HHS Public Access

Author manuscript

ACS Chem Neurosci. Author manuscript; available in PMC 2018 May 17.

Published in final edited form as:

ACS Chem Neurosci. 2017 May 17; 8(5): 955–960. doi:10.1021/acschemneuro.7b00042.

The Rodent Forced Swim Test Measures Stress-Coping Strategy, Not Depression-like Behavior

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Abstract

The forced swim test (FST) measures coping strategy to an acute inescapable stress and thus provides unique insight into the neural limb of the stress response. Stress, particularly chronic stress, is a contributing factor to depression in humans and depression is associated with altered response to stress. In addition, drugs that are effective antidepressants in humans typically promote active coping strategy in the FST. As a consequence, passive coping in the FST has become loosely equated with depression and is often referred to as "depression-like" behavior. This terminology oversimplifies complex biology and misrepresents both the utility and limitations of the FST. The FST provides little construct- or face-validity to support an interpretation as "depression-like" behavior. While stress coping and the FST are arguably relevant to depression, there are likely many factors that can influence stress coping strategy. Importantly, there are other neuropsychiatric disorders characterized by altered responses to stress and difficulty in adapting to change. One of these is autism spectrum disorder (ASD), and several mouse genetic models of ASD exhibit altered stress-coping strategies in the FST. Here we review evidence that argues a more thoughtful consideration of the FST, and more precise terminology, would benefit the study of stress and disorders characterized by altered response to stress, which include but are not limited to depression.

Graphical abstract

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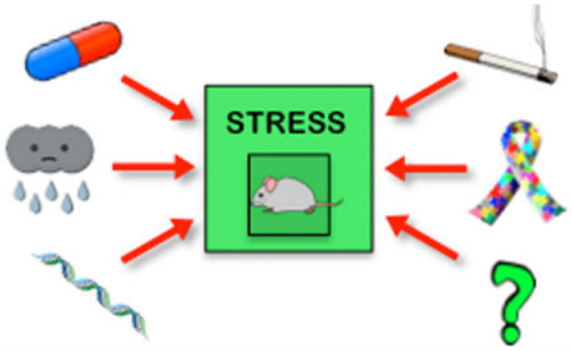
Author Contributions

K.G.C. conceived of the topic. K.G.C., A.B.C., J.A.B., and D.G.E. provided critical discussion, wrote, and edited the manuscript.

Notes

The authors declare no competing financial interest.



Keywords

Stress; behavior; autism; addiction; serotonin; antidepressants; Porsolt

INTRODUCTION

The forced swim test (FST) was originally introduced in 1977 by Porsolt and has been implemented and analyzed in several different ways.[1,2] In any form, the test is based on the observation that when rodents are faced with an inescapable aversive situation they can elect different strategies of coping that can be scored as either active or passive. Active strategies (climbing and swimming) predominate in the initial exposure to the swim but these are typically replaced over time with the appearance of a passive strategy (floating). The key observation that brought the test into widespread use was the discovery that effective antidepressants in humans had the ability to increase the amount of active strategies adopted by the animal in the FST. Thus, the major advantage of the FST has been its predictive validity: a drugs' effectiveness in promoting active coping in the FST had potential to predict its efficacy as an antidepressant. This was a particularly important observation because it yielded a simple screen in animal models to identify similarly acting drugs.[3,4]

The utility of the FST was extended by observations that conditions that are thought to contribute to depression in humans tend to shift rodent FST performance toward a passive coping strategy. For example, stress in humans is a key risk factor for depression.[5–8] Likewise, in rodents, stressful conditions during development, or adult chronic mild stress or repeated injections of the glucocorticoid corticosterone promote passive coping.[9–14] Thus, there is a possibility that the FST can have predictive validity to detect pro-depressant manipulations.

