

Prefrontal Lesion Reverses Abnormal Mesoaccumbens Response in an Animal Model of Schizophrenia

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Background: A neonatal hippocampal lesion induces postpubertal behavioral alterations resembling phenomena observed in schizophrenia. We have recently reported that nucleus accumbens neurons exhibit altered response to ventral tegmental area activation, but only when animals with this lesion reach adulthood. Because a prefrontal cortical lesion eliminates postpubertal abnormal behaviors in these animals, we investigated whether altered accumbens responses were reversed with this manipulation.

Methods: In vivo intracellular recordings were conducted in accumbens neurons in rats that had received neonatal hippocampal lesions combined with either adult prefrontal cortical lesion or sham treatment. Accumbens response to mesolimbic pathway activation was recorded in these animals.

Results: Accumbens neurons from animals with a neonatal hippocampal lesion and an adult prefrontal sham operation still showed altered accumbens response to mesolimbic stimulation. On the other hand, most animals with combined neonatal hippocampal and adult prefrontal lesions exhibited responses similar to those of naïve animals.

Conclusions: This result suggests that abnormal behaviors in these animals might be related to excessive prefrontal drive of accumbens neurons upon dopamine activation.

Key Words: Nucleus accumbens, prefrontal cortex, hippocampus, dopamine, schizophrenia, animal model

Animals with a neonatal ventral hippocampal (VH) lesion exhibit postpubertal behavioral abnormalities, such as exaggerated reactivity to stress, dopamine (DA) agonists (Lipska et al 1993), and *N*-methyl-D-aspartate (NMDA) antagonists (Al-Amin et al 2000). Other behavioral effects include cognitive deficits in working memory (Lipska et al 2002), latent inhibition (Grecksch et al 1999), and social interactions (Becker et al 1999). Neurochemical, anatomic, and molecular alterations in the mesocorticolimbic system have also been reported in these animals (Flores et al 1996; Lillrank et al 1999; Lipska and Weinberger 2000; Lipska et al, unpublished data). Because these deficits resemble phenomena observed in schizophrenia patients, this procedure has been proposed as an animal model of this disorder (Lipska and Weinberger 2000). It is conceivable that there are similar mesocorticolimbic alterations in animals with a neonatal VH lesion and in brains of schizophrenia patients.

The nucleus accumbens (NAcc) is a brain region that might link an abnormal VH with altered mesolimbic function. The NAcc receives dense synaptic inputs from the VH (Kelley and Domesick 1982) and DA projections from the ventral tegmental area (VTA) (Chang and Kitai 1985). In a previous study, we have shown that spontaneous membrane potential fluctuations that depend on VH inputs (Goto and O'Donnell 2001b; O'Donnell and Grace 1995) were not changed in neonatally VH-lesioned rats (Goto and O'Donnell 2002); however, responses of NAcc neurons to VTA stimulation were altered in young adult, but not prepubertal, animals. Instead of the depolarization with reduced firing typical of naïve (Goto and O'Donnell 2001a) and sham animals, animals with a neonatal VH lesion exhibited a dramatic increase in firing after VTA stimulation, which was reversed with subchronic antipsychotic treatment (Goto and O'Donnell 2002).

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Because subchronic antipsychotic treatment has also been shown to normalize DA-related behavioral alterations in these animals (Lipska and Weinberger 1994), it is possible that abnormal behaviors are linked to an improper activation of NAcc neurons after DA cell burst firing.

We have also shown that responses of prefrontal cortical (PFC) neurons to VTA stimulation were changed in adult animals with a neonatal VH lesion. Prefrontal cortical pyramidal neurons also exhibited an increase in action potential firing after VTA stimulation in these animals (O'Donnell et al 2002). Thus, it is possible that an abnormal PFC activation in response to VTA stimulation results in increased glutamatergic drive of NAcc neurons and that the enhanced NAcc firing is secondary to an abnormal PFC response. A critical role of the PFC in this model had been suggested by the reversal of behavioral deficits with an adult PFC lesion (Lipska et al 1998). If behavioral deficits in these animals are a consequence of their abnormal VTA-PFC-NAcc activation, then a PFC lesion should prevent altered NAcc neural responses. In this study, we examined this possibility with in vivo intracellular recordings from NAcc neurons in animals that received combined neonatal VH and adult PFC lesions.

