cal reorganization following any nerve injury that results in degeneration. With subsequent regeneration, inputs progressively reestablish cortical representations and replace inputs that appear after nerve injury. When regeneration follows nerve crush, representations of reinnervated skin areas become sequentially reestablished, and normal features of cortical topography, including preinjury skin-to-cortex correspondences, can be recovered. In contrast, cortical topography is aberrant after nerve transection, repair, and regeneration primarily because many cortical neurons have multiple receptive fields or fields out of topographic sequence (2). Peripheral regeneration thus reestablishes cortical activation from deafferented skin regions after both crush and transection injuries, but the likelihood of replicating preinjury topography is quite different for these injuries. Presumably this difference largely reflects the extent to which normal peripheral innervation patterns are reestablished after regeneration. In view of the good sensory restoration which usually follows nerve crush injuries (*1*), it seems reasonable to conclude that sensory recovery is more readily ensured when preinjury skin to cortex correspondences are reestablished. Recovery of preinjury state may not, however, be the only means of restoring sensory function since sensory impairments after regeneration can be significantly rectified by sensory therapy (*8*). Recovery may be promoted by sensory experience even when regeneration creates abnormal skin to cortex correspondences.

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3. Skin areas innervated by the median nerve have been defined from peripheral nerve recording studies and from cortical mapping studies following median nerve transection and ligation.
4. Mapping methods have been previously described (*5, 6*). Briefly, electrodes angled perpendicular to the cortical surface were lowered to the middle layers and receptive fields were defined from multiple unit responses to light tactile stimuli in monkeys anesthetized with ketamine hydrochloride (25 to 50 mg/kg, injected intramuscularly). Penetrations were closely spaced across the entire hand representation and adjacent cortex. Since there is no central sulcus in owl monkeys, the hand representation is located over a flat, accessible region of cortex (Fig. 1A). Recording sites were marked on an enlarged photograph of the brain surface, and receptive fields were drawn on hand illustrations. Map borders were established midway between adjacent penetrations with receptive fields on different hand parts. If the receptive field straddled more than one hand part, the border distinguishing the involved representations was placed at the penetration location.
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7. After mapping in another experiment with a short regeneration period, the innervation field of the partially regenerated median nerve was defined with nerve recordings. The extent of reinnervation estimated by nerve recording closely corresponded to the extent of reinnervation estimated from the cortical map. This suggests that cortical reactivation closely follows peripheral reinnervation after crush injuries.
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Cortical Dopaminergic Involvement in Cocaine Reinforcement

Abstract. *Neuronal systems involved in the initiation of cocaine reinforcement were investigated by identifying brain sites where direct application of the drug was reinforcing. This was accomplished by allowing rats to self-administer picomolar concentrations of cocaine into discrete brain regions. The medial prefrontal cortex supported self-administration, while the nucleus accumbens and ventral tegmental area did not. Self-administration could be attenuated by including equimolar concentrations of the dopaminergic D_2-receptor antagonist sulpiride in the microinjection system. These results imply that cocaine reinforcement is mediated in part through a direct action on mesocortical dopaminergic receptors.*

Cocaine is a local anesthetic agent that is used by millions of people (*1*). Parallels between the use of cocaine by humans and self-administration of the drug by animals have recently been established (*2*). Behavioral studies have shown that cocaine is a potent reinforcing stimulus that will maintain responding on operant schedules of reinforcement (*3*). Self-administration occurs in the absence of demonstrable physiological dependence (*4*), suggesting that cocaine-seeking in humans results principally from the reinforcing properties of this drug and not from a desire to postpone the discomforts of withdrawal.

