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Invited review

Coping with the forced swim stressor: Current state-of-the-art

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This article is dedicated to Dirk Hellhammer († december 1, 2018) a pioneer in psycho-endocrine research, who has left a legacy in the Trier Social Stress Test and Neuropattern™

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ABSTRACT

The forced swim test (FST) for rodents does not model despair or helplessness. It also is not a read-out for depression, anxiety, psychomotor retardation or autism, because these are anthropomorphic interpretations of the rodent's acquired immobility. Rather, the transition from swimming to immobility allows to examine the mechanistic underpinning of coping with inescapable stressors. However, in a recent detailed analysis of the FST application over the past 40 years, we noted a dramatic surge in the use of this test to phenotype animals as 'depressed'. As a follow up to that report, we now present an analysis of the use of the FST over the past three years. This literature analysis shows that the popularity of the FST is still increasing and that the majority of researchers qualifies the rodent's floating response as depressive-like behavior. However, over the past few years we also note a trend to interpret immobility rather as the expression of a coping strategy. In view of this result, we have sent a poll to the relevant authors to learn how consistent they are in naming FST behavior. Remarkably, we find a dramatic inverse correlation between their first qualification of acquired immobility as depressive-like behavior towards their current interpretation as coping strategy. In this contribution we have embedded our literature analysis and poll results in an update on the management of coping with inescapable stressors by processing in prefrontal cortical circuitry and glucocorticoid feedback.

'Two little mice fell in a bucket of cream. The first mouse quickly gave up and drowned. The second mouse wouldn't quit. He struggled so hard that eventually he turned that cream into butter and crawled out.'

Frank Abagnale Sr. and Jr., from the moving picture *Catch me if you can* (2002).

1. Introduction

About 40 years ago the forced swim test was designed for rapid screening of compounds with potential antidepressant activity [1]. Although this test was considered at that time very effective, one may conclude today that its *predictive* validity is disappointing, since it has not delivered novel antidepressants. The FST also does not have *face* and *construct* validity, because there is no single aspect modeled of depression, and the observed behavior is a 'dependent variable of the test situation itself' [2]. Rather, learning to become immobile in the FST may serve as model to examine the mechanistic underpinning of the coping strategy used by the rodent to achieve behavioral adaptation to inescapable stressors [3–5]. Accordingly, the action mechanism of glucocorticoids and dopamine in processing the acquired immobility response during coping with the forced swim stressor has been thoroughly investigated [6–8].

Three years ago we reported that about 4300 FST papers had been published and that half of them had used the test to phenotype genetically modified animals with or without a history of stress [3,4]. We also noted that anno 2015 one FST paper per day appeared and that labeling immobility as a depressive phenotype had become common practice. Since we are interested in changes in interpretation of FST behavior, we have examined the literature on the use of this test over the past three years. We also have sent a poll to the relevant authors who use or have used this test in order to learn their opinion on the interpretation of the FST data. In this contribution we will first present the results from our literature analysis and the outcome of the poll. Next, these results will be embedded in a state-of-the-art review of the science of coping with inescapable stressors. We will discuss the phenotypes identified with the forced swim and address management of stress-coping from prefrontal cortical control to glucocorticoid feedback.

2. Major depression

With a one-year prevalence of about 7 percent in developed countries [9,10], major depression is a common illness (See Box 1 for the

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depression symptoms [11]. Whether a symptom is present is indicated verbally by the patient, or in some cases based on the impression of a clinician [11]. The World Health Organization [12] states that depression is one of the leading causes of disease burden worldwide, associated with morbidity [13,14], and due to its relatively high suicide rates [15], also with mortality [16].

Box 1: The diagnostic criteria for major depressive disorder (APA 2013) [11].

Depression may be diagnosed if 5 (or more) of the following symptoms have been present
during the same 2-week period and represent a change from previous functioning. At least
one of the symptoms is either (**1**) or (**2**)

1 Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others. In children and adolescents, this can be irritable mood
2 Markedly diminished interest or pleasure in (almost) all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3 Significant weight loss when not dieting or weight gain (*e.g.,* a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
4 Insomnia or hypersomnia nearly every day
5 Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6 Fatigue or loss of energy nearly every day
7 Feelings of worthlessness or excessive or inappropriate guilt nearly every day (not merely self-reproach or guilt about being sick)
8 Diminished ability to think or concentrate, or indecisiveness, nearly every day
9 Recurrent thoughts of death, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for manic features in the presence or the past
C. The symptoms cause significant distress or impairment in important areas of functioning
D. The symptoms are not due to direct physiological effects of a substance/medical condition
E. The symptoms are not due to mood-incongruent delusions or hallucinations

