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Research Report

# Rewarded associative and instrumental conditioning after neonatal ventral hippocampus lesions in rats

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ABSTRACT

Sprague Dawley rats were submitted to bilateral ventral hippocampus lesions 7 days after birth. This corresponds to the Lipska and Weinberger's procedure for modeling schizophrenia. The aim of the present work was to test the learning capacity of such rats with an associative Pavlovian and an instrumental learning paradigm, both methods using reward outcome (food, sucrose or polycose). The associative paradigm comprised also a second learning test with reversed learning contingencies. The instrumental conditioning comprised an extinction test under outcome devaluation conditions. Neonatally lesioned rats, once adults (over 60 days of age), showed a conditioning deficit in the associative paradigm but not in the instrumental one. Lesioned rats remained able to adapt as readily as controls to the reversed learning contingency and were as sensitive as controls to the devaluation of outcome. Such observations indicate that the active access (instrumental learning) to a reward could have compensated for the deficit observed under the "passive" stimulus–reward associative learning condition. This feature is compared to the memory management impairments observed in clinical patients.



## 1. Introduction

Schizophrenia is a common human disorder (Austin, 2005). Its symptoms such as delusions, auditory–verbal hallucinations, and disorders of thought cannot be modeled in non-human species (Burns, 2006). In addition to such symptoms, impairments of cognitive functions are chronically present during the course of the disease (Breier, 2005; Danion et al., 1999). Patients show difficulties in binding the diverse aspects of complex memories (Boyer et al., 2007) and, paradoxically there occurs an abnormally strong binding between actions and consequences (Haggard et al., 2003). Transposed to lower animal models, the more natural forms of associative learning, when a number of environmental features have to be linked to each other, should be modified in another way as instrumental learning where an action becomes linked to its consequence. According to the here over reported memory perturbations of patients, the first of these two learning situations should be impaired and the second one should be preserved.

Rats with neonatal ventral hippocampus lesions have been proposed as a developmental animal model of the cognitive deficits of schizophrenia (Lipska and Weinberger, 2000). The emergence of abnormal behaviors, specifically after puberty, simulated the onset of the symptoms of the disease (Lipska, 2004). In this lesion model, a diversity of learning deficits was reported (Lipska, 2004). We recently reported minor deficits in

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conditioned emotional learning and in conditioned taste aversion which are two associative learning paradigms, both of which can be evaluated by the suppression of an ongoing drinking activity elicited by an aversive emotion, fear or disgust (Angst et al., 2007). Our knowledge about the hippocampus neonatal lesions have recently improved through studies showing modifications of the connectivity between the hippocampus and the nucleus accumbens (Flores et al., 2005a,b; Goto and O'Donnel, 2002, 2004). Even if the nucleus accumbens is involved in learning processes with aversive stimuli as outcomes (Schoenbaum and Setlow, 2003), it is probably more crucial for triggering actions according to rewarding outcome (Schultz et al., 2000). Therefore, we decided to test rats with neonatal ventral hippocampus lesions in learning paradigms based on rewarding outcome rather than the aversive one.

The technique used to lesion the rat pups is not as efficient as in adult rats because of the size of their head and the relative soft consistence of their skull. Thus, MRI was used to select those rats that showed hippocampus lesion of a satisfactory degree in site, symmetry and extent, before the beginning of the behavioral experiments. A Pavlovian associative learning was firstly implemented. In this paradigm, food was announced by either a light or a tone, which results in the exploration of the food receptacle before the delivery of that food (Holland and Petrovich, 2005). Once the rat had learned the contingency, it was reversed. The capacity to adapt to the reversed contingency could have been impaired by a prefrontal malfunction secondary to the hippocampus lesion (Joel et al., 1997). A different cohort of rats was subjected to an instrumental conditioning where they had to press a lever to be rewarded with a sweet beverage (Balleine, 1992). The conditioning paradigm included a test in outcome devaluation conditions that could have been affected by a modification of the prefrontal cortex or nucleus accumbens secondary to the lesion (de Borchgrave et al., 2002; Ostlund and Balleine, 2007).

