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Use of the forced swim test to assess "despair"

Dear Editors

In their recently published manuscript, "Chronic brain stimulation rewarding experience ameliorates depression-induced cognitive deficits and restores aberrant plasticity in the prefrontal cortex," [1] Chakraborty and colleagues describe subjecting rats to the forced swim test (FST), which involves dropping them into inescapable tanks of water and measuring how long they attempt to climb and swim before becoming relatively immobile, making only the motions necessary to keep their noses above the water line. The authors state that they use the FST to assess the animals' "despair" following early life injections of clomipramine hydrochloride (CLI) and, later, intracranial self-stimulation of the lateral hypothalamus - medial forebrain bundle (LH-MFB). From their FST results, the authors conclude, "repeated electrical self-stimulation of LH-MFB ameliorates behavioral despair … in neonatal CLI model of depression" [1]. They go on to say, "We speculate that brain stimulation rewarding experience could be evolved as a potential therapeutic strategy to treat affective disorders" and, "Our results support the hypothesis that chronic brain stimulation rewarding experience might be evolved as a potential treatment strategy for reversal of learning deficits in depression and associated disorders" [1]. The authors offered no discussion as to other possible interpretations of the animals' behavior or to the scientific controversy surrounding this behavioral test.

The FST, also called the Porsolt swim test, was popularized in the 1970s by Roger Porsolt as a potential method for screening antidepressant drugs. Porsolt observed that rats dosed with antidepressants would spend less time immobile while in the water, compared to rats that had not been given the drug, leading him to assert that a longer swimming time indicated a less depressed rat [2]. However, some have suggested that immobility in the FST is a learned or adaptive behavior, not one representing an internal state of "despair." Dutch scientists Molendijk and de Kloet argue that behavior during the FST instead measures an individual animal's coping in response to stress [3]. Therefore, an alternate interpretation in the present study could be that repeated electrical self-stimulation of LH-MFB promotes passive coping in rats given early life injections of CLI. If, by floating sooner and struggling less, the animal is saving energy in an attempt to prolong survival, then what is interpreted as "despair" in the FST may represent the enhancement of a positive evolutionary trait.

While the FST appears to show predictive validity for selective serotonin reuptake inhibitors (SSRIs), a class of widely-prescribed antidepressant compounds, these responses are typically seen after acute administration of the drug, contrasting with the chronic intake (weeks to months) needed to produce a clinically-relevant response in humans [4]. Use of the FST may also result in false positives. For example, the cannabinoid receptor agonist rimonabant has demonstrated "antidepressant-like" effects in FST experiments according to study authors [5–7]. However, rimonabant, which had been approved to treat obesity, was associated with increased psychiatric adverse events in users, including depression and risk of suicide, and rimonabant's market authorization was suspended in 2008 [8]. To better quantify the FST's predictive ability, empirical data is needed. A systematic review examining compounds used in FST experiments and their subsequently demonstrated efficacy or inefficacy in human depression should be conducted if this test is to continue to be used as a model for human depression.

The ubiquitous use of animal experimentation has been cited as "the ultimate source of attrition" in human neurobehavioral clinical trials [9], and the FST and similar tests have been specifically pinpointed as contributing to the lack of progress in the development of new therapeutics [10]. Yet, as in Chakraborty et al., anthropomorphic interpretations of experiments like the FST, presented with no alternative explanations for an animals' behavior, continue to be published in peer-reviewed scientific literature. Between June 2015 to June 2018, approximately 72% of published FST experiments report using the FST to score "depression-like" behavior and another 19% used it to infer "antidepressant-like" properties of compounds [3].

Public acceptance for experiments involving animals is predicated on the assumption that animals are used only when absolutely necessary, when their use is expected to benefit humans or other animals, and when pain and distress are minimized. The nature of the FST is that it is fundamentally stressful and sometimes used solely for this purpose. As no animal model has the ability to capture all aspects of model validity and because the use of other animals is also constrained by inherent species differences which limit the translation of physiological findings to humans, to gain reliable insights into in human depression and its comorbidities, it is this author's opinion that scientists and drug developers must focus their efforts on human-based experimental models. Examples are many, and include computational modeling using already well-defined biomarkers and the use of patient-specific stem cells for personalized medicine. Meanwhile, reviewers should challenge authors' interpretations of FST behavior to facilitate thoughtful discussion on this matter.

Compliance with ethical standards

Conflict of interest

The author declares no conflict of interest.

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