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Research report

# Effects of hippocampal damage on reward threshold and response rate during self-stimulation of the ventral tegmental area in the rat

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**Abstract**

The main purpose of this study was to explore the role of the hippocampus in motivated behavior. Rats with bilateral excitotoxic lesions of the hippocampus and controls were trained to lever press for electrical stimulation of the ventral tegmental area. Rate–intensity functions were generated from an ascending and descending series of current intensities. Lesion-induced changes in sensitivity to reward were distinguished from enhancements in motor output by calculating reward thresholds and maximal response rates from the rate–intensity functions. Rats with hippocampal damage showed lower reward thresholds and higher maximal response rates than controls. These results provide further evidence of hippocampal modulation of the nucleus accumbens, suggesting that lesions of this structure enhance sensitivity to reward and increase motor output. 

*Keywords:* Hippocampus; Nucleus accumbens; Intra-cranial self-stimulation; Dopamine; Reward; Motivation

## 1. Introduction

Although traditionally implicated in processes such as spatial memory [40,41], working memory [38], and response inhibition [1,18], accumulating evidence indicates that the hippocampal formation exerts an important modulatory influence over behaviors directly mediated by the nucleus accumbens (NACC). This modulatory influence has been consistently demonstrated in many studies of spontaneous and drug-induced locomotion. Thus, it has been shown that extensive lesions of the hippocampal formation produce increases in spontaneous locomotion [9,24] and result in heightened locomotor responses to psychostimulants and dopamine agonists [5,38,47,59,60]. This enhancement in drug-induced activity following extensive hippocampal damage: (i) occurs as a direct function of increased locomotion and not indirectly, from reductions in competing behaviors [59]; (ii) is dependent on the integrity of the mesolimbic dopamine (DA) projection, as 6-OHDA lesions of the NACC block this effect [59]; (iii) occurs specifically in response to pharmacological stimulation of dopamine D2 receptors, which is consistent with the possibility of underlying receptor-based changes [38]; and (iv) corresponds to increases in amphetamine stimulated DA release in the NACC [60]. It is presumed that these changes occur as a function of the degeneration of hippocampal efferents innervating the NACC [4,17,19,20,27,50,51,55,56,63].

Based partly on anatomical evidence of hippocampal efferents to various subcortical regions, it has been suggested that the hippocampus similarly modulates motivated or goal-directed behavior [25,39]. Evidence consistent with this possibility has recently been presented [48]. In comparison to controls, rats with hippocampal lesions had significantly higher breakpoints in a progressive ratio, food reward task. Addi-

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tionally, when sucrose pellets were substituted for the grain-based pellets, breakpoints of lesioned rats were differentially increased as compared to controls. As progressive ratio breakpoints are believed to reflect the amount of effort an animal will exert to obtain a reinforcer [22,23,35,53], these results were interpreted as indicating that the lesion had enhanced the incentive motivational properties of the delivered food pellets. Given the well known involvement of the NACC in rewarded behavior (see Ref. [3] for a review), it was speculated that, similar to locomotion, these behavioral changes occurred as a function of the loss of hippocampal modulation of this structure.

The primary purpose of this experiment was to further explore the role of the hippocampus in motivated behavior, with a specific emphasis on determining if the NACC and associated DA system were affected by extensive hippocampal damage. This was accomplished by using an intra-cranial self-stimulation (ICSS) paradigm, in which the mesolimbic DA system was directly activated by stimulation of the ventral tegmental area (VTA). It has been demonstrated that electrical brain stimulation of the VTA potentiates DA release in the NACC [13,14,43–45]. Electrochemical analyses have revealed that VTA stimulation induced DA release in the NACC increases as a function of increasing current intensity [2]. The advantage of the ICSS approach is thus one of neuroanatomical specificity; by stimulating the cell bodies of the VTA, the mesolimbic DA system is activated and DA neurotransmission is potentiated.

