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# Impaired memory following predatory stress in mice is improved by fluoxetine

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**Abstract**

The first purpose of the present study was to investigate possible effects of predatory stress (i.e., 5-min cat exposure) on short-term learning abilities in Swiss mice using the object recognition test (ORT). The second aim was to evaluate the effects of anxiolytics (i.e., diazepam and fluoxetine) on learning/memory abilities in the ORT following predatory stress. Results showed that predatory exposure impaired learning and produced amnesia of acquired information or impairment to retrieve learned information (48 and 96 h poststressor). The learning impairment in the ORT in stressed mice was restored by acute fluoxetine treatment, but not by diazepam that instead affected learning in nonstressed animals. Taken together, these findings indicate that this animal model of exposure of mice to unavoidable predatory stimuli produces early cognitive changes analogous to those seen in patients with acute stress disorder (ASD).


*Keywords:* Amnesia; Fluoxetine; Object recognition; Predatory stress; Trauma

## 1. Introduction

In rodents and humans, stress has effects on functions of new learning and memory that are mediated by the hippocampus (Diamond et al., 1999; de Quervain et al., 1998; Gluck et al., 1997; Lupien and Lepage, 2001), the amygdala (McGaugh, 2002) or the medial prefrontal cortex (Bremner, 2002), and on serotonergic activity (Neumaier et al., 2002). Evidence from a variety of studies (Gilbertson et al., 2001; McNally, 1998; Sutker et al., 1990; Vasterling et al., 2002) shows a relationship between exposure to a traumatic stress and deficits in memory, attention, visual spatial skills, in encoding and in retrieval on explicit memory tasks, as well as deficits in working memory (e.g., sustained attention, visuospatial memory, executive functions) in addition to hippocampal damage (Bremner, 1999; Diamond et al., 1996; Galletly et al., 2001). Alterations in hippocampal morphology and function are associated with numerous psychiatric disorders, e.g., posttraumatic stress disorder (PTSD). PTSD has been linked to decreased volume of the hippocampus (Bremner et al., 1995; McEven and Magarinos, 1997; Warden et al., 1996). Selective reuptake inhibitors for serotonin (SSRIs) produced an impact on this process in a beneficial way, blocking the effects of stress at the level of neurotrophic factors (Duman et al., 2001; Post et al., 1996). SSRIs have been successfully used in the clinical management of several anxiety disorders, including PTSD (Den Boer and Westenberg, 1995; Fichtner et al., 1997; Nagy et al., 1993; Van Ameringen et al., 1993). It is of particular interest that PTSD accompanied by memory impairment could be improved by treatment with SSRIs (Davis et al., 2001; Fernandez et al., 2001; Smajkic et al., 2001).

Acute stress disorder (ASD) (WHO, 1993; APA, 1994) is characterized by symptoms similar to those of PTSD that occur immediately in the aftermath of an extremely traumatic event (dissociative, arousal, intrusive and avoidance symptoms) (Barros et al., 2000; Bremner et al., 1998). Predatory exposure has been shown to induce anxiety-like behaviour in rodents (Adamec et al., 1999; Belzung et al., 2001; Belzung and Griebel, 2001; Blan-

*Abbreviations:* ASD, acute stress disorder; Dz, diazepam; Fx, fluoxetine; ns, nonsignificant; ORT, object recognition test; Phy, physiological saline solution; PTSD, posttraumatic stress disorder; PVC, polyvinyl chloride; RI, recognition index=$100\times T_n/(T_{ref}+T_n)$; SSRIs, selective specific reuptake inhibitors for serotonin; $T_n$, time spent exploring the novel object; $T_{ref}$, time spent exploring the reference object.

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chard et al., 1998, 1990) and can be used as a model of ASD (Adamec et al., 1997).

