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Research report

Behavioural characterization in rats using the elevated alley Suok test

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Abstract

Exploration of the long elevated alley (the rat Suok test) enables behavioural characterisation of anxiety, activity and neurological phenotypes in rats. Here we show that this new test is sensitive to different types of anxiety in rats, including drugs (pentylenetetrazole)-induced, light-induced and socially induced (encounter with an unfamiliar male) anxiety, as assessed by reduced Suok test horizontal, vertical, directed exploration and stops. High anxiety also leads to higher motor incoordination (as assessed by the number of falls and hind-paw slips), suggesting that this test may be used for combined profiling of anxiety, motor-vestibular anomalies and anxiety-induced motor incoordination in rats. This new behavioural paradigm may be widely used in neurobehavioural stress research, including modelling of stress-evoked states and pharmacological screening of psychotropic drugs.

Keywords: Anxiety; Exploration; Rats; Suok test; Elevated alley; Stress; Motor incoordination

1. Introduction

Analysis of spontaneous locomotion and exploration in rodents is an important part of neurobehavioural research [6,16,35,38]. Anxiety and/or fear have long been known to be induced by novelty, and therefore can be studied by assessing rodent behaviour in an unknown environment [9,10,13,41]. Based on the balance between two natural motivations: the tendency to explore and the initial tendency to avoid the unfamiliar, many popular behavioural anxiety tests subject rodents to different novel arenas and various sources of potentially threatening stimuli [2–4,8,34,36,37,44].

Although it is commonly thought that rat behaviour could be easily generalized to mice, recent data do not support this contention, indicating that mice ethologically "are not little rats" [12,14,19,46]. For example, mice are more exploratory and active than rats [14]. In contrast, rats are more social, display complex agonistic repertoire, including sophisticated sexual and social behaviours [45,46], superior spatial navigation and learning, sophisticated manipulatory movements and self-grooming [5,19,25], also demonstrating more complex and flexible behavioural responses to novelty situations [46]. Collectively, this allows to speculate that rats may be superior than mice, and differ behaviourally in novelty-based behavioural tests.

Recently, we developed a new rodent model of anxiety based on the elevated novel horizontal rod—the murine "ropewalking" Suok test [26], named after a ropewalker in Olesha's novel "The three fat men" (1928). Evoking two obvious threats (the fear of height and novelty), this test enables ethological analysis of animal behaviour, profiling both anxiety and anxiety-induced motor incoordination [26]. Here we report the rat Suok test (ST) based on ethological analysis of the animal's exploration in the elevated novel alley, and conceptually close to the mouse ropewalking test (Fig. 1).

In the present study, we first assessed anxiety induced in rats by a conventional anxiogenic drug pentylenetetrazole [33,43], in order to show that the ST is able to detect chemically-induced anxiety. We then applied the ST to anxious (light-exposed) and non-anxious (dark-exposed) rats, to demonstrate that our test is able to discriminate between

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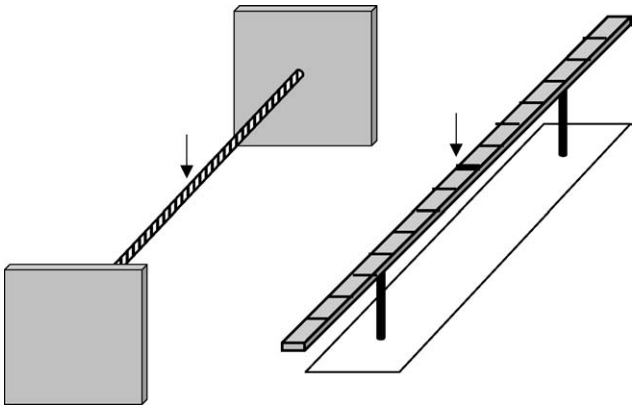

Fig. 1. The mouse (left) and the rat Suok test (right). Arrows indicate the placement point (snout facing either end).

different levels of evoked anxiety. In the third experiment, we used the ST to assess social anxiety in rats following an encounter with an unfamiliar male rat, showing that the test is able to discriminate between socially stressed and non-stressed rats.