Because hippocampal damage enhances both motor output and incentive motivation [48,49], an additional goal of this was to determine if lesions of this structure altered reward processes or motor performance. In order to distinguish changes in reward sensitivity from changes in motor performance, the ICSS curve shift method was used (for reviews, see Refs. [33,34]). Reward thresholds ($M_{50}$) and maximal response rates were determined from the rate–intensity functions generated by lesioned and control animals. These measures were selected because they have been shown to be sensitive to, respectively, manipulations of reward or motor performance in the ICSS task [10,37,52].

## 2. Methods

### 2.1. Subjects

Male Long-Evans rats ($N = 35$), approximately 90 days old at the start of the experiment, were used as subjects. The rats were housed individually in plastic buckets lined with cedar chip bedding and provided with food (Teklad, Harlan, Indianapolis, IN) and water ad libitum. The vivarium was maintained on a 12/12 h light/dark cycle (lights on at 07:00) at a temperature of 22°C. All behavioral testing took place between 08:00 and 17:00. All procedures were carried out in accordance with the *NIH Guide to Care and Use of Laboratory Animals*.

### 2.2. Surgery

All rats were anesthetized with chloropent (2.5 mg/kg) and fitted into a stereotaxic frame (David Kopf, Tujunga, CA). Rats were randomly assigned to receive either a bilateral hippocampal lesion ($n = 15$), or to serve as controls ($n = 20$). Lesion of the hippocampal formation was accomplished via the method of Sutherland and Macdonald [54]. For subjects receiving a bilateral lesion, a mixture of colchicine and kainic acid (2 $\mu$g colchicine and 0.1 $\mu$g kainic acid per 0.5 $\mu$l of 0.9% saline) was infused (0.5 $\mu$l over 5 min) into three sites in each hemisphere using a 30 gage stainless steel cannula connected to a 10 $\mu$l syringe (Hamilton, Reno, NE) that was mounted on an infusion pump (Harvard Apparatus, South Natick, MA). Stereotaxic coordinates were measured relative to bregma, with the incisor bar adjusted to ensure flat skull. Lateral coordinates were taken from the midline suture. All ventral coordinates were taken from the top of the skull. The coordinates were: AP $-$ 3.3 mm, L $\pm$ 1.5 mm, V $-$ 3.7 mm, AP $-$ 4.2 mm, L $\pm$ 3.2 mm, V $-$ 3.2 mm, AP $-$ 5.2 mm, L $\pm$ 5.0 mm, and V $-$ 7.5 mm.

During the same surgery, polyimide insulated stainless steel bipolar electrodes (Plastics One, Roanoke, VA; bare diameter, 0.25 mm) were bilaterally implanted into the VTA of both lesioned and control rats using the following coordinates: AP $-$ 4.4 mm from bregma, L $\pm$ 1.2 mm from the midline suture, V $-$ 8.5 mm from the skull surface. Bilateral implantation was deemed necessary in order to increase the probability of correct electrode placement. The electrodes were anchored to the surface of the skull using stainless steel screws and cranioplastic cement.

### 2.3. Apparatus

An operant chamber (Model E10-09, Coulbourn Instruments, Allentown, PA) equipped with a response lever was used for all behavioral training and testing. A white light was located 15 cm above the lever and was illuminated during all training and testing procedures. Trains of 200 ms, 60 Hz sign-wave pulses were administered via a constant current stimulator. Current intensity ($\mu$A) was adjusted manually. Data collection, trial length, and session length were controlled by a microcomputer (Spider, Paul Fray, Cambridge, UK).

