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

Table 2. Differences in rotation (mean ± standard error) induced by cocaine (20.0 mg/kg) and *d*-amphetamine (1.0 mg/kg) in left- and right-sided rats. "Preference" indexes each rat's directional preference independently of variations in the total number of rotations; it is calculated by multiplying rotation in the preferred direction by 100 and dividing by total rotations. In the cocaine experiments, both males and females showed significant differences (*t* tests, $P < 0.01$) between left- and right-sided rats on both net rotations and preference.

Group	Cocaine			Amphetamine		
	N	Net rotations	Preference (%)	*N*	Net rotations	Preference (%)
Female						
Left	13	89.1 ± 15.8	79.3 ± 4.7	19	53.6 ± 9.7	85.2 ± 3.8
Right	14	179.4 ± 18.1	96.3 ± 2.1	19	59.4 ± 8.1	90.1 ± 3.6
Male						
Left	19	126.6 ± 18.9	92.8 ± 2.3	15	32.0 ± 6.3	88.6 ± 3.1
Right	13	43.7 ± 11.1	77.7 ± 4.5	15	27.3 ± 6.5	84.4 ± 3.9

a photoelectric position sensing device that differentiated between incomplete and full (360°) rotations (*12*). Left and right full rotations were separately totaled, and the net rotational difference (that is, rotations in the dominant direction minus rotations in the opposite direction) was determined for each rat.

Cocaine elicited rotation in both sexes (Table 1). Maximal effects were produced by doses of 20.0 mg/kg, although females were more sensitive than males across all doses. Further scrutiny of the data revealed that right-biased females rotated more than left-biased females and that left-biased males rotated more than right-biased males (Table 2). Differences in preference indicate that the sidedness effects are not simply due to different levels of motor output.

The effects of cocaine were consistent from one week to the next: 16 male and 16 female rats tested with 20.0 mg/kg were retested a week later, and, in all instances, the direction of rotation was the same in both tests; the effects from week to week were also quantitatively correlated with each other (female: net rotation, $r = 0.69$, $P < 0.01$; percent preference, $r = 0.91$, $P < 0.001$; males: $r = 0.64$ and 0.67, $P < 0.01$).

Amphetamine-induced rotation has been studied in several laboratories (*7, 9*); as with cocaine, female rats are more sensitive to amphetamine than male rats are (*9*). Large differences between the responses of left- and right-biased rats to *d*-amphetamine have not been observed, however. Relative to cocaine, such differences with *d*-amphetamine (1.0 mg/kg) are small, comparable to those reportedly occurring when rats are tested without any drug at night (*10*). Comparison of the effects of cocaine and *d*-amphetamine was more directly explored by testing rats one week with one drug and the next week with the other drug. Eight male and eight female rats received cocaine hydrochloride (20.0 mg/kg) first and another eight male and eight female rats received *d*-amphetamine sulfate (1.0 mg/kg) first. In all instances, the direction of rotation was the same under both drugs, but the quantitative effects of the two drugs were not significantly correlated with each other (net rotation and preference—females: $r = 0.30$ and 0.09, $P > 0.1$; males: $r = 0.27$ and 0.21, $P > 0.1$).

Cocaine is a potent inhibitor of dopamine reuptake in the striatum (*13*). This action is responsible for the efficacy of cocaine in inducing rotation in rats with unilateral lesions of the substantia nigra (*14*). It appears likely that the same mechanism is involved in the rotation of naïve rats, although cocaine also inhibits reuptake of norepinephrine and serotonin (*15*) and these actions may contribute to the final effect (*16*). Cocaine is a local anesthetic, and behavioral effects of other local anesthetics have been reported (*17*). Lidocaine was tested according to procedures used with cocaine and amphetamine and found to be inactive in doses ranging from 5.0 to 80.0 mg/kg (*18*). As lidocaine is approximately equipotent with cocaine as a local anesthetic but is inactive as an inhibitor of monoamine uptake (*19*), the possibility seems remote that the local anesthetic action of cocaine is in any way related to its effects on rotational behavior.

A variety of drugs, including other stimulants, dopamine agonists, opiates and hallucinogens, have been tested in this laboratory (*11*) for their effects on rotation in female rats. The maximum effect of cocaine on mean net rotations in female rats was at least 30 percent greater than observed previously with any other drug. Indeed, three right-biased rats made more than 400 net rotations per hour, an amount of responding that is larger than that frequently observed after administration of various drugs to animals with unilateral nigrostriatal lesions (*20*).

This extreme efficacy of cocaine, along with the differences between left- and right-sided rats, suggests that cocaine is affecting a fundamental mechanism that regulates brain asymmetry. This mechanism may have to do specifically with the importance of dopamine reuptake for the regulation of dopamine neuron activity and hence striatal dopaminergic asymmetry, or more generally with the importance of monoamine uptake in multiple brain regions and neurotransmitter pathways. Of interest in this regard are reports of sex differences in anatomical asymmetries in the cortex (*21*) and the hippocampus (*22*). In both structures, the left sides are thicker than the right sides in females and the right sides are thicker than the left sides in males. Because both the cortex (*23*) and the hippocampus (*24*) modulate the intensity of rotation, the uniqueness of cocaine's effects on rotation may be attributable to actions (*16*) in structures other than striatum.

Cocaine is a much used and abused drug. Our finding that sensitivity to cocaine can be largely determined by an interaction between sex and sidedness may have potentially important implications for understanding interindividual differences in susceptibility to cocaine addiction. Further studies should reveal the extent to which such generalizations can be made.

