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Factors influencing behavior in the forced swim test

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Abstract

The *forced* swim test (FST) is a behavioral test in rodents which was developed in 1978 by Porsolt and colleagues as a model for predicting the clinical efficacy of antidepressant drugs. A modified version of the FST added the classification of active behaviors into swimming and climbing, in order to facilitate the differentiation between serotonergic and noradrenergic classes of antidepressant drugs. The FST is now widely used in basic research and the pharmaceutical screening of potential antidepressant treatments. It is also one of the most commonly used tests to assess depressive-like behavior in animal models. Despite the simplicity and sensitivity of the FST procedure, important differences even in baseline immobility rates have been reported between different groups, which complicate the comparison of results across studies.

In spite of several methodological papers and reviews published on the FST, the need still exists for clarification of factors which can influence the procedure. While most recent reviews have focused on antidepressant effects observed with the FST, this one considers the methodological aspects of the procedure, aiming to summarize issues beyond antidepressant action in the FST. The previously published literature is analyzed for factors which are known to influence animal behavior in the FST. These include biological factors, such as strain, age, body weight, gender and individual differences between animals; influence of preconditioning before the FST: handling, social isolation or enriched environment, food manipulations, various kinds of stress, endocrine manipulations and surgery; schedule and routes of treatment, dosage and type of the drugs as well as experimental design and laboratory environmental effects. Consideration of these factors in planning experiments may result in more consistent FST results.

Keywords

Forced swim test; Depression; Behavior

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1. Introduction

Major depressive disorder is a global medical problem due to its high prevalence and incomplete responsiveness to treatment [1]. Screening of novel antidepressants is an important practice in modern research due to the limited efficacy and large number of side effects of existing treatments [2]. The forced swim test (FST), also known as the 'behavioral despair' test, was developed in 1978 by Porsolt et al. [3] as a rodent model for predicting the clinical efficacy of antidepressant drugs.

The basic FST involves two sessions with animals placed in a cylinder containing 25 ºC water, from which they cannot escape. The first session is a 15-min pretest that is followed 24 h later by a 5-min test session. The pretest is a stressor which is thought to induce a state of behavioral despair [4] or passive stress coping strategy [5], since the animals become more immobile as the test session progresses. The typical posture of immobility is characterized by floating in the water with only movements necessary to keep the nose above the surface. The immobility time and also the latency to the initial immobility period [6] are the primary dependent measures. A wide range of antidepressant drugs injected between the pretest and test periods decrease the duration of immobility in the test, i.e., makes the rats more active [7].

In 1996, Detke and coauthors added evaluation of active behavior during the FST — climbing: vertical movements against walls; swimming: horizontal movements across the water surface; and diving. This modified version facilitates differentiation between the major classes of antidepressant drugs in rats [8]. Treatment with norepinephrine-targeting antidepressants selectively increases climbing in the FST, while drugs influencing serotonin neurotransmission enhance swimming behavior. Adding measurement of the latency to immobility to the standard procedure increases the sensitivity of the FST in both mice and rats [6,9].

The FST is also used for assessment of depressive-like behavior in animal models of psychiatric disorders [10–12]. The behavioral and biochemical characteristics of animals in a state of learned helplessness produced by a period of inescapable swimming during the FST have led some investigators to believe this condition itself provides a useful animal model of depression [13,14]. Forced swim provokes neurochemical and endocrine alterations [15,16] and is used as a stressor by itself [17,18].

Despite the simplicity and sensitivity of the FST procedure, large differences even in baseline immobility rates have been reported between different working groups, which complicate the comparison of results across studies. To illustrate this, some examples of differences in immobility scored in control animals of the two most commonly used strains of rats, Sprague–Dawley and Wistar, are presented in Table 1.

In this review, we have analyzed the published literature included in the PubMed MEDLINE database for factors that may influence rodent behavior in the FST and attempt to describe those variables that should be considered in studies employing the FST. First, factors which are known to influence FST results were chosen (e.g. physical environmental factors such as light and noise; biological factors such as age, sex, and strain; and manipulations before test,

such as housing and handling). As the FST was developed for the rat, and active behaviors estimated mostly for the rat, keywords for this search included “factor of interest + forced swim test + rat”. Sometimes, due to a low number of search results, (less than 10), keywords were changed to “factor of interest + forced swim test”, and results from other species, mostly mice, were included. If the search yielded more than 1000 results (as in the case of antidepressant treatment), only reviews were considered.

2. Biological factors in the FST

2.1. Strain of animals

Behavioral strategies in the FST can vary significantly with animal strain [53–55]. Even obtaining Wistar or Sprague–Dawley rats from different suppliers may yield different findings [4]. A significant decrease of struggling between first and second sessions of the FST was observed in *spontaneously hypertensive* (SHR) and Wistar Kyoto (WKY) but not in Fisher 344 or Lewis (LEW) rats [55]. Strain differences also exist in antidepressant efficacy [28,56,57].

Certain specific rat strains are also known to develop more depressive-like behavior in response to the FST, including the Flinders Sensitive Line and WKY. Taken together with results from other behavioral tests for anxiety, anhedonia and other assays, these strains of rats have been proposed to serve as possible animal models of a predisposition to depression [58–60]. Nevertheless, WKY rats have blunted responses to the serotonergic antidepressant fluoxetine and atypical increases in both climbing and swimming after treatment with the noradrenergic antidepressant desipramine [28,57]. In spite of the fact that Long Evans rats are a popular strain for assessing behavior particularly in animal models of depression, they display contradictory results in the FST. Chronic mild stress produced a greater increase in immobility in the FST in Long Evans rats than in Sprague–Dawley rats [54]. However, when the FST is done as a single 15 min session, Long Evans rats are less immobile than other widely used rat strains such as Sprague–Dawley, Wistar, and Fisher 344 rats [61]. In control Long Evans animals, the second swim session of the FST does not produce an increase in immobility behavior, depicting a potential strain-specific behavioral strategy [54]. In the modified FST, Long Evans rats display more interindividual variability in swimming behavior and have more baseline immobility, then Wistar rats [41,62]. After olfactory bulbectomy, a popular rodent model of depression, Wistar rats develop depression-like symptoms in the FST while Long Evans do not.