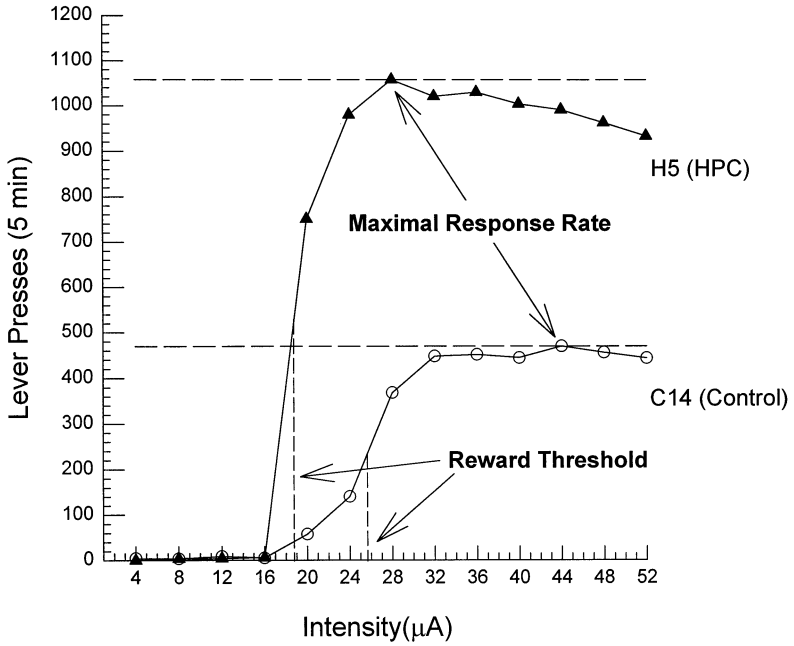


Fig. 1. Representative rate–intensity curves taken from one hippocampal lesioned rat and one control rat. Reward thresholds and maximal response rates are illustrated.

### 2.4. Procedure

Screening and shaping for self-stimulation began following 1 week of post-operative recovery. This phase consisted of rewarding the rat with stimulation at every instance an approach was made toward the lever, and when the lever was pressed. Each animal was screened in a range of 40–50 $\mu$A. The initial electrode used during the screening procedure was randomly chosen. If the rat was not responsive to the stimulation, or if stimulation-induced side-effects appeared (e.g. gross head movements to one side, circling in the operant chamber), the shaping procedure was reinitiated using the contralateral electrode.

Once a rat had begun to freely press the lever, it was allowed to self-stimulate for three daily sessions of 1 h each. Current intensity was held constant at 40 $\mu$A. Each rat had to maintain at least 1000 lever presses per session for inclusion in the study. During this phase, seven controls and five lesioned animals were unable to meet the response criterion, and were not included in the study.

Following the completion of the training procedures, the rats were given eight sessions (65 min each) from which rate–intensity curves were generated. During these sessions, the current intensity was increased from 4 to 52 $\mu$A in 4 $\mu$A steps every 5 min (i.e. an ascending series) or decreased from 52 to 4 $\mu$A in 4 $\mu$A steps every 5 min (i.e. a descending series). Both series thus involved a total of 13 steps. Three priming pulses were delivered at the beginning of each 5 min interval. The number of lever presses was automatically recorded for each current intensity. Lever presses were collected over four ascending sessions and four descending sessions in an ascend–descend–ascend order. The interval between sessions was a minimum of 48 h.

### 2.5. Histological evaluation

At the conclusion of behavioral testing, all animals were deeply anesthetized with chloropent and perfused intracardially with 60 ml of 0.9% saline followed by 180 ml of 10% formalin solution. The brains were removed from the skull and placed into 30% sucrose/formalin solution for at least 1 week. The brains were then sliced at 40 $\mu$m on a freezing microtome. Every other brain slice throughout the lesion and electrode placement areas was collected for cresyl violet staining. Sections were examined using light microscopy in order to determine lesion extents and electrode placements.

### 2.6. Measurements and statistics

#### 2.6.1. Dependent measures

Rate–intensity functions were generated for each rat for the ascending and descending current series. Reward threshold ($M_{50}$) was defined as the stimulation intensity ($\mu$A) required to yield 50% of the asymptotic maximum response rate, and was geometrically derived from the rate–intensity functions. Maximal response rate was defined as the highest number of lever presses per 5 min interval. Fig. 1 illustrates an ascending rate–intensity curve for a representative lesioned and control animal, and depicts the reward thresholds and maximal response rates of these animals.

