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The effects of acute and chronic stress on motor and sensory performance in male Lewis rats

Gerlinde A.S. Metz[a,b,*], Martin E. Schwab[b], Hans Welzl[c]

[a]*Department of Psychology and Neuroscience, University of Lethbridge, Lethbridge, Canada*
[b]*Brain Research Institute, University and ETH Zurich, Zurich, Switzerland*
[c]*Institute of Anatomy, University of Zurich, Zurich, Switzerland*

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Abstract

Any behavioral testing induces stress to some degree. A meaningful interpretation of behavioral results can be difficult if stress, caused by handling or the testing situation, modifies the experimental outcome. Especially for neurological animal models, it is important to know how stress affects motor and sensory performance. Therefore, we investigated the effects of varying degrees of stress on several motor and sensory tasks that are frequently used to assess functional recovery after lesion-induced impairments in adult rats. Acute, subchronic, and chronic stress impaired ladder walking and prolonged the duration of grasping a bar. Stress also altered walking patterns by increasing the base of support and foot rotation and reducing stride length. Furthermore, chronic stress induced hypersensitivity to painful stimuli, but did not significantly influence the latency to remove sticky papers from the hindpaws (sticky paper test). In the light–dark (L/D) test, stress reduced the latency to enter the dark compartment and enhanced the number of transitions supporting that cold swim stress modifies the animal's level of anxiety. These data point towards a critical influence of acute or chronic stress on motor control and sensory performance of rats, suggesting that stress might be a critical intervening variable of the outcome of behavioral tests.

Keywords: Locomotion; Testing strategy; Swim stress

1. Introduction

Situations that elicit a stress response drastically change the state of an organism. Ideally, these changes should help to quickly analyze the situation and to prepare adequate behavioral reactions. On a physiological level, stress response mechanisms also provide the necessary energy for a sudden increase in motor activity (for review, see Ref. [26]). The stress response, however, has evolved mainly to cope with short-lasting stressors. Long-lasting (chronic) stress overburdens these physiological mechanisms, eventually leading to functional or organic disturbances, including also the nervous system (e.g., Refs. [24,29]).

Such effects of stress on behavior are well documented in animals and man. Depending on the stressor's strength and duration, performance in learning tasks is improved or attenuated (for review, see Refs. [18,21]). Stressors also change reflex activity, sensory perception, and locomotor activity. A stressful environment could enhance the startle reflex in man (e.g., Ref. [14]) and rats (e.g., Ref. [22]). Further, whereas acute exposure to stress induced analgesia in various species (for review, see Refs. [2,6,28]), chronic exposure of rats to repeated cold stress lowered their threshold for the sensation of painful stimuli, leading to a state of hyperalgesia [17]. Finally, general locomotor activity in an open field decreased in chronically stressed rats [9].

In view of the wide range of behavioral processes that are influenced by stress, one would also expect that sensory–motor activities are affected in humans. Movie clichés, such as the difficulty to open a door with a key when being stalked by an aggressor (i.e., performing skilled movements when under extreme stress), seem intuitively right to us. The stress response is coordinated by hormones whose receptors are located throughout the body including the brain. The involvement of receptors for cortisol or corticosterone in cognitive behavior is well documented ([23] for review).

* Corresponding author. Department of Psychology and Neuroscience, University of Lethbridge, 4401 University Drive, Lethbridge, Alberta, Canada T1K 3M4.

E-mail address: gerlinde.metz@uleth.ca (G.A.S. Metz).

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However, receptors for the stress hormone, cortisol, or corticosterone in rodents can be found not only in areas that are involved in cognitive and sensory function, but also in brain structures participating in the control of motor activity such as the motor cortex, basal ganglia, cerebellum, and ventral spinal cord [4,5].