The underlying physiological substrates associated with inter-strain differences in FST behavior and variation in antidepressant sensitivity in the FST are not clear. In spite of significant differences in FST behavior, no unidirectional inter-strain differences in physiological responses to the FST were found [53].

2.2. Body weight and age

Animals of a range of bodyweights have been used in the FST in different studies. In the original work of Porsolt et al. [3], the authors used rats weighing 160–180 g. In more recent protocols for the FST, the use of rats ranging in weight from 180 g to 280 g has been

suggested [63]; other protocols propose a weight range of 275–450 g [64]. In a paper by Detke et al. (1996) describing the modified method [27], rats weighing 150–175 g were used. Some studies requiring long-term treatment maintain animals on treatments for several weeks, and as a result, the rats are larger than 400 g [33]. Body weight of rats has a significant effect on their behavior in the FST, and statistical subtraction by one-way multivariate covariance analysis (MANCOVA) of body weight difference has been used to account for variation in weight of animals used in the FST [37].

The parameter of age should also be considered in parallel with weight. There is a significant difference between the behavior of younger and older animals in the FST [35,65,66]. The ability to float is first seen in rat pups at 21 days of age and stabilized beginning at 26 days of age [67]. Older Sprague–Dawley rats (18–20 months old) were found to be more immobile in the FST then young adult rats (3–4 months old) [68]. In the study of Martinez-Mota et al. [69], adult male rats (90 days old) exhibit more immobility and less activity as compared to adolescent animals (35–37 days) in the pre-test session, but more immobility and climbing behavior in the test FST session.

Sensitivity to some antidepressants is profoundly altered by age. Chronic treatment with paroxetine, a selective serotonin reuptake inhibitor, has typical antidepressant-like effects in the FST in adult rats, but not in adolescent rats [70]. The response to treatment with tricyclic antidepressants or noradrenalin and serotonin reuptake inhibitors is stronger in the FST with 4-week old mice than in 40-week old mice [71]. Social isolation as well as treatment with reserpine, an antihypertensive and antipsychotic drug, increases FST immobility in 17–21-day-old Swiss Webster mice but not in 26–30-day-old animals [72].

2.3. Gender

Male and female rats exhibit different behavior during the FST. Female rats swim more during the pretest session than males, but exhibit a longer floating duration in the test session, while males have more climbing during both pretest and test sessions [46]. Female rats in proestrous and estrous phases (the rat estrous cycle is 4–5 days in length) exhibit more immobility than animals in the diestrous phase [52]. Additionally, female rats in proestrous or estrous-phase display increased active behaviors [73], more swimming and climbing, and less immobility after sham ovariectomy [74]. Other studies, however, indicate that female rats grouped together in proestrous and estrous phases of the cycle and in metestrous and diestrous phases did not differ in their behavior in the FST, but both groups displayed more immobility than males [34,75]. Chronic mixed modality stress (consisting of isolation, restraint, and social defeat) during adolescence shortened time spent in active behavior in the FST only in female but not in male Wistar rats [76]. In another study [53], no gender-based differences were observed in the FST between the sexes in five inbred strains of rats: Brown–Norway, Fisher 344, Lewis, SHR and WKY.

Gender-related differences have been observed also in the effect of drug treatment on FST behavior. Desipramine-induced antidepressant effects were noted to be significantly increased in male rats but not in females in one study [77]. Chronic treatment with another tricyclic antidepressant, clomipramine, was effective in the rat FST only for high novelty seeking males and low novelty seeker female rats [31]. Female rats maintained on a creatine-

enriched diet displayed increased activity in the FST, whereas creatine-fed male rats showed no consistent change in behavior in the FST [33].

2.4. Individual differences

Due to significant inter-group variability, this parameter is an important point of interest in the interpretation of FST results [24,39]. Inter-individual variations in behavior in the FST within otherwise identical animals could interfere with the consistent use of this test. For example, mice of the same strain that receive no treatments can have large variations in immobility duration [65]. Swim-test susceptible rats, which have reduced struggling in the FST and/or increased immobility, have also been shown to have inter-individual differences in other behaviors: high voluntary ethanol intake, enhanced stress-induced ethanol drinking [78], suppressed reactions in response to uncontrollable electric shock [79] and poor performance on spatial memory tasks [80]. When rats are divided into high and low sucrose intake groups, based on their preference for drinking sucrose solution versus water (a measure of hedonic trait), chronic social defeat stress-induced depressive-like behavior in the FST is seen only in rats with high sucrose intake [81].

In other studies, behavior in the FST was evaluated in rats divided into three groups according to time spent in the open arms of an elevated plus-maze chamber. The elevated plus-maze is a widely used behavioral test for anxiety [82], based on a tendency exhibited by rats to avoid open spaces: typically, the closed arms are explored for a longer duration than the open arms. The most anxious animals (those spent less time in the open arm) have less immobility in the second FST session versus the first, and a higher latency to immobility, while the other groups exhibit more immobility in the second FST session versus the first and a lower latency to immobility [39]. D-cycloserine, a partial agonist of the glycine binding site on N-methyl-D-aspartate receptors, decreased immobility in the FST in anxious but not in rats which spent more time in the open arms [83].