*2.6.2. Data analysis*

Analyses of variance (ANOVAs) [61] were conducted on all the dependent measures in order to determine if there were group differences in self-stimulation behavior. Rate–intensity functions were initially analyzed using one between subjects factor, Group (lesion and control) and three within subjects factors: test session (1–4), current sequence (ascend or descend) and current intensity (13 steps). As this initial analysis indicated that self-stimulation differed significantly as a function of current sequence (Sequence; $F = 38.91$, $df = 1, 21$, $P < 0.001$), ascending and descending current series were analyzed separately for all dependent measures. Thus, reward thresholds and maximal response rates were analyzed using Group and Session as factors. When appropriate, comparisons between the lesioned and the control group were performed using Dunnett's $t$-test.

## 3. Results

### 3.1. Histology

Damage to the hippocampal formation was very similar to that previously described [55]. Histological analyses revealed that all lesioned animals that received kainic acid/colchicine lesions had extensive bilateral damage to the hippocampal formation (see Fig. 2). The fimbria/fornix was either completely destroyed or extremely shrunken for all subjects in this group. The CA subfields, dentate gryus, and subiculum were completely destroyed in eight rats Approximately 10% of the CA3 subfield in the left hemisphere was spared in one animal, and the most ventral portion of the subiculum was spared bilaterally in the remaining animal. Additional damage to the deep layers of the entorhinal cortex (layers 3–6) was also evident in nine rats. However, there were no significant correlations between extent of entorhinal damage and response thresholds or maximal response rates.

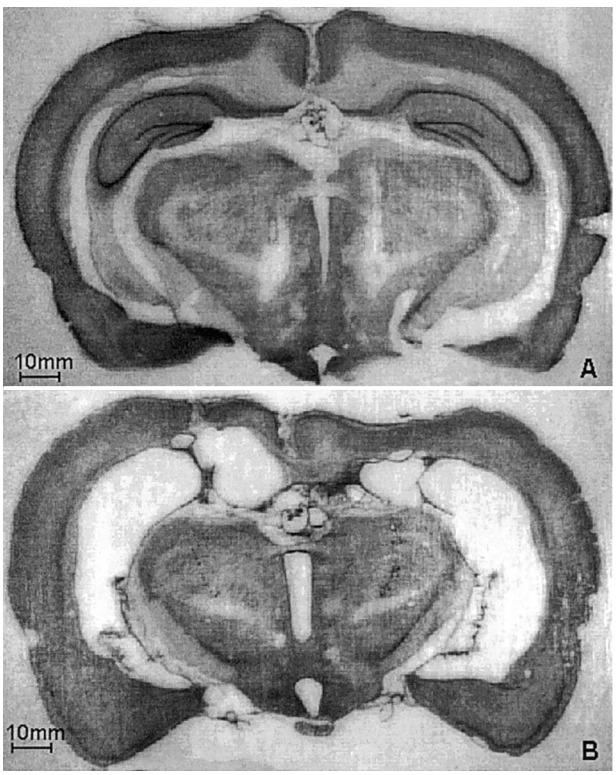


Fig. 2. Coronal sections showing a representative control (a) and kainic acid/colchicine lesion of the hippocampus (b).

Damage to non-target structures included thinning or loss of the anterior portion of the body of the corpus callosum. In one animal, there was slight damage to the anterior portion of the stria medullaris and the ventral mediodorsal thalamus. Varying amounts of thinning and damage to the parietal-cingulate cortices overlying the lesion site were evident in all animals. There were no significant correlations, however, between extent of cortical damage and levels of performance.

Histological analyses of electrode placement revealed that the electrodes were primarily localized within the anterior-dorsal portions of the VTA. Fig. 3 illustrates the distribution of electrode placement of both control and lesioned animals for sites that supported ICSS.

