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9. Statistical analyses were computed only on those subjects above the age of 3 years 9 months, who displayed reliable ipsilateral responses. This included 15 adults 13 to 40 years old, 11 children 7 to 10 years old, 12 children 5 to 7 years old, and 7 children 3.75 to 5 years old. In addition 7 children 2 to 3.75 years old were tested. All subjects were right-handed. A pilot series conducted on several adults showed no systematic difference in commissural transmission between the left- and the right-handed or between left and right finger stimulation within a given subject.
10. Separate analyses of variance computed for the ipsilateral and contralateral responses revealed that only the ipsilateral response (all components) varied with age. Thus the ipsi-contralateral differences could not be attributed to changes occurring in the contralateral response (Fig. 1). Others have also reported little difference in the latency of early contralateral activity to shock stimulation between 4 years of age and adulthood. Changes in body length seemed to account for the relative consistency across age [see J. E. Desmedt, E. Brunko, J. Debecker, *Electroencephalogr. Clin. Neurophysiol.* **40**, 43 (1976); P. Laget, J. Raimbault, A. M. D'Allest, R. Flores-Gueuara, J. Mariani, *ibid.*, p. 499].
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Lateralization of Norepinephrine in Human Thalamus

Abstract. *Norepinephrine has a strongly lateralized distribution in the human thalamus. In the pulvinar region the left hemisphere is rich in norepinephrine, whereas in the somatosensory input area the right hemisphere has a higher concentration of this catecholamine. Such naturally occurring left-right differences in concentration of a neurotransmitter represent a new aspect of hemispheric specialization.*

In this report we provide evidence of a significant, naturally occurring lateralization in the distribution of a neurotransmitter system in the human brain. These findings add a new dimension to laterality concepts—that of left-right (L-R) variations in the "chemical neuroanatomy" of the central nervous system—the significance of which we think might be correlated in the future with functional and behavioral effects. The introduction to a recent symposium on hemispheric specialization and lateralization in the nervous system suggests that, "the lateralization problem impinges upon the entire spectrum of brain-behavioral research from the synapse to the sentence" (*1*). Here we provide strong evidence of the chemical laterality.

Recently developed assay procedures enable us to analyze rapidly and accurately the concentration of norepinephrine (NE), epinephrine, dopamine, and ascorbic acid in brain tissue samples weighing between 0.5 and 50 mg. Using small punches from coronal slices we initiated a detailed mapping of these compounds in selected areas of human brain. Occasional bilateral punching, designed to check the precision of the assays and our neuroanatomical expertise (or lack thereof), gave analyses with surprising L-R differences in certain areas. These differences far exceeded the estimates of uncertainties in the assays or punching techniques. The clinical histories did not provide any evidence of hemineurological dysfunction which might account for such results. Accordingly, we began studies of tissue samples from accurately placed bilaterally symmetric punches. The data from five brains are summarized herein and primarily concern the L-R distribution of NE in the thalamus, an area in which we have been particularly interested because of the possible involvement of catecholamines in somatosensory pathways.

Brains were obtained after routine autopsy with the time between death and autopsy varying from 9 to 16 hours (average, 12 hours). Immediately upon removal the whole brains were placed in a −70°C freezer and kept at this temperature until ready for sectioning. The temperature of the specimen was then allowed to rise until slicing could be accomplished; however, the brain remained in the frozen state at all times. These procedures are qualitatively similar to those used by other investigators in postmortem neurochemical studies (*2*). Coronal slices 3 to 4 mm in thickness were cut, placed on a glass plate over Dry Ice, and photographed in color. Samples were removed from the desired areas with a sharpened punch. These samples routinely weighed 30 to 40 mg and were about 3 to 5 mm in diameter. The slice was rephotographed after punching and anatomical assignments were confirmed from the photographs. Standard whole brain and special thalamic atlases were used as required (*3*). Tissue punches were immediately returned to the −70°C environment until analyzed. Catecholamine (*4*) and ascorbic acid (*5*) concentrations were determined by liquid chromatographic procedures with electrochemical detection. The analyses were conducted blind, in that the analyst did not know the side or exact location from which a given sample was obtained.