When animals are divided according to those that exhibit greater motor activity in a novel environment (high responders) versus those that are less active (low responders), high responders spent more time swimming in the rat FST [38]. Treatment with the norepinephrine reuptake inhibitor desipramine resulted in a significant decrease in immobility in the rat FST only in low responders, while the selective serotonin reuptake inhibitor fluoxetine caused a significant reduction in immobility in both groups [22]. In another rat study, [31] the tricyclic antidepressant clopiramine reduced floating and increased swimming only in high responder males, while in females, reduced floating and increased climbing were shown only for low responders.

3. Preconditioning and treatments

3.1. Preconditioning

3.1.1. Handling—Short-term handling daily for 5 days prior to the FST did not affect immobility time in rats, but long-term handling (2 months daily before the FST) increased immobility time in the study [84] (Table 2).

3.1.2. Housing—Exposing laboratory animals to physical or social stimulation greater than they would receive under standard housing conditions either had no effect on immobility [36,85] or had an antidepressant-like effect (Table 2).

Rats housed in an enriched environment exhibited less immobility [3] and more swimming and climbing in the FST [37]. Dietary supplementation with escitalopram, a selective serotonin reuptake inhibitor, had antidepressant effect in the rat FST only if combined with a running wheel in the cage [111]. The different sizes and design of enriched cages, duration of enrichment exposure and whether the animals were housed separately or in groups, may be responsible for the absence of any effect of enriched housing [36,85].

Housing either individually or in groups is an important factor. In general, social isolation is known to induce anxiety and depression-like symptoms in rodents. Short or long term isolation may modify immobility behavior in the mouse FST [65] (Table 2). An increase in FST immobility time was found in rat weanlings housed separately for 6 weeks [23]. Rats, isolated for 3 months from weaning, had the highest level of immobility and the lowest level of swimming and climbing [37]. However, in other studies, no effect of isolated rearing was found on rat FST behavior [36,43]. Probably, antecedent procedures, such as surgery or other behavioral testing performed before the FST might make the animals more prone to the depressogenic impact of isolated rearing. In adulthood, rats showed no impact of social isolation on FST rates [60,72]. The tricyclic antidepressant desipramine reduced immobility time in the FST only for rats housed individually [36].

3.1.3. Diet—Several studies have reported that chronic or acute food restriction increases immobility time [21,87] and abolishes the effect of escitalopram treatment in rats [29]. In other studies, food deprivation for 24 h had no effect on rat FST behavior estimated during only one swim session [89]. The behavioral consequences of food restriction may be related to the way in which food restriction is implemented: chronic caloric restriction caused reduced immobility in the mouse FST [88] (Table 2). Reduced effectiveness of escitalopram, an antidepressant of the selective serotonin reuptake inhibitor class in the FST was found in food-restricted rats [29].

A palatable high-fat diet increased immobility in the mouse FST [112]. Applied in the period from weaning to puberty, a high fat diet increased active behaviors in male rats during the first FST session, but induced more immobility in females during the second session of the test [113]. Rats exposed to early life stress or maternal separation stress, show depressive-like behavior in the FST, which is reduced by a high fat diet in the post-stress period [114,115]. A creatine-enriched diet potentiated antidepressant action of fluoxetine in the rat FST [34].

3.1.4. Stressors—The FST is a stressor itself in different experimental paradigms [17,116,117]. Alternatively, it has been used for assessment of depressogenic effects of various kinds of stress. Stressful events may enhance the occurrence of depression [118], and would be expected to have depressogenic action in the FST. However, published studies yield inconsistent behavioral results on the effect of stress on the FST (Table 2).

Unpredictable chronic mild stress resulted in more frequent active behavior during the pre-test session, but also a greater decline of active behaviors from pre-test to test session in the rat FST [54]. In other studies, chronic mild stress reduced immobility time in adult male Wistar rats [44,45], hypothetically because of an increase of impulsivity. But the effect of chronic mild stress is age dependent: exposure to chronic mixed modality stressors during adolescence decreased latency to float and time spent struggling in female, but not male, Wistar rats [76].

Social defeat either increased immobility in the rat FST [90,91] or had no impact on the rat behavior [24]; it also did not influence mouse FST behavior [92]. The variation in these findings may be explained by inter-individual differences in reaction to this type of stressor [24,81].

Chronic foot-shock stress (used in a learned helplessness model of depression), or inescapable foot shock, significantly increased immobility duration in the FST in mice [93]. Surprisingly, variations of inescapable foot shock differentially affect FST results. Mild electric shock enhanced the antidepressant effect of the tricyclic antidepressant clomipramine in the rat FST, while moderate shocks of higher intensity or duration reduced it [52]. In the same study, application of severe shocks increased the immobility time in untreated animals and counteracted the antidepressant action of clomipramine. In females, the effects of electric shock application varied as a function of the estrous cycle [52]. Increased immobility time in the rat FST, provoked by unavoidable chronic foot shock [95,96], was prevented by treating rats with the tricyclic antidepressant imipramine [94]. In mice, chronic foot shock resulted in increased immobility when they were tested before foot shock on that day, but if the FST was scheduled immediately after the foot shock, immobility decreased in the chronically stressed mice, but not in the control animals [97]. Another type of electric shock, electroconvulsive therapy, has an antidepressant effect in the rat FST [3,119], as well as in humans.

The effect of *chronic restraint stress* (immobilization for several hours daily in a special restraint chamber for several days) varies possibly due to the influence of hyperlocomotion induced by this type of stressor in the rat [120]: it can decrease immobility (antidepressant-like effect) [95], produce depressive-like behavior in the FST [26,40] or have no significant impact on immobility time [98]. Notably, acute restraint stress produced increased immobility in both weanling [99] and in adult rats [98].