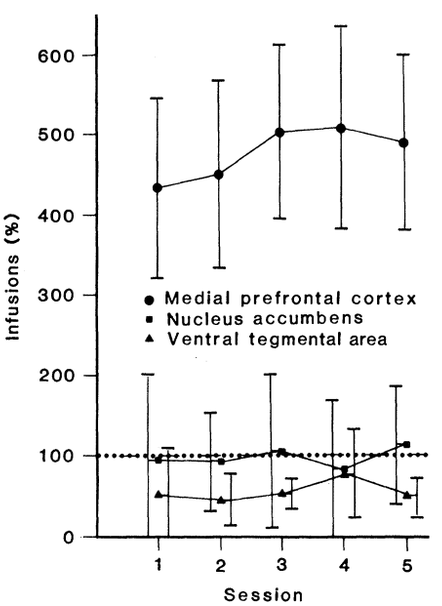

Fig. 1. Intracranial self-infusions of cocaine hydrochloride (100 pmole per microinfusion), presented as the percentage of infusions of vehicle (artificial cerebrospinal fluid), by rats with cannulas implanted into the nucleus accumbens, ventral tegmental area, or medial prefrontal cortex. Values are means ± standard deviations for five animals per group.

Even though little is known about the neuronal mechanisms mediating cocaine reinforcement, neuropharmacological investigations suggest an involvement of the biogenic amines. Cocaine inhibits reuptake of norepinephrine (*5*), dopamine (*6*), and serotonin (*7*) in vitro and increases the turnover of dopamine in rat brain (*8*). Pimozide, a dopaminergic receptor antagonist, attenuates the intravenous self-administration of cocaine by rats while the noradrenergic receptor blocker phentolamine does not (*9*), suggesting a role for dopaminergic neurons in this behavior. More recently, 6-hydroxydopamine lesions of the nucleus accumbens were shown to decrease the rate of intravenous self-administration of cocaine (*10*), further implicating mesolimbic dopaminergic neurons. We attempted to directly explore the neuronal circuitry involved in cocaine reinforcement by using an intracranial self-administration (ICSA) methodology. We report that the application of cocaine into the medial prefrontal cortex results in the initiation of reinforcing neuronal activity.

Experimentally naïve male Fischer 344 rats 90 to 150 days old were stereotaxically implanted unilaterally with 22-gauge guide cannulas into the nucleus accumbens, ventral tegmental area, or

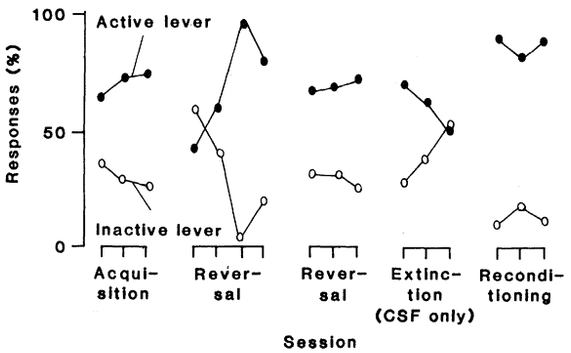

Fig. 2. Percent responding for intracranial microinjections of cocaine hydrochloride into the medial prefrontal cortex in a two-lever choice procedure. Responding rapidly increased on the active lever. When the active and inactive levers were reversed, the rat switched to the new active manipulandum. Extinction resulted in a loss of this preference and reconditioning in a rapid return to appropriate responding. Similar results were obtained with two other animals, the only difference being the length of time necessary to meet the criterion (> 75 percent responding on the active lever) for the first reversal; *CSF*, cerebrospinal fluid.

medial prefrontal cortex (*11*). The animals were housed individually in cages on a reversed 12-hour light-dark cycle and given free access to food and water. Intracranial microinjections were delivered by an adaptation of the electrolytic microinjection transducer system (*12*), which was mounted directly on the animal's head. Microinfusions were produced by passing a direct current (200 μA) between a silver anode and a platinum cathode contained in an airtight drug reservoir. The resulting evolution of hydrogen gas forced a reproducible volume of the drug solution out through a 28-gauge injection cannula (*13*). A small quiescent current (6 μA) prevented the redissolution of hydrogen evolved during previous infusions. A flexible lead connected the microinjection system to a counterbalanced mercury commutator, allowing unrestrained movement of the animal during testing. Depression of a lever on one wall of the experimental chamber resulted in a 5-second microinjection of 100 nl of cocaine hydrochloride. A red stimulus light directly above the lever signaled the availability of reinforcement. After successful completion of the response requirement, the light was extinguished, the drug was delivered, and a tone was presented for 30 seconds.

