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Short report

Olfactory discrimination and memory deficits in the Flinders Sensitive Line rodent model of depression

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ABSTRACT

Major Depressive Disorder (MDD) is a heterogeneous psychiatric disorder with broad symptomatic manifestations. The current study examined, for the first time, olfactory memory and discrimination in the Flinders Sensitive Line (FSL) rodent model of depression. Male FSL rats and controls were trained on an Olfactory Discrimination (OD) and a Social Interaction (SI) test. On the OD test, the FSL and controls performed similarly at the shortest inter-trial interval (5 min), however, with extended delay of 30 min, the FSLs had a recall and odour discrimination deficit. At the longest delay (60 min) both groups performed poorly. The FSL rats i.) had a deficit in olfactory discrimination suggesting impairment in olfactory memory and recall; ii.) were less likely to socialize with unfamiliar rats. The data suggests that FSL animals have an impaired olfactory information processing capacity.

1. Introduction

Major depressive disorder (MDD) is the most prevalent psychiatric disorder in the world (Ormel et al., 2008) affecting approximately 350 million people worldwide at any given moment (World Health Organisation WHO, 2015). MDD imposes immense burdens on the sufferers' and the caretakers' lives, and there is ever-rising economic costs associated with depression (Greenberg et al., 2015). The aetiology and the symptoms of MDD are heterogeneous, and current conventional treatments combine pharmacotherapy and psychotherapy and approximately 70–75% of the diagnosed patients can experience remission.

Anhedonia and decreased motivation levels are considered core symptoms in clinical depression, and the phenotypes in animal models corresponding are deficits in the Sucrose Preference Test, or on the Forced Swim Test, respectively. However, another key aspect often described in clinical depression is olfactory dysfunction, and this phenotype is neglected in experimental models. Olfactory memory recall and sensitivity is significantly worse in MDD patients (Grapsa et al., 2010; Kohli et al., 2016; Pause et al., 2001) and it is still disputed whether this loss of olfaction ability is a part of the cause or a part of the symptomology of MDD. Olfactory function is governed by the olfactory system which encompasses parts of the limbic and mesolimbic system (Sivam et al., 2016; Wilson et al., 2004). Areas such as the olfactory bulb, the amygdala and the hippocampus are actively involved in goal directed behaviour but also in the formation of olfactory memories. This link between the two systems indicates that there may be a link between the onset of anhedonic symptoms and a decrease in olfactory function. Alleviating olfactory dysfunction may lead to a better prognosis for MDD patients, and conversely, reversing anhedonic tendencies may alleviate olfactory function.

The current study explored olfactory discrimination and social interaction using the Flinders Sensitive Line (FSL) rats, a validated model with spontaneously emerging depressive-like behavioural and physiological phenotype (Overstreet and Wegener, 2013; Thiele et al., 2016). The results indicate that FSL animals are capable of learning and discriminating between novel odours at short intervals, however, they had robust recall and odour discrimination deficit at longer delays compared to controls. The FSLs were also less likely to explore and interact socially with an unfamiliar rodent. Taken together, the data suggests that the FSL animals have an impaired olfactory information processing capacity, and are less motivated to explore novelty, both indicating potentially a dysfunctional limbic system. The animal model lends itself to future investigations of the therapeutic effect of medial forebrain bundle Deep Brain Stimulation on the olfactory deficits associated with MDD.

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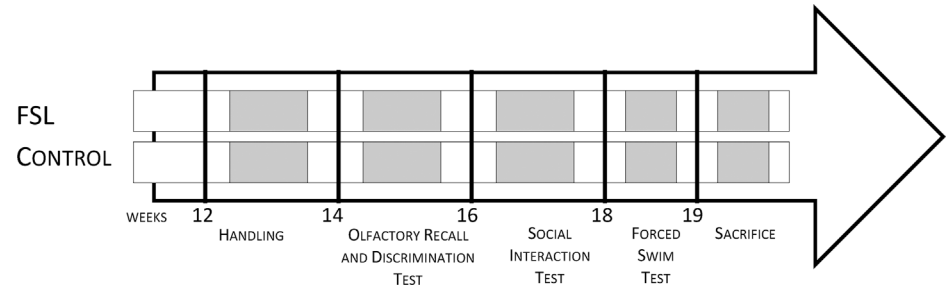
Table 1
Timeline of the behavioural tests. Grey blocks indicate participation in the procedures.



2. Method

2.1. Subjects

Male Flinders Sensitive Line (FSL) rats were used from the in-house breeding colony (Freiburg University Medical Centre, n = 6), and gender matched Sprague-Dawley (SD, the same background as FSLs) rats acted as controls (Charles River, n = 6). Animals were 10 weeks old at the start of the study and the same cohort of animals were used for all procedures. Subjects were housed 3 rats per cage, on a 12 h:12 h light-dark cycle, at 21 ± 1° C, 50–60% relative humidity, and had ad libitum access to standard rat food and water. For design see Table 1. The study was approved by the veterinary board for research in animals of the University of Freiburg and was carried out in accordance with the EU Directive 2010/63/EU concerning the protection of animals used for scientific purposes.