The observation that behavior in the FST is influenced not only by antidepressants but also potentially "prodepressant" manipulations suggests that the neural networks that control coping strategies in response to acute stress likely overlap heavily with those impacted in depression. For example, these networks probably include the hypothalamic–pituitary–adrenocortical (HPA) axis. Responses to acute stress are governed in large part by the HPA axis and dysregulation of the HPA axis often occurs in depressed patients.[6,15] Reduced hippocampal volume is one of the hallmarks of depression and the hippocampus is a key feedback regulator of the HPA axis.[16–20] Brain networks involved in the neural limb of the

stress response such as the extended amygdala and septal complex, as well as hindbrain serotonin- and norepinephrine-containing nuclei may also contribute to both depression and stress-coping strategy.[21–23] There is likewise evidence for overlap in cortical processing. For example, while deep brain stimulation (DBS) of Brodmann Area 25 alleviated depressive symptoms in patients,[24] high-frequency DBS of the rat ventromedial prefrontal cortex, the rodent correlate of Area 25, promotes active coping in the FST.[25–28] Thus, employed in conjunction with a larger behavioral profile and interpreted carefully, the FST is an important tool that can provide unique insight into the neurobiology of stress coping, which is relevant, but not equivalent, to major depressive disorder.

However, as a result of these interesting characteristics, performance in the FST is now routinely labeled as “antidepressant-like” or “depression-like” (Figure 1). That is to say, behavior in the FST is often egregiously overinterpreted. While it is likely that behavior in the FST is relevant to the biology of depression, there are many factors that can influence performance in the FST that have nothing do to with depression. Specifically, the term “depression-like” to refer to FST behavior is pointedly incorrect for three key reasons.

1. The FST actually measures coping strategy to an acute inescapable stress, not something like a pathological internal state of mind. Coping strategy is *measured* in the FST; “depression-like” is an *inference* that may or may not be correct (Figure 2).
2. “Depression-like” is jargon, used to acknowledge the limitations of the model system. However, “depression-like” is easily misunderstood by those less familiar with animal research including students, researchers in other fields, clinicians, patient advocates, and funding agencies.
3. The neurobiology underlying stress-coping strategy revealed in the FST is likely relevant to additional clinical conditions where there is poor behavioral response to acute stress. In this review, we highlight autism spectrum disorder as well as substance use disorder as contexts where the FST may be useful (Figure 1).

The FST has been closely and exclusively associated with depression research despite poor construct validity. Specifically, the shift from active to passive coping strategy that occurs over time when rodents are exposed to an inescapable swim appears to be normal, meaning typical of most rodents. Since the 1990s, it has been argued that the transition to floating behavior is an adaptive coping strategy to conserve energy, rather than a coping failure.[29,30] The term “depression” typically connotes clinically relevant depression or major depressive disorder, which is an impairment of the normal state. Major depressive disorder is a chronic disorder that often develops and persists over time, and in part, is defined by its extended duration. Sometimes pathological depression is initiated within the context of normal feelings of depression, or intense sadness, precipitated by a major stress such as the loss of a loved one. Normal depression could be argued to be an adaptive emotion that promotes rumination on loss serving to understand the cause and to motivate strategies to mitigate future loss. Similar to normal pain or normal anxiety, the experience of normal depression is unpleasant but is only considered to be pathological when it persists with sufficient intensity to result in the pervasive disruption of daily behavior. Moreover, while normal (transient) depression is widely experienced, this state only becomes pathological in a subset of

individuals. The FST falls short of a test for depression because these features of the pathological state of major depressive disorder are poorly represented.

The FST also lacks face validity for depression, in that there is little similarity between the clinical symptoms of depression in humans and the behaviors measured in the test. While it could be argued that passive coping strategies to stress are characteristic of depression, the connection between swimming and the human condition begs an abstraction at best. Behavior in the FST is a reaction to the acute stressful stimulus of being placed in a container without an escape route, and human depression reflects a chronic subjective emotional state rather than a reaction to an individual stimulus. Most importantly, depression is a pathological subjective internal emotional state and, to date, the subjective internal emotional state of nonverbal species is not knowable. Do rodents in the FST experience despair, sadness, frustration, or emotional exhaustion and are these equivalent to being depressed or depressed-like? A fundamental premise underlying neurobehavioral research involving animals is that nonhuman species likely experience emotion that is parallel to humans in many ways. However, the problem is in ascertaining exactly what those emotions are without a means of communication. In fact, the diagnosis of major depressive disorder in humans is exceedingly difficult in the absence of subjective report. Therefore, it is impossible to conclude with certainty that the FST is a measure or a test of depression, or a “depression-like” state.