The present study was designed to determine whether exposure to species-relevant inescapable stress (i.e., a 5-min cat exposure) leads to acute changes in cognitive functioning using a hippocampus-related memory task, the object recognition test (ORT) (Prickaerts et al., 2002). ORTs are widely used in rodents to test aspects of working memory and to characterize processes of amnesia (acquisition, consolidation, retrieval). In many animal models of learning and memory, the learning component consists of a stressful stimulus or food deprivation to ensure that animals are motivated to perform the task and to obtain a reward (Dodart et al., 1997). To circumvent problems with stress or food in memory tasks, the ORT was developed. It is based on the natural tendency of mice to explore an unknown object longer than a familiar one (Poucet, 1989). An animal showing impaired memory will spend the same amount of time exploring familiar and novel objects (Messier, 1997; Dodart et al., 1997). The ORT is useful to test recognition memory in mice, allowing the assessment of acquisition, consolidation or retrieval of information. In a second phase we investigated the effects of anxiolytic drug treatments (diazepam, fluoxetine) on the impairment of learning abilities following predatory exposure.

## 2. Animals, materials and methods

### 2.1. Ethics

All procedures described here fully comply with French legislation on research involving animal subjects. This research protocol adhered to recommendations by the European Community Council for the Ethical Treatment of Animals (no. 86/609/EEC).

### 2.2. Animals

Subjects ($n = 36$) were naïve, male, Swiss mice aged 9 weeks at the time of testing. Animals were bred and provided by Janvier-CERJ (France). Prior to experimental testing, they were housed in groups of three in standard-sized Plexiglas cages ($30 \times 20 \times 14$ cm) permitting free access to food and water. All animals were maintained under standard laboratory conditions (21–23 °C) and kept on a 12-h light/dark cycle (light onset at 7 a.m.).

### 2.3. Drugs

Diazepam (1 mg/kg) and fluoxetine hydrochloride (10 mg/kg) (synthesized by Sigma Aldrich, Saint Quentin Fallavier, France) were prepared as suspensions in physiological saline containing one drop of Tween 80 (0.1%). They were injected intraperitoneally in a volume of 20 ml/kg, 30 min before test.

### 2.4. Predatory exposure

Mice were randomly assigned to the exposed or control groups. Subjects of the exposed group were confronted individually with a cat during a 5-min session. The cat (male, age 3 years; Iffa Credo, L'Arbresle, France) was placed in the exposure apparatus ($42 \times 56 \times 42$ cm) first. The mouse was placed in a Plexiglas ball (diameter = 17.5 cm) containing numerous holes, and introduced into the exposure apparatus. After 5 min of exposure to the cat, the mouse was put back in its cage. Mice from the control group were handled gently and briefly in their home cage. Predatory stress or handling took place between 1000 and 1500 h.

### 2.5. Object recognition test

The apparatus consisted of an illuminated (100 lx) grey PVC box ($20 \times 21 \times 32$ cm) covered with Plexiglas. The objects used were small plastic kitchen hooks of different colours and shapes, eliciting the same exploration time.

The ORT consists of three sessions, lasting 5 min each. During the first session, each subject was placed in the box empty of any object, for a 5-min habituation period. Test 1 (second session) took place 30 min after the end of the habituation period. Two identical objects (reference objects) were fixed on the wall, so that the mouse could stand up to explore it. Test 2 (third session) took place 1 h after the end of Test 1. One of the reference objects was replaced with a novel object. The time spent exploring the reference object ($T_{ref}$) and the novel object ($T_n$) was recorded. A recognition index (RI) was calculated for each animal, expressed by the ratio $RI = 100 \times T_n/(T_{ref} + T_n)$ and compared to the value of 50% (the two objects identically explored). Between testing sessions, the box and the objects were cleaned with 10% ethanol-imbibed linen. The behaviour of the mouse was observed for 5 min each session via a closed-circuit TV camera by an observer in an adjacent room, blind to the treatments of the mice. The time spent exploring each of the reference objects (snout pointing toward the object at a distance $\leq 1$ cm) was recorded.