When studying the effects of stress on behavior, stress could possibly either directly affect the behavior under investigation or influence the performance by changing sensory–motor functions. Even when stress is not the experimental variable under investigation, the stress associated with a testing situation might modify the experimental outcome via its effect on sensory–motor functions. Therefore, we investigated the sensory–motor performance in standardized locomotor and sensory paradigms under basal conditions and after acute, subchronic, and chronic stress caused by forced swimming in adult rats. The results revealed massive functional impairments and motor abnormalities after acute as well as chronic stress.

2. Materials and methods

2.1. Subjects

Sixteen male Lewis rats (BRL, Füllinsdorf, CH) weighing 310 ± 20 g at the beginning of the experiment were housed in groups (three to five animals per cage) and maintained under a 12:12 h light–dark (L/D) cycle with lights on at 07:00 AM. Water and food were given ad libitum. Body weights were recorded daily before the beginning of experimental manipulations.

2.2. Experimental design

All tests and forced swim trials were performed during the light phase. At the beginning of the experiment (day 1), each animal's anxiety level was evaluated (Table 1). Based on the test scores, they were distributed to either the control group (chronic handling) or the stress group (chronic forced swimming; $N = 8$/group), so that both groups contained comparable mean anxiety levels. Previous to baseline testing, all animals were trained on the ladder beam (days 2 and 3) and introduced to the testing boxes to habituate to the environment. The baseline values of sensory–motor performance were then evaluated with a test battery on day 4. The test battery included ladder beam walking, footprint analysis, grip test, and sticky paper test (for description, see below). During days 5–18, animals were daily handled or forced to swim (chronic treatment). To evaluate acute, subchronic, and chronic effects of swim stress on sensory–motor performance, all animals were again submitted to the test battery on days 5, 11, and 19, respectively. One day after the end of the stress period (day 19), animals were again tested for anxiety to detect possible swim-stress-induced changes in anxiety scores. In addition, they were submitted to a hot plate test. Tests were carried out at the same time of day between the two daily swim stress procedures.

2.3. Swim stress procedure

Stress was administered twice daily at variable times of the day with an 8-h interval between treatments. To induce stress, animals were individually placed for 5 min in a bucket filled with water (17 ± 1°C) that was deep enough so that the animals' feet did not touch the bottom. After forced swimming, they were dried with a towel and returned to their home cage. Individual defecation rates were recorded after each swim stress treatment as a measure of stress levels. To assure the manifestation of chronic stress, animals were stressed over a 2-week-period. The time point at which a chronic stress situation is reached is at least 5 days after the beginning of daily stress induction (see Ref. [20]).

2.4. Light-Dark (L/D) test

All animals were tested for anxiety-like behavior in a L/D test (modified from Refs. [1,11]). After adaptation to the testing room (30 min), animals were individually placed into the center of the illuminated part (180 lx) of an open field (100×80 cm^2). A dark compartment (40×28 cm^2) was attached to one side with an opening (10×10 cm^2 diameter) facing the center of the open field. The latency to enter the dark compartment (L/D latency) and the number of transitions between the compartments (L/D transitions) were recorded in a single 5-min trial.

2.5. Horizontal ladder beam

Deficits in coordination between forelimbs and hindlimbs and accuracy of limb placement were examined by assessing the animal's ability to navigate across a 1-m-long runway in order to return to its home cage (modified from Ref. [32]). The floor of this runway consisted of regularly

Table 1
Experimental design

Day(s)	1	2–3	4	5–18	19
Procedure	–	ladder training	–	daily swim stress or handling	–
Test	anxiety (L/D)	–	–	–	anxiety (L/D)
	–	–	test battery	test battery (days 5 + 11)	test battery hot plate

spaced bars (distance between bars, 3 cm). Crossing this 'horizontal ladder' required that animals accurately place their limbs on the bars. Falling through the bars with one limb was counted as an error, and the number of errors per crossing was analyzed. During baseline training (days 2 and 3), animals had to cross the ladder five times each day. On test days, the average error scores of three crossings were determined. On day 19 (chronic stress stage), animals were also required to cross a runway with randomly assigned gaps 10 times (distances between bars ranging from 1 to 5 cm).

