



Rats with differential self-grooming expression in the elevated plus-maze do not differ in anxiety-related behaviors

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HIGHLIGHTS

- Male Wistar rats were divided according to time of grooming in the elevated plus-maze.
- Self-grooming behavior varies broadly among subjects.
- Groups do not differ in the expression of conditioned and unconditioned fear.
- No neurochemistry or neuroendocrine differences were observed between groups.
- Grooming expression in the EPM seems to be dissociated from anxiety-related behaviors.

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ABSTRACT

Individual differences are important biological predictors for reactivity to stressful stimulation. The extent to which trait differences underlie animal's reactions to conditioned and unconditioned fear stimuli, for example, is still to be clarified. Although grooming behavior has been associated with some aspects of the obsessive-compulsive disorder in humans, its relation with other anxiety disorders is still unknown. Given that grooming behavior could be a component of the whole spectrum of these disorders, in the present study we allocated male Wistar rats in low, intermediate and high self-grooming groups according to the duration of such behavior in the elevated plus-maze (EPM). These groups were then evaluated in unconditioned fear tests, such as the EPM and the open-field, and in conditioned fear tests, such as fear-potentiated startle and fear extinction retention. Additionally, we studied the expression of unconditioned behaviors in marble burying test and the sensorimotor gate function with prepulse inhibition test. Neurochemicals and neuroendocrine parameters were also evaluated, with the quantification of basal corticosterone in the plasma, and dopamine, serotonin and their metabolites in brain structures involved with fear processing. In general, rats classified according to grooming expression showed similar performance in all behavioral tests. Accordingly, corticosterone and monoamine concentrations were similar among groups. Thus, despite grooming expression elicited by different approaches – especially pharmacological ones – has been related with some aspects of anxiety disorders, rats with different expression of spontaneous self-grooming in the EPM do not differ in anxiety-like behaviors nor in neurochemical and neuroendocrine parameters generally associated with anxiety disorders.

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1. Introduction

Interindividual variation in terms of behavioral response and physiology can be found in laboratory animals with identical strain, breeder, age, sex and housing [1–3]. Although small within- and between-subject variability through an outbred animal population are expected, such individual differences can affect the performance in neurobiological and, particularly, behavioral tests.

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Nevertheless, the research on individual differences has opened new possibilities for better exploring the neurobiological basis of vulnerability to psychopathological disorders, and is also helping to solve some important questions on treatment-resistant patients [4,5].

Numerous studies have been using different methodologies to screen rodents, and to assign them to subgroups with differential expression of a specific behavior, for example, locomotion and rearing in an unfamiliar environment [6], expression of a specific conditioned fear response [7], or time spent in the open arms of an elevated plus-maze (EPM) [8]. In this direction, it has been shown that individual differences are important predictors for the reactivity to stressful stimulation [7–9]. The reasons and specific individual traits that can contribute to variations on the expression of defensive behaviors are still unclear, although being under intense investigation [10,11].

One little explored aspect in both screening and behavioral testing is the self-grooming behavior. Grooming consists of complex sequences of movements directed to clean and maintain the fur and skin of the head and body. These coordinated movement strings include wiping, licking, and scratching [12,13]. Moreover, grooming behavior can be triggered in different contexts, such as after peripheral stimulation or contamination or, yet, when animals face a novel/unfamiliar somehow stressful situation [12,14,15]. In this latter case, self-grooming is frequently classified as a displaced behavior, suggesting that the grooming/anxiety relationship deserves further evaluation [12].

As well as grooming behaviors are highly adaptive in most species, obsessive-compulsive behaviors occur in many humans without being pathological. However, both excessive grooming and obsessive-compulsive behaviors can result in physical and social impairment given their persistence despite negative consequences. In this respect, a spectrum of abnormal behavior resembling excessive grooming in both animals and humans may be related to some specific obsessive-compulsive disorder (OCD) symptoms [16,17]. Previous studies have suggested that excessive grooming behavior and its correlates, such as hair loss and skin lesions observed in animals, could share similarities with contamination fears that lead to compulsions such as repetitive hand washing, observed in some OCD patients [18–20]. Indeed, one of the most used treatments for OCD, the administration of serotonin-reuptake inhibitors (SRIs), when applied to rats exhibiting pharmacologically-induced excessive grooming, reduces the skin lesions resulted from exaggerated grooming behavior [20,21].