The limitations of the FST as a test for depression or “depression-like” behavior have been emphasized previously.[30–32] However, an important additional consideration is that treatment of the FST as a test of depression-like behavior negates the importance of this test in assessing stress coping behavior as it relates to a much broader range of neurobehavioral disorders than just depression. For example, autism spectrum disorders (ASD) are frequently associated with altered behavioral responses to acute stress and difficulty adapting to change. Similar to depression, there is also evidence for alterations of the HPA axis in ASD.[33,34] Moreover, accumulating evidence supports the contention that stress plays an important role in the severity of repetitive behavior, a core feature of ASD.[35] Likewise, stress is a factor that influences social interaction: another core behavioral feature disrupted in ASD. Taken together, an altered behavioral response to an acute stress has the potential to represent an endophenotype for ASD that could provide unique insight into the neurobiological underpinnings of this disorder.

There are now several genetic mouse models for ASD, some of these are based upon gene associations, copy number variants, or missense mutations found in human ASD. Others have less construct validity but provide face validity in their overall behavioral repertoire. Consistent with associations between ASD and altered behavioral responses to acute stress, many of these models exhibit altered behavior in the FST. Several ASD mouse models display enhanced active coping behavior in the FST and/or fail to show the normal adaptation from active to passive coping during the time-course of the test. These include Fragile-X Mental Retardation 1 (FMR1) knockout, Timothy Syndrome Type 2 (TS2-neo) mice, BTBR T+tf/J, and mice modeling 16p11.2 chromosomal microdeletion.[36–41] Of these, only the FMR1 knockout mice display generalized hyperactivity outside of the FST that could account for increases in active coping behavior.

Nonetheless not all genetic mouse models for ASD show uniform behavioral changes in the FST. For example increased passive coping in the FST has been observed with the Engrailed 2 (En2) null mice, male but not female growth-associated-protein-43 (GAP43) heterozygous knockout mice, Grik4 overexpressing mice and Npas4 deficient mice.[42–46] Of these only Grik4 overexpressing mice are hypolocomotive outside of the FST. Perhaps it is not surprising that these various mouse models of ASD show different behavior in the FST considering their variable relationship to the human disorder, diversity in genetics and overall behavioral profile. In fact, human ASD is characterized by a marked heterogeneity of behavioral features. However, the propensity of mice models related to ASD to exhibit altered stress coping behavior in the FST is striking, and suggests that the FST may provide a unique perspective to help to illuminate more generally the biological underpinnings of ASD. Moreover, they raise the possibility that the FST could be used to clarify how these differences in stress coping strategies influence or exacerbate the expression of the core behavioral features perturbed in mouse models of ASD that include social interaction, communication, and repetitive behavior.

It is imperative to point out that there is little rationale to interpret these alterations in stress coping strategies in genetic mouse models related to ASD with respect to depression, that is, as “depression-like” or “antidepressant-like”. In humans, there is little evidence to support the idea that depression is either over- or under-represented in ASD.[47] Although antidepressants may be highly prescribed in ASD, their efficacy is unsupported. In fact, individuals with ASD may be more likely to experience adverse effects from antidepressant treatments.[48,49] Randomized control trials do not show any compelling efficacy for tricyclic antidepressants in the treatment of ASD.[50] Likewise, “there is no evidence of effect of SSRIs in children with ASD and emerging evidence of harm”.[51]

While observations of altered stress coping in mouse models with ASD related genetic mutations have only been noted more recently, they add to a growing literature indicating that the FST is relevant to other disorders such as substance use disorder, which is also stress related. Stress clearly contributes to substance use disorder emphasizing the importance of understanding how these factors converge and/or overlap in the brain. In rodents, previous or current exposure to drugs of abuse changes coping strategies in the FST.[52–58] In addition, acute swim stress is sufficient to promote relapse to drug seeking.[59] Interpretation of behavior in the FST in the context of depression in addiction models is not trivial. While there are similarities between depression and the dysphoria associated with withdrawal, they are not equivalent and most antidepressants have little effect on relapse behavior.[60]

Moreover, there are additional known factors that can generate “false-negative” or “false-positive” effects in the FST when interpreted with respect to depression or antidepressants. Stimulants and sedatives have long been known to change behavior in the FST, and general changes in locomotor activity should always be evaluated in the absence of stress to interpret behavior in the FST more accurately.[61] Likewise factors that influence how stressful the swim may be perceived, i.e., age, metabolism, weight, and the ability to stay afloat, impact behavior in the FST.[62–64] These factors tend to receive little consideration when interpreting behavior in the FST with respect to depression.

