in lieu of more translatable biomarkers (Snyder et al., 2016). Assays historically employed with claims of *predictive validity* have certainly been successful for screening “me too” like mechanisms, but have not been particularly successful in translating novel mechanisms beyond what these assays were established and validated as predictive for. Even the clinically available drugs which demonstrated robust reversal of cognitive impairments in traditional behavioral assays in animals only modestly improve cognition in some patients (Husain and Mehta, 2011).

So where do we go from here? There is no single solution, however, recent advancements in new technologies aimed towards effective translation of animal paradigms to the clinic are beginning to pave the way for improved animal-to-human translation. For example, the rodent touchscreen platform enables a battery of tests to be administered under the same, controlled testing environment requiring responses directed to visual, spatial and auditory cues, specifically developed to be analogous to the human touchscreen test batteries (e.g., CANTAB) available to probe different cognitive domains (e.g., learning and memory, attention, executive functions) in clinical populations. Additionally, integrating behavioral assays with telemetry devices such as those that can correlate behavioral responses with biomarkers of EEG and physiology (e.g., blood pressure, heart rate, temperature) are also improving translational value. Sleep signatures are conducive to continuous data collection over long periods (hours/days/weeks) and can

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https://doi.org/10.1016/j.neubiorev.2020.07.008
Received 22 May 2020; Accepted 10 July 2020
Available online 15 July 2020
0149-7634/

be based on highly objective neurophysiological measures. Animal models used to study neurodevelopmental, neuropsychiatric and neurodegenerative disorders frequently report dysregulation of sleep and biological (diurnal, circadian) rhythms, suggesting common pathophysiologies across species (Mullington et al., 2016).

Imaging methodologies such as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) are available for animal studies, albeit expensive, but provide nearly identical translational measures of neuroanatomical changes, and in some cases with the same PET ligands validated and in use in clinical trials. Critically, any drug being evaluated for translational studies in animal models requires a knowledge of the drug exposure level and pharmacokinetics in the target tissue (e.g., brain) and ideally an understanding of its therapeutic window for efficacy relative to any confounding side effect (e.g., hyperactivity, sedation, impaired motor coordination). Improved translation that uses behavioral outcome measures as well as pharmacodynamic readouts will also need to demonstrate the drug's pharmacokinetic/pharmacodynamic (PK/PD) relationship and ideally with a translatable biomarker being used in clinical trials (Snyder et al., 2016; Sukoff Rizzo et al., 2019). Combinatorial approaches that leverage translationally relevant behavior, neuroanatomy, neurophysiology and neuropharmacology should be used to strengthen the interpretation of preclinical behavioral outcomes and develop a platform for translational success (Snyder et al., 2016; Silverman and Ellegood, 2018). Emphasis should be placed on strengthening the predictive validity of tasks by utilizing disease relevant models that also incorporate relevant ages, rather than otherwise normal, healthy young subjects (Sukoff Rizzo et al., 2019).

In conclusion, while we strongly believe in the value of behavioral measures in preclinical animal models and support the utility of well validated behavioral assays for phenotypic characterization, we also challenge the community to critically reflect on the assays being utilized and evaluate their strengths and weaknesses when addressing preclinical to clinical translation. There is no doubt that functional outcome measures, including behavior, are fundamental for translational studies to deliver better therapies to patients with brain disorders; but in order to achieve this, we collectively need to move toward improved predictive validity and push to advance novel behavioral approaches that promote translation.

Declaration of Competing Interest

The authors declare no competing interests. JLS is supported by National Institute of Neurological Disorders and Stroke R01NS097808 and MIND Institute's Intellectual and Developmental Disabilities Resource Center HD079125; JN is supported by Australian Research Council Future Fellowship FT140101327; AD-A is supported by National Institute of Mental Health R01MH121352; JWY is supported by National Institute of Mental Health UH3MH109168; SJSR is supported by National Institute on Aging R13AG060708, U54AG054345.

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