2.6. Footprint analysis

The animals' paws were inked and footprints of forepaws and hindpaws were made separately on paper covering a narrow runway (100×7 cm^2; modified from Ref. [12]). A series of at least eight sequential steps was used to determine the mean values of base of support, stride length, and limb rotation. Base of support was determined by measuring the distance between the left and right footprints of forepaws and hindpaws (core to core distance of the central pads). Stride length refers to the distance between the central pads of two consecutive footprints on each side. Limb rotation was defined as the angle formed by the intersection of the line through the print of the third digit and the print representing the metatarsophalangeal joint with the line through the central pad parallel to the walking direction.

2.7. Grip test

A Newtonmeter with a grip bar was horizontally fixed. The rat was held in a horizontal position and lowered towards the grip bar until the animal grasped it. Then a constant force of 200 *g* was given and the time until the rat dropped the grip bar (grip time) was measured. Three trials per animal and session were recorded and the maximum time was included in the analysis to correct for eventual habituation in each trial.

2.8. Sticky paper test

Somatosensory responsiveness was tested by cutaneous stimulation with a test modified from Schallert and Whishaw [27]. Small squares of self-adhesive tape (1.3×2.6 cm^2) were attached to the ventral side of the palm of both forelimbs. The rat was then returned to its home cage and the time to remove both pieces of paper from its paws was recorded. Each session consisted of two trials, and the mean value was taken for analysis.

2.9. Hot plate test

To measure pain thresholds, an animal was placed on a hot plate (55°C) and the latency for the appearance of heat avoidance behavior (lifting and licking a paw, hopping, or jumping) was recorded [31]. A trial was terminated when the animal did not respond within 30 s.

2.10. Statistical analysis

Data were analyzed with a statistical package (STATVIEW 4.53; Abacus Concepts, Berkeley, CA). Between-group comparisons (factor STRESS) were analyzed using a two-way analysis of variance (ANOVA) with repeated measures (factor DAYS). Data after stress induction were also expressed as a percentage of baseline values and analyzed with a one-way ANOVA. Post-hoc tests were used to adjust for multiple comparisons. Group comparisons were performed using unpaired *t* tests. Comparisons of repetitive measurements were done using the paired *t* test (e.g., for parametric data) or a Wilcoxon signed rank test (e.g., for nonparametric data). All values are given as means ± S.E.

3. Results

On day 1 and before the chronic stress treatment, baseline values of the two groups did not differ from each other on the sensory–motor test battery. Differences in several test scores were, however, apparent after acute (day 5), subchronic (day 11), and/or chronic stress exposure (day 19; see below). The rate of defecation increased after the stress procedure, and the lack of a reduction in defecation rate suggests that animals did not adapt to the stressor during the forced swimming period. Despite being chronically stressed, animals of the stress group did not significantly change their body weight compared to unstressed controls.

3.1. Chronic stress decreased L/D latency

Animals were evenly distributed to the control or stress group dependent on their L/D test scores measured on day 4. Mean escape latencies of controls remained unchanged from days 1 to 19 ($P > .05$, ANOVA; Fig. 1A). Chronic stress, however, drastically reduced escape latencies (from 98.1 ± 40 s in baseline to 15 ± 4 s after chronic stress, i.e., 40% of baseline; $Z = -2.5$, $P = .014$, Wilcoxon signed rank test; Fig. 1A). Chronically stressed animals also showed three times more L/D transitions on day 19 than unstressed controls (300% of baseline values, $t = -2.3$, $P = .04$, unpaired *t* test; Fig. 1B).

