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# Alterations of behavior and spatial learning after unilateral entorhinal ablation of rats

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## Abstract

The entorhinal cortex (EC) is the key input and output structure of the hippocampus. It plays a crucial role in sensory processing, memory and learning, as well as in mechanisms of epileptic seizures. Our previous studies on the 4-aminopyridin induced epilepsy model of rats showed that ablation of unilateral EC prompted weakening of limbic seizure manifestation, thus the possibility of therapeutical benefit of this kind of surgery can be risen.

Open field, elevated plus-maze and Morris water-maze test were performed to analyze changes of the basal activity level, exploratory behavior, and spatial memory capacity, respectively, of adult Wistar rats having undergone left EC excision.

Compared with the sham-operated control group, rats with lesions of the EC showed enhanced locomotor activity in the open-field test. The elevated plus-maze test revealed higher frequency of entries and more time spent in the open arms. Morris water-maze test suggested impairment of the spatial learning capacity following left lateral EC lesion. Therefore, our data showed that EC lesions induced hyperactivity, increased exploratory behavior, and impaired spatial learning.

Entorhinal cortex ablation, as a potential method for controlling epileptic seizures has multiple effects on animals' behavior and spatial learning. To determine the cost–benefit ratio of a potential surgical intervention needs further experimental and human investigations.

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*Keywords:* Entorhinal cortex; Hippocampus; Rat; Behavior; Spatial learning; Epilepsy surgery

## Introduction

Entorhinal cortex plays a key-role within the temporo-limbic functional anatomy. It relays multimodal processed information between the sensorial cortical areas and hippocampus by numerous ipsi- and contralateral connections (Burwell and Amaral, 1998a,b; Heinemann et al., 2000, Hjorth-Simonsen and Jeune, 1972; Swanson and Köhler, 1986). The role of EC has previously been investigated under pathological conditions like temporal lobe epilepsy (TLE). Apparently, EC is involved in the generation of TLE (Bailey et al., 2004; Calcagnotto et al., 2000; D'Antonuo et al., 2001) and plays a role in attention processes and motivation, in addition to spatial memory performances (Galani et al., 1998; Swanson and Köhler, 1986; Yaniv et al., 2003). These behavioral functions may be underlined by the network of the whole limbic system.

As far as TLE is concerned, the key-role of EC has been shown by our previous experiments of 4-AP induced acute seizure model on rats with unilateral EC ablation. Our results clearly showed the weakening of limbic seizure after EC ablation: intracellular c-fos protein expression was reduced in the hippocampus and dentate gyrus, the EEG recordings with deep brain electrodes found the epileptogenesis also disregulated and "slowed down" (Kopniczky et al., 2005).

There are many neurosurgical techniques which have been developed to influence epileptic seizure occurrences benefi-

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cially. Destruction caused by this type of surgery is accepted in favor of the better seizure control of the patient, but surgeons should try to minimalize the undesirable effects. A variety of epilepsy surgeries have been performed on the temporo-limbic structures, which are known to be the generator of epileptic foci. As the unilateral ablation of EC significantly reduces intracellular and electrophysiological phenomena associated to seizure (Kopniczky et al., 2005), the benefit of an eventual seizure-controlling neurosurgical intervention can be speculated. Having seen the "beneficial-preventing" effect of reducing epileptogenesis, we wanted to know the "cost" of unilateral EC ablation. Based on our preliminary experiments, we designed our experiments to investigate the effect of unilateral EC ablation on emotional behavior and spatial learning capacities in adult Wistar rats.

## Material and methods

### Animals

The animals were kept and handled during the experiments under a protocol accepted by the Ethical Committee for the Protection of Animals in Research, University of Szeged, Hungary. A total number of 50 male Wistar rats weighting 150–180 g were used (35 operated, 15 sham-operated control, SOC). The animals were housed in groups of five to six in cages in a room maintained at constant temperature (23 ± 1 °C) and on a 12-h dark–light cycle (lights on from 06.00 to 18.00) with free access to tap water and standard laboratory food.