Methods and Materials

Surgery

Pregnant Sprague-Dawley rats were obtained from Taconic Farms, (Germantown, NY), and surgery was conducted in 35 male pups at postnatal day (PD) 6–8. All experimental procedures were carried out according to the U.S. Public Health Service *Guide for the Care and Use of Laboratory Animals* and approved by the Albany Medical College Institutional Animal Care and Use Committee.

For neonatal VH lesions, pups were anesthetized with hypothermia by being placed in ice for 10–15 min before being mounted on a stereotaxic apparatus. After incisions were made in the skin, bilateral VH lesions were performed by administration of .3 μ L of ibotenic acid (10 μ g/ μ L in 0.1 mol/L phosphate-buffered saline, pH 7.4) to the VH (3.0 mm caudal to bregma; \pm 3.5 mm lateral from midline; 5.0 mm ventral from skull) at a speed of .15 μ L/min. The needle was kept in place for 3 additional min. Then, the incision was closed with clips and the

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pups were warmed up with heating pads ($\sim 37^{\circ}\text{C}$) until body temperature was completely recovered.

Adult PFC lesions or sham operations were performed when animals with a neonatal VH lesion reached PD 56. Animals were randomly selected for these procedures from within individual litters. Rats were anesthetized with equithesin (40 mL/kg, IP) and placed on the stereotaxic frame. Either ibotenic acid for lesion (.5 μL at a speed of .15 $\mu\text{L}/\text{min}$) or artificial cerebrospinal fluid (ACSF) for sham treatment were delivered bilaterally into the medial PFC (3.5 mm rostral to bregma; $\pm .7$ mm lateral from midline; 3.5 mm ventral from brain surface). Rats were allowed at least 2 weeks for recovery before recordings were conducted.

Electrophysiology

The animals were anesthetized with chloral hydrate (400 mg/kg, IP) and placed on the stereotaxic apparatus. Intracellular electrodes made from 1 mm O.D. Omegadot borosilicate glass tubing (resistance: 31–80 M Ω) were filled with 2 mol/L potassium acetate and 2% Neurobiotin (Vector Labs, Burlingame, California). Electrodes were lowered into the NAcc (1.4–2.1 mm rostral to bregma; 1.0–2.0 mm lateral from midline; 5.8–8.4 mm ventral from brain surface) with a hydraulic manipulator while their activity was monitored. Intracellular signals were amplified, filtered at .3–3 kHz, digitized at 10 kHz, and fed to a computer for off-line analyses. Once a stable impalement was obtained, baseline recordings (>5 min) were performed. Only neurons showing at least -50 mV resting membrane potential with overshooting spikes were analyzed and included in the study. All data handling was performed with custom-made software (Neuroscope).

Concentric bipolar electrodes with .5 mm between tips were used for electrical stimulation of the VTA (5.8 mm caudal from bregma; .5 mm lateral from midline; 8.4 mm ventral from brain surface; ipsilaterally to NAcc recording). Current pulses were generated by a stimulus isolation unit, and the stimulation protocol was controlled by the computer and current pulse generator. Ventral tegmental area stimulation was performed by the delivery of sets of five .5-msec, 1.0-mA current pulses at 20 Hz every 10 sec, to mimic DA cell burst firing.

Histology

Recording sites were marked with Neurobiotin ejected from intracellular electrodes by passing positive current. Animals were given a lethal dose of pentobarbital (100 mg/kg) and transcardially perfused with ice-cold saline followed by 4% paraformaldehyde. Brains were removed from the skull, cryoprotected in 30% sucrose, and sectioned with a freezing microtome. Serial 50- μm -thick sections were cut coronally. Neurobiotin-injected sections were further processed with an avidin–biotin reaction. The sections for locations of VTA stimulation, and neonatal VH and adult PFC lesions were stained with neutral red. All sites and lesions were identified according to the atlas of Paxinos and Watson (1998).

Results

Bilateral damage of the VH and PFC was observed in rats that received ibotenic acid injections into the VH at PD 6–8 and into the PFC at PD 56 (Figure 1). Ventral hippocampal lesions varied from structural disorganization to extensive cell loss and included the ventral part of the dentate gyrus, CA3, and CA1. There was no correlation between VH lesion size and electrophysiological changes; therefore, the data from all lesioned animals were pooled. Prefrontal cortex lesions encompassed prelimbic

and infralimbic cortices, and they extended in some cases to the anterior cingulate region. Sham-treated animals did not exhibit morphological changes in the PFC.