Nevertheless, the FST is a unique and valuable tool in the field of behavioral neuroscience. It constitutes a well-characterized assay providing insight into the neural limb of the stress response in the context of an acute, ethologically relevant stress. The value of the FST for the study of depression as well as other disorders would be considerably enhanced, not by technical tweaking, but by understanding its limitations. Interpretation related to subjective emotional state needs to be thoughtfully considered holistically, that is hand-in-hand with data from a suit of related behavioral tests as well as within the overall experimental context (Figure 2). For example, it would not seem meaningful to interpret a mouse model of ASD with a tendency for repetitive behavior as "antidepressed" if they exhibited persistent active coping in the FST. Likewise it is a tenuous proposition to diagnose a knockout mouse exhibiting passive coping in the FST as "depressed-like" in the absence of strong converging lines of evidence. Thoughtfully employed and interpreted though, the FST shows itself to be a powerful tool. As a good example, a recent study made an intriguing argument that manipulating housing conditions can impact affective state by using the FST in combination with observations on feeding behavior, HPA axis function, and antidepressant treatment.[65]

Similar to the FST, the tail suspension test (TST) measures the time spent employing active or passive behavioral coping, and this is sensitive to antidepressants.[66] The TST was developed as an alternative method that is easily scored while avoiding the hypothermic effects of water immersion. While we focus our discussion on the FST, many of the same observations extend to the TST, which similarly measures coping strategy while depression-like behavior is inferred. In fact, many of the same arguments cautioning against prepackaged interpretation could be applied to several behavioral paradigms that purport to measure a subjective emotional state. Foremost among these would be tests for "anxiety-like" state, which often measure exploration.

Construct validity is how well a test measures what it reports to measure. In this review we have argued that the FST does not have strong construct validity for as a test for depression. Make no mistake: the FST has no better construct validity as a test for ASD or substance use disorder. Rather the FST measures coping strategy to an acute stress and therefore has excellent construct validity for coping strategy to an acute stress (Figure 1). Evidence suggests that coping strategy to acute stress is relevant for understanding depression and the mechanism of action of antidepressants. Moreover, we review evidence that coping strategy to acute stress may also be relevant to other disorders such as ASD and substance use disorder; providing a basis to support face validity for using the FST in additional biological contexts. Predictive validity of the FST, arguably the most important experimental characteristic of a test, is considered very good for antidepressants of known pharmacological classes. However, for novel classes of antidepressants or for treatments relevant to ASD or substance use disorder, the predictive validity of the FST remains to be determined.

CONCLUSION

The emotional mind-state and physical actions are inextricably linked. The problem is that that linkage may not be simple, direct or constant. Many rodent behavioral assays depend on measuring patterns of locomotion: actions. What these assays reveal in terms of emotions

and mind-state needs demands careful consideration. The ease with which behavior in the FST (or TST) is equated to depression called “depression-like behavior” in the current literature is disquieting because it assumes a connection between animal behavior and human psychopathology that discourages critical thought. The FST is not a model nor a stand-alone test for any neuropathological condition. Rather is an interesting and unique test that gives insight into the neural networks that coordinate the behavioral response to an acute inescapable challenge, which may be impaired in depression, ASD, and other disorders.

Acknowledgments

Funding

Funding provided by the National Institutes of Health Grants DA021801 and HD036379, the Brain and Behavior Foundation NARSAD Independent Investigator Award, and the Sara Page Mayo Foundation for Pediatric Pain Research.