3.2. Stress caused deficits in ladder beam walking

Swim stress significantly increased errors on the ladder beam through acute, chronic, and subchronic testing sessions ($F = 11.4$, $P = .005$; STRESS × DAYS: $F = 5.6$, $P = .002$, ANOVA; Fig. 2). Post-hoc tests revealed that there were no group differences in baseline measurements on day 4 ($P > .05$, Scheffe; Fig. 2). The error scores in control rats

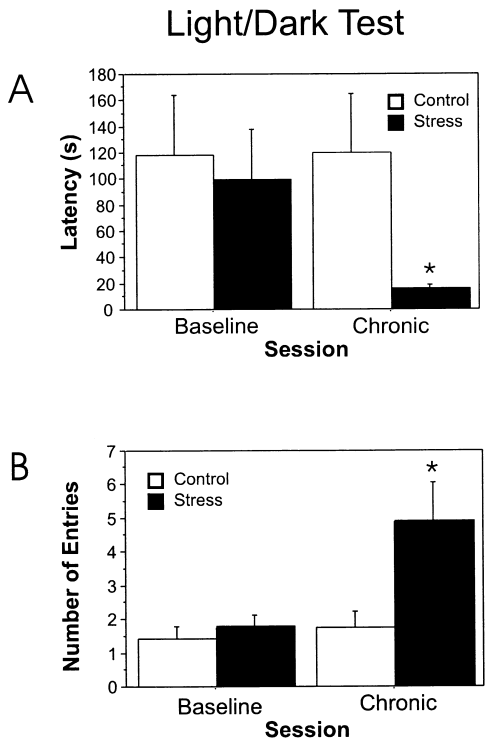

Fig. 1. Performance of control and stressed animals in the L/D test during the baseline session and following chronic stress (2 weeks of daily swim stress). Parameters measured were (A) latency of the first entry into the dark compartment and (B) the number of entries during a 5-min observational period. Stressed animals showed a much shorter latency to enter the dark compartment and a drastic increase in the number of entries as compared to controls ($P \leq .05$, unpaired t test).

remained unchanged for all subsequent sessions and showed no effect of the repeated testing. In contrast, error scores massively increased (up to 10 times of baseline values) in stressed animals following acute (900% of baseline values, $t = -2.6$, $P = .036$), subchronic (1100% of baseline values, $t = -3.3$, $P = .01$), and chronic stress (550% of baseline values, $t = -2.6$, $P = .037$, paired t test). The performance of rats after acute, subchronic, and chronic stress did not differ significantly from each other. Eventual training effects on the regular ladder present on day 19 (chronic) testing session were reduced when we used an irregular ladder ($t = -2.2$, $P = .04$ on regular, $t = -4.7$, $P = .003$ on irregular ladder, paired t test; Fig. 2). However, chronic test sessions on the regular ladder did not differ significantly from results obtained on the irregular ladder ($P > .05$, paired t test). After acute stress, but not following subacute or chronic stress, the stress group also differed from controls in the time taken to cross the runway (controls: 8.2 ± 0.3 s; stressed group: 45.5 ± 9.1 s; $P = .001$, unpaired t test).

3.3. Stress altered footprint patterns

Stress significantly increased the base of support from 2.6 ± 0.1 cm (acute) to 2.9 ± 0.3 cm (chronic; Fig. 3A). However, this increase was not significant among the stressed animals (STRESS × DAY: $F = 0.4$, $P > .05$, ANOVA). The acute, subchronic, and chronic testing sessions in controls and in stressed animals did not differ significantly from each other ($P > .05$, unpaired t test). In contrast, stress caused a decline in stride length (STRESS × DAY: $F = 5.9$; $P = .002$, ANOVA); stride lengths were significantly shorter in stressed than in control animals after acute ($t = 3.6$, $P = .003$), subchronic ($t = 3.9$, $P = .002$), and chronic stress ($t = 3.5$, $P = .004$, unpaired t test; Fig. 3B). Further, angle rotation increased with repeated testing (STRESS × DAY: $F = 3.5$, $P = .026$, ANOVA; see Fig. 3C), but this effect was significant only following acute and subchronic stress, and not after chronic stress ($t = -3.6$, $P = .003$; $t = -3.2$, $P = .007$; and $t = 1.9$, $P = .07$, respectively, paired t test). The results of the individual testing sessions were not significantly different from each other ($P > .05$, paired t test).

