of age, hypothalamic LHRH again peaks between days 22 and 28 (*7*). In addition, pituitary LH concentration increases toward puberty (*7*). Perhaps increased hypothalamic LHRH and pituitary LH account for the return of a response to naloxone on days 22 to 26 and during the peripubertal period. On the other hand, the male's increased sensitivity to exogenous LHRH toward puberty (*7*) might explain the heightened sensitivity to naloxone at this time.

Since LH release is modulated by estrogen and since we found that estradiol benzoate selectively blocked the naloxone-induced LH surge, patterns of serum estradiol and estradiol receptor concentrations during prepubertal life might also explain the variable LH response to naloxone in the female (*8*). Alternatively, the major effect of endogenous estrogens in modulating opioid-regulated LH secretion might be through a neurotransmitter system involving dopamine (*9*). We could reasonably assume that testosterone exerts a similar modifying influence in the male.

Although a different latency for the effects of estradiol benzoate on PRL and LH cannot be excluded, the failure of estradiol benzoate to alter the naloxone-induced decrease in serum PRL (at least within 48 hours of estrogen exposure) indicates that the opioids probably exert their control over LH and PRL secretion through different mechanisms.

Although it is well known that the opioids and their antagonists alter basal levels of circulating anterior pituitary hormones, we have presented evidence that implicates the opioids in a physiologically important context: the regulation of LH secretion during development and therefore in the onset of puberty itself. Furthermore, the data indicate an interaction between two widely divergent systems in the control of LH secretion: gonadal steroids and morphinelike brain peptides.

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4. Serum LH and PRL were measured with kits supplied by NIAMDD (National Institute of Arthritis, Metabolism, and Digestive Diseases), and hormone concentrations are expressed in terms of the NIAMDD RP-1 standards. Data were analyzed by one-way analysis of variance followed by Duncan's new multiple range test [D. B. Duncan, *Biometrics* **11**, 1 (1955)].
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A Test of Some Models of Hemispheric Speech Organization in the Left- and Right-Handed

Abstract. *A new method generates specific predictions concerning the expected frequencies of aphasia after unilateral injury to the brain in the left- and right-handed. These predictions are then compared with the observed data for all known studies between 1935 and 1973 to derive the best-fitting model of hemispheric speech lateralization in the left- and right-handed.*

Clinicians have long reported a higher incidence of aphasia in the left-handed (LH) than the right-handed (RH) after unilateral injury to the adult brain (*1*). These reports, many anecdotal, have led some investigators to hypothesize an incomplete functional lateralization of speech in the majority of the LH, which results in greater sensitivity to acute brain lesions (*2–4*). At the other extreme, some investigators have dismissed reports of a higher incidence of aphasia, hypothesizing left-sided dominance for speech in the vast majority of both LH and RH adults (*5*). These two polar views are contrasted with other reports of a more variable pattern of cortical speech representation in the LH. According to one of these positions, the cortical speech mechanisms in the LH are unilateral, though variable, with the majority being dominant on the left side (*6–8*). The other position proposes a more complex pattern involving different types of cortical speech organization; some of the LH are hypothesized to have variable unilateral hemispheric speech (left- or right-sided) and some bilateral speech (*9–11*).

If the incidence of aphasia after unilateral brain injury were demonstrated to be higher in the LH, it would at least suggest the presence of a different pattern of hemispheric speech; it would provide no information, however, on the type of organization (unilateral, bilateral, or both). I now present an approach designed to address both of these issues.

Table 1 presents a review of (to my knowledge) all twelve studies (1935 to 1973) that have reported the incidence of aphasia following unilateral brain injury (left- and right-sided) in LH adults. Five of the studies also reported frequency data for RH adults. The data have been recalculated to show the frequency of aphasia separately for left- and right-sided brain injury in each study and a composite frequency (proportion) of aphasia for combined lesions in each study (final column). The incidence of aphasia after brain injury on the left and right side in the LH, ranged from a low of 0.3 (study 9) to a high of more than 0.9 (study 2). The overall mean frequency across studies was 60 percent (187 of 313). Comparative frequencies for the RH ranged from a low of 33 percent (study 8) to a high of 38 percent (study 11) with an overall mean frequency of 35 percent (714 of 2070). This frequency difference (proportions) is significant and points to an almost twofold increase in the incidence of aphasia in the LH after unilateral brain injury. Moreover, the incidence of left-handedness approximates closely the estimates of left-handedness in the general population (313 of 2383 = 13 percent).