2. Materials and methods

Subjects were 48 male Wistar rats (3 months old, 240–280 g, University of Tampere, Finland; $n = 8$ in each group) maintained in a virus/parasite-free facility under conditions of controlled temperature ($22 \pm 2\,^{\circ}C$), humidity (60%), and a 12:12 h light–dark cycle (lights on at 7:00 h). The animals were housed in pairs in standard laboratory cages, with water and food available ad libitum. Rats were only occasionally handled during change of bedding. Animal care procedures were conducted in accordance with guidelines set by the European Community Council Directives. Behavioural testing was always conducted between 14.00 and 18.00 h. On the day of experiments, the rats were transported from their holding room to the experimental room and left undisturbed for 1 h prior to testing.

In Experiment 1, the rats were injected saline (control group) or pentylenetetrazole (Sigma, Finland, 15 mg/kg i.p.) and returned to their home cages until the ST testing. Pentyleneterazole was chosen as a reference drug with a known mechanism of anxiogenic action (blockage of the chloride ionophore at the gamma amino-butyric acid GABA-A receptors) without any non-specific motor defects at the relatively mild dose given [7,11,22,23]. The pre-treatment time for our experiments (30 min) has been chosen based on numerous data showing, in different models, that pentylenetetrazole is able to exert its anxiogenic effects in rats 15–45 min after i.p. administration [7,11,22,23].

In Experiment 2, we induced different levels of stress using the light (high stress) or dark (low stress) exposure in the light–dark paradigm [13], validated for rats and widely used in behavioural neuroscience [35,41]. The light–dark test was a Plexiglas box consisting of two compartments (30 cm × 30 cm × 30 cm each)—the transparent (light) and the black (dark) box. The light box was brightly lit with a 75 W lamp fixed 40 cm above the floor, and connected to the dark box by a sliding door (this door was not used in the present study). In order to induce high or low levels of stress, we exposed the rats for 5 min to the light or dark box, respectively, essentially as described previously [25]. Immediately after the exposure, each rat was tested in the ST.

In Experiment 3, the rats were exposed to social stress (encounter with an unfamiliar male rat) in a plastic box (30 cm × 30 cm × 30 cm) for 5 min. To minimize the effect of novel environment, the exposure was performed in a familiar plastic exposure box (three 10 min daily exposures prior to the day of experiments). To reduce inter-male aggression, able to be a confounding factor in our study, we used relatively young, 2–2.5-month-old naïve non-aggressive rats as opponents. No fighting or biting behaviours were recorded in our experiments between the animals (in addition, the exposure box was novel to the opponent rats, also reducing the probability of aggression). Control rats were exposed to the same empty familiar box for 5 min prior to the ST.

The ST was a white aluminium alley (240 cm × 5 cm × 1 cm), separated into 16 sectors (15 cm) by line drawings and elevated to a height of 20 cm from the cushioned floor by two vertical stands (Fig. 1). The experimental room was dimly lit during all tests. In all ST experiments, the rats were placed individually in the middle part of the test (snout facing either end) and their behaviours were observed for 5 min by an experienced observer (intra-rater reliability >0.9), scoring the number (frequency) of anxiety and motor-related behaviours, as summarized in Table 1 (also see Fig. 2 for details). During observations, the experimenter always sat at the same place, in front of and 2 m away from the apparatus. In addition, in all experiments, the latency (s) to leave the center of the ST was measured, reckoned as total 5 min observation time (300 s) in the rats (5–10%) not leaving the central zone. The lighting in the experimental room was similar to that in the holding room during these procedures.

Between subjects, each apparatus used in the present study (light–dark box, ST, plastic observation box) was thoroughly cleaned (wet and dry cloths). To remove olfactory stimuli, each apparatus was also cleaned with a 10% ethanol solution and dried with paper towelling. The procedures used in this study were in strict accordance with the European legislation and the guidelines of the National Institutes of Health on the use and care of laboratory animals. All animal experiments reported here were approved by the Ethical Committee of the University of Tampere.