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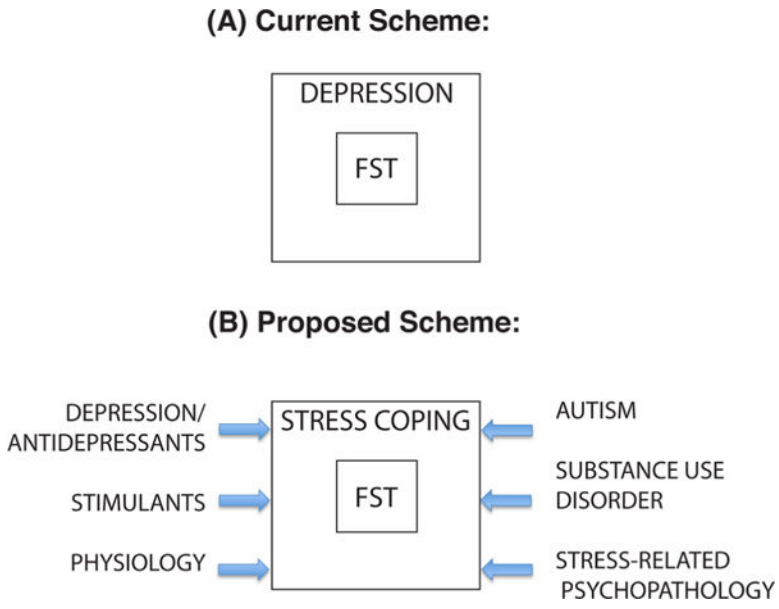

Figure 1.

(A) Current scheme: the forced swim test (FST) is interpreted in the context of depression/antidepressant action. However, the FST has poor construct and face validity as either a model or a test for depression, and not all of the factors that change coping strategy in the FST are relevant to depression. (B) Proposed scheme: The FST gives unique insight by measuring coping strategy to an acute, inescapable, ethologically relevant stress; but is not a model or a stand-alone test of any psychopathology. Rather, stress-coping strategy in the FST can be modified by factors relevant to depression and antidepressant efficacy, arousal state, metabolic state, as well as additional neuropsychiatric conditions including autism spectrum disorder (ASD) and substance use disorder. For stress coping, the FST has excellent construct validity. The observation that depression, ASD, and substance use disorder are all associated with altered response to stress lends face validity for use of the FST in each of these contexts.

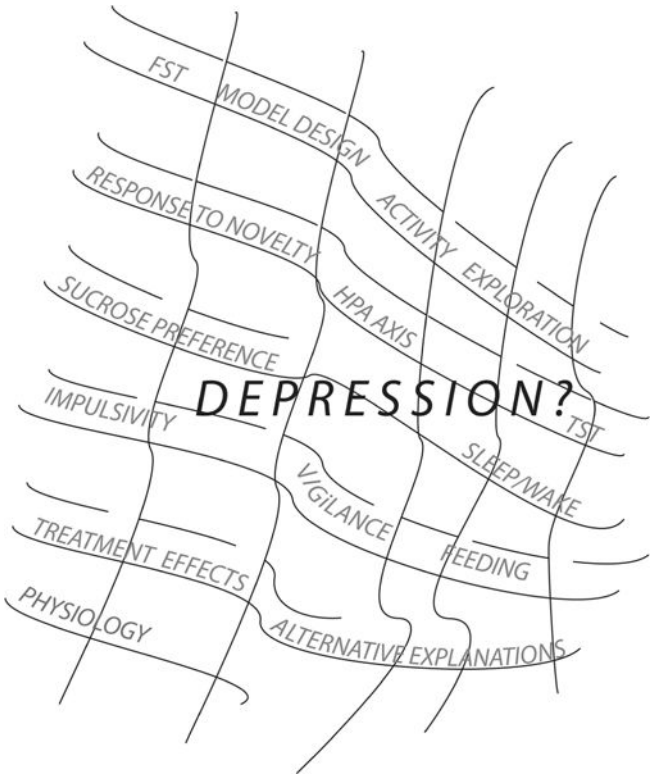

Figure 2.

"Facts are contained in the [data]. The fabric of speculation against which they are projected is thin indeed and has to be rewoven many times before it will stand much wear".[67] The mind-state of a rodent relevant to depression is the subject of speculation. Data from the forced swim test is an important thread of evidence that has to be carefully considered with respect to the entire behavioral and experimental context to support a compelling interpretation.