3.4. Stress increased grip time

Stress greatly affected grip time ($F = 9.4$, $P = .001$, ANOVA). In controls, the time to hold on to a grip with a constant pull (200 g) remained unchanged throughout the experiment. Baseline values were not different between the stressed and the control groups (unpaired t test; Fig. 4). Stressed animals held on to the grip significantly longer than controls after acute, subchronic, and chronic stress (all P values < 0.001, unpaired t test; Fig. 4). Compared to baseline values, the time to hold on to the grip was significantly increased after acute ($t = 3.8$, $P < .01$), subchronic ($t = -3.7$, $P < .01$) stress, but not after chronic stress ($t = -1.5$, $P > .05$, paired t test). The decline of the time measurements in stressed rats during the testing period was significant (STRESS × DAY: $F = 13.0$, $P < .001$, ANOVA). The time to hold on to the bar after chronic stress in these rats was

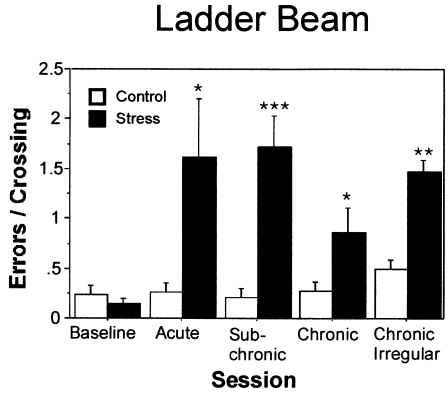

Fig. 2. Performance of control and stressed rats in the horizontal ladder beam paradigm. The number of foot falls (errors) during the traversal of the ladder was counted during a baseline session, and after 1 (acute), 7 (subchronic), and 14 (chronic) days of daily stress application. In the chronic testing session, the ability of the animals to cross a ladder with irregularly assigned bars was also tested (last column). At all experimental stages, the stressed animals exhibited significantly increased numbers of foot falls in comparison to control rats. Significant levels are given with asterisks: $*P \leq .05$; $**P \leq .01$; $***P \leq .001$ (unpaired t test).

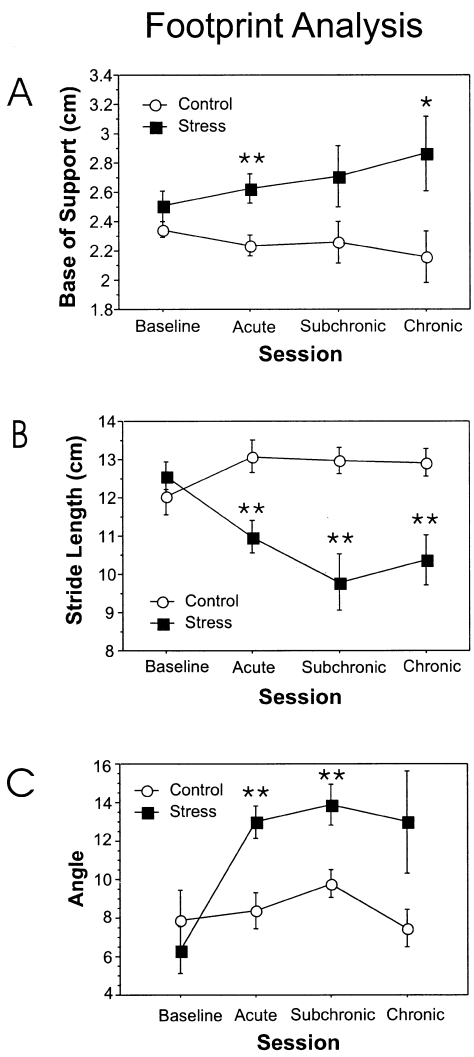

Fig. 3. Quantitative footprint analysis of control and stressed rats in a baseline session, and after acute, subchronic, and chronic stress induction. (A) Measurements of the base of support revealed enhanced distance between the left and right hindlimbs in stressed animals as compared to control rats. The increases were significant following acute, subchronic, and chronic stress. (B) Stride length measurements showed severe reduction in stressed animals throughout the entire time course. (C) The angle of foot rotation was significantly increased after acute and subchronic stress induction. Significant levels are indicated with asterisks: $**P \leq .01$ (comparison of stressed and control rats with unpaired t test).