As they stand, however, the results merely suggest that the cortical representation of speech is different among

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the LH; beyond that, they provide no additional information regarding the type of hemispheric organization (unilateral, bilateral, or both). Determining the type of organization will require a hypothetical model for each possible type of speech lateralization for which, after unilateral brain injury, the upper limit of aphasia can be quantitatively determined. The upper limit represents the maximum frequency of aphasia that could be expected under the assumption that aphasia always occurred after injury to the "dominant" speech hemisphere. In reality, however, this value would be lower because not all lesions confined to the dominant hemisphere encroach upon the speech areas. However, if the expected upper limit (EUL) is exceeded by the observed incidence of aphasia following unilateral brain injury, then that model of hemispheric speech would have to be rejected. By contrast, if the EUL value is lower, that model would have to be accepted until the best fitting model was found (*12*).

Table 2 presents an example of the model for 100 hypothetical RH persons in which the probability (rows) of left-sided speech is empirically estimated at .96 and the probability of right-sided speech at .04 (*11*). In addition, lesion side is hypothesized to be random in nature such that half of the injuries are on the left and half on the right (columns). If aphasia is assumed to invariantly follow injury to the dominant speech hemisphere, the EUL of aphasia in this model would be 48 (after left-sided damage) plus 2 (after right-sided damage) = 50 percent (50 of 100). This EUL value (50 percent) is compatible with the observed incidence of aphasia reported for the RH [mean ($\bar{X}$) = 35 percent] but not the LH ($\bar{X}$ = 60 percent). (The observed frequency will always be lower than the EUL value because lesions to the dominant hemisphere in the state of nature do not always encroach upon the speech areas.) In fact, the probability of acquiring aphasia after unilateral injury to the dominant speech hemisphere in the RH across studies was only .70 (observed/EUL = 35 percent/50 percent).

The task is now to find that speech-brain model which best fits the observed incidence of aphasia in the LH across all studies. On a priori grounds, such a model would have to include at least some proportion of bilateral hemispheric speech in order to account for the fact that the observed rate (60 percent) exceeded the maximal EUL value of 50 percent for right-handers. In another report (*12*), the only model not rejected by the observed data was one that postulated the existence of three types of hemispheric speech organization in the LH in the general population: (i) a unilateral left-sided group (P = .40), (ii) a unilateral right-sided group (P = .20), and (iii) a bilateral group (P = .40). The maximal EUL of aphasia predicted by this model was 70 percent, which is above the observed value of 60 percent and therefore acceptable as a tentative approximation. There are, however, two major problems with this approach. (i) Each of the hypothetical speech-brain models was tested against data in which lesion side was not random, but favored the left side (56 percent versus 44 percent) (Table 1). (ii) Conclusions based on a test of the models were confined to either acceptance or rejection and not to a determination of the best-fitting model. For example, if two models generated EUL values higher than the observed data (failure to reject), one would be unable to determine which model provided the closer fit to observed data. This problem could be solved, in part, if one could estimate the likelihood of acquired aphasia, given a lesion to the hemisphere dominant for speech in the LH. That value for the RH, based on more than 2000 cases, was estimated at P = .70 (*13*). If this estimate could be used for the LH, one would multiply this value by the EUL value in each cell in which lesion side and dominant speech side intersected. This adjusted value, when summed, would generate the expected likelihood of aphasia for each model.

Table 3 presents the speech-brain model that best fits the observed data of Table 1. This model has been adjusted for lesion asymmetries in the observed data as well as for a determination of the expected likelihood of aphasia. The EUL value was 85 percent [Σ(8.40 + 6.60 + 39.20 + 30.80)/100], and the expected likelihood value was 60 percent {Σ[.7(8.40) + .7(6.60) + .7(39.20) + .7(30.80)]/100}. The expected likelihood of aphasia in this model is identical to the overall mean observed frequency of aphasia across studies. This model reveals three different types of cortical speech organization in the LH: (i) a unilateral left-sided group (P = .15), (ii) a unilateral right-sided group (P = .15), and (iii) a bilateral group (P = .70).