### The neurosurgical technique of unilateral left entorhinal cortex ablation

The animals were anesthetized with Calypsol® (100 mg/kg) plus atropine (0.01 mg/kg) given intraperitoneally (i.p.). The head of the animal was fixed in a stereotaxic frame, and following a vertical skin incision, the soft tissues and the temporal muscle were cut and kept aside in order to expose the temporo-basal region of the skull on the left side. The bone was cut and removed with a dental drill, a temporobasal craniectomy was performed just before the transverse sinus and rhinal sulcus were identified. The lateral area of the entorhinal cortex (LEA) can be found inferior to the rhinal sulcus down to the temporal basis and back to the transverse sinus, the planning of surgical excision was referred to the parameters defined by Burwell and Amaral (1998a,b). The surface of the LEA was electrocoagulated and a 2 mm long (anteroposterior diameter), 1 mm large (dorsoventral diameter) and 1 to 2 mm deep cortical (subcortical) parenchyma was aspirated with micropipette-suction. Once, the ablation was achieved, a little piece of temporal muscle was laid on the surface of cortical excision for ensuring safe hemostasis. Afterwards, the bone defect was covered with layers of the temporalis muscle and fascia, finally the skin was closed with clamps. In sham-operated animals of controls (SOC) the same procedure was performed except for coagulation and aspiration of the cortex, i.e. the meninges and the brain were left intact.

Histological proof of the surgical ablation was performed on the third day, while behavioral recordings and tests were performed during the third and fourth weeks after the operation. The distribution of subgroups is detailed below.

### Histological description of the entorhinal cortical lesion

Three entorhinal cortex ablated (ECA) and 3 sham-operated control (SOC) animals were investigated 3 days after the surgery. The animals were anesthetized with diethyl ether and perfused through the heart with 4% paraformaldehyde in 0.1 M phosphate buffer (PB, pH 7.4). The same transcardial perfusion fixation method was applied to other experimental rats unless otherwise indicated. The brains were kept in fixative overnight, then washed in phosphate-buffered saline (PBS, pH 7.4), cryoprotected in 25% sucrose and 25 μm sections were prepared using a freezing microtome. Tissue sections were processed for the immunohistochemical detection of synapsin I (rabbit anti-synapsin I, Alexis Corporation; 1 : 1000 dilution) and the microglia antigen CD11b specific mouse antibody (Serotec; clone MRC OX-42; 1 : 100 dilution), using the streptavidin–peroxidase method with 3,3′-diaminobenzidine tetrahydrochloride (DAB) substrate.

### Open-field test

The open-field apparatus was a square open-field cage with a side length of 60 cm, surrounded by a 0.4 m high wall. The floor of the cage was divided in 36 (6 × 6) small squares. A 60 W light was situated 1 m above the arena floor. Sessions started at 9 a.m. All animals were carried to the experimental room in their home cages. Each animal was placed in the center of the open field and was observed for 5 min.

The locomotor activity (horizontal activity) defined as number of squares crossed and rearing frequency (vertical activity) defined as number of times the animals stood on their hind legs were evaluated. Furthermore, defecation and the number of grooming episodes were also counted.

### Elevated plus maze

The elevated plus maze has been widely used as an anxiety paradigm and represents a test based on unconditioned responses to a potentially dangerous environment. The plus maze comprises two (opposite) closed and two open arms, each arm located on a central pole. The combination of height, luminosity and open space is assumed to induce fear or anxiety in the animal. The degree of anxiety was assessed by measuring the time spent on the open and closed arms and the total number of entries made into each arm.

### The apparatus

The elevated plus maze consists of two closed arms (10 × 40 cm) and two open arms (10 × 40 cm) forming a cross, with a quadrangular center (10 × 10 cm). The maze was placed 50 cm

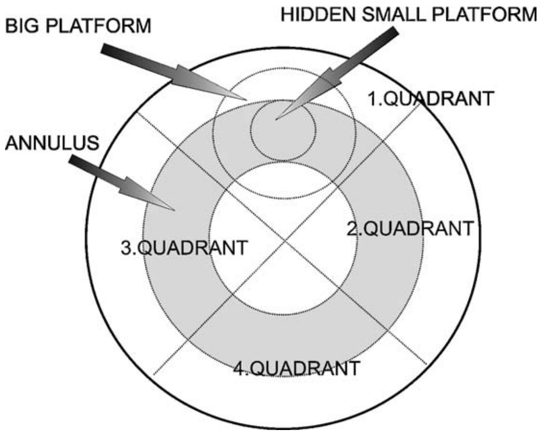

Fig. 1. Schematic drawing of Morris water maze.

above the floor. A 60 W light was situated 1 m above the plus-maze apparatus. Sessions started at 9 a.m. All animals were carried to the experimental room in their home cages. The rats were placed on the center facing an open arm. Each animal was observed for 5 min.