The symptoms of depression are heterogeneous and descriptive and they do not provide an etiological model of the illness. Current research suggests that predisposing genetic factors and (early) life events play a key role in the etiology of depression [11,17] along with an altered responsiveness of the stress system [18,19], cognitive malfunctioning [20] and disturbances in neurotransmitter- [21], neuropeptide [22], and neurotrophic systems [23–25]. The common pharmacological- and psychological treatments of depression are at best modestly effective and about one third of the patients is therapy resistant [26,27]. This is in part due to the heterogeneous presentation of depression [28], which complicates the selection of the best possible treatment strategy. Moreover, progress is also hampered by the incomplete knowledge of the mechanism the treatment should target.

A major goal of current research is to reach out beyond a descriptive notion of major depression and to move to a model of this mental illness that takes the etiological mechanism into account [17]. For this purpose the Research Domain Criteria (RDoc) have been formulated by the National Institute of Mental Health in 2018: https://www.nimh.nih.gov/research-priorities/rdoc/definitions-of-the-rdoc-domains-and-constructs.shtml#part_154187. The RDoc strategy concerns the integration over different levels (*units of analysis*) of biological complexity - from genome to circuits, behavior and self-reports-, which will produce criteria that may help translation of *psychological constructs to domains of human behavior*. Obviously, stress hormone action on coping and adaptation is fundamental for this approach [22,29]. As noted by Bruce McEwen [30]: “cortisol acts in 6 RDoc units of analyses from gene to behavior; the hormone can alter arousal and regulatory circuitry and affects psychosocial, cognitive, positive- and negative valence systems. Accordingly, it seems therefore that the RDoc framework does not yet fully recognize the role of stress and stress hormones in coordinating the domains over the various units of analysis in neuroendocrine, immune and metabolic interactions.”

Van Praag introduced many years ago the concepts of functionalization and verticalization (*prioritizing psychic dysfunctions*) in psychiatric diagnosis. Functionalization of diagnosis refers to a ‘*conglomerate of interacting dysfunctions, within the psychic apparatus in the provinces of affectivity, cognition and motor regulation*’. In this way anxiety / aggression-driven depression was identified as a possible subtype of depression [31]. Another innovation was pioneered by the late Dirk Hellhammer using an approach entitled Neuropattern™. These are patterns (conceptual endophenotypes) of co-occuring neuroendocrine, biological, psychological and symptomatic features that signal striking changes in the activity and reactivity of brain circuits involved in coping with stress and which are defunct in stress-related psychiatric disorders such as depression. This approach can provide at least 13 distinct individual-specific patterns which can be used for rational personalised psycho- and neuropharmaceutical therapy recommendations [32].

In view of these considerations the development of valid animal models for the study of vulnerability to these various dysfunctions in depression will be indispensable. Although it is obvious that the forced swim test (FST) is not a model for depression, the FST may provide an opportunity for study of the mechanism underlying coping with inescapable stressors, which -if persisting- may enhance vulnerability to depression.

3. The forced swim test

The FST was presented first by Roger Porsolt and his colleagues [1] as an animal behavioral model that resembles *depressive illness* and that is *selectively sensitive to clinically effective antidepressant treatments* (page 730). Box 2 provides a description of this test. For more detailed information on FST protocols, we refer to the publications by Porsolt [1,33] and Cryan et al [34].

About three years ago we have presented a detailed analysis of the use of the FST over the past 40 years [3]. We found an increase in the use of the FST over the years. More importantly we noted a dramatic surge in the proportion of papers in which the FST was used to label animals as being depressed. This is surprising, because the FST lacks face and construct validity to assess depression or depressive-like behavior.

Box 2
A description of the FST. Adapted from De Kloet and Molendijk [4].

In the original version of the FST, a rodent is placed in a beaker (width: > 20 cm; depth ~15–18 cm) filled with water of 24 ± 2 degrees ◦C from where escape is not possible. The rodent is let to swim for 15 minutes. After the session, the animal is removed from the water, dried, and placed back in the home cage. Twenty-four hours later, the rodent again is placed in the beaker. During this second swim experience, that usually lasts 5 or 6 minutes, most animals start showing passive behavior soon. When this occurs, the animal is said to be *immobile* or that it *floats*. The time from placement in the cylinder to immobility / floating, is regarded as the main outcome measure of the FST experiment. Over the years, the original version of the FST has undergone some modifications. A major modification is the use of the test to measure immobility in a single session, thus without the 15 minutes pretest, in particular for mice.