This more complex model of unilateral and bilateral speech is at variance with those positions which hypothesize a unitary representation of speech in the LH, either unilateral (*5*) or bilateral (*2, 3*).

Table 1. Observed incidence of aphasia in the left-handed in relation to the side of the lesion. Proportions are shown in parentheses.

Study		Cases	Left side		Right side		Total frequency of aphasia (proportion)
No.	Reference		Aphasia	No aphasia	Aphasia	No aphasia	
1	*17*	8	4 (.7)	2 (.3)	2 (1.0)	0 (0)	.75
2	*18*	12	5 (.8)	1 (.2)	6 (1.0)	0 (0)	.9
3	*19*	20	5 (.5)	5 (.5)	5 (.5)	5 (.5)	.5
4	*20*	10	5 (1.0)	0 (0)	4 (.8)	1 (.2)	.9
5	*21*	9	6 (.9)	1 (.1)	2 (1.0)	0 (0)	.9
6	*22*	14	7 (.6)	5 (.4)	0 (0)	2 (1.0)	.5
7	*23*	13	5 (.8)	1 (.2)	5 (.7)	2 (.3)	.8
8	*5*	33	13 (.7)	5 (.3)	1 (.1)	14 (.9)	.4
9	*24*	63	11 (.4)	19 (.6)	8 (.3)	25 (.7)	.3
10	*3*	58	28		20		.8
11	*9*	59	27 (.7)	10 (.3)	13 (.6)	9 (.4)	.7
12	*25*	14	2 (.5)	2 (.5)	3 (.3)	7 (.7)	.4

Table 2. Unilateral model. Expected incidence of aphasia (upper limit) among the RH where speech hemisphere is left (96 percent) and right (4 percent) and lesion side is random. The expected incidence (upper limit) of aphasia = (48 + 2)/100 = 50 percent.

Speech hemisphere	Lesion hemisphere		Total
	Left	Right	
Left	48*	48	96
Right	2	2*	4
Total	50	50	100

*Aphasia.

Table 3. Bilateral and variable unilateral model (best-fitting model). Expected upper and likely incidence of aphasia among the LH where speech hemisphere is left (15 percent), right (15 percent), bilateral (70 percent), and lesion side is asymmetric.

Speech hemisphere	Lesion hemisphere		Total
	Left	Right	
Left	8.40*	6.60	15
Right	8.40	6.60*	15
Bilateral	39.20*	30.80*	70
Total	56.00	44.00	100

*Aphasia.

The model is also at variance with those currently popular positions which hypothesize a variable unilateral (left- or right-sided) representation of speech in the LH (*6-8*). This type of position would generate an EUL value identical to that of the RH (50 percent), which would not account for the raised incidence of aphasia reported for the LH (*14*). The results demonstrate that this increased incidence could be produced only by an increase in the number of the LH who, because of an incomplete functional lateralization of speech (bilateral), are more sensitive to the effects of an acute unilateral brain lesion. The model would also help explain clinical reports of a raised incidence of aphasia in the LH after injury to the left hemisphere (*5*). Approximately 85 percent of them would be expected to have at least partial representation of speech in the left hemisphere.

This model would also be compatible with studies that have reported a more dramatic remission of aphasia in the LH following unilateral brain injury (*1, 4*). If the majority of the LH (approximately 70 percent) have bilateral representation of speech, this atypical organization would spare them from the more severe and prolonged effects of a unilateral lesion that would be seen in an RH person whose speech mechanisms are more laterally differentiated (*15*). Would the recovery course in those LH (approximately 30 percent) who are predicted (Table 3) to have a more variable unilateral representation of speech (left- or right-sided) be similar to that of RH patients? Recent evidence linking familial left-handedness (in sinistrals) to bilateral cortical speech (*16*) provides one approach, albeit indirect, to these questions.