## 2. Results

### 2.1. *Size of the lesions*

We selected 24 rats with bilateral ventral hippocampus lesions resembling those previously published (Chambers

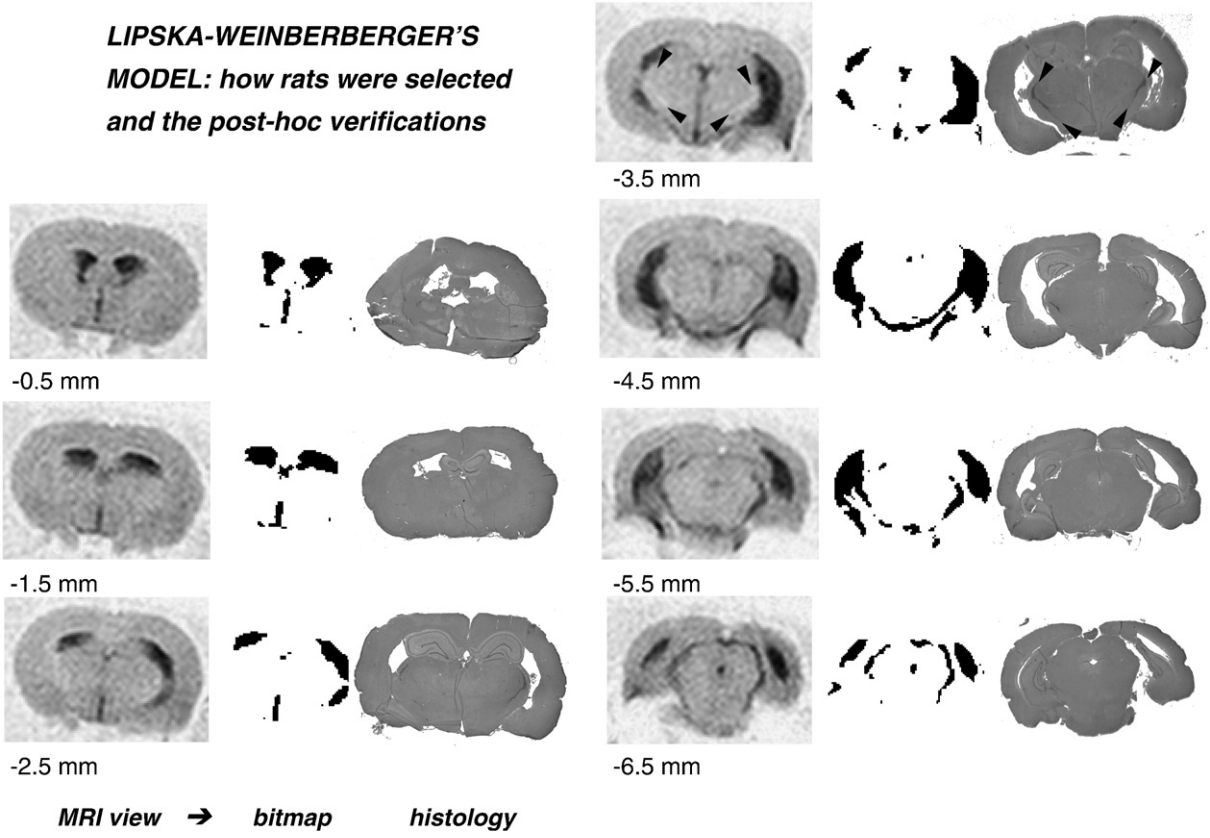


**Fig. 1 – Magnetic resonance images (MRI) and their corresponding histological slides of the brain of a typical rat used in the instrumental conditioning experiment. There are three series of images presented in this figure. The left most corresponds to inverted images of 7 frontal MRI sections where a lesion was visible. The digitized areas of the same images are shown at the right of these MRI sections. They were used to compute the volumes of the lesions on each side of the brain. Photographs of the corresponding histological slides were placed at the right of each of these digitized areas. The approximative rostro-caudal position of each slide is indicated relative to the bregma below each MRI picture. On the RMI as well as the histological slice corresponding to –3.5 mm from the bregma, black arrows are used to point out a thin layer of tissue, hyporeactive to RMI (containing less water than that observed in other parts of the brain) and more dense in the histological slices.**