Correlational analyses revealed no significant relationship between site of electrode placement (measured as mm posterior to bregma) and response thresholds or maximal response rates. Additional ANOVAs were performed to determine if significant differences in threshold or maximal response rate existed between subjects with electrode placement in the right or left hemisphere. No significant differences in performance as a function of hemispheric placement were detected.

Fig. 4 shows mean rates of self-stimulation in lesioned and control animals as a function of ascending (top) and descending (bottom) current intensities. As clearly illustrated in this figure, lesioned animals responded very differently than controls to both the ascending (Group X current intensity; $F = 10.65$, $df = 12, 252$, $P < 0.001$) and descending series (Group X current intensity; $F = 10.05$, $df = 12, 252$, $P < 0.001$) of currents. Most evident from these rate–intensity curves is the group difference in response rates. Thus, lesioned animals responded at significantly higher rates at currents above 16 $\mu$A when presented with the ascending series, and maintained higher rates of lever pressing at current intensities above 28 $\mu$A on the descending series.

In confirmation of this group difference in self-stimulation, Fig. 5 illustrates explicit differences in both reward threshold and maximal response rate over the four ascending and four descending sessions. When considered over the self-stimulation test sessions, le-

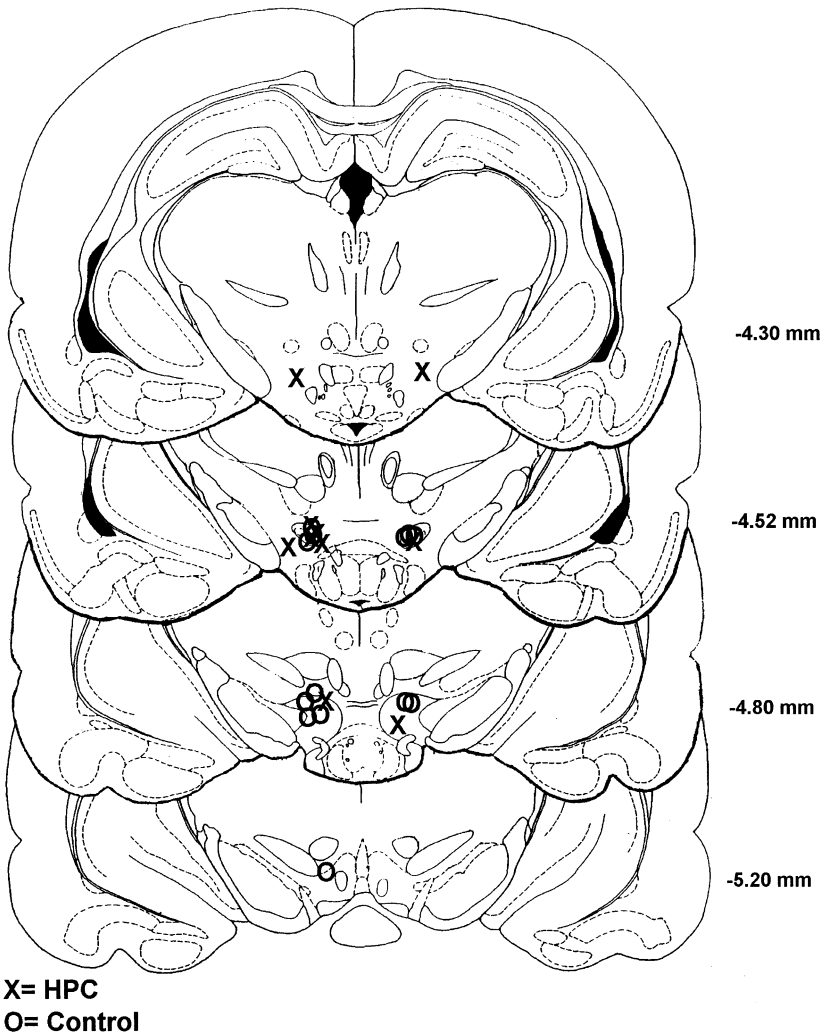


Fig. 3. Coronal sections showing schematic depiction of electrode placement for both hippocampal lesioned rats (X) and controls (O). Drawings are adapted from Paxinos and Watson [42].

sioned animals showed consistently lower reward thresholds than controls when presented with the ascending series of current intensities (Group; $F = 6.239$, $df = 1, 22$, $P = 0.02$). Animals with hippocampal damage also showed consistently higher maximal response rates for both the ascending (Group; $F = 13.366$, $df = 1, 22$, $P < 0.01$) and descending (Group; $F = 14.094$, $df = 1, 22$, $P < 0.001$) current series.

