Sex and Handedness Differences in Cerebral Blood Flow during Rest and Cognitive Activity

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4. Winter moth larvae were collected in Nova Scotia by Canadian Forestry Service personnel under the supervision of D. G. Embree, and were allowed to pupate in vermiculite. In late fall they were sent to the insect quarantine laboratory in Ottawa, which is supervised by J. S. Kelleher. The pupae were held in dark cold storage (7°C) and adults emerged in 1 to 2 weeks. Female moths were collected and processed under the supervision of A. C. Schmidt, plant quarantine entomologist. Abdominal tips of 2- to 3-day-old female moths were clipped and soaked in methylene chloride for 24 hours. The solution then was removed with a disposable pipet and shipped to Geneva, New York, in two batches of crude extract from 5000 abdominal tips each.
5. W. L. Roelofs, in *Crop Protection Agents, Their Biological Evaluation*, N. R. McFarlane, Ed. (Academic Press, New York, 1977).
6. Packard GLC columns were as follows: 3 percent OV-101 (methyl silicone) on 100- to 120-mesh Gas-Chrom Q, 2-m glass column (inside diameter, 4 mm); 10 percent XF-1150 (50 percent cyanoethyl, methyl silicone) on 100- to 120-mesh Chromosorb W-AW-DMCS, 2-m glass column (inside diameter, 2 mm); 3 percent CHDMS (cyclohexanedimethanol succinate) on 100- to 120-mesh Gas-Chrom Q, 2-m glass column (inside diameter, 4 mm). Capillary GLC columns included a 45-m Carbowax 20 M and a 49-m OV-101 column used with splitless injection programmed from 80° to 190°C at 30° per minute after an initial hold of 2 minutes.
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10. Flight tunnel as in J. R. Miller and W. L. Roelofs, *J. Chem. Ecol.* **4**, 187 (1978). Males were tested with 30 μg of synthetic **1** on a rubber septum (A. H. Thomas Co.) at ~ 1 lux, 3 hours into the scotophase of a photoperiod of 14 hours of light and 10 hours of darkness. Males were acclimated to tunnel condition for 2 hours before they were tested. Initially, 33 males were tested, with 33, 29, and 27 males exhibiting wing fluttering, upwind flight 150 cm to the source, and source contact with attempted copulation, respectively.
11. At temperatures above and below the optimal range, males were typically inactive, often lying on their sides and exhibiting very little movement, even when touched. Within the optimal range, nonpheromone-stimulated basal activity was significantly increased, with males exhibiting upright posture and frequent periods of walking and wing fluttering.
12. Field trapping was conducted (6 November to 21 December 1981) in an orchard containing Cortland, McIntosh, and Red Delicious apples. Zoecon 1CP traps with synthetic lures were hung in trees in a Latin square design of three replicates with traps randomized each of 19 count days (Monday, Wednesday, and Friday at 1000 EST). A virgin female approximately 72 hours old was used in each replicate on 16 November, but only one male was captured compared to 141 males captured on that night in the traps baited with **1**. On two occasions, lure traps were checked hourly from dawn to dusk to determine flight occurrence. No males were taken during the daylight hours.
13. J. C. Miller, D. Kimberling, G. E. Daterman, unpublished results.
14. Individuals of the genus *Ennominae* (Geometridae), similar in external morphology and size to *O. brumata*, exhibited flight activity at 7°C and had a mean thoracic temperature of 17°C [G. A. Bartholomew and B. Heinrich, *J. Exp. Biol.* **58**, 123 (1973); B. Heinrich, *Insect Thermoregulation* (Wiley-Interscience, New York, 1981)].
15. Supported by NSF grant PCM 78–13241 and by PHS grant AI-12020. We thank J. Franclemont for identification of the Bruce spanworm specimens caught in New York.