Table 1
Changes over time in the interpretation of behavior observed in the FST: data for June 2012 - June 2015 and June 2015 - June 2018.

	2012–2015 (N = 97)	2015–2018 (N = 285)	Difference (interaction)[a]
Antidepressant response	ρ = -.65***	ρ = .10	***
Depressive-like behavior	ρ = .66***	ρ = -.24***	***
Other[b]	ρ = -.12	ρ = .55***	**

** statistically significant at $P <$ .01, *** statistically significant at $P <$ .001.
[a] The interaction effects, indicating change in interpretation over the two time-frames, were also significant when we compared the time-frames June 2012 *vs.* June 2015 vs.1978–2015.
[b] The category *other* includes the following interpretations: stressor, anxiety, immobility (without further connotation), and mixed interpretations.

Porsolt already noted that the immobility response in the FST is the '*dependent variable of the test situation itself*' [2]. Moreover, the response to the FST is instantaneously, while the pathogenesis of depression extends over weeks or months. Furthermore, the animal's transition to floating is said to demonstrate despair as a consequence of learned helplessness, but these are no major symptoms of the depressive phenotype either. Other proposals labeled the animal's behavior as psychomotor retardation [33,35] or anxiety [36], but these opinions are also not supported by scientific facts. Commons et al. [5] demonstrated that the animal's response to FST could easily be interpreted also as autism like-behavior and substance abuse.

In our previous reports [3,4], we arrived at the conclusion that the FST presents a unique paradigm to investigate the mechanistic underpinning of 'coping with an acute inescapable stressor'. If the situation is appraised as inescapable the rodent will acquire immobility after initial attempts to escape by swimming, struggling and climbing. This switch from an active to passive coping style favors energy conservation until a new option to escape is presented. In the original version of the FST the immobile animal is saved by the experimenter after the 15 min initial test and the animal learns that remaining immobile is associated with a survival option. It was shown 30 years ago that the consolidation of this acquired immobility response was disrupted by glucocorticoid antagonists, opioid antagonists and various types of antidepressants [37–39,4].

4. Use and interpretation of the FST from June 2015 to June 2018

In 2015 we published a rapport on the use of the FST and the interpretation of the results derived from this test [3]. In this rapport we show that the FST attained ever increasing popularity and that a growing proportion of papers labels the observed immobility as depression-like behavior. Here we update this rapport and investigate potential changes in the interpretation of the behavior that can be observed in the FST from 2015 onwards.

Between June 2015 and June 2018, about 2100 papers have been published that reported the use of the FST. This estimate is based on a PUBMED search (final search date 22-08-2018) using the search terms Porsolt swim test OR forced swim test. We find that the yearly number of papers that report on the use of the FST increased from June 2015 to June 2018 from about 430 in 2015 to about 600 in 2018. This is in line with the trend that we observed earlier [3].

We took a random sample of 285 papers (18%) from all FST-papers published between June 2015 and June 2018. Sample size of this random selection was chosen in order to provide a representative overview [40]. We estimate from this sample that in 71.9% of the papers, the FST is used to score depression-like behavior, while in about 19.1% the FST was used to infer on the anti-depressant-like properties of certain compounds or procedures. In the remaining 9.0% of the papers, the FST was used to stress the animal (3.2%), or to assess its coping capacities (2.1%), endurance or fitness (1.8%), or learning capacities (0.4%). In 0.7% of the papers, the FST was used as a read-out for immobility, without further connotation.

The interpretation of the behavior observed in the FST changed from June 2015 to June 2018. Authors tended to interpret the floating behavior increasingly less often as representing depression-like behavior (Spearman's rho (ρ) = -.24, 95% CI = -.39 to -.08, $P <$ .01) while the use of alternative interpretations increased over time (ρ = .55, 95% CI = .43 to .67, $P <$ .0001). This was particularly due to an increased tendency to use the FST as a read out for *coping behavior* (ρ = .76, 95% CI = .68 to .84, $P <$ .0001). No change was observed in the proportion of papers that scored an antidepressant response using the FST (ρ = .09, 95% CI = -.07 to .27, P = .26).

The interpretation of FST results not only changed from June 2015 to June 2018 but also relative to a prior period of equal length; from June 2012 to June 2018. We find that a smaller proportion of FST papers in which the observed behavior was labeled as depression-like behavior in the years 2015–2018 relative to the years 2012–2015. The inference that behavior in the FST reflects a response to an anti-depressant increased over the time-frame 2015 - June relative to the downward trend observed in the time frame prior to that. Alternative interpretations of the observed behavior (*e.g.,* as coping) also were used increasingly more often in recent-, relative to earlier years. For estimates of the strength of these associations and the statistical significance of their differences we refer to the Table 1.