## Morris water-maze test

The setup consists of a round water pool (2 m in diameter) containing opacified water (temperature: 26 °C) with a hidden escape platform. The subject must learn the location of the platform using contextual, local and distant cues. Theoretically the water pool is divided into four quadrants, small platform, big platform, and annulus (Fig. 1).

During the training period animals were tested 2 times a day (morning session—from 9.00 to 11.00 am. and afternoon session from 13.00 to 15.00 pm) for five consecutive days. During one session a rat was placed in one quadrant of the pool and allowed to swim until the small platform was found. Rats were left on the platform for 15 s. If the platform was not found within 2 min, the animals were directly placed on the platform for 15 s. The starting point was randomly rotated for every trial. The hidden platform was located in a fix position with respect to the surrounding area. After the training period, a test was administered on day 6 (reference day). During this trial the platform was removed from the pool and the swimming path was recorded for 2 min for each animal. The animal behavior was tracked by a video camera and analyzed by video software. The events registered were as follows: swimming speed, distance traveled by, latency to reach the platform, entrances and time spent in the goal area (small platform and the surrounding area), entrances and time spent in annulus.

## Statistical analysis

Statistical analysis of the data was made by repeated measure analysis of variance (ANOVA) and paired *t*-test. For significant ANOVA values, groups were compared by Tukey's test for multiple comparisons with unequal cell size. A

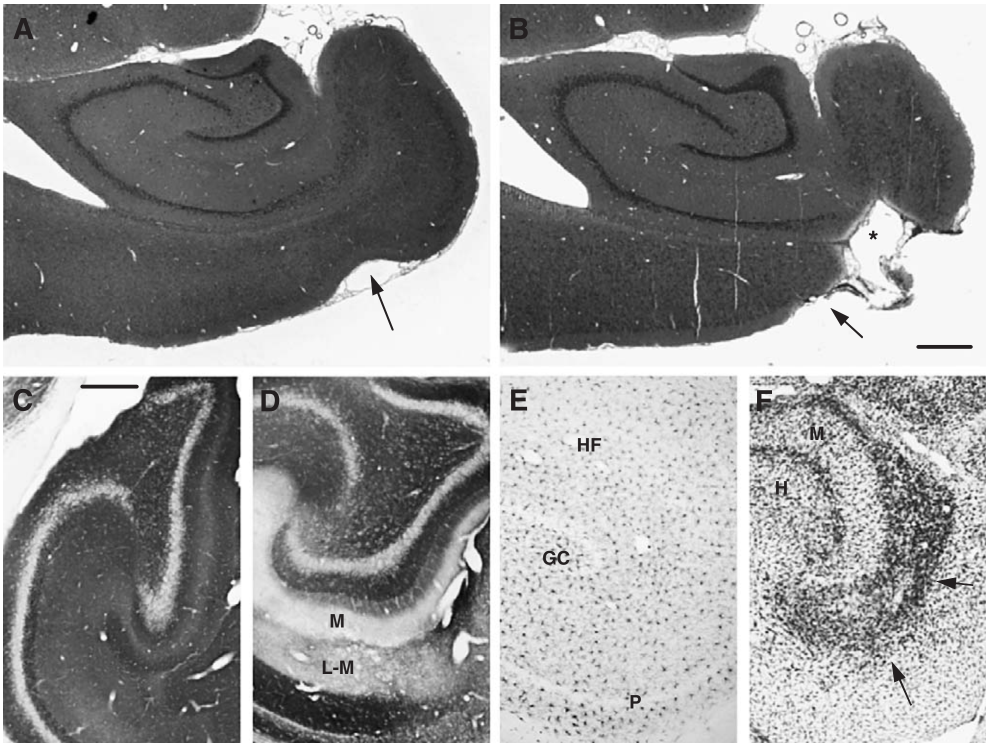

Fig. 2. The histological consequences of unilateral entorhinal cortex ablation (A,C,E: non-operated; B,D,F: operated). A and B: H-E stained paraffin embedded thin sections—arrow points to rhinal sulcus, asterix shows the lesion; etalon: 1 mm. C and D: mouse anti-rat CD11b stained microglia in the hippocampus; on the side of the lesion arrows sign the strong microglia proliferation of the ending area of perforant path. E and F: terminal degeneration of perforant path proved by dropout of synapsin I immunoreactivity in the molecular layer (M) of the dentate gyrus and in stratum lacunosum-moleculare (L-M) of CA1 region of hippocampus on the side of the operation.