## 4. Discussion

The main results of this experiment indicated that extensive damage of the hippocampal formation produced profound changes in responding for electrical stimulation of the VTA. In comparison to controls, lesioned animals were more sensitive to the stimulating current, as indicated by significantly lower thresholds. These animals also consistently exhibited higher maximal response rates during self-stimulation tests. Collectively, these novel results extend previous demonstrations of the involvement of the hippocampal formation in motor output and rewarded behavior [5,9,17,24,48,49] by demonstrating that lesions of this structure can dramatically alter behaviors traditionally ascribed to the mesoaccumbens DA system [2,13,14,29,43–45].

In understanding the observed group differences in responding, it is important to note that lesioned animals showed lower reward thresholds when responding to the ascending, but not the descending series of current intensities. The presentation of ascending or descending current intensities during ICSS produces, respectively, positive or negative contrast effects [21,28,57]. It has been shown that reward thresholds are lower during the presentation of an ascending current series, in comparison to random or descending current series [12,28]. Rats with hippocampal lesions have previously been described as being 'extremely sensitive' to contrast effects engendered by shifts in reward [31], and

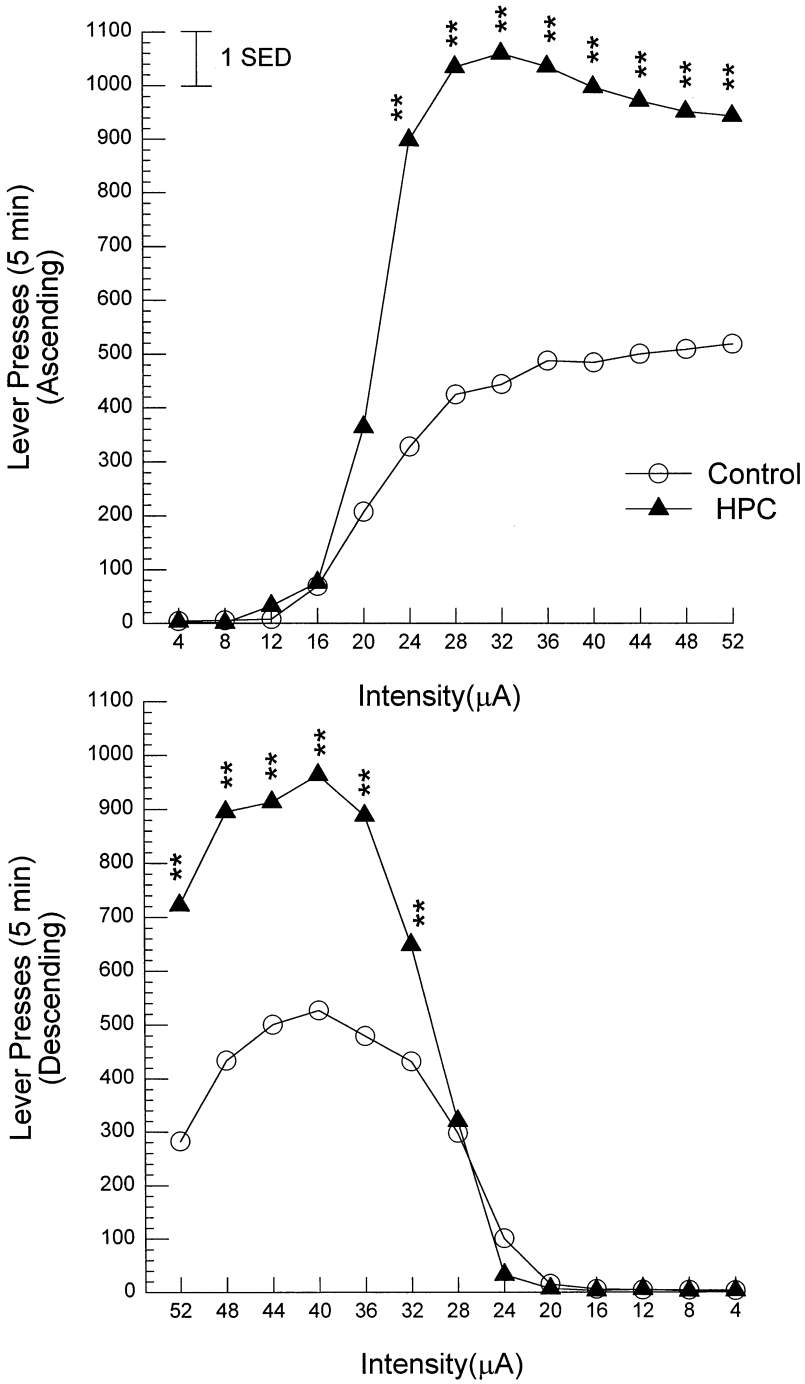


Fig. 4. Mean response rates for both lesioned and control animals across each current intensity for both ascending and descending current presentations. The vertical bar represents the standard error of the difference in means. Significant group differences are indicated by ** (Dunnett's $t$-test, $P < 0.01$).

it has recently been reported that rats with extensive hippocampal damage were more sensitive than controls to 'increases' in the qualitative aspects of reward [48]. The current results confirm these earlier observations, and, in the case of ICSS, suggest that lesioned animals may be more sensitive to positive, rather than negative, contrasts.

Analyses also indicated that lesioned animals had significantly higher maximal response rates than controls. There are at least two possible interpretations of this group difference. First, maximal response rates for ICSS are usually considered to be a measure of motor performance [33]. Rats with hippocampal damage, produced by a variety of different methods, have been