In vivo intracellular recordings were obtained from 17 rats with combined neonatal VH + PFC lesions (referred to as "LESION" in the following text), and 12 rats with combined neonatal VH lesion + PFC sham operation (referred to as "SHAM" in the following text) at PD 56 or older. Six other rats had been eliminated from the study because of misplacement of either PFC or VH lesion. Out of 52 NAcc neurons, 36 (69%) exhibited spontaneous transitions from resting membrane potential (DOWN state) to a sustained depolarized (UP) state in LESION animals (Figure 2A; DOWN: -79.6 ± 4.2 mV; UP: -68.1 ± 6.5 mV; frequency of UP transitions: $.67 \pm .26$ Hz; mean \pm SD). A similar percentage of NAcc cells ($n = 17/23$; 74%) showed membrane potential fluctuations in the SHAM group (Figure 2B; DOWN: -80.4 ± 4.2 mV; UP: -67.3 ± 7.1 mV; frequency of UP transitions: $.64 \pm .20$ Hz). Histograms of these membrane potential fluctuation distributions were fitted to dual Gaussian functions (Figure 2), indicating a bimodal membrane potential. The proportion of neurons showing membrane fluctuations was not different between groups (χ^2 test: $p > .05$). DOWN and UP membrane potentials and frequency of UP transitions were also similar in LESION and SHAM animals (unpaired t test: $p > .05$). Furthermore, UP state duration was also similar in both groups (387 ± 283 msec in LESION animals; 384 ± 229 msec in SHAM animals), and the coefficient of variation of intervals between UP events was not significantly different between groups (LESION: $.38 \pm .15$; SHAM: $.33 \pm .27$). The latter measure reflects regularity in UP states and is higher in animals with a neonatal VH lesion compared with sham and naïve animals (Goto and O'Donnell 2002). Thus, spontaneous NAcc activity in this abnormal set of animals might not be affected by a PFC lesion.

Ventral tegmental area stimulation with trains of pulses mimicking DA cell burst firing evoked membrane depolarizations in NAcc neurons in both LESION ($n = 27$) and SHAM ($n = 11$) animals (Figure 3). There were no statistically significant differences in peak amplitude (Figure 3A; 10.2 ± 5.8 mV in LESION; 11.3 ± 3.5 mV in SHAM; unpaired t test: $p > .05$) or duration measured as decay to half of peak amplitude (Figure 3B; 615 ± 333 msec in LESION; 468 ± 134 msec in SHAM; unpaired t test: $p > .05$) of responses. A striking difference, however, was observed in action potential firing during these evoked depolarizations (Figure 3C). As we have previously demonstrated in animals with a neonatal VH lesion (Goto and O'Donnell 2002), most PFC SHAM animals exhibited spike firing during the VTA-evoked depolarizations (Figure 3D; $n = 7/11$; 64%). On the other hand, only 7% ($n = 2/27$) of NAcc neurons recorded exhibited action potential firing during the VTA-evoked depolarizations in LESION animals (Figure 3E). These proportions were significantly different between groups (Fisher exact test: $p = .0007$). This absence of firing is similar to what was observed in naïve animals (Goto and O'Donnell 2001a), which suggests that an intact PFC is necessary for the abnormal NAcc response to VTA stimulation in the neonatally VH lesioned rats.

Discussion

A neonatal VH lesion alters mesocorticolimbic responses to activation of DA projections in adult, but not prepubertal, animals (Goto and O'Donnell 2002; O'Donnell et al 2002). In naïve animals, VTA stimulation has been shown to induce membrane depolarization in NAcc neurons while reducing ac-

