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Phencyclidine Exacerbates Attentional Deficits in a Neurodevelopmental Rat Model of Schizophrenia

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Schizophrenia is characterized by severe abnormalities in cognition, including disordered attention. In the rat, neonatal ventral hippocampal (NVH) lesions induce behavioral abnormalities at adulthood thought to simulate some aspects of the symptomatology of schizophrenia. Here, we compared the effects of NVH and adult ventral hippocampal (AVH) lesions on attentional performance as assessed by the five-choice serial reaction time task (5-CSRTT). NVH-lesioned rats were slower to acquire the task than AVH-lesioned and control animals. When training was complete, NVH- and AVH-lesioned animals exhibited stable but disrupted performance under standard conditions, thus emphasizing an implication of VH in visual attentional processes. Variations in task parameters induced a significantly greater disruption in NVH- and AVH-lesioned groups as compared to controls. NVH-lesioned rats were also hyper-responsive to the disruptive effects of a high dose of phencyclidine (PCP) (3 mg/kg). In contrast, amphetamine (0.4–0.8 mg/kg) had a similar effect in control and VH-lesioned rats. Thus, NVH-lesioned rats were impaired in the acquisition of stable performance in the 5-CSRTT, and were hypersensitive to the cognitive-impairing effects of PCP.
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INTRODUCTION

Neuropathological changes in the hippocampus have been frequently observed in schizophrenia (Zaidel *et al*, 1997; Weinberger, 1999; Csernansky *et al*, 2002). These brain abnormalities have been proposed to result from abnormal neurodevelopmental processes (Weinberger, 1986). An animal model simulating neurodevelopmental lesions of the hippocampus has been developed by Lipska and co-workers (Lipska *et al*, 1993; Lipska and Weinberger, 1993). This model, based on the long-term effects of postnatal day-7 lesions of the ventral hippocampus, provides preclinical evidence for the neurodevelopmental hypothesis of schizophrenia. Neonatal ventral hippocampal (NVH) lesions in rats have been shown to induce postpubertal emergence of behavioral abnormalities thought to simulate some aspects of both the positive and negative symptomatology of schizophrenia. These include hyper-responsiveness to stress, novelty, dopamine agonists and glutamate antagonists (Lipska *et al*, 1995a, 1993; Flores *et al*, 1996; Black *et al*, 1998; Brake *et al*, 1999; Al-Amin *et al*, 2000, 2001). NVH-lesioned rats also exhibit deficits in social behavior (Sams-Dodd *et al*, 1997; Becker *et al*, 1999) and altered reward sensitivity (Le Pen *et al*, 2002).

Traditionally, schizophrenia has been viewed as an illness comprised primarily of positive and negative symptoms, but it is now recognized that cognitive impairments are also a central feature of this disorder, and not secondary to drug effects or other symptoms (Breier, 1999; Weinberger and Gallhofer, 1997). Cognitive deficits are common across all subtypes of schizophrenia and include deficits in abstraction, executive function, verbal memory, language function, vigilance, and attention (Sharma, 1999; Joober *et al*, 2002; Hughes *et al*, 2003).

Regarding cognitive processes, NVH-lesioned rats exhibit a postpubertal emergence of deficits in sensorimotor gating (Lipska *et al*, 1995b; Le Pen *et al*, 2000), in latent inhibition (Grecksch *et al*, 1999), and also in spatial learning and working memory (Chambers *et al*, 1996; Lipska *et al*, 2002). More recently, we extended these results by demonstrating lesion-induced deficits in spatial and associative learning (Le Pen *et al*, 2000).

To further explore the neurodevelopmental aspects of this model and its validity, we investigated the effects of neonatal and adult VH lesions on attentional processes. As attention subsumes several distinct underlying processes (Robbins and Everitt, 1995; Sarter and Bruno, 2000) including sustained attention, selective attention, and

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executive control, we have used the five-choice serial reaction time task (5-CSRTT) in rats. This test provides independent measures of these different processes in rats (Carli *et al*, 1983) and exhibits closed analogies with the continuous performance test and Leonard's 5-CSRTT used in humans to assess attentional processes (Mirsky and Rosvold, 1960; Leonard, 1959, 1961). In the 5-CSRTT, rats must detect and respond to a series of brief visual stimuli that are presented in one of five locations in a spatial array. Attentional demands of the task can be increased by reducing brightness or duration of the stimulus, decreasing the time between stimulus presentations, or interpolating unpredictable white noise. Thus, we have assessed and compared the performance of neonatal and adult VH-lesioned rats in the 5-CSRTT under normal conditions and after increasing attentional demands. Finally, the effects of two classic psychotomimetic drugs (phencyclidine (PCP) and amphetamine) on rats' performances have been evaluated.

METHODS

All animal experiments were approved by local animal protection authorities

Animals

Sprague–Dawley rat pups were obtained at 3–4 days of age as whole litters together with their mother and adult male Sprague–Dawley rats were obtained at 50 days of age (BRL, Füllinsdorf, Switzerland). After weaning, rats were housed in groups of four in holding rooms at controlled temperature (20–22°C) with a 12-h light/12-h dark cycle (ON: 06.00 h; OFF: 18.00 h). Behavioral testing occurred during light cycles between 10.00 and 16.00 h.

Surgical Procedure

Neonatal rats. On the seventh day of age and at a body weight of 15–20 g, male pups within each litter were randomized to Sham or Lesion status, anesthetized by isoflurane inhalation (4% for induction and 1.5–3% for maintenance) through a mask, mounted on a stereotaxic Kopf instrument with an adapter for small animals (Harvard Biosciences) and additionally taped on a heating pad placed on the platform. The skin overlying the skull was incised and 0.3 μl of either ibotenic acid (Sigma, St Louis, MO, USA; 10 μg/μl) or artificial cerebrospinal fluid was bilaterally infused over a 2-min period by a micro-infusion pump (PHD Programmable, Harvard Biosciences) using an injection cannula (0.3 mm diameter) aimed at the ventral hippocampal formation (AP −3.0 mm, ML ± 3.5 mm, and DV −5.0 mm relative to bregma). After completion of the infusion, the cannula was left in place for an additional 3-min period before being slowly removed. Then, the skin overlying the skull was sutured and the animals were allowed to recover on a heating pad before being returned to their mother (female pups were removed from the litter). Eighteen days after surgery (ie PND25) rats were weaned and housed four per cage until further testing.