The results showing thalamic cate-

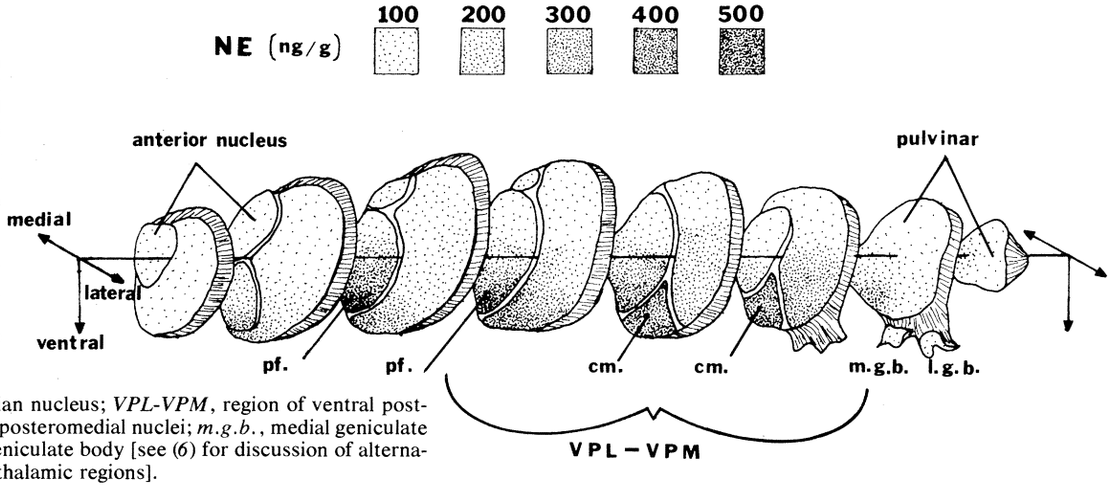

Fig. 1. Regional norepinephrine (NE) distribution in human thalamus. The NE values were averaged over both thalami from five separate brains, but are represented here on a single (left) thalamus. Although precise anatomical localization is not intended, general subdivisions and nuclei of interest are designated on the diagram: *pf*, parafascicular; *cm*, centromedian nucleus; *VPL-VPM*, region of ventral posterolateral and ventral posteromedial nuclei; *m.g.b.*, medial geniculate body; *l.g.b.*, lateral geniculate body [see (*6*) for discussion of alternative nomenclature of thalamic regions].

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cholamine patterning are intriguing in their own right. Regardless of any L-R differences, NE has a highly variable distribution in the thalamus. Figure 1 shows that NE is concentrated in the so-called ventral tier of the lateral nuclear mass and, especially, in the VPL and VPM (V.c.e., V.c.p.i.) areas (*6*). Maps constructed by Brown and Goldman (*7*), showing the distribution of catecholamine in the cortex of rhesus monkeys, reveal that the largest NE concentrations are centered in somatosensory cortex—that region with clearly established connections from the thalamic VPL-VPM areas. High concentrations of NE are also found more medially in the centromedian (CM, n. centralis) and parafascicular (Pf) regions (about 400 ng/g).

Dopamine concentrations in the thalamus are somewhat low (10 to 30 ng/g) and moderately uniform in distribution. With no evidence of any thalamic areas with high concentrations of dopamine, and with such low concentrations of this substance in contrast to NE, we suggest that DA does not have neurotransmitter functions of its own in the thalamus, but is probably present only as a precursor of NE. The ascorbate concentrations, as expected, are 10 to 100 times greater than those of NE, but show no surprising gradients. We do not have enough data on the epinephrine analyses to make any meaningful comments on its distribution.