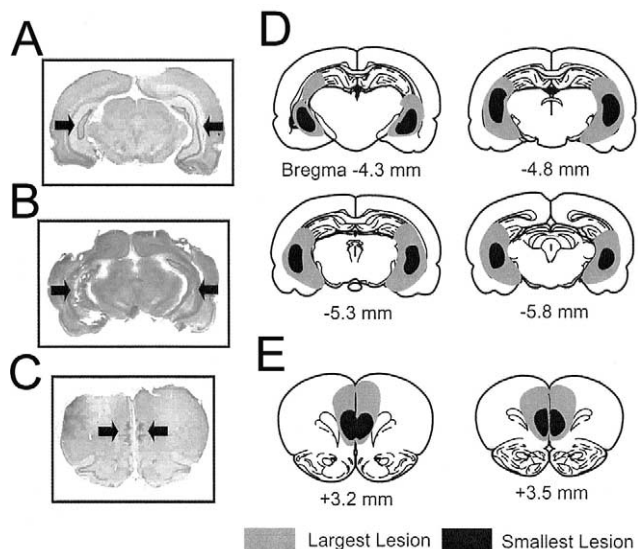


Figure 1. Histology of ventral hippocampal (VH) and prefrontal cortex (PFC) lesions. (A) A small neonatal VH lesion inducing hippocampal structural disorganization. (B) Example of a large lesion, with cell loss and hippocampal shrinkage. (C) Adult PFC lesion including infralimbic and prelimbic areas. The section was taken from the same animal shown in A. (D) Schematic diagrams showing largest (gray) and smallest (black) neonatal VH lesions at four different rostrocaudal levels. (E) Similar diagrams showing largest and smallest adult PFC lesions.

tion potential firing (Goto and O'Donnell 2001a). In adult animals with a neonatal VH lesion, however, the VTA-evoked depolarization was accompanied by an increase in spike firing (Goto and O'Donnell 2002). A PFC lesion in adult animals that had received a neonatal VH lesion significantly reduced the

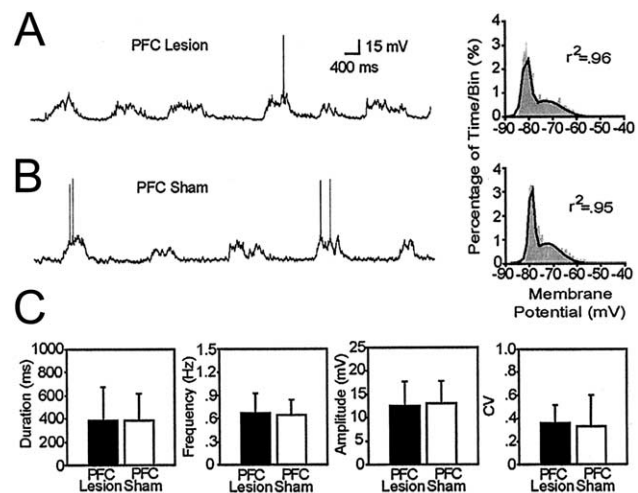


Figure 2. Electrophysiologic recordings in nucleus accumbens (NAcc) neurons from rats with combined neonatal ventral hippocampal lesion and prefrontal cortex (PFC) lesion or sham treatment. (A, B) Representative tracings of spontaneous NAcc neuron activity recorded from a PFC-lesioned (A) and a sham-treated (B) rat, showing typical spontaneous membrane potential fluctuations. (C) Bar graphs summarizing duration, frequency, and amplitude of UP events, as well as variability of intervals between these events for NAcc neurons in PFC lesioned and sham animals. Membrane potential histograms at right reveal a bimodal distribution. The dark lines are the dual Gaussian functions that best fit to the histograms.

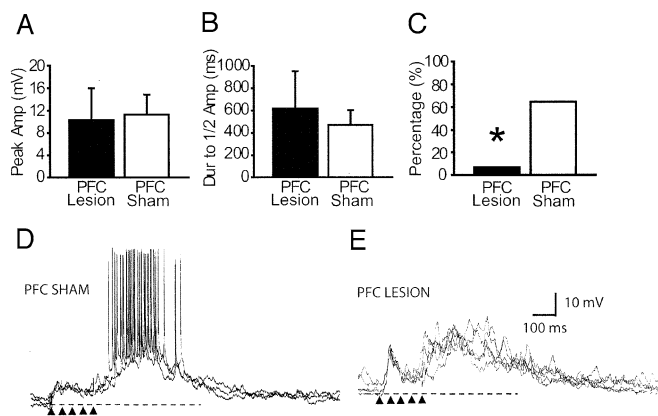


Figure 3. Nucleus accumbens responses to ventral tegmental area (VTA) stimulation with trains of pulses. (A, B) Bar graphs comparing decay time to half of peak response and peak amplitude between prefrontal cortex (PFC) lesion and sham groups. No difference could be observed. (C) Bar graph comparing proportion of neurons exhibiting action potential firing in response to VTA stimulation. * $p = .0007$ (Fisher exact test). (D, E) Overlays of responses in sham-treated (D) and PFC-lesioned (E) rats. In the neonatally VH-lesioned animal combined with PFC lesion, high frequency firing could not be observed during the VTA-evoked depolarization.

proportion of NAcc neurons exhibiting action potential firing during the VTA-evoked depolarization.