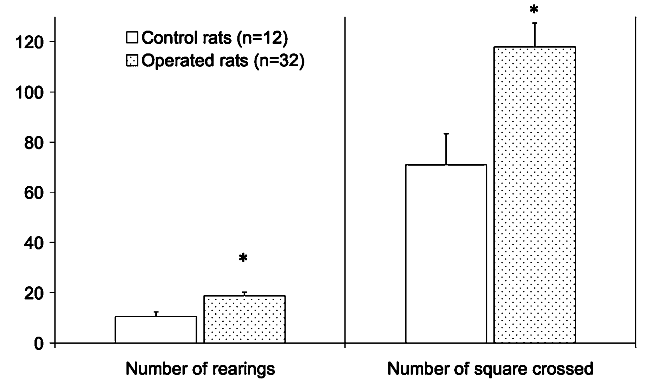

Fig. 3. Vertical (number of rearings) and horizontal (number of squares crossed) locomotor activity was tested in open field. Operated animals moved and explored more in the open-field compared to control rats as indicated by the enhanced vertical and horizontal locomotor activity. Vertical lines on the top of the bars denote the S.E.M. $^*p<0.05$ vs. control group.

probability value less than 0.05 was considered statistically significant.

## Results

During the time of our daytime observations, like in our previous studies, no spontaneous epileptic activity was detected on rats with unilateral EC ablation.

### *Description of the histological consequences of entorhinal cortex ablation*

Histological analysis of the lesion confirmed the complete removal of the lateral ECA. There was no noticeable neuronal loss in the hippocampal region at the side of the ECA. Immunohistochemical analysis revealed the disappearance of synapsin I immunoreactivity, and appearance of microglia proliferation in the molecular layer of the dentate gyrus and in stratum lacunosum-moleculare of hippocampal regions CA1-3 (Fig. 2). These changes confirmed the secondary degeneration of the perforant path axons at the side of the lesion three days following surgery.

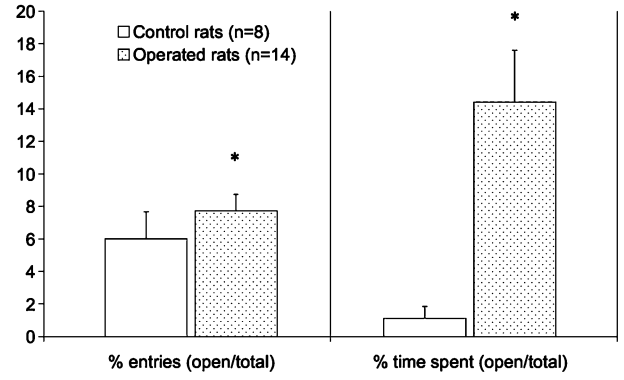

Fig. 4. The number of entries in the open arms and the time spent in the open arms was tested with elevated plus-maze test. Operated rats show lower anxiety level in the elevated plus-maze test as compared to control group. They performed more open arm entries and they spent more time in the open arms. Vertical lines on the top of the bars denote the S.E.M. $^*p<0.05$ vs. control group.

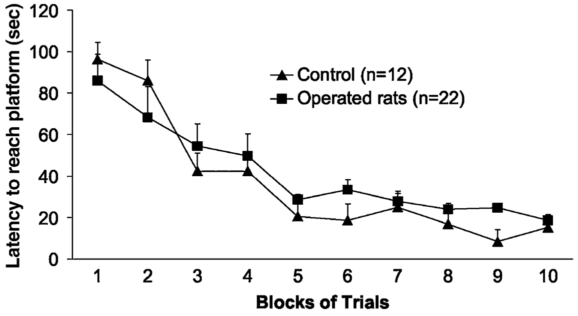

Fig. 5. Latency to find the hidden platform. Over the training period the ability to find the hidden platform progressively improved in both groups. Vertical lines denote the ± S.E.M.

### *Behavioral studies*

The data acquired about spontaneous exploratory activity in the open-field test showed that lesions of the entorhinal cortex results in a significant increase in horizontal ($F_{(1,\ 43)}=7.26$) and vertical locomotor activity ($F_{(1,43)}=8.69$) compared with the control group (Fig. 3). Furthermore defecation and grooming were also counted, but no statistically significant results were observed.