Adult rats. We anesthetized 56-day-old rats with ketamine 80 mg/kg (Ketalar, Parke-Davis) and xylazine 10 mg/kg (Rompun, Bayer). The animals were mounted on a stereotaxic Kopf instrument and the skin overlying the skull was incised. Then, 2 × 0.2 μl of either ibotenic acid (Sigma, St Louis, MO, USA; 15 μg/μl) or artificial cerebrospinal fluid was bilaterally infused over a 2-min period by a micro-infusion pump (PHD Programmable, Harvard Biosciences) using an injection cannula (0.3 mm diameter) aimed at the ventral hippocampal formation (AP −4.8 mm, ML ± 5.2 mm, and DV −7.0 and −5.0 mm relative to bregma). After completion of the infusion, the cannula was left in place for an additional 3-min period before being slowly removed. This procedure was adapted from Lipska *et al* (1993) in order to induce lesions similar in volume and location to those obtained after neonatal injections of ibotenic acid. Following infusion, the skin overlying the skull was sutured and the animals were allowed to recover on a heating pad before being returned to their home cage.

Five-Choice Serial Reaction Time Task

For the 5-CSRRT, animals were maintained under a schedule of restricted access to food (1 h a day after experimentation) in order to maintain 85% of free feeding body weight. Except during testing, water was always available *ad libitum*.

Apparatus. Five-choice operant chambers (Med Associates Inc., St Albans, VT) housed in sound insulated and ventilated enclosures were used for all experiments. Each chamber consisted of an aluminum enclosure (25 × 30 cm) containing on one wall a food hopper and house light and on the opposite wall an array of five square holes (2.5 × 2.5 × 2.5 cm) arranged on a curved panel and raised 2.5 cm from the grid floor. A LED (standard conditions: 150 lx) was positioned at the rear of each hole. All apertures in the chamber, including the food hopper, were controlled by a photocell placed across the entrance. Operant chambers were controlled by the Kestrel Control System (Conclusive Solutions, Harlow, UK).

Training. Training began with the illumination of the house light and delivery of a food pellet. A nose-poke into the magazine tray started the first trial, which consisted of an intertrial interval (ITI, 5 s) followed by the random illumination of one of the five lights for a fixed interval (stimulus duration, SD). If a nose-poke was registered in the illuminated niche before the end of either the SD, or a fixed interval after this period (limited hold, LH) a further pellet was dispensed and a 'correct trial' registered. An incorrect nose-poke (incorrect trial) or failure to respond within the allotted time (missed trial) resulted in a time-out (TO) period during which the house light was extinguished for 5 s. Responding to one of the five niches during the ITI (premature response), or after a correct trial was registered (perseverative response), resulted in a further TO. Finally, if a rat responded into a niche during a TO, the TO was restarted. Each training session ran for either 100 trials or 60 min, whichever was shorter.

Task acquisition. Rats were initially given access to a handful of pellets (45 mg Noyes Formula P Food Pellets) in

their home cage for 2 consecutive days. Training commenced with daily 60-min sessions, in which subjects were placed in the operant chambers and both the food hopper and five light niches were filled with approximately five pellets each. On subsequent days, no food was placed in the chambers before sessions began.

Initially, stimulus parameters were such that SD was set at 30 s and ITI, TO and LH were 5 s. Training continued until the rats achieved 80% correct responses ([correct/(correct + incorrect)]*100) and less than 20% omissions on 2 consecutive days. Then, SD was progressively reduced to 15 s. After 2 consecutive days of consistent performances at this criterion, SD was further reduced to 5 s, then 2 s. To finally reach 1 s, rats must have reached the target criterion for 3 consecutive days. At 1 s SD, to avoid overtraining, rats with good performance were only tested twice a week.

To compare acquisition of this task between the different groups of rats, the number of days to reach the next level of SD was evaluated. Arbitrarily, when SD was 30 s, day 1 was considered when 10 correct trials had been registered for a rat.

After the exclusion of rats following histological examination, we have noticed that five NVH-lesioned rats never reached the 2 s SD criterion even after a large number of training sessions. Moreover, at 1 s SD, some rats (one in the adult lesion group, and three in the neonatal sham group) completed only 60% or less of the total number of trials indicating very low performances. A Pearson χ^2 test revealed no significant effect of lesion on the proportion of rats that failed to acquire the task in both adult and neonatal groups ($\chi^2 = 0.87$, NS and $\chi^2 = 0.96$, NS; respectively). In addition, a Breslow and Day (BD) test for homogeneity of odds ratios indicated that the profiles obtained in adult or neonatal operated animals were similar (BD coefficient = 0.37, NS). Therefore, to compare groups with homogeneous performances, rats that failed to acquire the task properly were excluded from the analysis and presentation.

Acquisition data and data under standard conditions were analyzed using a three-factor ANOVA (lesion status × age at lesion × training stage or day, respectively) with repeated measurements on factors training stage or day respectively, followed when appropriate by separate two-factor ANOVA or by the Fisher's PLSD *post hoc* test.

Task manipulation. Training continued until subjects had achieved stable performances (more than 80% correct responses and less than 20% omissions) for at least a 2-week period.

To assess the effects of changing the stimulus parameters, rats were exposed to (1) standard or reduced stimulus intensity (SI), respectively, in arbitrary units (SI = 255: normal intensity; SI = 1: low intensity), each presented randomly 50 times during the test session, (2) standard or reduced stimulus duration (SD = 1 or 0.05 s, respectively, with equal numbers of each SD randomly presented during the session), (3) a distracting white noise (85 dB, 0.5 s duration) or no noise presented at the end of the ITI (simultaneously with the visual target stimulus) in a random and counterbalanced procedure, (4) standard (5 s) or longer (10 s) ITI duration, each presented randomly 50 times during the session.