5. A poll on (changes in) FST interpretations

We wanted to know whether the above presented changes in interpretations of FST results also were evident in the opinion of researchers. This was investigated by means of a non-random poll among researchers who use or have used the FST and who have been citing our work [3,4].

Through PUBMED, Web of Science and Google scholar we identified articles that cited one of our papers on the FST [3,4]. The total number of citations to these articles was 159. After deletion of duplicate citations and reading title and abstract of these papers to ascertain eligibility, we discarded 75 records. Among the discarded records were for instance reviews or studies on humans that did not report the primary use of the FST. We extracted the email addresses of the corresponding and/or senior authors of the remaining 84 articles, and we sent them an email in which we asked them the following:

1 Since when are you using the FST?
2 How many papers have you published in which the FST was used?
3 How did you initially interpret FST results?
4 How do you in your current or latest research interpret FST results?
5 Were there comments from reviewers on the chosen interpretation of the FST results?

Fifty-two percent (n = 44) of the authors, to whom we sent out the poll, responded. There was a wide variety with regard to the experience these authors had with the FST (range number of papers published in which the FST was used = 1–40 papers [average = 6]). Some of them published their first paper using the FST in 1982, others in 2017. Seventeen (39%) of the authors mentioned to have received reviewer comments on their interpretation of the FST.

Overall the authors reported differences in interpretation of the behavior from first- to current/latest use (χ^2_{25} = 51.5, $P <$ 0.01). The

Table 2
Poll results. Percentage of use and 95% Confidence Interval (CI) for each interpretation of the behavior observed in the FST by first *vs.* current or latest use.

	First use % (95% CI)	Latest use % (95% CI)	*Z*-value[a]
Antidepressant response	9.8 (2.0 – 23.8)	2.4 (0.1–12.8)	1.59
Depressive-like behavior	65.9 (49.5 – 80.0)	12.2 (4.1–26.6)	7.25***
Coping/learning/acquired immobility	14.6 (5.5 – 29.1)	56.1 (39.8–71.5)	7.53***
Other[b]	9.8 (2.7 – 23.2)	29.3 (16.5–45.6)	4.20***

*** statistically significant at $P < .001$.
[a] We calculated a *Z* and *P*-value for the difference between the observed proportion that a given interpretation is used ('latest use') vs. the observed proportion a given interpretation was used ('first use').
[b] The category *other* includes the following interpretations: stressor, anxiety, immobility (without further connotation), and mixed interpretations.

observed and significant differences were in line with what we observed in the survey of the literature: more and more authors stated to interpret immobility as for instance coping or acquired immobility and fewer as depression-like behavior or something related to this (*e.g.,* despair). Details from our poll can be found in Table 2.

The results from this poll and the survey of the literature, together show the dynamic nature of how immobility, as observed in the FST, is interpreted. Currently the trend is such that it is increasingly less often labeled as depression–like behavior.

A limitation that is worth mentioning here is that social desirability bias cannot be excluded as the driving force underlying the pattern of results derived from our poll. Self-reported data was used after all and the authors who were approached probably knew our stance with regard to the questions that we asked them [41].

6. Coping with stressors

Here we will review in the next sections the progress in understanding stress-coping with reference to the FST. We first discuss the phenotype of rodents displaying either an active or a passive behavioral response to the inescapable stressor. Then, the implication of brain circuitry, dopamine and the glucocorticoid stress hormone in management of stress-coping is examined.

6.1. Stress-coping phenotypes

Henry and Stephens defined the *active* fight-flight and the *passive* conservation withdrawal mode as two evolutionary successful coping strategies [42]. In line with this concept Koolhaas et al. [43] identified highly aggressive short attack latency (SAL) mice as *pro-active* rather than *active* copers because of their tendency to take the initiative in fights *vs* the *reactive (passive)* copers that actually had a lower threshold to 'freeze' during such violent confrontations. In their analysis the Koolhaas lab extensively phenotyped the animals with the two opposite coping styles. Among numerous other parameters, pro-active coping is characterized by high sympathetic activity and low stress-induced glucocorticoid secretion with a pro-inflammatory and auto-immune bias, while the re-active (passive) ones show the opposite pattern where parasympathetic activity is prominent with high glucocorticoid secretion [44,45]. This led Mechiel Korte to distinguish these two divergent rodent phenotypes prosaic as Hawks *vs* Doves [46].