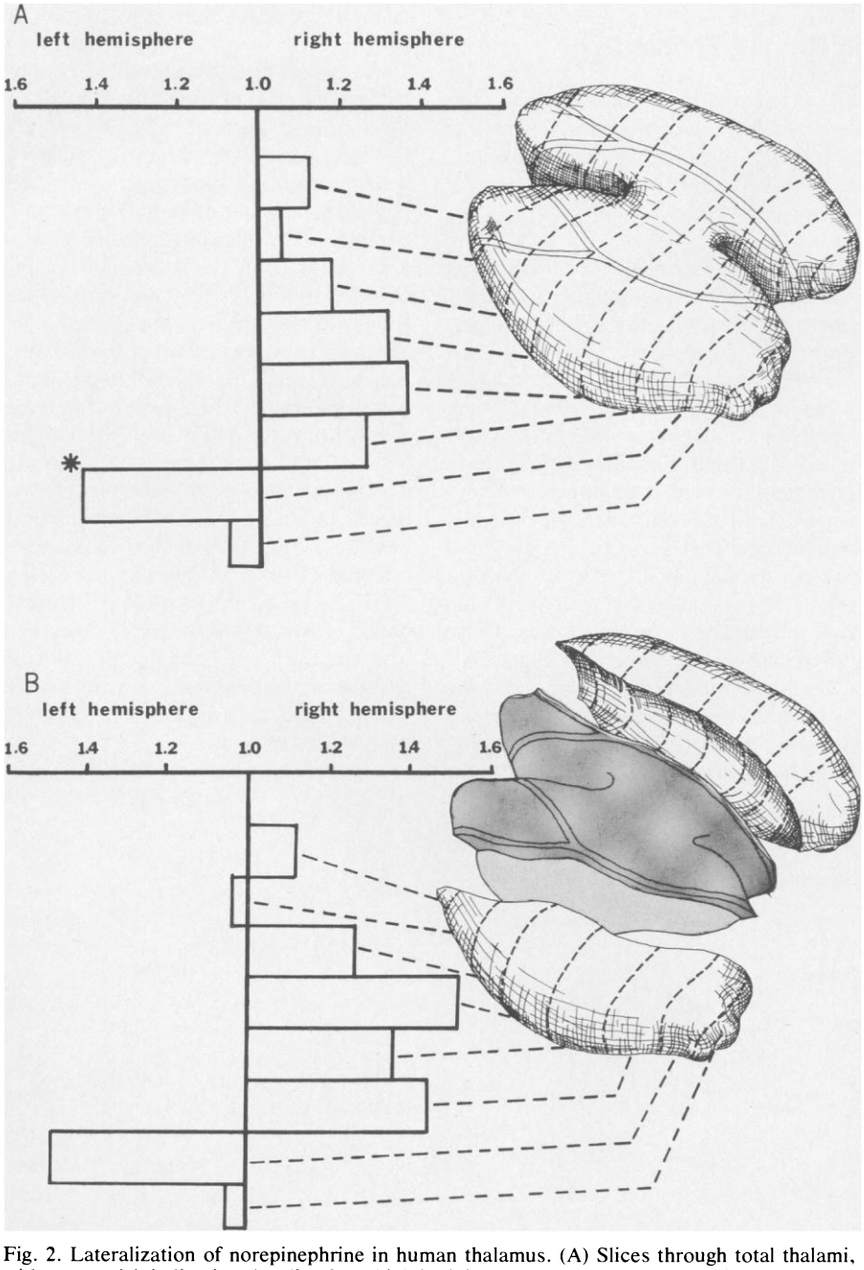

Fig. 2. Lateralization of norepinephrine in human thalamus. (A) Slices through total thalami, with an asterisk indicating the slice for which individual assay data are present in Table 1. (B) Slices through lateral mass only.

The lateralization phenomenon, documented only for NE, is shown in Fig. 2, A and B. The left side of Fig. 2A shows the results for the total thalami in terms of the NE concentration ratio in the L and R halves for each of the indicated anterior to posterior slices. The ratios are the means from the analyses of five brains. The dotted lines in Fig. 2 extending to the right show the approximate regions which the individual slices comprise. Beginning posteriorly, it is clear that the pulvinar region on the left is rich in NE and there is a decided swing to "right-rich" as one proceeds anteriorly through VPL-VPM. As one goes more anteriorly, the extent of right lateralization decreases until there is very little lateralization in the most anterior regions. Each of the individual brains, plotted in this fashion, shows similar trends. It should be noted that the lateralization is very marked, reaching ratios of 1.4 to 1.5 in this averaged representation and even higher in some individual brains.

In Table 1, columns 1 and 2 show the NE concentrations for the left and right punches, respectively, taken from the pulvinar slices of each of the five brains. Column 3 shows each calculated ratio and column 4 the hemispheric prominence or "richness" of the NE distribution. The algebraic mean of all the ratios in column 3 corresponds to the diagram ratio for the asterisk-marked slice in Fig. 2A (1.53, left-rich). Only six individual ratios out of a total of 30 for this slice deviate from the left-rich pattern. Three of these (1.14 R, 1.04 R, and 1.13 R) are less than the ratio of 1.00 ± 0.20 which we consider as insignificant lateralization. Furthermore, the individual ratios marked L are much more strongly oriented. Only two out of 24 of these left-rich ratios are insignificant (less than 1.00 ± 0.20) and many are 1.5 or greater.

In addition to the anterior region, the dorsomedial portions of the thalami have relatively insignificant NE lateralization and, hence, "dilute" the observations. In Fig. 2B, only the lateral mass sections are compared (the gray-stippled region of the slice diagram qualitatively illustrates the dorsomedial regions left out of this comparison). The L-R differences are identical to those of the whole thalamus, but more strongly accentuated. Thus, it appears significant that those regions with the highest concentrations of NE (the general ventral tier, but including CM and Pf) show the strongest lateralization.