In all cases rats were given 100 trials and 60 min to complete the session (except for the session on ITI duration, which lasted more than 60 min). Task manipulation occurred on Tuesdays and Fridays. For the rest of the week all subjects were run under standard conditions.

Data were analyzed using a three-factor ANOVA (lesion status × age at lesion × stimulus parameter) with stimulus parameter as a repeated measure factor followed when appropriate by separate two-factor ANOVA or by the Fisher's PLSD *post hoc* test.

Psychotomimetic challenges. Following manipulation of stimulus parameters, baseline performance was re-established for a week. The effects of two classic psychotomimetic drugs (amphetamine, a dopamine agonist, and PCP, a glutamate receptor antagonist) were evaluated using standard stimulus parameters (SD = 1 s; ITI, TO, and LH = 5 s). D-amphetamine and PCP were dissolved in 0.9% saline and administered in a volume of 5 ml/kg body weight, 10 min prior to the start of the test session. Drug challenges occurred on Tuesdays and Fridays. The other days of the week were devoted to training sessions under standard conditions. First animals received PCP (0, 0.3, 1, or 3 mg/kg, s.c.) and then amphetamine (0, 0.4, or 0.8 mg/kg, i.p.) according to a Latin Square design. Rats were kept in training under baseline conditions for a week between the PCP and the amphetamine experiment. Doses of amphetamine and PCP used in the present experiments were selected from previous reports in the literature (eg Cole and Robbins, 1987; Harrison *et al*, 1997; Jin *et al*, 1997).

Data were analyzed using a three-factor ANOVA (lesion status × age at lesion × drug dose) with repeated measurements on factor drug dose, followed when appropriate by separate two-factor ANOVA or by the Fisher's PLSD *post hoc* test.

Locomotor Activity

Locomotor activity was assessed in a Digiscan actimeter (Omnitech Electronic Inc., Colombus, OH) monitoring horizontal and vertical movements of the animals. The individual compartments (40 × 40 × 30 cm) were located in a dimly lit and quiet room. Horizontal and vertical activity counts were recorded for a 60-min period, and were expressed as the total number of horizontal and vertical beams crossed by the animal. Locomotor activity data were analyzed using a two-factor ANOVA (lesion status × age at lesion), followed when appropriate by separate two-factor ANOVA or by the Fisher's PLSD *post hoc* test.

Rating of Lesion Size (according to Sams-Dodd *et al*, 1997)

At the completion of behavioral evaluation, rats were killed by decapitation. Brains were rapidly removed and after fixation in formalin solution (10% in NaCl for at least 1 week), 40-μm sections were sliced with a freezing cryostat. The sections through the lesioned area were mounted and stained with cresyl violet. The extent of the lesion on each

side of the brain was rated as follows: 0—no discernible cell loss in the hippocampal formation, 1—small, 2—medium, 3—large area of cell loss within the ventral hippocampal formation. Scores for both sides were added to yield a total score ranging from 0 to 6.

RESULTS

Histology

One NVH-lesioned rat was excluded because of extrahippocampal damage (cortex) and another one because of unilateral lesion. Thus, following histological examination and removal of animals that did not acquire the 5-CSRTT properly, 7 and 10 control and 9 and 11 lesioned rats were included for data analysis in the neonatal-lesioned and the adult-lesioned group, respectively. It has to be noted that rats excluded from the analysis because of their poor learning performances exhibited lesion scores similar to those obtained for rats included in the analysis.

Neonatal- and adult-lesioned rats exhibited mean lesion scores of 3.5 ± 0.4 and 3.4 ± 0.2, respectively, indicating (1) a similar extent and location of the lesion in adult- and neonatal-lesioned animals (Figure 1), and (2) that the cell loss was restricted to the ventral part of the hippocampus. Some animals exhibited cavitation around the site of injection. In control rats injected with artificial cerebrospinal fluid, the hippocampus was morphologically intact (lesion score 0).

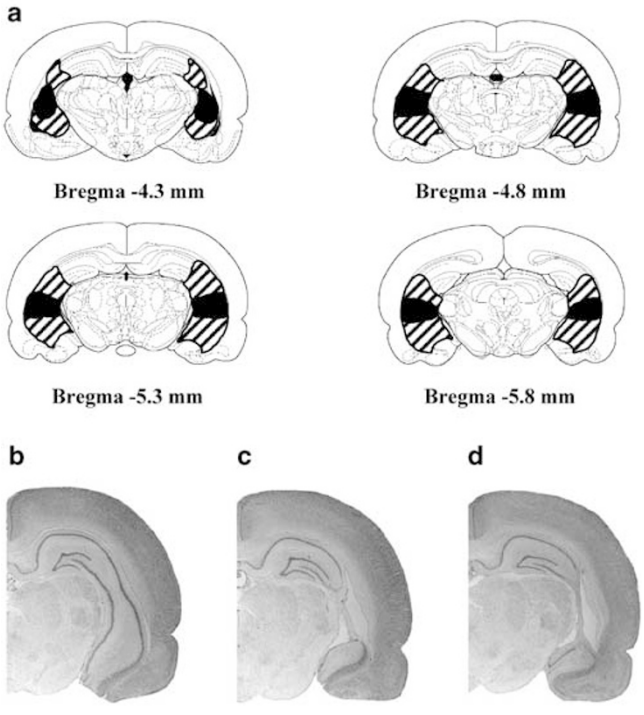

Figure 1 Lesion boundaries in the ventral hippocampus of rats infused bilaterally with ibotenic acid. (a) Schematic drawing of the ventral hippocampus with boundaries of the largest (stripes) and smallest (black) lesions. Representative photomicrographs of cresyl violet-stained coronal section through the brains of rats that had received sham (b), neonatal (c), or adult (d) lesions of the ventral hippocampus.