### 2.6. Experiment 1: behaviour of nonexposed animals in the ORT

A control group of 12 subjects was tested in the ORT. They were not exposed to the cat and remained untreated.

### 2.7. Experiment 2: effects of predatory exposure on memory in the ORT

Thirty minutes after the learning session (Test 1), subjects ($n = 8$) were confronted individually with a cat during a 5-min session. One hour after Test 1 the effects of cat exposure on the recent learning in the ORT (short-term memory) was assessed (Test 2).

### 2.8. Experiment 3: effects of predatory exposure at different time intervals on learning in the ORT

To evaluate the effects of predatory stress on learning, the predatory exposure in mice took place 48 h ($n=8$) and 96 h ($n=8$) before the ORT.

### 2.9. Experiment 4: effects of diazepam and fluoxetine in the ORT following predatory exposure

Diazepam and fluoxetine were administered 30 min before Test 2 in the ORT (49 h after cat exposure). Forty mice were allocated to the following five groups:

(a) Naïve + saline (Phy): animals were not exposed to a cat and received physiological saline solution.
(b) Naïve + diazepam (Dz): animals were not exposed to a cat and received diazepam.
(c) Naïve + fluoxetine (Fx): animals were not exposed to a cat and received fluoxetine.
(d) Exposed + saline (E-Phy): animals were exposed to a cat 48 h before the ORT, and received physiological saline solution 30 min before Test 2.
(e) Exposed + fluoxetine (E-Fx): animals were exposed to the cat 48 h before the ORT, and received fluoxetine 30 min before Test 2.

Since acute administration of diazepam induced impairment of learning (Itoh et al., 1991) in the ORT in naïve Swiss mice, we did not test the effects of diazepam in exposed mice.

### 2.10. Statistical analysis

Behavioural data and comparisons between all exposure groups and controls were done using Student's $t$ tests. As some samples displayed nonnormal distribution and nonhomogeneity of variances, data were analysed using nonparametric statistics (Wilcoxon test). Significance was assumed at the value $P<.05$.

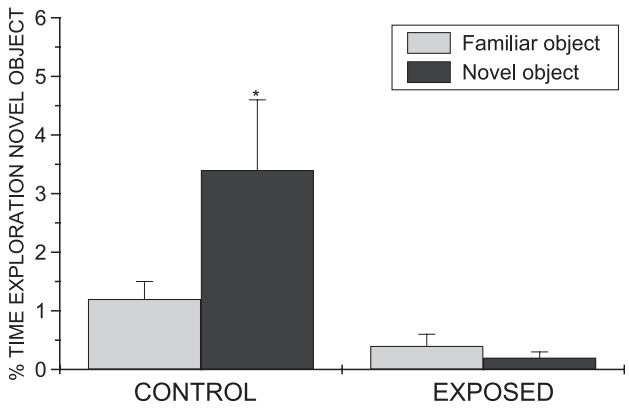


Fig. 1. Effects of unavoidable cat exposure on the time spent by Swiss mice exploring a familiar object and a novel object on Test 2 of the ORT (Experiment 2: effects on memory). The mice were exposed to a cat between Tests 1 and 2 of the ORT. Data represent mean ± S.E. $*P<.05$ (vs. control group).