significantly reduced as compared to acute ($t = -4.0$, $P < .01$, paired t test) and subchronic stress induction ($t = -3.8$, $P < .01$, paired t test), but did not differ from baseline values ($t = 1.5$, $P > .05$, paired t test). The grip time remained elevated in the stress group even after a further stress-free period of 4 weeks (6.4 ± 1.4 vs. 17.0 ± 2.3 s; $P = .008$, paired t test).

3.5. Stress increased latency to remove sticky papers

With each testing session, the time until both sticky papers were removed from the forepaws declined in both groups,

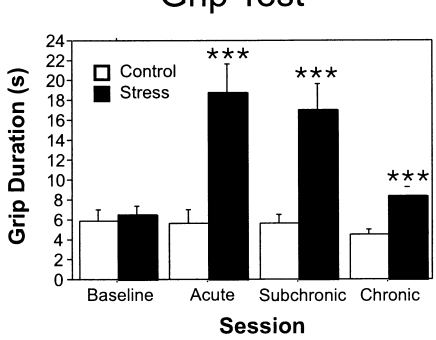

Fig. 4. The maximal duration to hold a handle with a weight of 200 g was assessed with a grip test. In contrast to control animals, stressed rats showed significantly increased time measurements after acute, subchronic, and chronic stress induction. ($***P \leq .001$, unpaired t test).

suggesting a training effect. The decline in time measurements during the testing period was significant in controls ($F = 8.9$, $P < .05$), but not in stressed animals ($P > .05$, ANOVA). In control animals, the enhanced speed of paper removal during the repeated testing led to a significant difference between acute and subchronic time points ($t = 4.0$, $P < .05$) and acute and chronic time points ($t = 3.2$, $P < .05$, paired t test). However, stressed animals did not show this training effect as their time measurements during the testing sessions did not differ significantly from each other (all P values > 0.05, paired t test). The time to remove the papers in the stress group was significantly prolonged at the subchronic ($t = 2.8$, $P < .3$) and chronic ($t = 3$, $P < .02$), but not the acute time point ($P > .05$, paired t test compared to baseline). The latency of stressed animals tended to be longer than that of controls only after subchronic stress, although not significant ($P > .05$, unpaired t test; Fig. 5).

3.6. Chronic stress lowered pain threshold

The latency of the animals' responses to a heat stimulus on a hot plate was recorded on day 19 (chronic stress).

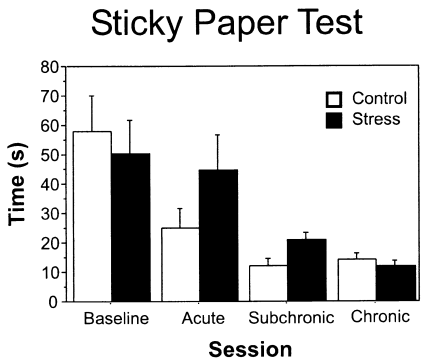

Fig. 5. The sensitivity to cutaneous stimulation was assessed in the sticky paper test in controls and stressed rats. The time to remove adhesive labels from both forelimbs was measured and revealed increased measurements after acute and subchronic stress induction as compared to control animals. The differences are not significant, however (unpaired t test).

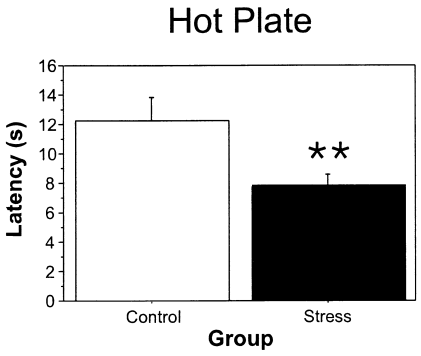

Fig. 6. Latency measurements in a hot plate test in control and stressed animals. These time measurements were performed after chronic stress induction and showed latencies in stressed animals to thermal sensation (** $P \leq .01$, unpaired t test).