Assuming that self-grooming behavior could be associated with some aspects of OCD [18–20], and OCD and other anxiety-related disorders may share overlapping brain circuitries [22], male Wistar rats screened according to the duration of self-grooming in the EPM were evaluated in a series of experiments regarding unconditioned and conditioned fear responses and compulsive-like behaviors. Because some OCD patients present deficits in the interface between information acquisition and motor expression [21,23], the rats displaying different levels of grooming were also assessed in the prepulse inhibition test (PPI) to evaluate the sensorimotor gating function. In addition, basal concentration of plasma corticosterone, and dopamine, serotonin and their metabolites in several brain structures related to fear processing and/or OCD pathophysiology were analyzed.

2. Methods

2.1. Animals

One-hundred and seventy-five male Wistar rats, weighing 290–310 g, from the animal house of the University of São Paulo,

campus of Ribeirão Preto, were used. These animals were housed in groups of four per cage under a 12:12 dark/light cycle (lights on at 07:00 AM) at 23 ± 1 °C, and given free access to food and water. Rats were handled only during cage cleaning in order to minimize known handling effects on grooming expression [24]. All procedures were approved by the Committee for Animal Care and Use of University of São Paulo at Ribeirão Preto (No. 11.1.1649.53.4) and were in accordance with the United States National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Selection of rats according to self-grooming behavior in the elevated plus-maze

At the beginning of each experiment, rats were exposed to a 5-min session in the EPM. The EPM apparatus consisted of two open arms (length: 50 cm/width: 10 cm), perpendicular to two closed arms of equal dimensions and surrounded by 40 cm high walls. The EPM was elevated 50 cm from the floor, and located inside a room with constant background noise (50 dB) and controlled luminosity (30 lux at the level of the open arms of the maze). The maze was cleaned with 20% ethanol before each test. Experimental sessions were conducted between 09:00 AM and 13:00 PM. All motor activity was monitored during the EPM test and subsequently scored by an observer using the ethological analyses software ANY-maze (version 4.7; Stoelting, Wood Dale, IL, USA). The animals were sorted by total time spent in self-grooming in any part of the apparatus. Face and head washing, body and genital grooming, scratching and paw licking were included as components of grooming behavior. Three groups, with similar number of animals each, were then formed considering the overall grooming response across experiments: Low Grooming (LG – including animals with total grooming duration between 0 and 14.7 s); Intermediate Grooming (IG – 14.9 to 32.9 s) and High Grooming (HG – 33.0 to 124.0 s). Independent sets of animals were used for each experiment described below, unless specifically pointed in the experimental design.

2.3. Experiment 1: unconditioned fear responses

2.3.1. Elevated plus-maze test

As described previously, EPM was used to select animals regarding their grooming expression. Additionally, traditional anxiety-related parameters were evaluated in the present experiment. Rats were placed individually in the center of the EPM and left for a 10 min period of free exploration. The frequency of open arms and closed arms entries (an arm entry or exit being defined as all four paws into or out a section, respectively) and the relation between time spent in open and closed arms were recorded. Although 10 min of test was recorded, the behavioral data presented correspond to the first 5-min of the EPM test.

2.3.2. Open-field test

The open-field (OF) apparatus consisted of a circular transparent acrylic arena (60 cm diameter, 50 cm height) placed on a dark plywood floor (floor divided into 12 sections, 8 peripherally and 4 centrally located, with central area with approximately 30 cm diameter). The apparatus was located inside a room with constant background noise (50 dB) and luminosity at the OF floor set at 30 lux. Three days after EPM exposure, the same groups of rats were placed individually in the center of the OF and left for a 10 min period of free exploration. The total grooming time, total distance travelled, total immobility time and time in the center of the OF were recorded.

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