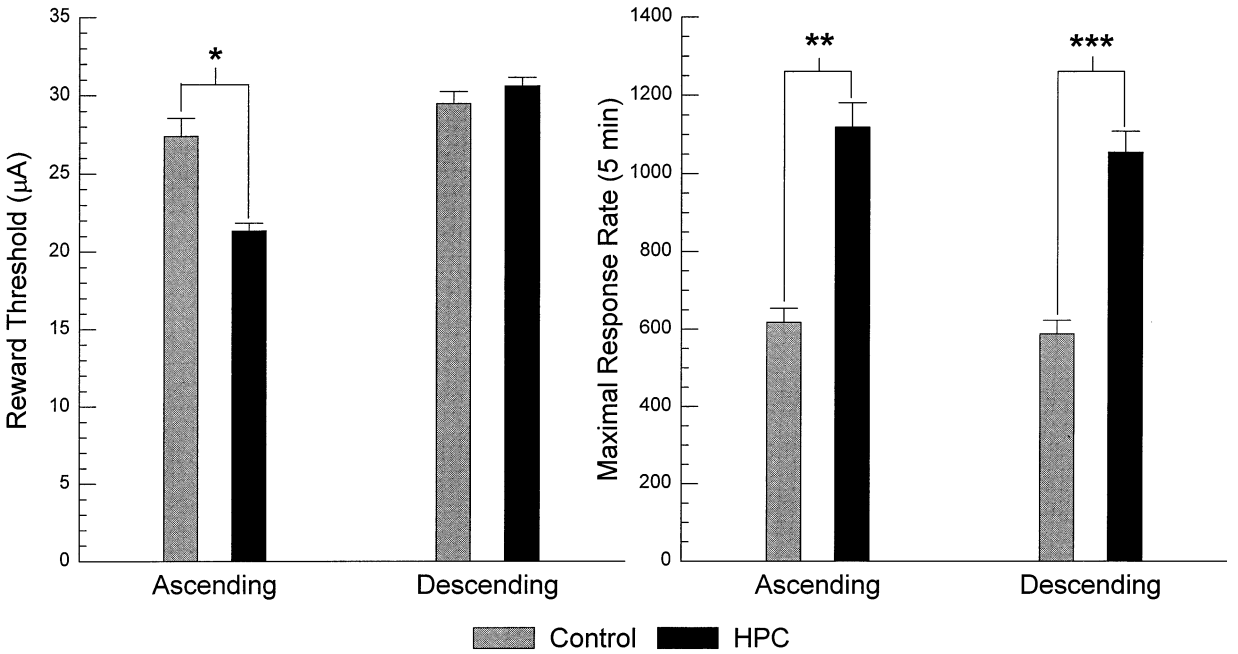


Fig. 5. Mean reward threshold and maximal response rates for both ascending and descending sessions. Vertical bars represent the standard error of the mean. Significant group differences are indicated by *, ** and *** ($P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively).

reported to display increased motor output in response to activating situations, food reward, and following drug administration [5,8,9,17,24,38,48,49,59,60]. These results may thus be another example of the enhancement in motor output resulting from hippocampal damage.

A second possibility relates to the hypothetical properties of inverted, U-shaped response functions that have been generated in self-stimulation [64] and self-administration experiments [26,35,36,62]. Thus, at low current intensities on the ascending limb of the curve, responding probably reflects the rewarding properties of the stimulation, in that higher currents elicit increasing rates of responding. At higher current intensities (on the descending limb), responding often begins to decline from asymptotic values, thus indicating rewarding, as well as additional rate-suppressing properties of the stimulation (for example, Fig. 4, top). For example, at higher current intensities, animals may develop behaviors that are incompatible with lever pressing, or responding may slow as a function of the development of additional, aversive properties of the stimulation [33,34,57]. Given the consistently higher maximal response rates in lesioned animals, these results may support the possibility that either the motoric side-effects or potential aversive properties of higher intensity currents were reduced by hippocampal damage. In this context, it seems unlikely that this result can be attributed to simple differences in current spread from the site of stimulation between lesioned and control animals. It should be recalled that electrode placements overlapped in both groups, and diffusion of electrical excitation is mainly influenced by the resistance of the stimulation medium [64]. There is no evidence to suggest that brain resistance was altered as a function of the lesions.