The animals were tested for self-administration every third day for 8 hours. Concentrations of 0 to 5000 pmole of the drug dissolved in artificial cerebrospinal fluid were tested in the three brain regions. A two-lever discrimination procedure was used to demonstrate that self-administration resulted from the reinforcing properties of cocaine and not from a nonspecific increase in motor activity. For these lever-reversal experiments, an identical but "inactive" lever was installed on the opposite wall of the chamber, with responses being recorded but having no scheduled consequences. When responding stabilized, active contingencies were alternated between the right and left sides of the chamber. Since cocaine blocks the initiation and conduction of nerve impulses (*14*), it might be argued that cocaine ICSA results from a nonspecific neuronal block mediating its reinforcing properties. Therefore, to determine the nature of these reinforcing properties, sulpiride, a dopaminergic D_2-receptor blocker (*15*), was mixed in equimolar concentrations with cocaine in the microinjection system.

While microinjections of cocaine into the nucleus accumbens or ventral tegmental area did not maintain responding at any concentration tested, microinfusions into the medial prefrontal cortex resulted in a rapid acquisition of lever-pressing (Fig. 1). Responding was dose-dependent and was maintained on fixed-ratio schedules of reinforcement (*16*). In the lever-reversal experiments the animals quickly discriminated between the active and inactive levers and maintained this discrimination when the active contingency was alternated between the two levers (Fig. 2). The addition of sulpiride to the cocaine solution markedly decreased self-administration without affecting operant rates of responding (Fig. 3).

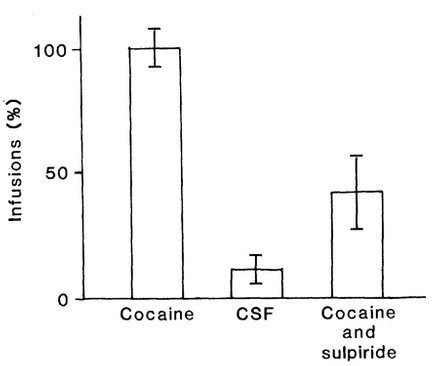

Fig. 3. Effects of sulpiride on the intracranial self-administration of cocaine into the medial prefrontal cortex. The decrease in ICSA is not likely to result from a nonspecific behavioral depressant action of sulpiride since the drug did not affect baseline responding. Values are means ± standard deviations for double determinations in three animals; *CSF*, cerebrospinal fluid.

Microinfusion of cocaine into the medial prefrontal cortex is a positively reinforcing stimulus that maintains responding in a dose-dependent manner. This conclusion is supported by the rapid acquisition of the lever-pressing response for infusions of 50 to 100 pmole of the drug, the regular spacing of infusions, the maintenance of responding on intermittent schedules of reinforcement, and the ability of the animals to discriminate between active and inactive response levers. Since responding occurred primarily on the active manipulandum during several reversals, the self-administration did not result from a generalized nonspecific behavioral stimulant action of the drug. The reinforcing properties of cocaine are probably mediated by subpopulations of neurotransmitter receptors rather than through a nonspecific neuronal block, since self-administration of the drug into the medial prefrontal cortex was attenuated by a specific dopaminergic receptor antagonist. These receptors may be excitatory or inhibitory to cocaine reinforcement. Increasing or decreasing the concentration of cocaine can decrease the rate of responding maintained by cocaine injections in rodents and primates (*17*). Therefore, the administration of sulpiride could shift the dose-response curve for ICSA to the left or right, making the microinfusion of cocaine more or less reinforcing. While these results are in general agreement with the dopamine theory of stimulant reinforcement (*18*), they do not exclude the possibility that other neurotransmitters are also involved, since a number of putative neurotransmitters have been identified in the prefrontal cortex (*19*).