Five-Choice Serial Reaction Time Task

Task acquisition. The rate of acquisition of the 5-CSRTT by neonatal- and adult-lesioned animals is illustrated in Figure 2. A three-way ANOVA revealed a significant effect of age at lesion ($F(1,33) = 14.3$, $p < 0.001$), a significant effect of lesion ($F(1,33) = 22.7$, $p < 0.001$), and a significant effect of training stage ($F(3,99) = 23.2$, $p < 0.001$). There was also a significant age $\times$ lesion interaction ($F(1,33) = 12.3$, $p < 0.01$), indicating that neonatal and adult lesions differentially affected performance at the various stages of training. *Post hoc* comparisons revealed that, in contrast to AVH-lesioned or control animals, NVH-lesioned rats needed more time to reach a consistent performance criterion at each stage of the training (30 s, $p < 0.01$; 15 s, $p < 0.01$; 5 s, $p < 0.05$; 2 s, $p < 0.01$).

Performance under standard conditions. Figure 3 shows the mean performance of adult- and neonatal-lesioned rats in the 5-CSRTT over a 10-day period under standard conditions. Rats were tested once daily for 10 days when stage SD 1 s was reached. Both control and VH-lesioned rats were able to acquire stable responses as revealed by no significant day effects and no significant interactions with factor day upon percent correct and correct latency. However, VH lesions significantly decreased accuracy (percent correct responses) ($F(1,33) = 14.9$, $p < 0.001$), increased correct latency ($F(1,33) = 7.9$, $p < 0.01$), and also largely tended to increase the number of perseverative responses ($F(1,33) = 3.98$, $p = 0.054$). These effects occurred independently of lesion age as indicated by a lack of significant age or age $\times$ lesion interactions across any of the parameters studied.

Task manipulation

Increased ITI: The effect of increasing ITI on accuracy and correct latency is illustrated in Figure 4a and b. Accuracy was significantly decreased by the lesion ($F(1,33) = 5.3$, $p < 0.05$) and by the increase of ITI

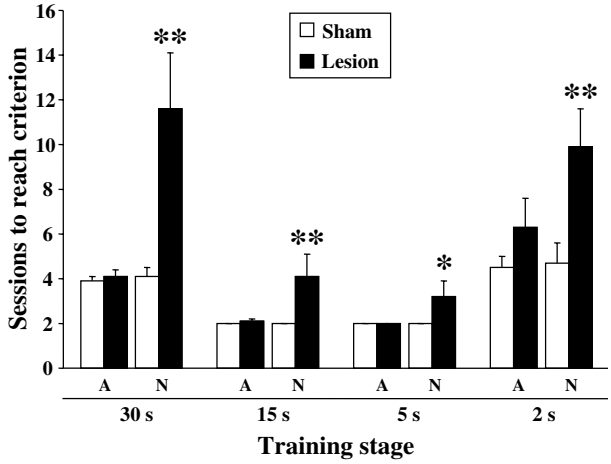

Figure 2 Effect of neonatal (N) or adult (A) ventral hippocampal lesions on acquisition of the 5-CSRTT. The success criterion is defined as the number of days to reach 80% correct responses with <20% omissions with a SD of 30, 15, 5, and 2 s. *$p < 0.05$ and **$p < 0.01$ compared to respective sham animals.

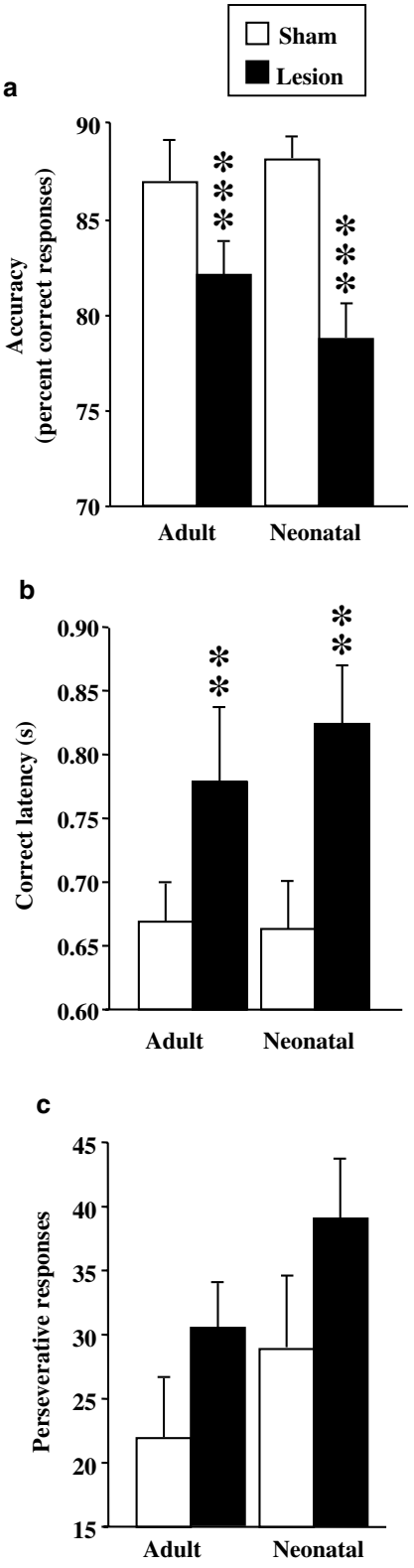

Figure 3 Effect of ventral hippocampal lesions performed neonatally or at adulthood on mean performance over 10 consecutive days of testing under standard test conditions in the 5-CSRTT. Data shown are for percentage correct responses (a), correct latency (b), and perseverative responses (c). $^{**}p<0.01$ and $^{***}p<0.001$ compared to controls.

