weeks only with respect to brain weight. As seen in Fig. 1b, 4 weeks of ECS followed by 4 weeks of sham treatment led to normalization. The significant increase of synaptin, D2, and the 14-3-2 isoantigens was therefore a reversible phenomenon.

In conclusion, we found an increase of synaptin, D2, and 14-3-2 in the rat brain. This increase was seen in forebrain after ECS three times weekly for 4 weeks, and in occipital cortex after ECS three times weekly for 8 weeks. The occipital cortex showed a decrease of those proteins after 4 weeks of ECS, which may indicate a reversible delay of development of this area of the brain. The reversible increase of 14-3-2 may indicate increased neuronal preparedness for glycolytic demands. The reversible increase of forebrain synaptin may indicate an increase of synaptic vesicles, and the reversible increase in forebrain D2 may indicate increased synaptic remodeling. These findings are in accordance with the concept that ECS leads to a sustained change in postsynaptic nerve transmission (*6, 7*). Furthermore, the increased amount of D2 measured in the cerebrospinal fluid of patients recovering from psychotic (endogenous) depression, regardless of the type of therapy (*23*), indicates that the present model for the study of ECS may prove valuable in the search for the etiology of affective illness.

OLE STEEN JØRGENSEN
*Psychochemistry Institute, University of Copenhagen, Rigshospitalet, DK 2100 Copenhagen Ø, Denmark*
TOM G. BOLWIG
*Department of Psychiatry, University of Copenhagen, Rigshospitalet*

### References and Notes

1. Medical Research Council, *Br. Med. J.* **1**, 881 (1965).
2. J.-O. Ottosson, *J. Nerv. Ment. Dis.* **135**, 239 (1962).
3. T. G. Bolwig, M. M. Hertz, O. B. Paulson, H. Spotoft, O. J. Rafaelsen, *Eur. J. Clin. Invest.* **7**, 87 (1977).
4. T. G. Bolwig, M. M. Hertz, E. Westergaard, *Acta Neurol. Scand.* **56**, 335 (1977).
5. G. Nordin, J.-O. Ottosson, B. E. Roos, *Psychopharmacologia* **20**, 315 (1971).
6. A. R. Green, D. J. Heal, D. G. Grahame-Smith, *ibid.* **52**, 195 (1977).
7. K. Modigh, *ibid.* **49**, 179 (1976).
8. G. T. Pryor, L. S. Otis, M. K. Scott, J. J. Colwell, *J. Comp. Physiol. Psychol.* **63**, 236 (1967).
9. J. M. Musacchio, L. Julou, S. S. Kety, J. Glowinski, *Proc. Natl. Acad. Sci. U.S.A.* **63**, 1117 (1969).
10. E. Bock and O. S. Jørgensen, *FEBS Lett.* **52**, 37 (1975).
11. E. Bock, O. S. Jørgensen, L. Dittmann, L. F. Eng, *J. Neurochem.* **25**, 867 (1975).
12. E. Bock and K. B. Helle, *FEBS Lett.* **82**, 175 (1977).
13. E. Bock, *J. Neurochem.* **30**, 7 (1978).
14. O. S. Jørgensen and E. Bock, *ibid.* **23**, 879 (1974).
15. O. S. Jørgensen, *ibid.* **27**, 1223 (1976).
16. C. M. Jacque, O. S. Jørgensen, N. A. Baumann, E. Bock, *ibid.*, p. 905.
17. B. W. Moore and V. J. Perez, in *Physiological and Biochemical Aspects of Nervous Integration*, F. D. Carlson, Ed. (Prentice-Hall, Englewood Cliffs, N.J., 1968), pp. 343-360.
18. V. J. Perez, J. W. Olney, T. J. Cicero, B. W. Moore, B. A. Bahn, *J. Neurochem.* **17**, 511 (1970).
19. V. M. Pickel, D. J. Reis, P. J. Marangos, C. Zomzely-Neurath, *Brain Res.* **105**, 184 (1978).
20. E. Bock and J. Dissing, *Scand. J. Immunol.* **4** (Suppl. 2), 31 (1975).
21. O. S. Jørgensen and E. Bock, *Neurochem. Res.*, in press.
22. H. G. M. Clarke and T. Freeman, *Clin. Sci.* **35**, 403 (1968).
23. O. S. Jørgensen, E. Bock, P. Bech, O. J. Rafaelsen, *Acta Psychiatr. Scand.* **56**, 50 (1977).
24. This investigation was supported by a grant from "Den Laegevidenskabelige Forskningsfond for Storkøbenhavn, Faerøerne og Grønland." The skillful technical assistance of G. Centerwall is highly appreciated.