In the elevated plus-maze test the total number of entries made into each arm was nearly equal in the two tested groups (SOC: 6±1.7, operated: 7.7±1). However, the operated rats showed more open arm activity than the control animals: more time spent ($F_{(1,21)}=9.62$) and more entries in the open arms ($F_{(1,21)}=9.34$) were detected (Fig. 4).

In the Morris water-maze test, during the training period (first 5 days) animals learned to locate the position of the submerged (hidden) platform by using spatial cues within and around the pool. The latency to find the hidden platform improved throughout the training, however no significant difference in the performance of the operated and control animals was observed (Fig. 5). No significant difference was found in the “distance traveled” between experimental groups (operated animals: 2282 cm on the first day—679 cm on the fifth day; control animals: 2576 cm on the first day—308 cm on the fifth day; data not shown). The mean speed of swimming was constant during all trials (30–35 cm/s, data not shown), this allowed us to express our data in terms of “latency to reach platform” in seconds.

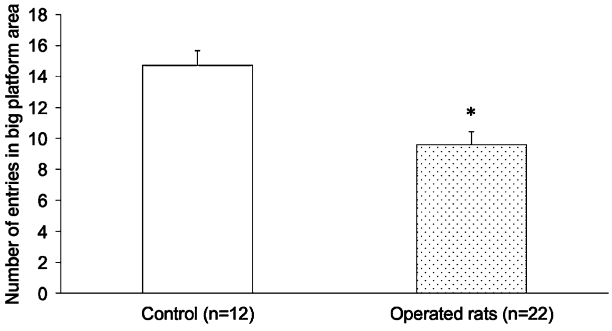

Fig. 6. Number of entries in big platform area. The number of entries in the big platform area was significantly less in entorhinal cortex operated rats. Data are given as mean±S.E.M. $^*p<0.05$ vs. control group.

Recall of the location of the platform was tested during the 6th day (reference day) when the platform was removed from the pool. The number of entries into the big platform area was significantly less in the group of rats with entorhinal cortex lesion ($F_{(1,33)}=14.35$; Fig. 6) indicating that their spatial search pattern was impaired. No significant differences were obtained regarding time spent and number of entries in the small platform area, quadrants and annulus.

## Discussion

Data from our experiments clearly showed that left lateral EC lesions induced hyperactivity and increased exploratory behavior associated with reduced signs of anxiety. The Morris water-maze tests of spatial learning and memories detected significant impairment of modalities of spatial memory recall.

The hippocampus and adjacent cortical structures, including the entorhinal, perirhinal, and parahippocampal cortices, appear to serve as an integrated memory system (Maren and Fanselow, 1997; Poucet et al., 2003; Steward et al.,1977). This extended hippocampal system is believed to influence memory and consolidation through an extensive set of reciprocal connections with widespread areas of the neocortex (Burwell and Amaral, 1998a,b; Hjorth-Simonsen and Jeune, 1972; Poucet et al., 2003). Numerous reports show that lesions to hippocampal afferents, such as entorhinal cortex exert an effect not only on memory but also on other behavioral aspects (e.g. exploratory activity, locomotion) in rodents (Dasheiff and McNamara, 1982; Fass, 1983; Glasier et al., 1995; Steward and Scoville 1976, Steward, et al., 1977).

The *open-field test* is based on the conflict between the exploration of a new environment and the aversion to open spaces from which escape is prevented by a surrounding wall. The stimulus of the novel environment may simultaneously induce anxiety and exploratory behavior. We detected an increased exploratory activity as shown by the increased number of horizontal and vertical motion of operated rats.

This is in line with behavioral studies performed with rats with bilateral EC ablation or hippocampal lesion. Previous studies using different experimental protocols have shown results similar to that presented here. For example, pronounced but transient increase in open-field activity was detected, which peaked between 5 and 7 days post lesion and returned to near normal preoperative levels at about 11 days (Steward et al., 1977). Our group of rats was about 14–21 days after unilateral EC lesion, however the increase of the exploratory activity was significant. Others studied the effect of “progressive” (destroying different portions of EC during two occasions of 11–15 days interval) vs. “serial”(performing total EC destruction of different sides on two different occasions) entorhinal lesions on open-field activity (Fass, 1983). They found that “progressive” (but not “serial”) lesion enhance the above mentioned behavioral recovery. They refer to the possible role of spatial and temporal pattern of sprouting in the hippocampus.