Other researchers have examined extensively rats that are rapid learners of shuttle box active avoidance behavior *i.e.* Roman High Avoidance (RHA), in comparison with Roman Low Avoidance (RLA), which learn slow and display a more passive (freezing) response [47]. The RLA line shows much higher emotionality than RHA's. The latter RHA rats display little anxiety in a novel environment, express novelty-seeking and increased impulsivity, but surprising are less aggressive [48,49]. As is the case with the SAL mouse line, male rats of the pro-active behaving RHA line actively cope with the non-escapable swim stressor, while the reactive (passive) RLA rats show the passive coping style, particularly in the retest [47]. RHA animals are resistant to antidepressants in the FST and show much less FST-induced HPA-axis activity and lower prolactin release than their RLA counterparts [48,47,50]. HPA axis activity associated with FST behavior was extensively investigated in five different rat strains by Armario et al. [51,52]. These experiments identified alike the RLA's, the Wistar Kyoto strain (rather than spontaneous hypertensive rats) as the strain predisposed for passive coping.

The FST has also been used to pre-select animals for their coping performance as criterion to test their vulnerability to subsequent stressors. One recently published example by Mul et al [53] is based on exposure to the FST for 5 consecutive days when all mice were found to show a passive coping style; this repeated FST procedure did not produce dysregulation of emotional, homeostatic or psychomotor functions, however. In a variation of this approach by Wislowska-Stanek et al. [54], rats were divided according to their immobility times after first exposure to the FST. The passive copers appeared more vulnerable to challenges related to the function of the VTA dopamine system, which includes exposure to social isolation or a restraint stressor. This phenotype was associated with increased dopamine turnover and release in the VTA – amygdala terminal area, where also increased expression of cocaine- and amphetamine (CART) related peptide was found.

In conclusion, the distinction in active and passive coping styles observed in the FST represents two very different phenotypes, which are labeled in their response pattern to psychosocial stressors as pro-active and reactive, respectively. The two distinct phenotypes can be predicted by genetic factors and are associated with widely divergent patterns of e.g. stress-induced HPA-axis and autonomous activity, prolactin release and dopamine signaling. Accordingly, the FST procedure can be used to rapidly select animals with an extreme different phenotype for further study of stress vulnerability and resilience.

6.2. Stress-coping management

Mice of the DBA2 *vs* C57Bl6 inbred strains also showed large differences in active vs passive coping with the inescapable stressor encountered in the FST [55]. This difference was demonstrated in the initial tests as well as at retest 24 h later. In their pioneering research, the Cabib lab reported that the passive C57Bl6 mice showed swim-activation of the amygdala - hippocampal circuitry by using c-fos expression as marker. The actively coping DBA's were found to rely heavily on an amygdala - dorso-lateral striatal (DLS) dopaminergic mechanism, which is also prominent in stereotypical, habit and addictive behavior [56,55,8]. The effects that were visualized by c-fos expression, show a profound lateralization, though, and the changes are most prominent in the left DLS. Interestingly, lesioning of the left DLS or local treatment with D2 antagonists abolishes retention of the acquired immobility in the DBA's, while hippocampal lesions interfere with memory performance of the C57 Bl6 mice [55]. In addition, downregulation of left DLS-D2 receptors by previous food deprivation also interferes with memory consolidation c.q. retention of acquired immobility [56].

It is generally thought that the ventromedial prefrontal cortex (mPFC) is central to top-down control of stress-coping because of its

function in decision-making, planning and cognitive flexibility. Depending on the nature, activity and duration of the stressor various neuronal ensembles in mPFC are recruited in circuits serving executive behavioral and physiological reactions. Thus, the mPFC projects to circuitry in the extended amygdala *i.e.* bed nucleus striae terminalis (BNST), the various amygdala nuclei and parts of the striatum, hypothalamic and thalamic nodes and connects via these hubs to neuroendocrine, autonomic and behavioral output pathways in the paraventricular nucleus (PVN) and peri-aquaductal grey (PAG). Simona Cabib et al. pointed out that the passive coping response to uncontrollable stress evolved upon the switch from prelimbic-mPFC (pl-PFC) regulating goal-directed towards stimulus-response behavior by the infralimbic (il)-PFC – DLS circuit [8].