3.1.4.1. Maternal deprivation: Effect of early maternal deprivation, e.g. separation of rat pups from their mother for several hours a day in the early postnatal period appeared to have a greater input from genetic predisposition than by experimental design or age of animals. The relatively mild procedure of temporary removal of the dam (while all the pups left in their home cage) increased immobility time, and decreased climbing time of adult Wistar male rats [50]. Whereas male pups of Fisher rats periodically isolated in another cage during first two weeks of life, have increased swimming activity in the FST in adulthood in Ref. [100]. In other studies, maternal deprivation did not alter immobility in prepubescent Wistar–Kyoto and spontaneously hypertensive rat lines [102] or adult Wistar rats [101]. In the study of Marais et al, [121], depressive-like behavior was seen in maternally separated

Sprague–Dawley rats only after additional chronic stress. Other types of early life stress, such as housing with limited bedding, enhanced depressive-like behavior as indicated by longer immobility in the rat FST [85]. Mother rats also had a long-term behavioral impact of separation from their pups, displaying increased immobility and shortened swimming duration in the FST [115].

3.1.4.2. Prenatal stress: Offspring from dams exposed to stress during pregnancy demonstrated depressive-like behavior in the FST [19,20,25,103]. However, in the studies of Rayen et al. [104], offspring of prenatal stressed rats spent significantly less time immobile in adolescence compared to the control group; although, only one swim session was used. Rats born by Cesarean section with 10–15 min of anoxia were significantly more immobile during the FST in adulthood [122]. Prenatal stress reduced the ability of hormone replacement to normalize depressive-like behavior in ovariectomized female rats [107]. Discrepancies in behavioral consequences of early life and prenatal stress could be produced by differences in experimental protocols as well as in strain or age of the animals during the FST [66].

3.1.5. Endocrine manipulations—Ovariectomy in rats has been reported to increase "the index of depression" [105] and increase immobility [106], while decreased immobility has also been noted [35]. These discrepancies may be explained by time-dependent changes in FST behavior after ovariectomy [74]. Hormone-replacement therapy decreased the duration of immobility [106] and improved other behavioral parameters in ovariectomized rats [74,123]. In the study of Rachman et al., [123] distinct behavioral profiles were found for ovariectomized rats and their counterparts treated with estrogen. Non-treated ovariectomized rats had initial attempts to active escape, including diving, but afterwards spent the rest of time immobile. Estrogen replacement therapy was associated with significantly reduced climbing behavior, which was followed by long periods of swimming; no immobility was observed. Both natural estrogen 17β-estradiol and synthetic steroidal estrogen ethinyl-estradiol produced a decrease in immobility and an increase in swimming behavior in ovariectomized female rats; this effect appeared 60 min after administration and lasted for 48–72 h [124]. Even endogenous estrogens originating from the brain significantly affect FST behavior. Ovariectomized females treated with the aromatase inhibitor letrozole to prevent estrogen synthesis in the brain, displayed enhanced immobility and decreased active behavioral responses during the FST [125]. Age, length of treatment, type of estrogen and other factors which might impact the effect of estrogens on FST behavior are described in a recent review by Estrada-Camarena et al. [74].

Estrogens may potentiate the antidepressant action of classic antidepressants. The combination of sub-optimal doses of estrogen or estrogen derivatives ethylestradiol or diethylestradiol with sub-effective doses of tricyclic antidepressant desipramine or selective serotonin reuptake inhibitor fluoxetine resulted in augmented antidepressant-like effects in the FST of ovariectomized female rats [126–128]. Estrogen treatment of orchidectomized male rats also produces antidepressant-like effects and restored the antidepressant action of fluoxetine and desipramine [129]. The antidepressant-like actions of estrogen may be blocked by antagonists for estrogen receptors [130] and, interestingly by 5-HT_{1A} receptor

antagonists [131] and enhanced by 5-HT_{1A} receptor agonists [131]. These data confirm participation of the serotonergic system in the antidepressant-like actions of estrogens [132].

Castrated male rats demonstrated increased depressive-like behavior, they struggled significantly less and spent more time immobile then did intact, or dihydrotestosterone treated rats [107,133]. A similar increase in immobility time, observed in the FST of castrated mice, normalized with testosterone supplementation [134]. Martinez-Mota et al. [47] noted that while orchidectomy itself did not alter depressive-like behavior in the rat FST, it blocked the action of the noradrenergic antidepressant desipramine. In intact male rats, subcutaneous testosterone application induced a dose-dependent reduction of immobility [135]. Administration of testosterone or its metabolites –dihydrotestosterone or 17beta-diol-3alpha-diol – 1 h before mouse FST reduced immobility and increased climbing time for both aged (24 months old) males and females [136]. Testosterone is thought to exert antidepressant action mediated by aromatization to estrogen-like compounds: gonadectomized males rats receiving estradiol demonstrate an increased time until immobility and spend a shorter total time immobile compared with gonadectomized rats receiving placebo or dihydrotestosterone supplements [133]. Interestingly that rats, chronically treated with the anabolic androgenic steroids nandrolone or stanozolol – drugs that mimic the effects of testosterone and dihydrotestosterone in the body – show increased immobility time in the FST along with other depression-like signs [137].

Pregnancy or progesterone injection to ovariectomized rats reduced immobility behavior [108,109,138]. Acute progesterone administration between pre-test and test FST sessions did not alter behavior both in intact female or male rats, while chronic treatment with progesterone (8–10 days) decreased depressive-like behaviors in female rats but increased immobility in males [139].

In the mouse FST, progesterone injected subcutaneously at a high dose, 10 mg/kg, caused a significant increase in immobility period [140], but when administered at a 1 mg/kg dose, it had antidepressant-like action causing an increase in latency to immobility and decrease in immobility duration [141].