One final caution should be noted. This model of cortical speech organization in the LH represents merely the best fit with the observed data on the frequency of aphasia after unilateral injury to the brain. Although these studies comprise all of the known reports between 1935 and 1978, they represent only one of several inferential approaches to speech-brain asymmetry in the LH. It is, however, one approach that lends itself to more quantitative inferential test.

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13. This estimate also approximates closely the observed incidence of dysphasia after an operation on the left hemisphere in right-handed (73 percent) and left-handed (72 percent) patients as reported by Penfield and Roberts (*5*). It also approximates the value computed by M. Annett [*Cortex* **11**, 305 (1975)] and J. Levy [in *Hemisphere Function in the Human Brain*, J. Dimond and J. Beaumont, Eds. (Wiley, New York, 1974)].
14. Any model which postulated a unilateral or variable unilateral mode of speech (left- or right-sided) would generate an EUL value of 50 percent, regardless of differences in the proportions of speech representation between hemispheres.
15. The proportions derived from Table 3 closely approximate the findings of a recent study of bilateral intracranial arteriograms in left- and right-handers [F. Hochberg and M. LeMay, *Neurology* **25**, 218 (1975)]. The authors found that the right sylvian point angle was greater than the left by more than 10° in the majority of right-handed patients. However, in the left-handed patients, the majority (71 percent) had comparatively equal right and left sylvian point angles.
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Enduring Changes in Dopamine Receptor Cells of Pups from Drug Administration to Pregnant and Nursing Rats

Abstract. *A decrease in specific [^3H]spiroperidol binding to rat caudate tissue and a parallel decrease in sensitivity to apomorphine in eliciting stereotyped behavior was observed in the offspring of rat mothers treated with either haloperidol or α-methyl-p-tyrosine-methyl ester during pregnancy. In contrast, evidence of increased dopamine-receptor sensitivity was observed in the pups if haloperidol was administered to their mothers postpartum during nursing rather than during pregnancy.*

Although mechanisms for the storage and synthesis of dopamine are present at a very early stage of ontogeny (*1-3*), dopamine-containing neurons gradually develop their functions during fetal life and the first 4 weeks of postnatal life (*4*). The activity of tyrosine hydroxylase, the concentration of dopamine, and the activity of dopamine-stimulated adenylate cyclase in the striatum at birth, represent only 20 percent of adult levels for these neurochemical markers of dopaminergic activity, which achieve adult levels at the age of 3 to 4 weeks of postnatal life (*2, 5*). Cell bodies for dopaminergic neurons are extrinsic to the striatum, and changes in their neurochemistry reflect an ingrowth, proliferation, and development of terminals (*1*). The fetal and early postnatal periods in rats may, therefore, be vulnerable stages in the functional maturation of the central dopaminergic system (*6-8*). In the study described here we demonstrated that certain drugs, administered during these two periods related to the maturation of dopaminergic mechanisms, have pronounced prolonged effects on central dopamine receptors and on the response to a dopaminergic agonist.

To test the prenatal effects of drugs, we injected pregnant female Wistar rats intraperitoneally with either haloperidol (2.5 mg/kg-day) (*6*), α-methyl-*p*-tyrosine-methyl ester (α-MT) (50 mg/kg-day) (*9*), or saline. The injections were given for 16 days, beginning on day 4 or 5 after conception. No rat mother died during the treatment and none appeared to be ill or suffering from an adverse reaction. These doses of haloperidol and α-MT produced no apparent sedation, nor did they interfere with eating or drinking. Each pregnant rat was placed in a separate cage 4 to 5 days before she was expected to give birth. Within 12 hours after birth runts were discarded and all litters culled to ten pups. All pups were weighed at 1 week of age and weekly thereafter until they were killed. Dopamine receptor function was assessed in the pups by measurement of specific binding of [^{3}H]spiroperidol in caudate homogenate (*10*) by a modification of the method of Fields *et al.* (*11*). The stereotyped behavioral response to apomorphine was assessed with a five-point scale (*12*), which was a modification of a scale developed by Tarsy and Baldessarini (*9*). We also studied the effect of haloperidol on pups whose mothers were first allowed to give birth and then were

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