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Adaptive Changes of the Vestibulo-Ocular Reflex in Flatfish Are Achieved by Reorganization of Central Nervous Pathways

Abstract. *Flatfish provide a natural model for the study of adaptive changes in the vestibulo-ocular reflex system. During metamorphosis their vestibular and oculomotor coordinate systems undergo a 90° relative displacement. As a result, during swimming movements different types of compensatory eye movements are produced before and after metamorphosis by the same vestibular stimulation. Intracellular staining of central nervous connections in the flatfish with horseradish peroxidase revealed that in postmetamorphic fish secondary horizontal semicircular canal neurons contact vertical eye muscle motoneuron pools on both sides of the brain via pathways that are absent in all other vertebrates studied.*

Adaptive plasticity of the vestibulo-ocular reflex has been the subject of numerous studies, but so far causal explanations of the phenomenon at a neuronal level have not been successful (*1*). In those experiments the normal vestibulo-oculomotor coordinates of a specimen were altered to induce a discrepancy between oculomotor commands and the visual feedback produced by the head movement eliciting the reflex (*2*). The flatfish species constitutes a natural experiment on adaptive changes because a 90° relative displacement of the vestibular and ocular coordinate systems takes place during metamorphosis (Fig. 1). In early larval stages, the flatfish are pelagic and their swimming movements are like those of other fish. In a later metamorphic stage, the body tilts 90° to one side as they become the bottom-adapted adult flatfish (*3*). During this period the eye which would have faced the sea bottom migrates around the dorsal aspect of the animal toward the upper pigmented side. No other aspects of the fish's symmetry change, including the labyrinths, which remain in their original positions (*4*). As a result, the lateral semicircular canals become orientated vertically, while the orientation of the optic axes remain constant with respect to the environment (Fig. 1B) (*5*). Thus the optic axes and the horizontal semicircular canals are finally arranged perpendicular to each other. Nevertheless, the flatfish has a functioning vestibulo-ocular reflex which appropriately stabilizes the animal's visual world during head movements (*6*).

The extent of changes necessary for adaptation of the vestibulo-ocular reflex can be seen in the compensatory eye movements occurring during swimming. In an upright fish, when the body moves in a horizontal plane the head rotates around a vertical axis, thereby stimulating the lateral (horizontal) semicircular canals. This stimulus causes compensatory horizontal eye movements with one eye moving backward and the other forward (*7*). Since the adult flatfish propels its body by use of the same swimming movements, the lateral semicircular canals are stimulated similarly even though the head movement now occurs in a vertical plane. The observed compensatory movements of the two eyes are now rotations approximately around the optic axes in the same direction at the same time with respect to the visual environment (Fig. 2) (*8*). Given a normal vesti-

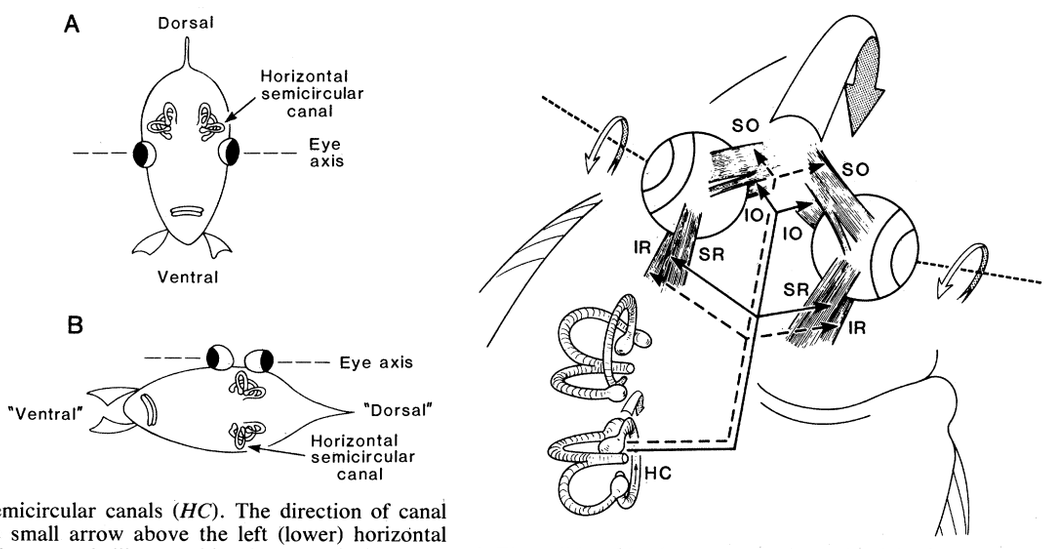

Fig. 1 (left). Spatial relationship of labyrinths and eye axes before metamorphosis (A) and in an adult flatfish (B). Fig. 2 (right). Extraocular muscle co-contractions required for the production of compensatory eye movements during a downward movement of the head. Backward rotations of the eyes (small arrows around the optic axes, which are symbolized by broken lines) would be produced by contractions of the superior rectus (*SR*) and inferior oblique (*IO*) muscles. The downward head movement (large arrow) eliciting these compensatory eye movements would activate the vertically oriented horizontal (lateral) semicircular canals (*HC*). The direction of canal displacement is shown by the small arrow above the left (lower) horizontal canal. Ampullopetal endolymph current is illustrated by the arrow inside the canal. The solid and broken arrows connecting labyrinth and eye muscles suggest the prospective excitatory and inhibitory connections required for an appropriately functioning vestibulo-ocular reflex. The horizontal canal pathways have to undergo a rearrangement leading to new extraocular motoneuron termination sites on both sides of the brain. Abbreviations: *IR*, inferior rectus; *SO*, superior oblique.