Control animals showed heat avoidance behavior on the average after 12 s (Fig. 6). Chronically stressed animals had a significantly shorter response latency ($P = .002$, unpaired t test), indicative of a lower pain threshold.

4. Discussion

The present study shows that stress induced by forced swimming in cold water changed sensory–motor performance of adult male rats in different behavioral paradigms. Most of these changes appeared after acute stress and continued through subchronic and chronic stress. In comparison to control rats, the number of errors on the ladder beam in stressed animals was increased. Also, stress enhanced the grip strength when holding on to a bar. Stress led to increase of the base of support and the angle of foot rotation, but decreased the stride length in footprint analysis. In contrast, the handled controls showed very little changes in parameters with repeated testing. Animals of both groups learned to remove sticky papers from the forepaws during the testing sessions. Our data indicate that this improvement was delayed in stressed compared to control animals.

Acute stress has been repeatedly shown to induce analgesia (for review, see Ref. [28]), whereas chronic stress leads to a hypersensitivity to pain, i.e., hyperalgesia [2,6,17]. Our results confirm these observations: Chronically stressed animals had a lower pain threshold in the hot plate test than handled controls. Acute stress has also been shown to enhance c-*fos* expression in sensory relay nuclei, whereas chronic stress led to increased c-*fos* levels in the forebrain and ascending and descending sensory relay nuclei, e.g., those mediating epicritic sensation (gracile and external cuneate nuclei), pain inhibition (central gray and raphe nuclei), and viscerosensory transmission in the solitary tract nucleus [7,20].

In the L/D box, stressed but not control animals showed a large decrease in the latency to enter the dark compartment. Avoidance of the aversive brightly lit compartment by quickly entering the dark compartment is considered as an indicator of anxiety [1,10]. However, stressed animals also left the dark compartment more often than controls. The enhanced number of transitions between the light and the dark compartment observed in the present experiments is in accordance with previous literature showing that chronic stress has anxiolytic effects leading to elevated transition counts [8].

There are several possible mechanisms on how stress could influence sensory–motor performance. In their immunohistochemical study on the distribution of type II glucocorticoid receptors in the brain, Ashima and Harlan [4] concluded that these receptors are not only expressed by neurons and glia in limbic and stress-related regions, but also in various cortical, brainstem, spinal cord, and cerebellar neurons involved in motor and sensory coordination. The presence of glucocorticoid receptors in areas involved in sensory and motor coordination, including the spinal cord [4,19], suggests that glucocorticoids could directly affect motor control. Although not directly comparable to chronic stress in adults, corticosterone treatment of infant mice has been shown to affect several brain structures including the cerebellum [15] and to reduce the ability in these mice to remain on a rotating bar as adults [16]. After chronic stress, changes might also be due to longer-lasting structural or functional changes. Such corticosterone- or cortisol-induced changes have been observed in the locus coeruleus [24] as well as in the hippocampus [29]. In the present experiments, the acquisition of motor skills by the sensorimotor system, such as removing sticky labels from the paw, was slowed by stress. These data indicate that similar processes as demonstrated for cognitive function (e.g., Ref. [25]) may also lead to functional alterations in the motor system.

The tests we employed in the present study are part of test batteries used to study sensory–motor behavior in rats and mice after brain and spinal cord lesions. The present study investigated Lewis rats that are known to show a low responsiveness to stress in comparison to other rat strains [3,13,14,30]. The present study, however, showed impaired motor function in this rat strain even after chronic stress induction, indicating a limited capacity to habituate to repeated stress. Depending on the strain and the experimental conditions, various manipulations of animals might induce stress to a considerable degree and therefore influence the outcome of sensory–motor tests. While most experimenters are aware of the possibility that cognitive performance can be altered by stress, the present results show that acute and chronic stress can also strongly influence the outcome of sensory–motor tests in adult rats.

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