Radley and coworkers distinguished more than 10 years ago the role of the il- and pl-PFC during emotional stress in control of PVN function by placing discrete lesions in these areas. Briefly, they found that the pl-PFC primarily regulated HPA axis activity by inhibiting the neuroendocrine CRH cells in the paraventricular nucleus (PVN), while il-PFC rather restrained autonomic functions via adjacent PVN cell groups [57] Pioneering work by the Jim Herman lab [58] have further outlined some features of the il-PFC projectome. During a chronic (uncontrollable) stressor the glutamatergic mPFC output is attenuated because of atrophy of the mPFC neurons and an impairment of the glucocorticoid-dependent break on the inhibitory GABA-ergic control of excitatory output within the mPFC. Both actions synergize and the result is a weakened il-PFC excitatory outflow during chronic stress, and thus suggesting a less restrained autonomic and neuroendocrine stress reaction [59,60,58].

The PFC input to the avBNST activates GABA-ergic cells that either innervate the hypothalamic PVN for neuroendocrine control and the vlPAG for expression of passive coping [61–63]. Lesioning the BNST advances the onset and increases duration of immobility in the FST retest [64]. In line with this, Johnson et al [61] reported that inhibition of the pl-PFC glutamatergic input of the avBNST increased passive coping in the tail suspension test (stimulation of glutamatergic avBNST input decreased passive coping). a finding that is in line with the stress-induced pl-il switch [8]. The finding was confirmed with variations in the 'immobility' response when the rats were exposed to the shock prod burying test. Actually, the important discovery was made that variations in activity of the pl-PFC top-down excitatory outflow via the GABA-ergic avBNST hub was expressed as a variation in 'gating' of passive coping that is mediated via the vl-PAG rather than these manipulations directly modulate active coping via the dl- and L-PAG.

About 20 years ago Bandler and Keay et al. [65,66] found that active coping responses are triggered by electrical or chemical stimulation of the dorsolateral and lateral columns (dl-PAG and L-PAG). C-fos activation of these PAG columns was observed during active coping with an *escapable* stressor and was associated with sympathetic activation of heart rate and pressor responses. In contrast, passive coping was evoked upon stimulation of the vl-PAG and is characterized by c-fos activation of this column during either *inescapable* physical (*e.g.* pain, tissue damage, hemorrhage) or psychological stressors. Activation of this vl-PAG pathway causes hypotension and bradycardia as hallmarks of quiescence and parasympathetic activation.

The passive coping style represents decreased responsiveness to environmental stimulation, while quiescence and immobility would allow for recovery and wound healing. However, Koolhaas and colleagues [44] assigned to the passive (in their case reactive) coping animals a phenotype that is guided by the environment. Such animals are more successful upon dispersal than the active copers. In contrast, the active coping trait features an optimal performance if conditions are predictable in the animal's own territory. Both views are not necessarily in contradiction: the Bandler/Keay *c.s.* view considers performance in the immediate aftermath of a challenge, while Koolhaas et al. highlights the performance of animals in psychosocial interactions.

The effect of psychological stressors on the PAG columns suggests control that is exerted by input from the PFC, hypothalamus and amygdala [65,66]. Information processing by the mPFC neurons is modulated by *e.g.* hippocampal contextual and amygdala-triggered emotional inputs, while valuation of the nature of the stressor is processed by the ventral tegmental area (VTA) striatal pathways. For modulation from different brain areas the BNST was found to be a critical node in this pattern of coping with stress [67]. In this respect confronting the rodent with the FST enhances dopamine release in the VTA as part of a scenario to control the stressor. Next, when after some time the animal appraises the situation as uncontrollable, DA release decreases in parallel with acquiring the passive coping style [68,8]. Chronic exposure to unpredictable stressors indeed reduces VTA-DA dopaminergic activity and is paralleled by a number of behavioral features including passive coping in the FST [69,70]. In support, optogenetic inhibition of the VTA dopaminergic cells causes immobility in the FST, while activation had the reverse outcome; the rats attempted to swim and escape again as part of their active coping repertoire [6].

In contrast, a paradigm of 10 days social defeat activated VTA-DA neurons [71], but reduced sucrose preference [72,23,73,74]. Interestingly, optogenetic inhibition of the VTA-DA cells in this social defeat model led to a reversal of this phenotype [75]. Thus, it seems that the role of VTA-DA in coping is different under conditions of a predictable (daily immobilization, repeated social defeat) *vs* an unpredictable chronic stress experience. Indeed, daily chronic immobilization for 12 days enhanced active behavior, particularly if the last immobilization was applied shortly before the FST. In these chronically stressed rats, a higher efficacy of de dopamine antagonist haloperidol was observed in suppression of active coping behavior. This finding suggests an increased role of dopaminergic transmission in active coping after chronic daily immobilization stress [76]. Accordingly, ventral and dorsal striatal pathways communicate via an intra-striatal spiraling cascade the motivation to act towards the actual motor response. Rat lines selected for a high apomorphine sensitivity indeed show the phenotype of active coping and stereotypical gnawing linked to the nigrostriatal A9-DLS projection [77].