The *elevated plus maze* is widely used as an anxiety paradigm and represents a test based on unconditioned responses to a potentially dangerous environment. The increased time spent in and number of entries in the open arm would be interpreted as a sign of increased exploratory activity but it can refer to decreased anxiety provoked by the stress of study itself. Steward and Scoville (1976) performed studies with plus maze to study the consequences of bilateral EC lesions on alternation capacity rather than on emotionality/anxiety-like behavior. They observed that EC lesion disrupts alternation performance, probably due to inability to recall which arm was chosen on preceding trial.

The *Morris water maze* is one of the most common behavioral tasks used to assess spatial (hippocampal) learning and memory in rodents. The animal must learn the location of the hidden platform using either distant or local cues. Performance in the Morris water maze depends on several mechanisms like attention, learning and memory, vision, and motor coordination. Our data did not show difference between the learning process (acquisition) of the two groups, however it did suggest an impairment of spatial memory recall of EC ablated animals. This had been also showed in animals of selective hippocampal lesions: rats with hippocampal damage were impaired in all spatial tasks. However, the rats with lesions of the EC or the subiculum were not impaired in the reference–memory procedure of the water-maze task and showed a deficit in reacting to a nonspatial change. The authors suggest a role for the entorhinal cortex and the subiculum in processing spatial information and indicate a hippocampal-independent role in memory process of the entorhinal cortex (Galani et al., 1998).

Short-term memory deficits after unilateral EC lesion has already been presented (Glasier et al., 1999a,b). They used Hebb–Williams maze, 7 weeks after electrolytic cortex lesion of Sprague–Dawley rats. In other experiments performed with water maze, EC ablation effected deficits in working memory (Glasier et al., 1995). Also, studies on retention presented difference of spatial navigation’s strategy only in the first day. This was interpreted as an incorrect strategy and use of cue integration. We have designed our experiments differently: using adult Wistar rats, the EC lesion was performed 3–4 weeks before the training period. Our results are in line with those referred to Glasier et al. (1999a,b).

Hippocampal place cells have been characterized by location-specific firing that reflects the environment so that different sensory information can be explored. Place cells use visual and motion-related cues (Poucet et al., 2003). Major part of information coming from the sensory cortex reaches the hippocampus via the EC. The work of Poucet et al. concentrates on the neocortical contribution of place cell spatial firing and demonstrate the relationship between place cell positional activity and spatial navigation performance. We hypothesize that the central role of place cells’ activity in space-related memory can offer an explanation to both the increased exploratory activity and the impaired capacity of water-maze navigation. Hippocampal place cells present stable, spatially determined, motion-related “firing-fields” which are continuously updated by keeping track of rat’s movements in space based on signal stemming from the vestibular and proprioceptive system. This mechanism is called “path integration”. It is possible that, after EC ablation, perforant path can not transfer sufficient amount of cortical information toward hippocampal place cells, which may result in pronounced exploratory activity as a compensatory mechanism. Furthermore, partial deafferentation of hippocampal place cells result in failure of space-related memory functions (Glasier et al., 1995, 1999a,b; Poucet et al., 2003). This can explain the decreased ability in water-maze navigation. Altogether, on the basis of our experiments, 3–4 weeks after unilateral entorhinal lesion, only mild deterioration in spatial memory performance occurred.

The amygdalo-entorhinal pathway has an important role in processing emotional relevant sensory information and it becomes activated during acquisition of fear-conditioning (Majak and Pitkanen, 2003). Manipulation of the neuronal activity of the EC affects emotional learning. For example lesion of the EC produce anterograde impairment in post-shock freezing (Majak and Pitkanen, 2003; Maren and Fanselow al., 1997). The enhanced open-field activity and the increased open arm activity in the plus-maze test underline the anxiolytic effect of EC lesion.

## Conclusion

In summary, entorhinal cortex ablation, which has been found to reduce epileptogenesis in the 4-AP induced acute seizure model (Kopniczky et al., 2005), has multiple effects on animals’ behavior and spatial learning. We found that EC ablation induces increased exploratory activity and anxiolytic effect, while spatial memory test revealed clear deficit regarding the ability of recall of search pattern learnt during the training period. These results suggest that determining the indication of a potential surgical excision of the entorhinal cortex for seizure control needs further pre-clinical and clinical investigations.

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