The antidepressant effect of progesterone injections is long lasting; it is present if the FST scheduled 24 h after the treatment in rats [142] and observed until the third day after withdrawal in mice [143]. Progesterone withdrawal protocols induced robust depressive-like behavior in the rat FST, which normalized with the tricyclic antidepressant amitriptyline, but did not with the selective serotonin reuptake inhibitor fluoxetine or the combined norepinephrine and serotonin reuptake inhibitor duloxetine [144].

The antidepressant action of progesterone may be mediated by mimicking and enhancing GABA effects, which is confirmed by blockade of its action by picrotoxin, a $GABA_A$ antagonist [138]. Progesterone injections reduced immobility duration even in progesterone receptor knockout mice (both males and females), confirming that progesterone receptors do not play a sole role in its antidepressant action [145].

Following adrenectomy, immobility was decreased in male and increased in lactating female rats [35,110]. Surgically thyroidectomized and iodine-deficient rats showed a significant increase in immobility [146].

3.1.6. Surgery and other manipulations—In spite of the fact that olfactory bulbectomy is a well-established model of depression [147], only Wistar, but not Long Evans rats develop depressive-like symptoms in the FST after bulbectomy [41]. The immobility response in the FST may be concealed by hyperactivity of bulbectomized animals shown in other behavioral tests, such as the open-field or elevated plus-maze [147]. Other kinds of surgical intervention have depressive-like effects in the rat FST. After chronic constriction injury of the sciatic nerve, a model of neuropathic pain in rats [148], swimming behavior was unchanged, but immobility time was extended replacing climbing attempts. Lesions in the habenula, a brain region impaired in depression [149] or in the bed nucleus of the stria terminalis, a limbic forebrain structure involved in hypothalamo–pituitary–adrenal axis regulation and stress adaptation [150,151] also resulted in increased immobility and inhibited escape-oriented behavior. However, when rat behavior was assessed 1–6 months after experimental traumatic brain injury, no differences were observed in the FST [152].

Transient inactivation by bilateral infusion of the $GABA_A$ receptor agonist muscimol into the infralimbic cortex, the rodent correlate of Brodmann area 25, which has increased metabolic activity in depressed patients, reduced immobility and increased climbing behavior in Sprague–Dawley and HAB (Wistar rats selectively bred for high anxiety-related behavior) rats [153]. High-frequency electric stimulation of the subthalamic nucleus (a therapeutic approach for Parkinson's disease treatment) caused a striking increase in immobility and decrease in climbing time in rats [154], which was reversed by the selective serotonin reuptake antidepressant, citalopram. The immobility time in the rat FST was significantly shortened after 10 days of repetitive transcranial magnetic stimulation [155]. The FST has also been also used to confirm depressive-like behavior produced by experimental parasitic infection with *Trypanosoma cruzi* in mice [156].

3.2. Treatments

3.2.1. Schedule—Routinely, antidepressant treatment is given between the pre-test and test sessions of the FST. This standard treatment regime consists of three doses of 23, 5 and 1 h before the test session is proposed for mimicking a state of subchronic drug exposure [157]. A cumulative dose of an antidepressant divided into two or three administrations decreases immobility behavior more efficiently than an equal amount given in a single dose [158]. The common routes of drug administration are via subcutaneous or intraperitoneal injection, however, it is also acceptable to introduce the drug orally or via direct administration into the CNS [64].

To avoid treatment influence on pre-test training session, it is not recommended to schedule any treatments before the first session. Chronic treatment can be placed between the two sessions [63] with more than 24 h between the first and second sessions. Even if pretest and test sessions are separated by up to 7 weeks, it does not appear to influence immobility responses to vehicle or antidepressant treatment [158].

Although the pharmacological effects of antidepressants can be seen in a few minutes, their therapeutic action in humans is observed only after several weeks of treatment. To align animal responses in FST behavior to clinical studies of antidepressant effects, longer treatment regimes (several weeks) have been used [159–161]. In this case, even low doses of antidepressants were effective in increasing the face validity of the test [7]. Chronic supplementation with creatine, an ergogenic compound involved in energy buffering, decreased immobility in the FST in female rats [33] and potentiated the effects of subeffective doses of fluoxetine [34].

3.2.2. Type and dose of the drug—Several reviews have been devoted to the effects of different antidepressants in the FST [7,65,162,163]. In most cases, antidepressant treatment produces stable reproducible results in the FST, which strengthens the predictive validity of the test.

It is worth noting that treatment with some non-antidepressant drugs: psychostimulants caffeine, amphetamine [3], tranquilizers [164], GABAergic, anticholinergics and others [158,165,166] may yield *false positive* results (e.g. a decrease in immobility which does not correspond to the specific antidepressant action of the drug) in the FST.

The most important *false negative* results (no change in immobility after treatment by drug with known antidepressant action) for the FST are produced by the selective serotonin reuptake inhibitors (SSRI), most commonly in the classic version of the FST. The modified version of the FST helped to overcome this problem [8,27,163]. First, increasing the depth of water from 15–18 cm to 30 cm not only decreased time of floating behavior but also promotes an SSRI-induced decrease in immobility. A possible explanation is that SSRI treatment specifically augments swimming behavior [27], whereas increased water depth forced rats to swim more. Second, modified scoring techniques allow discrimination between immobility and swimming, which has not previously been considered as an active behavior in the classic version of the FST. To exclude the possibility of false results, it is recommended to separately assess locomotor activity (for example, by the open field test) in order to determine whether the treatment of interest alters general activity levels [64]. However, some limitations should be considered when using mouse FST. False positives and false negatives have been reported more often in this case. The tail suspension test is likely more effective in evaluation of depressive-like behavior and antidepressant effects in mice [225].