The laterality we have demonstrated is

not due to analytical errors, nor is it artifactual. We are well aware of the difficulties associated with postmortem brain assays (*8*), but the L-R ratio comparisons that we used eliminate some of the problems. The data are essentially independent of the absolute amounts of NE in a given region. These absolute levels, do, of course, vary considerably among individual brain specimens. The liquid chromatographic assays for NE have given results for the past several years that are highly consistent with fluorometric, radioenzymatic, and other assays. Specifically, in the present analyses, a homogeneous sample of small animal or human brain can be analyzed by the liquid-chromatography method with a relative precision of ± 1 percent (that is, if absolutely identical bilateral punches were analyzed and they actually had no differences in NE content, the ratios of Fig. 2 should not exceed 1.00 + 0.01). Obviously, unavoidable punching dissymmetries have greater error limits than the analyses themselves. For example, as shown in Fig. 1, there are strong vertical gradients in NE concentration. Errors in dorsal-ventral as well as lateral placement of punches, together with freezing and slicing distortions, can result in ratio errors. It is reasonable to assume these will all be randomized. Inherent anatomical dissymmetries might produce skewing of the chemical results. If we assign an error margin of ± 10 percent (L-R ratios 1.0 ± 0.1), or even what we believe to be a completely unrealistic overestimate of ± 20 percent (ratios 1.0 ± 0.2), lateralization ratios far in excess of these limits occur (see Fig. 2). Furthermore, the same general L-R patterns emerge from each individual brain analysis as well as from the mean of all five.

The average age of the subjects from which we obtained brain specimens was 62 years. Their clinical histories gave no indication of neurological problems (nor, unfortunately, any meaningful handedness information) which might correlate with the results obtained. Partial vascular accidents prior to death could conceivably produce unusual distributions. However, vascular dysfunctions would be expected to produce more random disturbances in NE distribution or develop areas devoid of almost any catecholamines—wholly inconsistent with the overall patterns observed.

Thus we believe the results truly represent NE lateralization in the thalamus. As far as we know, the only other example of asymmetric neurotransmitter distribution in human brain is the verification of dopamine deficiency in contralateral caudate-putamen for a hemi-Parkinsonism patient (*9*). This was not an intrinsic chemical laterality but, as reported by Hornykiewicz (*10*), a clear example of the causal relation between dopamine deficiency and Parkinson symptoms. A possible natural L-R difference (about 10 percent) in rat striatal dopamine has been proposed by Glick *et al.* (*11*).

Clinical studies of patients undergoing thalamic surgery for dyskinesias or pain, for example, provide strong evidence for functional lateralization of the thalamus. Thus cryogenic surgery in left, but not right, pulvinar and ventrolateral regions produces postoperative difficulties in speech and other functions. The exact mechanisms of these disturbances are still open to question (*12*). We do not know whether neurotransmitter lateralization could play a role in such functionality. Our results show that the area of the thalamus which receives almost the entire somatosensory input (VPL-VPM or ventrobasal complex) has a strongly lateralized distribution of NE. Although the role of NE mediation in thalamic processing of somatosensory information is not at all established, the present results suggest their possible involvement with lateralized neuropsychological dysfunction in schizophrenic disorders (*13*).

We urge other investigators to examine this laterality phenomenon.

Table 1. Values for each of the paired punches taken for the pulvinar slice marked with an asterisk in Fig. 2A. The data are representative of all the slices shown in Fig. 2A.

Concentration of NE in the thalamus (ng/g)*		Ratio†	Hemispheric prominence
Left	Right		
	Brain No. 1		
118	58	2.03	L
86	23	3.74	L
34	21	1.62	L
24	9	2.66	L
45	12	3.75	L
	Brain No. 2		
29	33	1.14	R
21	12	1.75	L
23	21	1.09	L
16	11	1.45	L
19	15	1.27	L
	Brain No. 3		
79	42	1.88	L
185	148	1.25	L
250	183	1.37	L
56	50	1.12	L
174	135	1.29	L
391	299	1.31	L
122	162	1.33	R
	Brain No. 4		
46	29	1.59	L
11	16	1.45	R
15	12	1.23	L
62	29	2.14	L
82	85	1.09	R
290	122	2.38	L
160	120	1.25	L
	Brain No. 5		
32	9	3.55	L
130	46	2.83	L
15	17	1.13	R
25	36	1.44	R
87	57	1.53	L
55	35	1.57	L
Mean		1.53	L

*For tabulation simplicity individual values are rounded to nearest whole value in nanograms per gram. The variation in absolute values within a given brain slice primarily reflects the dorsal-ventral gradations within that slice which are apparent in the distribution pattern of Fig. 1. †Ratio always calculated with the larger value divided by the smaller, that is, ratio always < 1. Assignment of hemispheric prominence in last column made accordingly as L (left-rich) or R (right-rich).

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