The top-down PFC control implicates secretion of the glucocorticoid end products of the hypothalamus-pituitary-adrenal (HPA) axis, cortisol and corticosterone, which act via high affinity mineralocorticoid receptors (MRs) and lower affinity glucocorticoid receptors (GRs) (Box 3). MR activation during stress favors the selection of non-declarative (habitual) learning to cope with escapable stressors [78] by prioritizing the amygdala-DLS pathway at the expense of amygdala-hippocampal circuit underlying declarative learning [79–81]. An active coping style in the FST, characteristic for dominant individuals goes along with highest limbic MR expression, low HPA axis activity and a high sympathetic tone [82]. MR antagonists disinhibit HPA axis activity, reduce sympathetic tone, are anxiolytic and reduce aggression [83–87]. Blocking the MR interfered with habit learning and re-established the hippocampal cognitive program back into central stress-coping program. Cognitive performance became, however, slower and less effective after mineralocorticoid antagonist treatment [78–88]. In rodents the switch in coping style shows a sex difference; females actually prefer cognitive control rather than habit learning during stress [89].

While the MR activation is prominent during the initial phase of stress-coping, GRs become only activated with rising glucocorticoid concentrations and were found to facilitate memory storage of the selected coping response (Fig. 1). Thus, GR antagonists administered right after the initial 15 min FST interfered with memory storage [112,113] and this action was located in the hippocampal dentate gyrus [39]. Hans Reul and coworkers discovered in a series of elegant experiments that the facilitation of memory storage in the FST requires synergy with glutamate transmission. These experiments demonstrated in discrete neurons of the hippocampal dentate gyrus that not only glucocorticoid antagonists, but also specific genetic deletions in the underlying signaling pathway (*i.e.* MSK1/2) could prevent the consolidation of acquired immobility. The data suggest involvement of an epigenetic

Box 3
Mineralocorticoid receptors (MRs) and Glucocorticoid receptors (GRs).

Glucocorticoids have an important function in management of stress-coping and behavioral adaptation. This action of glucocorticoids is mediated in a complementary manner by MRs and GRs [90,29,91,92]. MRs are predominantly expressed in limbic-prefrontal neurons [93,94,95,96] and their activation by naturally occurring glucocorticoids enhances excitability [97]. There are also aldosterone-selective MR expressed in a discrete number of neurons in the n.tractus solitarii (NTS); this is because MRs are co-expressed in the NTS neurons with an enzyme(11β-hydroxysteroid dehydrogenase type 2) that degrades cortisol and corticosterone [98].

GRs are co-localized with MRs and widely distributed with highest density in stress regulating centers such as the PVN, the limbic-prefrontal cortical regions and the ascending aminergic neurons including the VTA-DA and striatal neurons [99,100,101]. The role of GRs is to provide energy substrates for tissues in need and to protect against the body's own initial defense reactions [102].

MRs and GRs occur as homodimers and heterodimers regulate gene transcription [103], but are also engaged in rapid non-genomic actions. MR activation promotes excitatory transmission [104,106,97] and downregulates the mGLu receptor [107]. GR activation suppresses stress-induced activation, involving trans-synaptic endocannabinoid [108]. MR- and GR-mediated signaling needs to be in balance for maintenance of homeostasis and health [109,111,29,92].

mechanism driven by histone modification, and immediate early gene activation as hallmarks of chromatine reorganization [114,115,7].

Chronic stress *per se* did not alter much the hippocampal dentate gyrus transcriptome, an additional challenge with an acute heterotypic stressor such as the FST -or even corticosterone itself for that matter [116,117]- revealed a pronounced difference in genomic organization. In particular the expression of genes with a role in chromatine reorganization, epigenetics, inflammatory cytokine pathways and synaptic plasticity was enhanced.

In conclusion, pioneering studies that combine optogenetic with tracing techniques have demonstrated the connectivity of the mPFC with downstream nodes that activate autonomic, neuroendocrine and behavioral output. Future studies will undoubtedly further unravel how the nature, duration and chronicity of a perceived stressor is appraised and which neuronal ensembles are recruited in the mPFC to ensure various degrees of connectivity. This connectome underlies coping with acute and chronic stressors congruent with domains of valence, emotional expression, cognitive operation and psychosocial interaction [118,119].