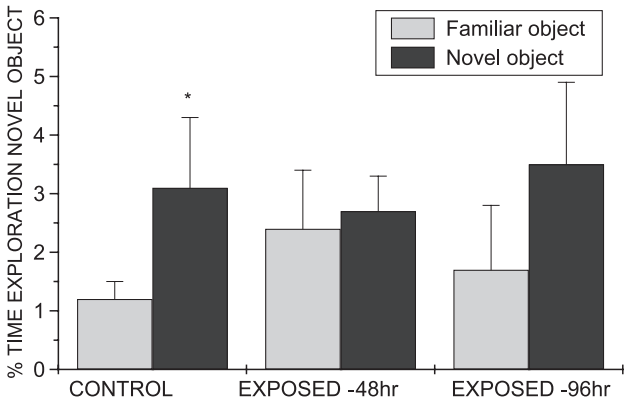


Fig. 2. Effects of unavoidable cat exposure on the time spent by Swiss mice exploring a familiar object and a novel object on Test 2 of the ORT (Experiment 3: effects on learning). The mice were exposed to a cat 48 or 96 h before the ORT. Data represent mean ± S.E. $*P<.05$ (novel vs. familiar).

## 3. Results

### 3.1. Experiment 1: behaviour of nonexposed animals in the ORT

Results showed that there was no significant difference in the time spent exploring the two objects in any group (Test 1). This was in contrast to Test 2 where naïve animals spent more time exploring the novel object ($w=23.5$, $P=.034$). The RI was found significantly different from 50% ($t=3.003$, $P=.013$).

### 3.2. Experiment 2: effects of predatory exposure on memory in the ORT

As shown in Fig. 1, mice exposed to a cat 30 min after Test 1 explored similarly the two objects on the Test 2 ($t=-1.583$, $P=.157$). The RI was found not different from 50% ($t=-1.011$, $P=.345$).

### 3.3. Experiment 3: effects of predatory exposure at different time intervals on learning in the ORT

As shown in Fig. 2, mice exposed to a cat 48 h before the ORT did not differentiate the novel object from the familiar one on Test 2 ($t=0.646$, $P=.538$). Mice exposed to a cat 96 h before the ORT explored the novel object more, but the difference was found nonsignificant on Test 2 ($t=1.947$, $P=.093$). The RI was not significantly different from 50% ($t=2.184$, $P=.065$).

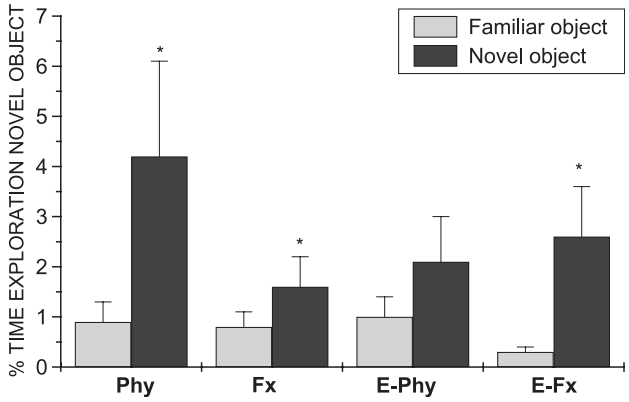


Fig. 3. Effects of diazepam (1 mg/kg) and fluoxetine (10 mg/kg) on exploration of novel object in Swiss mice confronted with unavoidable predatory stress 49 h before the ORT. We distinguish five groups: naïve + saline (Phy), naïve + fluoxetine (Fx), exposed + saline (E-Phy) and exposed + fluoxetine (E-Fx). Data represent mean ± S.E. $*P<.05$ (novel vs. familiar).

### *3.4. Experiment 4: effects of diazepam and fluoxetine in the ORT following predatory exposure*

As shown in Fig. 3, naïve mice that received physiological saline solution (Phy) differentiated the novel object from the reference one on Test 2 ($w=-21.5$, $P=.008$). The RI was significantly different from 50% ($t=4.267$, $P=.003$). Naïve mice that received fluoxetine (Fx) explored significantly more the novel object than the reference one on Test 2 ($t=2.413$, $P=.045$). The RI was not significantly different from 50% ($t=1.02$, $P=.342$). Naïve mice that received diazepam (Dz) did not differentiate the object on Test 2 ($w=-6.5$, $P=.219$). The RI was not significantly different from 50% ($t=0.269$, $P=.798$).