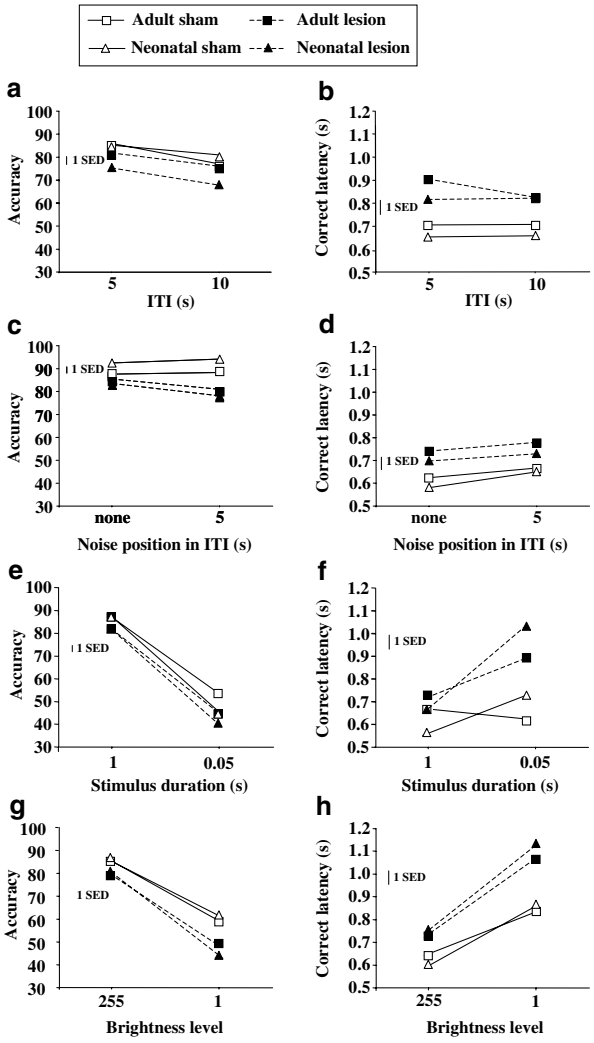

Figure 4 Effect of neonatal and AVH lesions on performances (percent correct responses and correct latency) under various task manipulations, such as variable ITI (a, b), white noise distractor (c, d), variable SD (e, f), and variable SI (g, h).

$(F(1,33)=11.7,\ p<0.01)$. No significant two- or three-way interactions were noted, indicating a similar effect of increasing ITI on both sham and VH-lesioned animals whatever the age of lesion. An increase of correct latency was also observed after both neonatal and adult VH lesion $(F(1,33)=5.3,\ p<0.05)$ but no significant two- or three-way interactions were found. Thus, increasing ITI had no significant effect on the increase of correct latency induced by the lesion in both adult- and neonatal-lesioned rats.

Interpolation of a white noise distractor: The effects of interpolating a white noise distractor on accuracy and correct latency are illustrated in Figure 4c and d. Here again, accuracy was decreased by the lesion $(F(1,33)=10.4,\ p<0.01)$ but no significant effect of age, or age $\times$ lesion interaction $(F(1,33)=0.3$, NS and $F(1,33)=2$, NS, respectively). A significant noise distractor $\times$ lesion interaction $(F(1,33)=7.9,\ p<0.01)$ indicated that the decrease in accuracy induced by the noise distractor was only observed in VH-lesioned rats. An increase of correct latency was also

observed in all groups after interpolation of a noise distractor ($F(1,33)=7.9$, $p<0.01$).

Reduced SD: The effect of reducing SD on accuracy and correct latency is illustrated in Figure 4e and f. Accuracy was significantly decreased by the lesion ($F(1,33)=8.3$, $p<0.01$) and by the decrease of SD ($F(1,33)=503$, $p<0.001$). No significant two- or three-way interactions were noted, indicating a similar effect of decreasing SD in both sham and VH-lesioned animals, irrespective of age at lesion. An increase of correct latency was also observed after VH lesions ($F(1,33)=9.7$, $p<0.01$) and following the decrease of SD ($F(1,33)=20.9$, $p<0.001$). A significant SD $\times$ lesion interaction was found ($F(1,33)=8$, $p<0.01$) indicating that the increase in correct latency induced by the reduction of SD was more pronounced in VH-lesioned rats, again, regardless of age at lesion.

Reduced brightness level: Figure 4g and h shows the effects of reducing SI on accuracy and correct latency. Accuracy was significantly decreased by the lesion ($F(1,33)=9.7$, $p<0.01$) and by the reduction of SI ($F(1,33)=400$, $p<0.001$). A significant SI $\times$ lesion was observed ($F(1,33)=6.5$, $p<0.05$) but no other two- or three-way interactions were found, indicating that the decrease of accuracy induced by the reduction of SI was more pronounced in VH-lesioned rats than in controls whatever the age of lesion. An increase of correct latency was also observed after lesioning ($F(1,33)=10.2$, $p<0.01$) and after decreasing SI ($F(1,33)=67$, $p<0.001$). No other significant two- or three-way interactions were found, indicating that the decrease of correct latency induced by the reduction of SI was more pronounced in VH-lesioned rats than in controls whatever the age of lesion.

Effect of psychotomimetics upon performance in the 5-CSRTT. The effects of amphetamine and PCP on 5-CSRTT under standard conditions are depicted in Figure 5a and b, respectively.

Amphetamine: Accuracy was significantly decreased by the lesion ($F(1,33)=7$, $p<0.05$) and by amphetamine ($F(2,66)=14.3$, $p<0.001$). No two- or three-way interactions were observed, indicating that the decrease of accuracy induced by amphetamine was similar in control and VH-lesioned rats whatever the age of lesion.

Amphetamine also decreased correct latency ($F(2,66)=23.7$, $p<0.001$), the number of correct trials ($F(2,66)=14.7$, $p<0.001$), and increased premature and perseverative responses ($F(2,66)=15$, $p<0.001$ and $F(2,66)=31.6$, $p<0.001$, respectively) (data not shown). All these modifications reached significant levels for 0.8 mg/kg of amphetamine except for correct latency, which was also significantly increased at 0.4 mg/kg. In addition, number of omission and magazine latency were not modified by amphetamine ($F(2,66)=1.9$, NS and $F(2,66)=0.5$, NS, respectively). No two- or three-way interactions were observed, indicating that these modifications induced by amphetamine were similar in control and lesioned rats whatever the age of lesion.