We have recently shown that PFC pyramidal neurons exhibit abnormal responses to VTA stimulation in animals with a neonatal VH lesion. As in NAcc neurons, PFC neurons exhibited increased action potential firing in lesioned animals (O'Donnell et al 2002), whereas sham-treated and prepubertal VH-lesioned animals yielded VTA-evoked depolarizations with decreased spike firing. Because PFC neurons project to the NAcc (Berendse et al 1992), it is possible that abnormally high firing in PFC pyramidal neurons results in excessive glutamate release in the NAcc and, consequently, in an increased cell firing in this region when both the PFC and NAcc receive the phasic DA signal associated with DA cell burst firing. Thus, the abnormal NAcc response could be secondary to a PFC alteration (Figure 4).

A number of mechanisms could explain an abnormal PFC response to VTA stimulation in animals with a neonatal VH lesion. Altered dendritic spine density has been found in PFC and NAcc neurons in rats with a neonatal VH lesion (Lipska et al, unpublished data). This might reflect the reorganization of excitatory synaptic afferents to these regions after elimination of VH inputs. Changes in alpha-amino-3-hydroxy-5-methylisoxazole propionate (AMPA) receptor subunits have been reported in the PFC, but not in the NAcc of animals with a neonatal VH lesion (Stine et al 2001). Because GluR3 flop receptors are associated with rapid desensitization (Karkianias and Papke 1999), the decrease of their mRNA levels observed in the PFC could be associated with increased PFC neuronal excitability; therefore, this could be related to the increased spike firing observed in our study. Another possible change in the PFC of neonatal VH-lesioned animals might be a decrease in gamma-aminobutyric acid (GABA) interneuronal activity. A reduction in GAD67 mRNA has been observed in these animals (Lipska and Weinberger 2000). Gamma-aminobutyric acid interneurons exhibit DA receptors (Khan et al 2001) and are innervated by DA terminals (Sesack et al 1995). Thus, it is possible that the decrease in PFC cell firing evoked by VTA stimulation in naïve animals is related to an activation of local inhibitory circuits. If these