Amphetamine has been self-administered into the nucleus accumbens of rats (*20*) and the orbitofrontal cortex of rhesus monkeys (*21*). This does not, however, contradict our findings. Amphetamine and cocaine may differ neuropharmacologically, since amphetamine inhibits catecholamine reuptake, releases newly synthesized catecholamines, and is a partial catecholamine receptor agonist (*22*), while cocaine has been reported to inhibit only catecholamine reuptake (*5–7*). Furthermore, the behavioral histories of the subjects may be important, since in both investigations of amphetamine ICSA (*20, 21*), the animals used were initially trained to press levers on schedules of intracranial electrical self-stimulation. We have attempted to engender responding with a similar method. Two rats with guide cannulas im-

planted in the nucleus accumbens were trained to press levers on a fixed-ratio schedule of food reinforcement (20 presses per food presentation) and then were tested for cocaine ICSA. Initially, moderate rates of responding were demonstrated, but after three experimental sessions the behavior underwent extinction. Behavioral history and the period of testing are important variables that must be considered in investigations with ICSA methodologies.

The cell bodies of origin for the neurons that constitute the mesolimbic dopaminergic system are located primarily in the ventral tegmental area. Some of these neurons terminate in the nucleus accumbens, while others pass through this structure to innervate the olfactory tubercle and prefrontal cortex (*23*). Lesions of the nucleus accumbens made with 6-hydroxydopamine decrease the rate of systemic cocaine self-injection (*10*). Similar lesions of the ventral tegmental area also disrupt the intravenous self-administration of cocaine, but the degree of attenuation is not correlated with the extent of dopamine depletion in the nucleus accumbens (*24*), suggesting that these lesions also destroy dopaminergic fibers that pass near the structure but terminate in other brain regions, such as the prefrontal cortex. This study implicates the dopaminergic innervations of the medial prefrontal cortex but not the nucleus accumbens or ventral tegmental area in the initiation of cocaine reinforcement processes.

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Cocaine-Induced Rotation: Sex-Dependent Differences Between Left- and Right-Sided Rats

Abstract. *Cocaine elicited dose-related rotation (circling) in naïve rats. The maximum effect was greater than observed previously with other drugs. Overall, females were more sensitive to cocaine than males. However, right-biased females were more sensitive than left-biased females, whereas left-biased males were more sensitive than right-biased males. The results suggest that sex-dependent differences in brain asymmetry may be an important determinant of cocaine sensitivity.*

Research conducted in several laboratories has established that normal rats have functional (*1*), neurochemical (*2*), and anatomical (*3*) asymmetries in several brain regions. An asymmetry in nigrostriatal function—characterized by hemispheric differences in striatal dopamine content (*4*), metabolism (*5*), and receptor activity (*5*)—has been related to spontaneous side preferences (*4*) and nocturnal (*6*) and drug-induced (*7*) circling behavior (rotation). Sex differences in the nigrostriatal asymmetry and differences between left- and right-sided rats have been suggested by the findings, respectively, (i) that female rats rotate more than male rats at night (*8*) and in response to *d*-amphetamine (*9*), and (ii) that right-sided female rats have greater side preferences than left-sided female rats (*10*). We now report sex-dependent differences between left- and right-sided rats in rotation induced by cocaine. The differences, substantially greater than observed previously with other drugs (*11*), suggest that brain asymmetry may be a major determinant of cocaine sensitivity.

Table 1. Cocaine-induced rotation (mean ± standard error per hour) in naïve rats. Two-way analysis of variance showed a significant effect of dose ($P < 0.01$), a significant difference between sexes ($P < 0.05$), and a nonsignificant interaction ($P > 0.1$).

Dose (mg/kg)	Female		Male	
	N	Net rotations	*N*	Net rotations
0*	8	3.1 ± 1.4	8	1.8 ± 1.0
5.0	6	4.2 ± 1.1	6	2.0 ± 1.4
10.0	6	12.8 ± 3.6	6	2.3 ± 1.0
20.0	27	135.9 ± 14.9	32	92.9 ± 16.3
40.0	8	129.0 ± 23.5	6	87.7 ± 21.4

*Saline

Naïve male and female Sprague-Dawley rats, approximately 90 days old, were individually tested for drug-induced rotation in the middle of their light cycle. Each rat was injected intraperitoneally with a drug or saline (0.1 ml per 100 g of body weight), harnessed by a flexible wire tightened around its abdomen, and placed in a cylindrical Plexiglas rotometer (*6*) for 1 hour. The wire harness was connected to a shaft which activated