4. Test design and environmental conditions

4.1. Experimental design

4.1.1. Test equipment and settings—*Tank dimensions* play a significant role in determining behavior in the FST. In Porsolt's original version of the test, the tank was 40 cm in height and 18 cm in diameter; it was designed to have depth of 15 cm water, shallow enough for the rat to feel the bottom with its hind paws and tail [3]; animals developed a floating posture quickly and this resulted in more immobility during the second test session. The modified version of the FST involved increasing water depth to 30 cm, so the rat was unable to touch the bottom of the tank, and had more active behaviors [8,167]. If the tank is

wider, swimming behavior is facilitated [64]. In mice, the total duration of immobility was shorter and the latency was longer in the FST carried out in chambers with a 10 cm diameter (as in the common version of the protocol for mice) in comparison to 20, 30, and 50 cm tank diameters. Increasing the diameter of the cylinder allows investigators to distinguish antidepressant drugs from other compounds (such as caffeine, anticholinergics, and antihistamines) which gave false positive responses in the FST performed using the classic cylinder size in the mouse FST [168]. However, reduced basal immobility in a wider tank abolished imipramine-induced reduction of 'behavior despair' in the mouse FST [169]. Another variation of the FST for mice was designed by introducing a small water wheel in a tank. On that apparatus, mice showed escape-oriented activity by turning the wheel; the number of rotations increased specifically by treatment with antidepressants but not with other drugs [170]. Desipramine, a tricyclic antidepressant that inhibits the reuptake of norepinephrine and serotonin, reduced immobility behavior in the rat FST (using a 20 × 20 × 50 cm tank, containing 20 cm of water at 25 ºC), but not in the Swimming Stress task (using a 50 × 50 × 50 cm tank, containing 38 cm of water at 30 ºC) [171]. Diazepam had no effect on immobility in the rat FST [3], but increased immobility in response to Swimming Stress [171].

The effect of *water temperature* on behavior in the FST has been investigated in several studies [172–175]. The preferred water temperature for the test is 23–25 ºC. If tested in cooler water, rats spent less time immobile both during pre-test and test sessions [173]. When the water is warmer (i.e., 30 ºC), rats were less active [172]. However, in another study, rats in 19 ºC water spent more time immobile and less time swimming in one 15-min session of swimming when compared with rats exposed to 25 ºC or 35 ºC water [176]. In mice, those that swam at 25 ºC demonstrated greater immobility than animals forced to swim in water at 35 ºC [177]. Amitryptiline-induced inhibition of immobility in mice was more persistent in 41 ºC water than in 26 ºC water [178]. Antidepressant effects of treatment with desipramine were detectable only if mice were tested in 30 ºC water temperature but not at 25 ºC [179].

4.1.2. Time effects

4.1.2.1. Schedule of test performance: A significant role of circadian rhythm has been reported in regulation of FST behavior [180,181]. In the mouse FST, the immobility duration was shorter at noon (12:00 PM–2 PM) than at midnight (12:00 AM–2:00 AM); in this experiment mice were kept under a 14/10 light/dark cycle (lights on at 4:00 AM and off at 6:00 PM) [182]. Escape-oriented activity was reduced in rats tested in the late evening, in this case in the dark phase (the FST is performed from 8:25 PM until 11:51 PM, animals were maintained on a 12 h light/dark cycle: lights on at 8:00 AM; lights off at 8:00 PM) compared to morning scores (the FST is performed from 8:25 AM till 11:51 AM, during the light phase) [183] in spite of the fact that biochemical measurements indicated that the animals were less stressed by the forced swim during the active (i.e., dark) phase of their circadian cycle. The antidepressant effect of selective serotonin reuptake inhibitor fluvoxamine was more easily observed in mice tested at 9:00 PM (in the dark phase) compared with tests scheduled for 9:00 AM, 1:00 PM, or 5:00 PM, in the light phase

(animals maintained with a 12 h light/dark cycle: lights on at 7:00 AM, lights off at 7:00 PM) [184].

There is may also be a *circannual rhythm* in the floating behavior of rats in the forced swim test: an increase in immobility behavior in the winter and a reduction in immobility in the summer has been observed [185]. In another study, female rats spent more time immobile when tested in February and May than in August and November [186]. The maximal effect of treatment with tricyclic antidepressants in the rat FST was found in March [187]. Interestingly, lowering barometric pressure (20 hPa below the natural atmospheric pressure) increased immobility time in rats [188].

4.1.2.2. Number of the swim sessions: Originally, two swim sessions were proposed for the rat FST [157]. The first 15-min training session is performed with naive rats and results in a long period of floating. The second 5-min test session is scheduled 23 h later; the rats tend to stay immobile for around 75% of the test period. Rats develop immobility much faster during the second test. Notably, in mouse FST a single 6-min test session is usually performed; the immobility time and latency of immobility during the last 4 min are estimated [164,189]. But some investigators have developed two session procedures with mice as well [190,191].

The behavioral change across the preconditioning and test exposures might reflect an ambient increase in behavioral despair indicative of mood change incurred by the reconditioning exposure. However, it also could involve an element of learning and memory [5,80] and be indicative of cognitive aspects of major depression in humans. If pre-conditioning procedures affect memory processing they could yield a false result. For example, there is unpublished data indicating that cycloheximide, a well known memory blocker, does reduce immobility in the FST; to eliminate this factor, a single 5-min session may be used [192]. In more recent studies, the FST is used not only for estimation of antidepressant effects of the drugs, but also for signs of depressive-like behavior produced by various manipulations: stress, surgery, endocrine-perturbation, selective breeding etc., that could potentially alter their baseline activity. In such cases, it is recommended that behavior during the pretest session be estimated as well [64]. In studies using chronic antidepressant treatment, a single 15-min test session has been used to avoid any confounding effect of a training swim on rats [161]. However, in earlier studies, the tricyclic antidepressant desipramine, the tetracyclic antidepressants maprotiline and mianserine and the norepinephrine–dopamine reuptake inhibitor nomifensine weren’t effective in rats which had not received the pretest session [162]. Antidepressant effects of fluoxetine treatment were detected at lower than the usual dose with several re-test sessions in the rat FST[49].