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Sex and Handedness Differences in Cerebral Blood Flow During Rest and Cognitive Activity

Abstract. *Cognitive activity resulted in increased flow of blood to the cerebral hemispheres. The increase was greater to the left hemisphere for a verbal task and greater to the right hemisphere for a spatial task. The direction and degree of hemispheric flow asymmetry were influenced by sex and handedness, females having a higher rate of blood flow per unit weight of brain, and females and left-handers having a greater percentage of fast-clearing tissue, presumably gray matter.*

Sex differences in cognitive functioning have been extensively documented (*1*). A consistent finding is that males perform better than females in spatial tasks, whereas females have greater verbal fluency (*2*). These findings have been linked to research on sex differences in hemispheric specialization of function (*3, 4*). Evidence on the effects of brain lesions shows that for most right-handers the left and right hemispheres are specialized for verbal and spatial functioning, respectively (*5, 6*). However, females are less likely than males to suffer speech impairment after left hemispheric damage (*4, 6*) or to have deficits in spatial function after right hemispheric damage (*6*). Furthermore, when verbal and spatial tasks are presented for initial processing by the right or the left hemisphere in visual, auditory, or tactile stimulation modalities, females tend to show less lateralization (*7, 8*).

Handedness also seems to have an effect on cognitive functioning and this effect in left-handed subjects has been attributed to a lesser degree of hemispheric specialization. Left-handed patients recover faster than right-handed patients from speech disorders resulting from cortical lesions (*9*), and a significant proportion of left-handed patients have verbal deficits after injuries to the right hemisphere (*6*). Likewise, studies of lateralization of function in normal subjects indicate that left-handers show smaller and sometimes reversed effects in comparison with right-handers (*7, 10*).

The neurophysiological basis of these sex and handedness differences is unknown. We present data of isotope clearance in humans showing sex and handedness differences in regional cerebral blood flow (rCBF) and in the amount and distribution of fast-perfusing tissue, presumably gray matter.

Using the ^{133}Xe inhalation technique (*11*), we measured rCBF in 62 normal healthy volunteers aged 18 to 26. The sample included 15 right-handed males, 15 right-handed females, 15 left-handed males, and 17 left-handed females (*12*). Measurements were taken from each subject during periods of resting, solving verbal analogies, and solving a spatial line orientation task (*13*). The order of tasks was counterbalanced across subjects (*14*). For each measurement, the subject inhaled trace amounts of ^{133}Xe mixed with air, and the clearance of xenon from the brain was measured by 16 sodium iodide crystal detectors, with collimators 19 mm in diameter and 21 mm in length, placed anteriorly to posteriorly over eight homologous regions (*15*) of each hemisphere. Each detector measures flow in a cylinder of tissue that includes primarily cortex and underlying white matter, and to a diminished extent deeper structures.

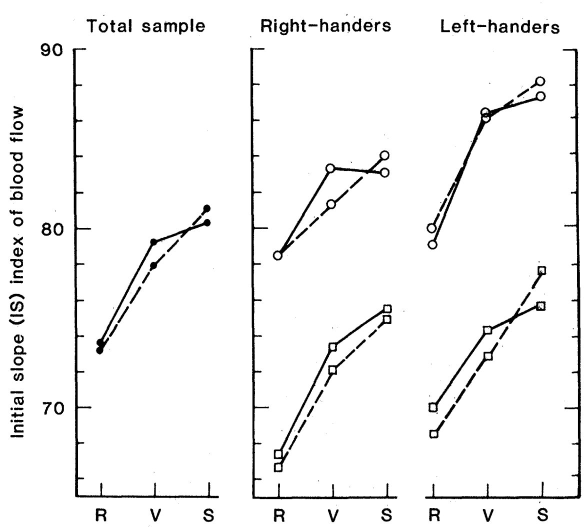

Fig. 1. Initial slope (*IS*) index of blood flow to the left (——) and right (- - - -) hemispheres for the total sample and for right- and left-handed females (○) and right- and left-handed males (□) during performance of resting (*R*), verbal (*V*), and spatial tasks (*S*).

Figure 1 shows the initial slope index of flow (*16*) for the total sample and for the four groups of subjects during the three experimental conditions.

Cognitive activity resulted in increased blood flow in all groups [$F(2, 116) = 40.33$; $P < .001$]. For each task, blood flow was increased in comparison with base-line flow ($P < .001$ for each); the increase in the overall flow was greater for the spatial than for the verbal task ($P < .001$). A significant interaction of task and hemisphere [$F(2, 116) = 14.16$; $P < .001$] indicated that the increase in flow was greater in the left hemisphere during the performance of the verbal task and greater in the right hemisphere during the performance of the spatial task (*17*). The four-way interaction (handedness, sex, task, and hemispheres) was also significant [$F(2, 116) = 5.25$; $P < .01$]. This interaction reflects a different pattern of blood flow changes in the two hemispheres in each of the four groups of subjects. Relative to base line, both groups of right-handed subjects showed greater increases in left hemispheric flow than in right hemispheric flow during performance of the verbal task, and the right-handed females also had greater increases in right hemispheric flow during performance of the spatial task. Thus, in right-handed females the laterality effect is stronger for this task. The laterality effect was weaker in left-handers; in left-handed males, the increase in blood flow was the same in both hemispheres for the verbal task, but was greater in the right hemisphere for the spatial task (*18*).