All results are expressed as mean ± S.E.M. Data were analysed by the Mann–Whitney *U*-test for comparisons between the experimental groups. A probability of less than 0.05 was considered statistically significant.

3. Results

Table 2 shows that more anxious pentyleneterazole-treated rats displayed reduced horizontal and vertical exploration, lower stopping activity, increased displacement grooming and higher levels of stress-evoked motor incoordination (falls and missteps). In addition, the inter-stop distance was significantly lower in this group, clearly demonstrating increased anxiety in these rats, compared to the saline-treated controls. In contrast, directed exploration, latency to leave the center as well as defecation/urination scores were unaltered in this experiment.

The light–dark exposure used in Experiment 2, in line with traditional interpretation of the light–dark paradigm, has been reported to induce two different levels of stress in rats [25,35].

Table 1
Summary of key behavioural parameters measured in the rat Suok test

Measures and behavioural domains		Description
I. Exploration (reduced by anxiety)		
HA	Horizontal activity	Number of sectors visited (4-paw criterion, Fig. 2A)
VA	Vertical activity[a]	Number of vertical rears[a]
SA	Stopping activity	Number of stops (complete cessation of movement (>2 s) except breathing)
HD	Head dips[b]	Down-directed exploration, number of exploratory looks down (Fig. 2C)
OR	Orientation[b]	Side-directed exploration (visual and olfactory scanning of environment and whisking, Fig. 2A)
DE	Directed exploration	Number of orientation and head dips (DE = HD + OR)
LL	Latency to leave[c]	Latency (s) to leave a 30-cm virtual central zone around the placement point (4-paw criterion)
ID	Inter-stop distance	Average distance between two stops (the number of sectors visited divided by the number of stops: ID = HA/SA)
II. Displacement (increased by anxiety)		
DA	Displacement[a]	Usually short bouts of forepaw and nose grooming. Measures include frequency and duration (s) of grooming
III. Vegetative behaviours (increased by anxiety)		
DB	Defecation	Number of defecation boli deposited
LD	Latency to defecate[b]	Latency (s) to the first defecation boli
UR	Urination[b]	Number of urination episodes
III. Motor coordination (reduced by anxiety)		
NF	Falls[b]	Number of falls from the rod
LF	Latency to fall[b]	Latency (s) to the first fall from the rod
MS	Missteps[b]	Number of hindpaw slips (Fig. 2D)
ML	Misstep latency[b]	Latency (s) to the first misstep (hindpaw slip, Fig. 2D)
MI	Motor incoordination index	Integral index, reflecting the number of falls and missteps (MI = NF + MS)

[a] Relatively rare behaviours in this test, but may be more frequent in some rat strains.
[b] Optional parameters (not assessed here).
[c] Latency to leave the center may be highly variable in this test, thus sometimes showing limited validity.

As expected, more anxious light-exposed rats demonstrated significantly lower directed exploration and more falls and missteps (motor incoordination index) in the ST compared to the dark-exposed control group. However, despite a general tendency to more anxiety behaviour in the light-exposed group (Table 2), horizontal and vertical exploration, stops, displacement grooming, latency to leave the center, inter-stop distance and defecation/urination measures did not differ significantly in both groups.

As can be seen in Table 2, social anxiety evoked in Experiment 3, significantly inhibited directed exploration and stops, also resulting in higher displacement grooming and poorer motor coordination (more falls and missteps). Additionally, there was a trend to less horizontal and vertical ST