4.1.2.3. Duration of the procedure: The frequency/duration of immobility of rats increased with time spent in the water [42] and over several re-test sessions [49], with a parallel decrease in latency to immobility. In spite of the fact that a prolonged single exposure of the rat to water induced marked hypothermia [193], Kitada et al. [194], using a 30-min FST instead of the classical 5-min test session, highlighted differences between antidepressant and non-antidepressant drugs in the last minutes of the test.

4.1.3. Scoring—Usually, FST behavior is videotaped and scored by researchers who are blinded to the treatment group. The reliability of the scores should be within 5–10% [64]. Subjective evaluation of behavior types is the major factor responsible for data variability between laboratories and within a working group [158]. Estimation of active behavior types facilitates discrimination between different classes of antidepressants [8], while also adding more discrepancy to the scoring results. It is important to place the video camera on the level of the water surface to clearly distinguish active and passive behavior. Presence of individual variations in behavior during the swimming period make even more difficult to distinguish swimming behavior from immobility then either swimming or immobility behavior from climbing.

One way to get around the inconsistencies of manual scoring and variations between different individuals scoring the tests, is the use of automated scoring software. Various principles are currently used for the development of automated FST scoring in rats and mice [195–201]. One factor that might contribute to variability is whether the video camera or automated system records the animal from an overhead view or from the side. This should be specified in studies. Use of automated analysis can help avoid observer-related artifacts and speed up both estimation of results and analysis of the data. However, automated analysis also needs adjustment to account for individual behavior patterns of the animal. Based on our unpublished observations, current systems allow clear differentiation of immobility and climbing behavior, but are less successful in distinguishing between immobility and swimming, which is important for the identification of serotonergic antidepressants [8].

4.1.4. Statistical analysis—For statistical analysis of two groups (control and treatment) a non-paired, two-tailed Student *t* test can be used [63]. Results from three or more groups should be analyzed using a one-way analysis of variance (ANOVA) along with further post-hoc tests (e.g., Bonferroni, Fisher's LSD or Student–Newman–Keuls). If the study design includes not only treatment, but also some pre-conditioning procedures, a multi-factorial ANOVA should be applied [64]. Sometimes even a large reduction in immobility time may not appear significantly different from the control group because of small group size or an inappropriate statistical approach. To compare results about treatment efficacy from different studies, treatments should cause at least a 20% reduction in immobility time [158].

4.1.5. Combination with other behavioral tests—Using behavioral test batteries provides more insight into the effects of studied treatments. However, behavior in the FST depends on its place in the order of the behavioral test battery. Rats that were tested first in the FST were less immobile and spent more time swimming than animals which received other behavioral tests on the previous day [202]. In mice, prior testing in the plus-maze did not alter immobility time in the FST [203]. Mouse FST results did not correlate with other behavioral scores from the plus-maze test for anxiety (in any test sequence), the holeboard test for exploration and locomotor activity, and the bicuculline seizure test [203,204].

4.2. Environment in the laboratory

Behavior in the FST is extremely sensitive to changes in the external environment before and at the time of testing. Some authors have noted that even movement by the researcher or a rat in another test tank can provoke active escape-oriented behavior [63]. Some other examples of the influence of environmental factors on FST results are listed below.

4.2.1. Light—Light is an important factor influencing rat behavior in the FST (Table 3). Standard illumination during the FST caused hyperlocomotion in chronically stressed mice, but red light illumination inhibited swimming in these animals [205].

A change in light phase duration from 10 h/day to 14 h/day leads to decreased floating time and increased swimming behavior in Wistar rats [206]. Similarly, a long photoperiod regimen (14 h of light:10 h of darkness) versus short (5 h of light:19 h of darkness) has an antidepressant effect in male rats [207]. However, chronic exposure to light, without a dark phase, increased depressive-like behavioral responses in the mouse forced swim test [208]. Exposure to dim (5 lx) light during the dark phase of the cycle increased depressive-like response in the mouse FST [209]. Some specific rat strains, developed to study circadian mechanisms involvement in mood and anxiety disorders, such as the diurnal fat sand rat [210] and Nile grass rat [211], showed depressive-like behavior when maintained under short-photoperiod conditions. These behaviors were ameliorated after treatment with bright light or antidepressants [212,213]. A single or repeated exposure to light shortened immobility duration in female rats [214,215]. In male rats, blue but not red light stimulation in the dark phase reduced immobility duration in the second FST session [216]. Exposure to infrared radiation may have potential antidepressant effects in the rat FST [217].

4.2.1.1. Effect of reversed dark/light cycle: In a study of Verma et al. [218], female Sprague–Dawley rats maintained in reversed light cycle spent more time immobile (lights on at 1200 h and off at 2400 h for normal light cycle; lights on at 2400 h and off 1200 h for reversed light cycle; all groups were tested between 1–4 PM). However, no phase-dependent behavior differences were found in males. Chronic stress had no statistically significant effects on depressive-like behavior in the FST in rats maintained in reversed light cycles during their dark phase. Increased climbing was observed in chronically stressed rats housed in a regular dark–light cycle, but not in the reversed light cycle [219].