2.2. Olfactory discrimination and recall test (OD)

The OD protocol (adapted from (Hackett et al., 2015)) used a grey open top box (65 × 65 × 50 cm) with two open Eppendorf tubes (1.5 ml) fixed around the centre (20 cm apart) each containing a swab with the odour (150 µl/swab). Mineral oil (Roth, Germany) was used as the control odour, as well as the vehicle to dilute the experimental odours in. The experimental odours (Odour 1; Odour 2) were diluted at specific concentrations to yield approximately 1 Pa. (Table. 2). The chosen odours were "neutral" (Devore et al., 2013). Before the experiment began, the subjects were habituated to the box and the control odour for five minutes a day for three consecutive days.

The test consisted of a five-minute encoding trial (Trial 1 or T1) consisting of exploration and familiarisation of odours presented. During T1 one tube contained the control odour (mineral oil) and the other Odour 1. The subject was then placed into a separate cage for a delay period of a specified duration (Table 2). After the delay, back in the test box for the recall trial (Trial 2 or T2), the animal had a further 5 min to investigate the familiar odour (Odour 1) and the novel odour (Odour 2). The test was conducted over three non-consecutive days; each day the delay period was extended. Odour recall capacity was calculated as the difference in time spent examining Odour 1 across the trials, in other words "Olfactory Recall" = (T1 Odour 1 duration) − (T2 Odour 21 duration). Odour discrimination was calculated as the difference in time spent with odour 2 vs. odour 1 during trial 2, in other words "Olfactory Discrimination" = (T2 Odour 2 duration) − (T2 Odour 1 duration). The visit duration of odour investigations was measured manually. A visit was defined as a direct movement of the nose towards the Eppendorf and the time the nose remained in proximity was measured. Activity was recorded using a digital recording camera (Sony Corporation, Japan).

Table 2
The six odours used in the olfactory recall and discrimination test and for which day of the experiment they were used. The dilutions shown are the required dilutions to create 1 Partial pressure (Pa.) of odour.

Day	*Delay period (minutes)*	*Odour one*	*µL in 10 ml*	*Odour two*	*µL in 10 ml*
1	5	Acetic Acid	0.2	Butanol	3.2
2	30	Octanal	14.8	Limonene	20.4
3	60	Hexanal	2.2	Geraniol	250

2.3. Social interaction test (SIT)

The three-chamber SIT measures sociability and preference for social novelty, has been adapted from Kaidanovich-Beilin et al. (2011). The transparent SIT box (100 × 45 × 45 cm) consisted of three partially separated zones, Zone 1, Middle, and Zone 2. Zones 1 and 2 contained Cage 1 and 2, respectively. The cages were cylinders (diameter: 20× height: 25 cm) made of transparent bars separated by small gaps that allowed only noses and paws to pass between. The "strangers" used in the test were 12 FSL male rats of a similar size and weight that were housed in a separate room. Before testing began, the subjects and the strangers were habituated to the social interaction box for 10 min a day for three days to reduce anxiety.

The procedure involved two trials; first, the subject was placed into the 'Middle' zone with open access to both Zones 1 and 2. In this initial trial (Trial 1 or T1) Cage 1 contained Stranger 1 and Cage 2 was empty. The subject was given 10 min to interact with Stranger 1 and explore the apparatus before returning to its home cage for a 5-min inter-trial interval. Following the inter-trial-interval the subject returned to the Middle zone for Trial 2 (T2) lasting 10 min during which Cage 1 still contained the familiar rat (Stranger 1), and Cage 2 contained Stranger 2, a novel rat.

Social Interaction behaviour was interpreted by assessing the time an animal spent with Stranger 2 in T1, and then looking at how this value changed when in T2 it had access to both the familiar Stranger 1 and the novel Stranger 2 rat. The expected preference to interact with the novel stranger was quantified as the difference in time spent with Stranger 2 compared with Stranger 1 in T2. "Interaction" was defined as movements of the nose towards the other rat, including sniffing or direct contact with the cage. The formula used for the calculation was: "Novel stranger interaction" = (T2 Stranger 2 duration) − (T2 Stranger 1 duration). Activity was recorded with a digital camera (Sony Corporation, Japan).

2.4. Forced swim test (FST)

The FST protocol used has been described previously in more detail (Thiele et al., 2016). The subjects were placed into a transparent plastic cylindrical tank (diameter: 20–40 cm; height: 65 cm), filled with water (26 ± 1 ° C) up to 10 cm from the rim of the tank. The rats were unable to reach the base of the tank with their tails and unable to reach the rim of the tank with their paws. Each subject was assessed between 14h00-16h00, during the light period of the light-dark cycle. The subject was