Blood flow rates were higher in females than in males [$F(1, 58) = 15.55$; $P < .001$]. The size of the difference for IS was 15 percent (*19, 20*). This difference existed for both handedness groups, under all three conditions, and for every detector. The effect did not diminish when the influences of hemoglobin levels, diastolic and systolic blood pressure, and the partial pressure of CO_2 were taken into account using analysis of covariance. Such a sex difference in blood flow also has been reported by Shaw *et al.* (*21*), and its explanation is unclear (*22*). An interpretation of the functional significance of this difference would depend on whether it is accompanied by sex differences in neuronal activity and cerebral metabolism, which are highly coupled in the normal brain (*23*). Sex differences in metabolism could be directly tested in humans by use of positron emission tomography (*24*). Autoradiographic techniques in animals (*25*) could establish whether such sex differences are uniquely human.

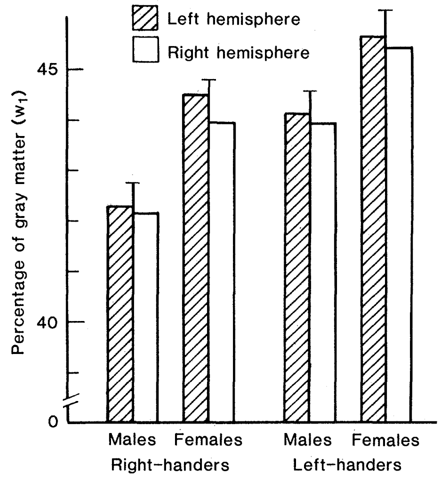

Fig. 2. Percentage of gray matter (w_1) in right- and left-handed males and females.

The isotope clearance method enables the calculation of w_1, which represents the percentage of tissue with fast perfusion and clearance. In the normal brain, the value of w_1 is assumed to represent gray matter, which has a perfusion rate approximately four times and a clearance rate approximately seven times that of white matter (*11, 19*). Earlier reports have indicated that w_1 is higher in the left than in the right hemisphere (*21, 26, 27*); this was also found in our study [$F(1, 58) = 12.15$; $P < .001$]. In addition, left-handers had a higher overall w_1 than right-handers [$F(1, 58) = 5.86$; $P < .025$] and females had a higher overall w_1 than males [$F(1, 58) = 6.87$, $P < .025$] (Fig. 2).

The finding that cerebral blood flow increases during cognitive activity is consistent with earlier results (*28*). Greater increases in the left hemisphere during the performance of verbal tasks (*29*) and greater increases in the right hemisphere during the performance of spatial tasks (*19*) also have been reported. These earlier effects were obtained with right-handed males. Our present results indicate that factors affecting the direction and degree of hemispheric specialization also affect patterns of hemispheric activation during cognition. However, although left-handers and females have been reported to show weaker hemispheric cognitive specialization of verbal and spatial functions, the right-handed females in our sample showed a stronger lateralization of cerebral blood flow than the right-handed males. This finding corroborates data obtained with electroencephalography, another measure of brain activity (*30*). Whether a lesser degree of hemispheric cognitive specialization in females is compensated for by greater activation of the hemisphere specialized for a particular task requires further testing.

Our findings that females and left-handers have a higher rate of hemispheric blood flow and a greater percentage of fast-perfusing tissue shows that brain organization in these groups, as indexed by our physiological measures, differs from that in right-handed males. The observations that the percentage of fast-perfusing tissue is greater in the left hemisphere than in the right and that this holds for both sexes and both handedness groups suggest possible differences in the gray and white matter distributions of the two hemispheres. If necropsies reveal that the gray and white matter distributions are consistent with inferences from blood-flow studies, investigations designed to specify the psychological correlates of the anatomic diversities could provide new insights into the relation between brain anatomy and function.