4.2.2. Noise—One hour of noise exposure had no effect on FST behavior tested immediately or 24 h later in adult male rats [220], while female rats that received inescapable loud noise (60 tones of 2000 Hz/120 dB) a day before the FST procedure had increased immobility duration in the study [221]. However, decreased immobility response in the rat FST also can be found after prior noise exposure [222]. A white noise generator is recommended for masking occasional loud noises that would potentially startle the animals during the swim sessions [189].

4.2.3. Odor—When tested in the water soiled by another rat, rats are less immobile than rats in fresh water [61,222,223]. This effect was thought not to be due to fecal or urinary contamination, but because of exposure to an “alarm substance”, possibly a pheromone

[224] released during the forced swim [222]. In another study, exposure to urine from stressed rats increased immobility [96]. Therefore, given the possibility for urine, feces, alarm substances or any other nonspecific cues to confound tests for subsequent subjects, the prudent recommendation (and most prevalent practice) is to use fresh water with every subject.

5. Conclusions

The FST, in its classical or modified version, provides a unique opportunity to assess antidepressant efficacy in a rapid, low-cost, and reliable manner. Its strong predictive and discriminative validity serves for reliable assessment of neurological mechanisms of antidepressant action. A large and growing number of studies also use the FST to assess depressive-like behavior in animal models of mood disorders.

To summarize, there are several suggestions which may help to improve quality of the study. The animals designated for FST should originate from one supplier and/or one breeding place. For interpretation of the results, it may be valuable to note the phase of the ovarian cycle for females. Other behavioral techniques for example, for overall activity of the animals, preferably should be placed after the FST, as they may influence the FST behavior. In case of pre-conditioning procedures, it may be beneficial to score behavior in the FST during both pre-test and test session. In terms of procedural recommendations, it is important to place the video camera on the level of water surface to clearly distinguish active and passive behaviors; a dark background should be used for light colored animals and a light background for dark colored ones. FST procedure should be performed in an isolated experimental room to avoid sounds/movements from other animals. If several animals are tested in parallel, water tanks should be separated with non-transparent barriers. The researcher should consider the impact of factors of handling, housing, and laboratory environment and report all procedural steps in detail.

With the expanding use of the FST as an assay for both depressive-like behavior and antidepressant activity, procedural aspects of the test become an important issue especially with respect to the comparison of observed results between studies. Animals of different strains, age and gender can differ in their baseline behavior in the FST and their response to treatment; pre-procedure conditions such as handling and housing may also alter their behavior in the FST. Surprisingly, various kinds of stress, endocrine manipulations and surgery produce a wide range of behavioral changes in the FST which may open new directions for understanding details of how the FST functions, as well as providing vital information on the neurobiology of depression. Due to the high sensitivity of results to environmental and biological factors as well as to variations in estimation of results (“the observer” factors), the FST should be standardized and the above-mentioned factors should be considered during study design and execution.

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HIGHLIGHTS

- The forced swim test (FST) is a rodent behavioral test for antidepressant efficacy.
- Variability in the FST results complicates the comparison across studies.
- The available literature was analyzed for factors influencing the FST behavior.
- The role of biological factors, preconditioning and experimental design is described.

Table 1

Immobility (floating) time (sec)[a] in the modified FST in control or vehicle-treated Sprague–Dawley and Wistar male rats.

Sprague–Dawley	
0–100 s	[19–26]
100–200 s	[9,27–35]
200–300 s	[36–38]
Wistar	
0–100 s	[39–42]
100–200 s	[43–50]
200–300 s	[51,52]

[a]Approximated from illustrations.

Table 2

Some examples of preconditioning influence on the FST results.

Type of preconditioning	Effect	Source
Handling	Depressogenic[a]	[84]
	No effect	[84]
Enriched environment	Antidepressant-like[b]	[3,37]
	No effect	[36,85]
Social isolation	Depressogenic	[23,37]
	No effect	[36,43,60,72]
Food restriction	Depressogenic	[21,86,87]
	Antidepressant-like	[87,88]
	No effect	[89]
Chronic mild stress	Depressogenic	[76]
	Antidepressant-like	[44,45]
	No effect	[76]
Social defeat stress	Depressogenic	[24,90,91]
	No effect	[24,92]
Chronic foot-shock stress	Depressogenic	[52,93–96]
	Antidepressant-like	[52,97]
Chronic restraint stress	Depressogenic	[26,40,98,99]
	Antidepressant-like	[95]
	No effect	[98]
Maternal deprivation	Depressogenic	[50]
	Antidepressant-like	[100]
	No effect	[100–102]
Prenatal stress	Depressogenic	[19,20,25,103]
	Antidepressant-like	[104]
Gonadectomy	Depressogenic	[74,105–107]
	Antidepressant-like	[35]
Pregnancy/progesterone Adrenectomy	Antidepressant-like	[108,109]
	Depressogenic	[35]
	Antidepressant-like	[35,110]

[a] Increase in immobility or decrease in active behaviors, and/or decrease in latency to immobility comparatively to control group.

[b] Increase in active behavior or decrease in immobility, and/or increase in latency to immobility comparatively to control group.

Table 3

Effect of light exposure on the FST behavior.

Type of exposure	Effect	Source
Bright light during testing	Antidepressant-like[b]	[205]
Increasing light phase of the day	Antidepressant-like	[206,207]
Chronic 24 h light exposure	Depressogenic[a]	In mice [208]
Decreasing light phase of the day	Depressogenic	In specific rat strains [210,211]
Reversing light/dark phases of the day	Depressogenic	[218]
Light treatment	Antidepressant-like	[211–213,215,216]

[a] Increase in immobility or decrease in active behaviors, and/or decrease in latency to immobility comparatively to control group.

[b] Increase in active behavior or decrease in immobility, and/or increase in latency to immobility comparatively to control group.