Exposed mice that received physiological saline solution (E-Phy) did not differentiate the object on Test 2. The RI was not significantly different from 50% ($P=$ ns). Exposed mice that received fluoxetine (E-Fx) explored the novel object significantly more from the reference one on Test 2 ($w=-18$, $P=.008$). The RI was significantly different from 50% ($t=9.083$, $P=.0001$).

## 4. Discussion

In the present study, exposure of mice to an unavoidable ethologically relevant predatory stress was found to be associated with impairment of learning as evidenced in the ORT. Results from pharmacological experiments showed that the administration of the 5-HT reuptake inhibitor fluoxetine improved the recognition memory in Swiss mice exposed to the predator.

The predatory exposure stress did not cause any noticeable physical harm that could explain the observed differences. One limitation of this study could be that the experiments took place under light conditions, while cats naturally predate in dark conditions. We used the Swiss strain, as it is among the most commonly line used in psychopharmacological studies, and it has been shown to be more sensitive than other strains to the administration of anxiolytics (Griebel et al., 2000).

Experiment 1 showed that naïve mice were able to discriminate between an unknown and a familiar object. In the second experiment, mice exposed to a predator after the learning session were not able to retrieve recently learned information suggesting that stress interfered with the encoding of memory. In the third experiment, 48 or 96 h after predatory exposure, mice were not able to differentiate the two objects on the test session. Thus, predatory stress in Swiss mice induced impairment in the encoding, storage or retrieval of stored information.

Numerous studies showed that acute stress has different effects on learning/memory in rodents and in humans. A bimodal response to stress was observed. A better registration of memories concerning the events occurring during the acute stress period was described by some authors (Diamond et al., 1999; Diamond and Park, 2000; Jodar et al., 1995, 1996; Garcia, 2001; Vedhara et al., 2000), whereas others put in evidence of amnesic effects (Newcomer et al., 1999; Mizoguchi et al., 2000; Raghavendra et al., 1999; Holscher, 1999; Cabib and Castellano, 1997). According to the intensity of the applied stress the learning/memory abilities will be impaired (in a traumatic stress) or improved (in a nontraumatic stress). In the present study, the learning component in the ORT did not consist of any stressful stimulus, did not implicate somatomotor activity, but it measures short-term memory. Performance of the stressed group was impaired relative to that of the control group. These results are similar to those of Park et al. (2001) who found impaired habituation to a novel environment in the open field in rats exposed to a cat, and impaired spatial learning and memory. Stress appears to reduce the efficiency of hippocampal-related processing but does not produce the equivalent of a complete hippocampal lesion (Diamond and Park, 2000; Park et al., 2001). In the present study, ORT impairments following cat exposure may possibly reflect impairments in attentional mechanisms (novelty detection).

Traumatic stress can cause a range of functional deficits. Our findings of impaired memory in mice following predatory stress may parallel human work in that people with PTSD exhibit impaired cognitive functioning (Bremner, 1999; Bremner et al., 1993, 1995; Yehuda et al., 1995). SSRIs, including fluoxetine, are effective in the treatment of the entire spectrum of posttraumatic symptoms (Fernandez et al., 2001; Hidalgo and Davidson, 2000; Van der Kolk, 1994), and may affect the serotoninergic activity particularly in the hippocampus (Belzung et al., 2001). As such, the present results with fluoxetine indicate an effect on stress, rather than learning (no positive effect in naïve mice). It can reasonably be suggested that fluoxetine opposes the negative impact of traumatic stress on memory. However, our findings

do not parallel human work as such effects are usually described as long-term posttraumatic effects (PTSD-like), whereas here we deal with short-term effects (ASD-like).

## 5. Conclusion

Previous studies showed that the acute unpredictable predatory stress produce in mice behavioural and neurochemical changes consistent with increased anxiety. The present findings, taken together, indicate that acute unpredictable predatory stress induces short-term memory changes ameliorated by fluoxetine treatment.

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