7. Concluding remarks

In this special issue, we present a survey showing that the number of reports on application of the FST in phenotyping rodents is still increasing. We note that the majority of the papers (about 72%) qualifies the behavior of the floating rodent as depressive-like, but without evidence for face, predictive or construct validity. We have asked a selected group of 84 authors who use or have used the FST on how they interpret behavioral performance of the rodents in their first and last use of the FST: the majority of the responding authors (65,9%) rated acquired immobility first as depressive-like behavior, while today this number sharply declined to 12,2% favoring the interpretation of coping strategy (56,1%) (Table 2).

This analysis is embedded in the current state-of-art in understanding the stress coping mechanism during the forced swim. Using optogenetics and tracing techniques the top-down organization of the stress coping circuitry is becoming rapidly understood. Neuronal ensembles in the mPFC area convey information downstream via hubs in the stress connectome in a time- and context dependent manner leading to the actual expression of active and passive coping strategy via different PAG columns. These hubs are also target for the glucocorticoid stress hormones that has its MRs and GRs activated in a complementary manner to modulate information processing from optimizing the coping response to its memory storage for future use (Fig. 1).

The FST certainly is a powerful paradigm to examine the mechanism underlying coping with inescapable stressors. This includes the study of the prefrontal-based coping circuit and glucocorticoid feedback [120,59,63,58,121,122]. It also includes the inoculation of this coping

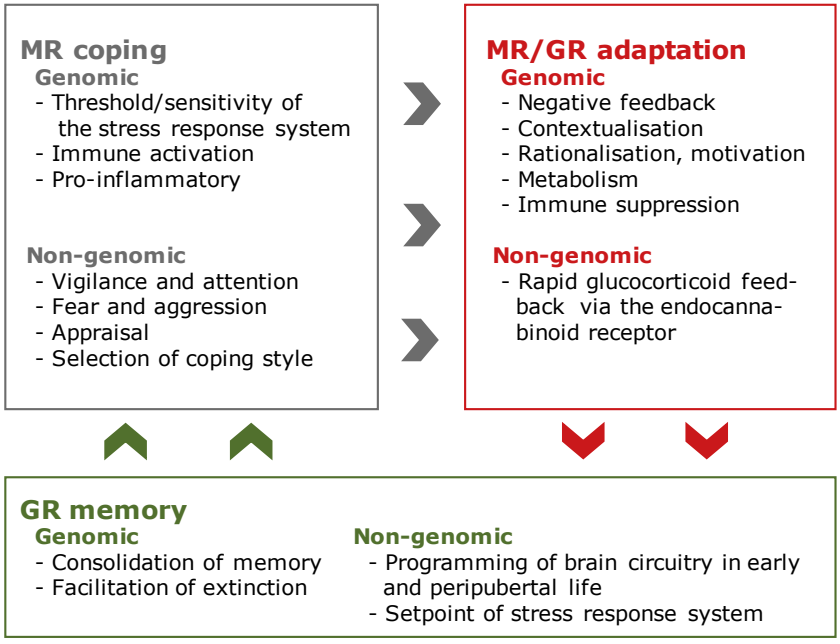

Fig. 1. MR, GR and stress coping. Flow diagram shows the three different phases of glucocorticoid action mediated by MR- and GR-mediated actions in the brain. MR activation affects the initial appraisal process and the selection of coping style. GR activation promotes behavioural adaptation and memory storage. In appropriate contexts the memory trace is retrieved again on demand via MR. Accordingly, MR- and GR-mediated processes need to be in balance for homeostasis and health. Data from [29,92,133,134].

circuitry by life experiences that leave their mark on critical hubs in e.g. the midbrain raphe nuclei [123] and in circuits that shift in time from processing salient to executive brain functions [124,118]. The programming effects involving epigenetics of the GR are best known [7,125]. Early life effects on PAG-mediated panic behavior also have been reported [126]. It is thought that resilience is favored if a later life event matches the early life experience [127–129]. Upon a mismatch between early and later life events vulnerability may increase, and recent evidence suggests that such changes can be reset by anti-glucocorticoids [130–132]. Whether this glucocorticoid-susceptible match/mismatch concept holds for inescapable stressors, such as tested in the forced swim, remains to be examined.

Conflict of interest

Marc Molendijk has no potential competing (financial) interests to report. Ron de Kloet is on the scientific advisory board of Dynacorts Therapeutics, and owns stock of Corcept Therapeutics.

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