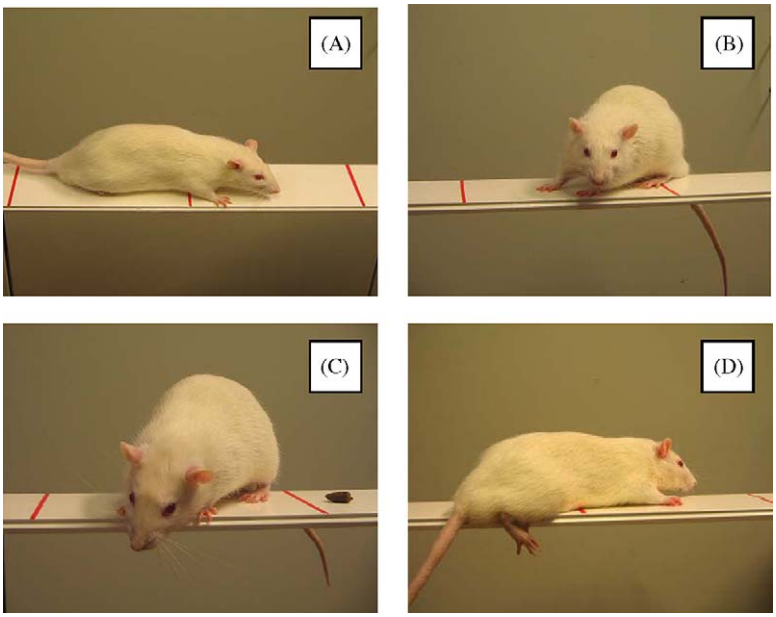

Fig. 2. Specific behaviours in rats tested in the Suok test: (A) horizontal locomotion, (B) side-directed exploration, (C) look down (also note defecation bolus deposited), (D) motor incoordination episode (hindpaw slip).

Table 2
Behavioural performance of rats subjected to the Suok test for 5 min (n = 8 in each group)

Experiments and measures	Non-anxious (control) group Saline-treated	Anxious group PTZ-treated	*P*<
Experiment 1: Pentylenetetrazole (PTZ)-induced anxiety			
Horizontal activity	49 ± 8	18 ± 3	0.001
Vertical activity	2.3 ± 0.5	0.9 ± 0.3	0.05
Stopping activity	14 ± 1.5	8.5 ± 0.7	0.05
Directed exploration	18 ± 2	19 ± 2	NS
Latency to leave center (s)	91 ± 34	126 ± 32	NS
Displacement grooming	0.1 ± 0	1.2 ± 0.2	0.05
Defecation boli	0.4 ± 0.3	0.1 ± 0.1	NS
Urination	0.3 ± 0.2	0.1 ± 0.1	NS
Average inter-stop distance	3.5 ± 0.6	2.2 ± 0.3	0.05
Falls and missteps	2.0 ± 0.4	3.6 ± 0.4	0.05
Experiments and measures	Non-anxious (control) group Dark-exposed	Anxious group Light-exposed	*P*<
Experiment 2: Light-induced anxiety			
Horizontal activity	81 ± 9	71 ± 7	NS
Vertical activity	0.3 ± 0.2	0	NS
Stopping activity	19 ± 2	19 ± 2	NS
Directed exploration	25 ± 3	15 ± 2	0.001
Latency to leave center (s)	18 ± 8	27 ± 9	NS
Displacement grooming	0	0	NS
Defecation boli	0.6 ± 0.4	1 ± 0.3	NS
Urination	0.3 ± 0.2	0.3 ± 0.2	NS
Average inter-stop distance	4.3 ± 0.5	3.7 ± 0.4	NS
Falls and missteps	2.6 ± 0.4	4.3 ± 0.4	0.001
Experiments and measures	Non-anxious (control) group Unexposed	Anxious group Exposed	*P*<
Experiment 3: Socially-induced anxiety			
Horizontal activity	74 ± 4	62 ± 7	NS[a]
Vertical activity	1.7 ± 0.5	0.4 ± 0.3	NS[a]
Stopping activity	22 ± 2	17 ± 1	0.005
Directed exploration	20 ± 1	12 ± 1	0.0005
Latency to leave center (s)	28 ± 13	53 ± 14	NS[a]
Displacement grooming	0	0.8 ± 0.1	0.05
Defecation boli	0	0	NS
Urination	0.2 ± 0.2	0.3 ± 0.2	NS
Average inter-stop distance	3.4 ± 0.2	3.6 ± 0.4	NS
Falls and missteps	2.4 ± 0.2	3.7 ± 0.2	0.005

Data are expressed as mean ± S.E.M. *P*: difference between groups (*U*-test). NS: non-significant difference ($P > 0.05$).
[a] Robust trend: $P = 0.07$–0.08.

exploration and a longer latency to leave the center in the stressed rats, indicating their anxious behavioural profile. Urination/defecation scores and the average inter-stop distance were unaltered in both groups (Table 2).