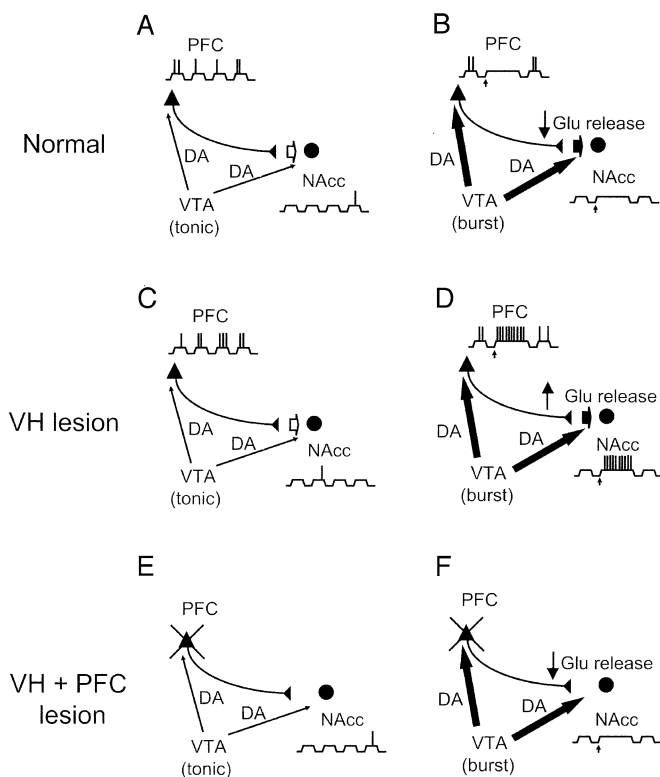


Figure 4. Schematic diagram illustrating the proposed mesocortical and mesolimbic alterations induced by a neonatal ventral hippocampal (VH) lesion. **(A, B)** In normal animals, tonic dopamine (DA) release might contribute to the oscillatory nature of membrane potential activity in prefrontal cortex (PFC) and nucleus accumbens (NAcc) neurons. With burst firing of DA cells, a sustained membrane potential depolarization with decreased spike firing is evoked in the PFC and NAcc. Decreased firing in PFC neurons resulted in reduction of glutamate (Glu) release in the NAcc. **(C, D)** In animals with a neonatal VH lesion, tonic DA release does not affect membrane potential activity in PFC and NAcc neurons differently from naïve rats; however, DA cell burst firing results in high frequency action potential firing during a sustained membrane potential depolarization in PFC neurons. This yields an increased Glu release in the NAcc that causes increased firing in NAcc neurons during ventral tegmental area (VTA)-evoked depolarization. **(E, F)** Increased Glu release in the NAcc evoked by VTA burst firing was blocked by a PFC lesion. The filtering mechanism by combined membrane depolarization and decreased spike firing was restored in these animals.

interneurons are reduced in number or their activation is impaired, the VTA-evoked depolarization might result in increased action potential firing. Indeed, postmortem studies have repeatedly reported a decrease in specific subpopulations of PFC GABA neurons (Beasley and Reynolds 1997; Pierri et al 1999) and reduced level of GAD67 mRNA (Volk et al 2000) in schizophrenia patients. A third possibility to consider is a change in DA D_1 receptors in the PFC resulting in an endogenous sensitization to DA (Laruelle 2000). A recent imaging study indicates increased D_1 receptor binding in the PFC in schizophrenia patients (Abi-Dargham et al 2002). This might induce alterations of DA-dependent synaptic plasticity (Gurden et al 1999, 2000) through synergism with NMDA receptors (Wang and O'Donnell 2001), altering excitability of PFC neurons to synaptic inputs. In normal conditions, VH inputs to the NAcc can gate PFC inputs (O'Donnell and Grace 1995), and VTA burst stimulation can sustain UP states while reducing the probability of firing. In

animals growing with an abnormal VH, the hippocampal gating in the NAcc is likely to be disrupted, and a different set of afferents might drive NAcc UP states (Goto and O'Donnell 2002). Also, burst VTA stimulation elicits a plateau depolarization in both the PFC and NAcc in these animals, but with enhanced action potential firing in both areas. Our results here indicate that the increased firing in the NAcc is dependent on the increased firing in the PFC. The cellular mechanisms responsible for enhanced action potential firing in the PFC remain to be determined. An enhanced PFC firing is not, at first sight, consistent with the idea of hypofrontality in schizophrenia; however, there is mounting evidence from brain imaging studies suggesting that the dysfunctional PFC typically described as "hypofrontality" might actually arise from an overly active PFC (Callicott et al 2000; Manoach 2003). Thus, our model (primarily relevant to positive symptoms) might also apply to negative symptoms.

The possible mechanisms discussed above are not mutually exclusive. In fact, given the influence that the PFC has on VTA burst firing (Au-Young et al 1999), it is likely that an increased PFC neuronal excitability results in enhanced VTA DA cell firing that, in turn, sustains PFC activity. Ventral tegmental area projections to the PFC can sustain persistent depolarizations along with reduced firing in naïve animals (Lewis and O'Donnell, 2000); activating this projection in animals with a neonatal VH lesion causes enhanced PFC cell firing (O'Donnell et al 2002) that can in turn further excite VTA neurons. The resulting vicious circle of activation (Laruelle 2000) could trickle down to structures targeted by both the VTA and PFC, such as the NAcc, resulting in abnormal activation and loss of the normal filtering of irrelevant information that VTA activation exerts. In our experiments, a PFC lesion would block this altered corticostriatal activity, which has been suggested for positive symptoms in schizophrenia (Carlsson and Carlsson 1990; Robbins 1990), thereby restoring some functionality to the system. This procedure would be the equivalent in this animal model to the prefrontal lobotomy performed in schizophrenia patients before the advent of antipsychotic drugs (Moniz 1937). The findings also link hippocampal pathology with PFC dysfunction and abnormal DA responses, all important components of schizophrenia pathophysiology.

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