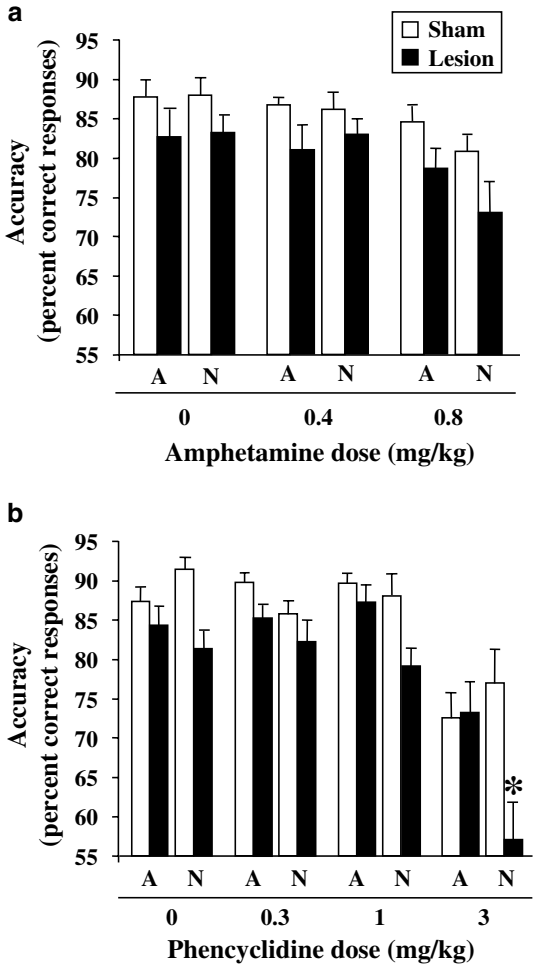

Figure 5 Effect of amphetamine (a) and PCP (b) on performances in the 5-CSRTT in rats with neonatal (N) or adult (A) ventral hippocampal lesions. $*p<0.05$ in comparison with respective controls.

Phencyclidine: We show a significant decrease of accuracy with lesion ($F(1,33)=13.1$, $p<0.001$) and with PCP dose ($F(3,99)=36.8$, $p<0.001$). A significant age $\times$ lesion interaction was observed ($F(1,33)=5.4$, $p<0.05$), indicating that NVH-lesioned rats were more sensitive to the disruptive effect of PCP compared to sham and adult VH-lesioned rats. A significant lesion and age $\times$ lesion $\times$ PCP interaction ($F(1,33)=13.1$, $p<0.001$ and $F(3,99)=2.9$, $p<0.05$ respectively) followed by separate ANOVA for each PCP dose revealed that hypersensitivity to PCP observed in NVH-lesioned rats was only seen at 3 mg/kg (significant age $\times$ lesion interaction: $F(1,33)=5.8$, $p<0.05$).

PCP also induced an increase of correct latency, missed trials, premature and perseverative responses ($F(3,99)=28.5$, $p<0.001$, $F(3,99)=47.7$, $p<0.001$, $F(3,99)=4.8$, $p<0.01$, and $F(3,99)=7$, $p<0.001$, respectively), and a decrease in the number of correct trials ($F(3,99)=60$, $p<0.001$) (data not shown). All these modifications reached significant levels for 3 mg/kg of PCP except for premature and perseverative responses, which were also significantly increased at 1 mg/kg. No two- or three-way interactions were observed, indicating that these modifications induced

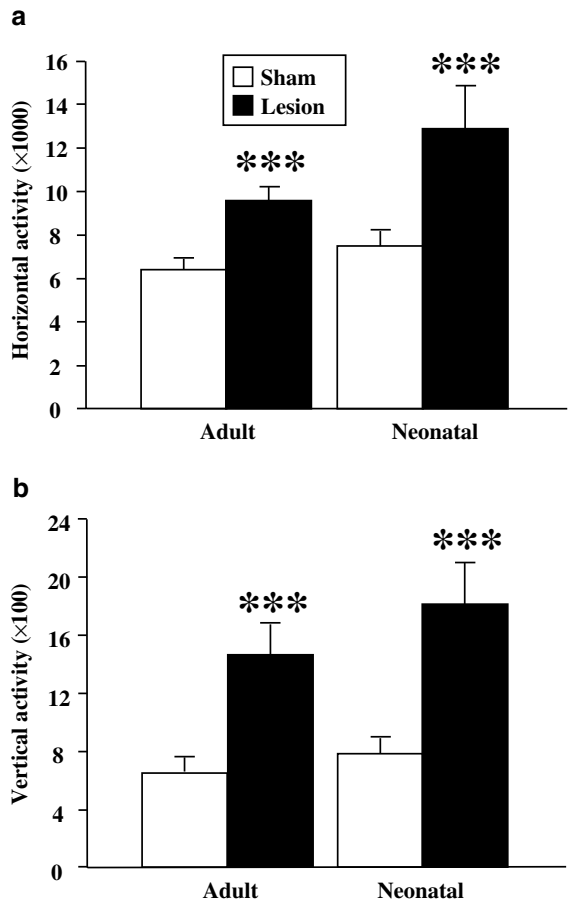

Figure 6 Effect of neonatal or AVH lesions on spontaneous horizontal (a) and vertical (b) activity within an open field chamber over a 60-min period. ***$p<0.001$ in comparison with controls.

by PCP were similar in control and lesioned rats whatever the age of lesion.

Locomotor Activity

Spontaneous horizontal (Figure 6a) and vertical (Figure 6b) activity was significantly increased in lesioned rats as compared to sham-operated animals ($F(1,33)=13.7$, $p<0.001$ and $F(1,33)=19.7$, $p<0.001$, respectively). No significant effect of age or age × lesion interaction was observed for the two parameters studied, indicating that the increase of both horizontal and vertical spontaneous activity induced by the lesion was similar whatever the age at lesion.

DISCUSSION

In the present study, we investigated the effects of neonatal and AVH lesions on attentional processes as assessed by the 5-CSRTT. We compared control and lesioned rats for their task acquisition, baseline performance, and for their response to various parametric manipulations or psychotomimetic drugs administration.