4. Discussion

Ethological analysis of mouse and rat exploratory behaviours provides an avenue for studying the neural basis of stress-related brain disorders [18,20,21,39]. Since recent data suggest that that rat behaviour is characterized by high level of complexity (relative to the mouse) and ability to alter behavioural strategies [45,46], it was interesting to assess in detail the rat ST performance. Is this paradigm able to detect anxiety in rats tested in different stress situations? As can be seen in Table 2, there was a general pattern of ST behaviour demonstrated by anxious rats including lower horizontal, vertical and directed exploration, and shorter inter-stop distance. In addition, anxious rats tended to display more displacement grooming and motor-vestibular deficits (as assessed by increased falls and hindleg slips in this test, Table 2), consistent with similar results in the mouse ST [26] and some other models (see [30–32,42] for details).

Notably, the rat ST performance differed from that reported previously in mice [26] in a number of ways. For example, while urination was equally ineffective index in both species, the ST defecation was a sensitive measure of anxiety in mice [26] but not in rats (Table 2). The latency to leave the ST central zone was also a robust behaviour in

mice, but a weak index in rats. Inter-stop distance was a good ST index of anxiety in mice, showing only slight sensitivity to anxiety induced in rats in the present study (Table 2). In contrast, vertical exploration (occurring only occasionally in mice and failing to detect anxiety [26]) was reduced in all our experiments in rats ($P < 0.05$: Experiment 1; trend: Experiments 2 and 3), generally consistent with increased anxiety in rodents [17,36,41].

Overall, mice produced more stops and directed exploration in the ST, confirming recent similar findings in the open field and the elevated plus maze [16,39]. However, relative to the rats, the mice subjected to the ST displayed less directed exploration compared to their respective non-stressed controls. In addition, although self-grooming behaviour may be a behavioural marker of stress in rodents [15,24,25], there have been only few ST grooming bouts in mice, but a robust displacement grooming activity in rats (Experiments 1 and 3; Table 2). Collectively, these data support the idea that the ST performance is more "locomotory" in mice, and more "exploratory" in rats [14].

In contrast to anxiety measures, motor incoordination index (falls + missteps) demonstrated consistent and non-specific increase in all anxious rat groups. Although strong relationship between anxiety and motor-vestibular disturbances has long been known in humans (see review in [40,42]), anxiety-evoked motor incoordination has only recently been reported in mice [30–32]. Our study is the first report demonstrating similar phenomenon in rats (Fig. 2). Indeed, Table 2 clearly shows that anxious rats consistently tend to display more falls and missteps then do their less anxious controls, indicating the ST potential utility to assess anxiety-induced motor-sensory defects in rodents.

Other potential applications of this test may be ethological analysis of the age-related motor and emotional behavioural alterations in rats, as well as behavioural phenotyping of various mutant or selectively bred rat strains, especially those displaying abnormal emotional and/or motor behaviours (e.g., [1,17,29]). Moreover, given high sensitivity of the rat exploration to various pharmacological manipulations [3,15,23,36,37], the ethologically-oriented analysis of their ST performance may be used in psychopharmacology research, including screening of novel anti-stress drugs. Our preliminary results using anxiolytic drugs diazepam and ethanol in the rat and mouse ST [27,28] suggest that this may indeed be likely. Finally, the ST may assist to explore cognitive and motoric structure of rat behaviours and motor-sensory integration (for example, assessing firing patterns of neurons responsible for exploration and navigation).

In conclusion, the present novel behavioural paradigm enables combined profiling of anxiety, activity and motor anomalies in rats. It is a one-trial test based on animal spontaneous behaviour, using natural stimuli and not requiring prior training or food/water deprivation. Finally, the ST examines a wide range of behaviours—from exploration to displacement and vegetative behaviours, and may therefore be a useful tool for neuroscience research, enabling high-throughput experimental modelling of various stress disorders in rats.

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