The differences in reward thresholds between lesioned and control animals may be due to the destruction of the glutamatergic hippocampal efferents innervating the NACC [15,16,58]. A diminished excitatory glutamatergic signal to the NACC may, by default, amplify the inhibitory mesolimbic DA signal. This lack of glutamatergic modulation would theoretically result in a heightened expression of DA-mediated reward sensitivity. Thus, it would be reasonable to assume that administration of glutamate receptor antagonists might produce changes in reward sensitivity similar to that of a hippocampal lesion. MK-801, which is widely known to block NMDA receptors, significantly lowers reward thresholds for lateral hypothalamic [46] and medial forebrain bundle self-stimulation [6]. Considering these similarities in reward changes produced by both NMDA receptor blockade and hippocampal lesions, it is possible that glutamate release from hippocampal afferents in the NACC (or, at least, NMDA receptor activation) is partially involved in modulating reward thresholds.

Considered together with previous research on the effects of hippocampal lesions on motivated behavior [25,48], these results provide additional evidence indicating that damage to this structure profoundly alters sensitivity to the hedonic properties of a non-natural reinforcer. As such, these results may provide some intriguing additions to our understanding of the neural substrates involved in addiction. Specifically, it seems possible that as hippocampal damage enhances sensitiv-

ity to ICSS, it may have similar effects on responding for drugs of abuse. In this context, it is interesting to note that in addition to showing neuropathological changes in the hippocampus [11,30], schizophrenics also exhibit an incidence of psychostimulant abuse that is two to five times higher than that of the general public [7,32].

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