Task Acquisition

At long SDs (training stage 30, 15, and 5 s), control, adult VH-lesioned and neonatal VH-lesioned rats were successfully trained in the 5-CSRTT. However, NVH-lesioned rats required more trials than control or AVH-lesioned subjects to reach the criterion at each training stage. Thus, NVH-lesioned rats exhibited a clear deficit in the initial acquisition of the stimulus light-reward association. This acquisition deficit could result from a difference in exploratory drive between neonatal and AVH-lesioned rats. This is unlikely since both adult- and neonatal-lesioned rats exhibited similar increases in locomotor activity in a novel open-field. This deficit could also be explained by the fact that NVH-lesioned rats may be less motivated to learn the task. Indeed, latency to collect the earned food pellets, a sensitive index of the level of primary motivation (Carli and Samanin, 1992; Harrison *et al*, 1997), was slightly higher in NVH-lesioned rats than in AVH-lesioned and control rats. Moreover, we have recently shown that, in contrast to adult-lesioned rats, neonatal-lesioned animals exhibited deficits in reward sensitivity (Le Pen *et al*, 2002). In addition, NVH-lesioned rats are also impaired in their capacity to acquire and retain information in tests of spatial and avoidance learning (Le Pen *et al*, 2000) whereas AVH lesions have a smaller impact on these procedures (Moser *et al*, 1995; Stubley-Weatherly *et al*, 1996; Hock and Bunsey, 1998). Thus, the slower acquisition of the task in NVH-lesioned rats may be best explained by reward and mnemonic process deficits, both of which are required to learn the initial association between stimulus presentation, operant response, and reward.

Offspring of mothers that show poor levels of pup licking and grooming also exhibit poor spatial learning and locomotor performances (Liu *et al*, 2000; Gomez-Serrano *et al*, 2001). According to these results, cognitive deficits seen in NVH-lesioned rats during the acquisition phase could result from reduced maternal care. However, a recent study of the behavioral outcome of NVH lesions in two strains of rats exhibiting differences in the frequency of maternal behavior has revealed no difference of maternal care towards lesioned or control pups (Wood *et al*, 2001). Nevertheless, NVH-lesioned rats were significantly more affected by increases in arched-back nursing compared to controls (Wood *et al*, 2001). Thus, increased maternal interactions perceived to be beneficial in some models could actually lead to some of the deficits seen in NVH-lesioned rats.

In the second part of the training, when SD was reduced to 2 s, several NVH-lesioned rats failed to reach the criterion. Moreover, NVH-lesioned rats that reached the criterion required significantly more sessions to do so than controls and rats lesioned at adulthood. In addition, AVH-lesioned rats also tended to need more sessions than controls to reach criteria. Altogether, these deficits already reflect an effect of VH lesions on attentional processes.

Effects of Lesions upon Baseline Performance in the 5-CSRTT

When stable performances had been reached at 1 s SD, subjects with neonatal and adult VH lesions were less likely,

and slower to make a correct response as compared to controls. An almost identical pattern of deficits can be observed after lesions of the basal forebrain cholinergic systems, which are known to be crucial for sustained and executive control of performance (Robbins and Everitt, 1995; Sarter and Bruno, 2000). More interestingly, adult and neonatal VH lesion-induced deficits in accuracy were smaller than those found after lesions of the entire medial prefrontal cortex (mPFC) and more similarly to those obtained after lesions of the dorsal or ventral portions of the mPFC (cingulate and prelimbic-infralimbic (PRL-IL) areas, respectively) (Muir *et al*, 1994, 1996; Passetti *et al*, 2002). Similarly to PRL-IL lesions, these deficits resulted from an increase in incorrect responses. However, in contrast to PRL-IL lesions, VH lesions increased the latency to respond correctly to a lower extent than following complete mPFC lesion. In addition, the increase in perseverative responses observed in both NVH- and AVH-lesioned rats was lower than that obtained after entire mPFC or PRL-IL lesions. This is best explained by an inability for lesioned animals to withhold multiple inappropriate nose-poking behavior in an aperture in which a correct response had been emitted. Perseverative responses have already been observed in a delayed alternation task after inactivation of the VH (Maruki *et al*, 2001) and in a spontaneous alternation task, after VH damage (Stevens and Cowey, 1973). Interestingly, in acute and chronic schizophrenic patients, deficits in executive function associated with an increase in perseverative error scores have been demonstrated in the Wisconsin Card Sorting Test, a task sensitive to prefrontal cortical and also hippocampal dysfunction (Goldberg *et al*, 1987; Weinberger *et al*, 1992; Corcoran and Upton, 1993; Goldberg and Weinberger, 1994), and in a two-choice visual task with reinforcement (Lyon and Gerlach, 1988). Moreover, in the rat, bilateral knife-cut lesions of the perforant path also induced an increase of perseverative responses, implicating the entorhinal cortex/hippocampal circuitry in perseveration (Kirkby and Higgins, 1998). To summarize, given the connectivity between VH and the entorhinal cortex, in addition to the projections from the VH to mPFC (including PR and IL areas) (Swanson, 1981; Wyss, 1981; Jay and Witter, 1991; Gabbott *et al*, 2002), VH lesion-induced perturbations in these circuitries may result in perseverative responses and a reduction in accuracy as observed in VH-lesioned rats upon baseline performance in the 5-CSRTT. These results also emphasize for the first time a role for the VH in visual attentional processes.