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14. The six possible orders of resting, verbal, and spatial tasks were presented to the 62 subjects in such a way that at least ten subjects performed the tasks in each possible order, but the specific assignment of task order was chosen at random for each subject.
15. The standard detector placement is described (*26*).
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17. The effects were significant for each task separately in an analysis of covariance, with baseline flows serving as covariates. The effects of task difficulty were evaluated by entering performance data as covariates. This did not influence the results reported above. The subjects found the two tasks about equal in difficulty (although the verbal task was considered slightly more difficult by 38 of the 62 subjects).
18. The task-hemisphere interactions were significant for right-handed females [$F(2, 28) = 12.20$; $P < .001$], reflecting a greater left hemispheric increase in blood flow for the verbal task and a greater right hemispheric increase for the spatial task; task-hemisphere interactions were also significant for left-handed males [$F(2, 28) = 9.42$; $P < .001$], reflecting a symmetrical increase for the verbal task and a greater right hemispheric increase for the spatial task.
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Destruction of Noradrenergic Neurons in Rabbit Brainstem Elevates Plasma Vasopressin, Causing Hypertension

Abstract. *When A1 noradrenergic neurons in the caudal ventrolateral medulla of rabbits are destroyed electrolytically or by local injection of the neurotoxin kainic acid, the concentration of vasopressin in plasma increases, causing hypertension. The A1 neurons may tonically inhibit the activity of vasopressin-secreting neuroendocrine cells through a direct hypothalamic projection.*

The A1 cells are a population of norepinephrine-containing neurons in the caudal ventrolateral medulla oblongata (*1*). Destruction of the area containing these neurons by electrolytic lesioning or by local administration of the neurotoxin kainic acid produces a striking cardiovascular syndrome characterized by acute hypertension, peripheral vasoconstriction, bradycardia, and florid pulmonary edema (*2*). The A1 cells do not project to the spinal cord, as was originally supposed (*3*). Rather, their axons ascend to the hypothalamus, with a major projection to supraoptic and paraventricular nuclei (*4, 5*). In these nuclei the terminals of A1 cells are concentrated around large neuroendocrine cells, which secrete arginine vasopressin (AVP) into the circulation (*5, 6*).

These anatomical observations suggest that A1 neurons may regulate the release of AVP by supraoptic and paraventricular neurons. Furthermore, they suggest that the cardiovascular syndrome observed after lesions of the A1 area may be related to increases in circulating vasopressin, a potent vasoconstrictor (*7*). We sought to determine whether A1 lesions elevate the concentration of AVP in plasma and, if so, whether this elevated AVP contributes to the hypertension associated with the lesions.

First we determined the effects of injecting kainic acid into the A1 area on mean arterial pressure (MAP) and plasma AVP. Male New Zealand White rabbits were anesthetized with urethane (1.4 g/kg, intravenously), paralyzed with curare (2 mg/kg, intravenously), and mechanically ventilated with oxygen-enriched air. A catheter was inserted into one femoral artery for continuous monitoring of arterial pressure. Samples of arterial blood (1.5 ml) were withdrawn at specified times for measurement of plasma AVP (*8*). The volume withdrawn was immediately replaced with saline. The rabbit's head was held in a Kopf stereotaxic apparatus, the dorsal surface of the medulla was surgically exposed, and mi-

Table 1. Effects of neurotoxic (kainic acid) and neuroexcitatory (L-glutamate) agents on MAP and plasma AVP in rabbits. Each agent was injected in the amount of 1 nmole dissolved in 0.25 μl of saline. Values are means ± standard errors.

Treatment	Number of rabbits	MAP (mmHg) Before injection	MAP (mmHg) Five minutes after injection	AVP (pg/ml) Before injection	AVP (pg/ml) Five minutes after injection
Kainic acid to A1 area	10	117 ± 6	149 ± 7*	14 ± 4	70 ± 10*
Saline to A1 area	8	106 ± 6	106 ± 5	10 ± 2	14 ± 2
L-Glutamate to A1 area	7	111 ± 6	110 ± 7	12 ± 4	13 ± 4
Kainic acid to spinal trigeminal nucleus	5	124 ± 3	125 ± 3	20 ± 7	13 ± 2
Kainic acid to A1 area after cervical spinal cord transection	5	95 ± 2	128 ± 9*	38 ± 8	142 ± 45†

*Significantly different from value measured before injection ($P < .01$, Student's t-test). †$P < .05$.