Effects of Task Manipulation

Challenges known to exacerbate deficits in attentional function were used (see Carli *et al*, 1983; Robbins *et al*, 1989; Jones *et al*, 1995). In summary, reducing the SD (a manipulation used to increase the attentional load) did not differentially affect the accuracy of VH-lesioned rats, and varying ITI (making the presentation of the stimuli temporally unpredictable) had the same effect in both sham and lesioned subjects. However, interpolating a distracting white noise immediately prior to the stimulus presentation induced a selective impairment in the ability of VH-lesioned rats to recognize the visual targets. Lesioned animals may thus be unable to ignore irrelevant or distracting stimuli, pointing to an impairment of selective attention function similar to that observed after mPFC lesions (Muir *et al*, 1996). Interestingly, NVH lesions have also been shown to induce a disruption of latent inhibition (Grecksch *et al*, 1999). This reflects a deficit in the ability to ignore irrelevant stimuli, a process depending on the integrity of the hippocampal formation (Gray *et al*, 1995). Acute schizophrenic patients also exhibit deficits in the ability to ignore irrelevant stimuli in a latent inhibition procedure (Baruch *et al*, 1988). There are also data to suggest that in chronic schizophrenic patients, latent inhibition deficits are present but masked by antipsychotic medications (Leumann *et al*, 2002). In addition, in stable chronic schizophrenics, higher levels of neuroleptics are associated with lessened distractibility in a reaction time task (Strauss *et al*, 1985), and an increased susceptibility to distraction while trying to process auditory information has been observed (Gold and Harvey, 1993).

Reducing the brightness level induced a selective impairment in the ability of VH-lesioned rats to detect the visual targets. This sensitivity to reduced SI has been suggested by some to reflect visual dysfunction rather than attentional impairment (Robbins *et al*, 1989; Muir *et al*, 1992a, b) whereas for Jones *et al* (1995) sensorimotor deficits could not be responsible for these results. In our study, in good agreement with Jones *et al* (1995), deficits in visual function seem unlikely to be responsible for the observed effects since neonatal and adult VH-lesioned rats did not exhibit visual impairment in the cued platform task of the Morris water maze paradigm (Le Pen *et al*, 2000). In good agreement with this hypothesis, it has also been shown in a latent inhibition paradigm that NVH-lesioned rats acquired the conditioned reaction similarly to controls where conditioned stimuli were a combination of light and sound (Grecksch *et al*, 1999).

Influence of Psychotomimetic Drugs upon Performance

As previously reported (Jin *et al*, 1997), PCP increased correct latency, and both premature and perseverative responses, and also reduced choice accuracy. Interestingly, PCP exacerbated accuracy deficits in NVH- but not AVH-lesioned rats. Other experiments have already shown an exacerbation of NVH lesion-induced abnormal behaviors in rats by PCP. These include hyper-responsiveness to PCP-induced locomotion (Hori *et al*, 2000; Kato *et al*, 2000) and PCP-induced retention deficits in a forced swim test used as a model of learning and memory (De Pablo *et al*, 1989; Hori *et al*, 2000).

Whether PCP-induced accuracy deficits are specific to attentional processes is an issue to be considered since systemically administered PCP has multiple effects on CNS function. Indeed, in our studies, and as already reported in the literature (Iwamoto, 1984; Hutson *et al*, 2000; Jacobs *et al*, 2000), PCP (3 mg/kg, s.c.) induced an increase of locomotion, stereotypies and ataxia and decreased rearing in Sprague–Dawley rats (data not shown). All these effects could contribute to the decrease in accuracy. However, this is unlikely since accuracy impairments induced by PCP (3 mg/kg, s.c.) in a 3-CSRTT were reversed by administration of a selective and high-affinity sigma antagonist that was inactive on PCP-induced hyperactivity in mice (Jin *et al*,

1997) and on PCP-induced ataxia and rearing behaviour in rats (Takahashi *et al*, 2001). In addition, drug effects on accuracy have been shown to be dissociable from drug effects on locomotion or stereotypies. Indeed, nicotine increased accuracy of SD rats in the 5-CSRTT (Mirza and Bright, 2001) at a dose that also increased locomotion and stereotypies (Ksir, 1994). And Grottick and Higgins (2000) have shown that subchronic nicotine treatment increased accuracy in the 5-CSRTT whereas sensitization to nicotine-induced locomotor activity has been observed after the same treatment (Benwell and Balfour, 1992). Finally, in our studies, PCP (3 mg/kg, s.c.) induced similar levels of locomotion and stereotypy in both control and NVH-lesioned rats (data not shown) even when a hyper-responsiveness to PCP-induced attentional deficits was seen in NVH-lesioned rats.

The present results also replicate previous findings showing that systemic administration of d-amphetamine increases the speed of responding, premature and perseverative responses and also mildly decreases accuracy (Cole and Robbins, 1987; Harrison *et al*, 1997). However, we showed that, in contrast to PCP, amphetamine did not increase accuracy deficits seen in lesioned rats, whatever the age at lesion. Previous experiments performed in NVH-lesioned rats have shown that cognitive impairments observed in the radial-arm maze were not exacerbated by amphetamine (Chambers *et al*, 1996) in contrast to hyperlocomotion (Lipska *et al*, 1993; Wan *et al*, 1996).

Thus, in good agreement with previous studies, we demonstrated that PCP, but not amphetamine, is able to exacerbate the cognitive deficits observed in NVH-lesioned rats.

These results obtained in NVH-lesioned rats can be compared with those obtained in schizophrenic patients, where PCP and ketamine (another NMDA receptor antagonist) have been reported to exacerbate both the positive and cognitive symptoms (Luby *et al*, 1959; Javitt and Zukin, 1991; Steinpreis, 1996; Malhotra *et al*, 1997; Jentsch and Roth, 1999), whereas amphetamine exacerbates positive symptoms (Angrist and Van Kammen, 1984; Lieberman *et al*, 1987; Wolkin *et al*, 1994) and can both improve or have no effect on negative symptoms (Goldberg *et al*, 1991; Sanfilipo *et al*, 1996). However, others have also reported an absence of ketamine effects on memory and cognition in schizophrenic patients (Laporte *et al*, 1996).

In conclusion, our study is the first that emphasizes an implication of the ventral hippocampus in visual attentional processes. In addition, our experiments suggest that NVH lesions in rats can simulate some aspects of the attentional and cognitive deficits observed in schizophrenic patients. This NVH lesion model of schizophrenia is also able to mimic the exacerbation of cognitive deficits seen in psychotic patients after PCP, but not amphetamine, challenge.

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