16 August 1978; revised 8 January 1979

## Differential Behavioral and Biochemical Effects of Right and Left Hemispheric Cerebral Infarction in the Rat

Abstract. *Following ligation of the right middle cerebral artery, rats were hyperactive for 2 to 3 weeks whether activity was measured by running wheel revolutions or open field observations. Assays of brain catecholamines revealed 30 percent reductions of norepinephrine in the injured and uninjured cortex and locus coeruleus and a 20 percent reduction of dopamine in the substantia nigra. In contrast, rats with left middle cerebral artery ligations did not become hyperactive and did not show any significant change in catecholamines in any of the brain areas studied. Right and left hemispheric infarctions were comparable in their locations and extent of tissue damage. This lateralization of behavioral and biochemical response to cerebral infarction may be the consequence of anatomical or physiological asymmetries in the brain.*

Ligation of the right middle cerebral artery in the rat leads to a reduction in norepinephrine (NE) concentration in the ipsilateral and contralateral cortex and brainstem and during a 40-day postoperative period there is a complete or partial return of NE to control levels (*1*). Fluorescence microscopic studies revealed a decrease in the number of fluorescent varicosities or intensity of fluorescence in both the ipsilateral and contralateral cortex and brainstem concomitant with the decrease in catecholamine concentrations (*2*). These changes in catecholaminergic neurons have been accompanied by several transient alterations in behavior, including increased spontaneous activity and a biphasic change in both shock-induced aggression (*1*) and intracranial self-stimulation (*3*). These behavioral changes were related to the biochemical changes by the finding that the period of spontaneous hyperactivity could be blocked pharmacologically either by postoperative daily treatment with the NE uptake blocker desmethylimipramine or by preoperative destruction of NE neurons with 6-hydroxydopamine (*4*).

Since all of the previous behavioral, anatomical, and biochemical experiments were done on animals with right middle cerebral artery ligation, and recent studies have reported asymmetries in brain catecholamine content (*5, 6*), the present study was undertaken to determine the behavioral and biochemical effects of left middle cerebral artery ligation.

Sprague-Dawley male rats (approximately 300 g) were housed individually in cages with food and water freely available and a regular schedule of 12 hours of light, 12 hours of dark. The cages (*7*) consisted of a stationary compartment and a running wheel with free access to either compartment. The running wheel could move freely in either direction and was connected to a cyclometer which was read at 24-hour intervals. Under chloral hydrate anesthesia (350 mg per kilogram of body weight, intraperitoneally), either the right or left middle cerebral artery was ligated under a dissecting microscope with a 6-0 ophthalmic suture. The surgical approach was made through a frontoparietal craniotomy extending from the coronal suture posteriorly to the periorbital area arteriorly and from the protrusion of the zygomatic arch inferiorly to the ridge separating the dorsal and lateral aspects of the skull superiorly. The suture was passed through the dura, behind the vessel, and out through the dura again, and the vessel and overlying dura were tied together; the artery was then severed distal to the tie with dural scissors. The ligature site, which was just above the rhinal fissure, varied slightly from animal to animal, but the surgical approach was the same on each side; there appeared to be no anatomical differences in the size or course of the artery on the two sides.

Two series of experiments were done to determine the effect of left middle cerebral artery ligation on spontaneous activity. In the first series, 33 rats were placed in the activity cages and allowed to acclimatize for 3 weeks before being


0036-8075/79/0817-0707$00.50/0  

randomly selected for either right or left cerebral infarction or sham operation. Although the number of daily revolutions of the running wheel increased during the first two preoperative weeks, daily activity levels were relatively stable by the third week and were used as the preoperative baseline. Because there was little fluctuation in day-to-day activity for any given rat, while there was as much as a tenfold difference between rats, the postoperative activity for each rat was compared with its preoperative baseline. By 4 days after surgery the animals with right hemispheric lesions ($N = 12$) were more active than either the sham-operated animals ($N = 7$) or those with left hemispheric lesions ($N = 14$) (Fig. 1A). Mean daily activity of these animals reached about 150 percent of control levels by 12 days after surgery and then slowly declined until 17 days after surgery, when activity returned to preoperative base line. In contrast, the activity of the sham-operated and left hemisphere–infarcted animals slowly returned to base-line levels by 10 days after surgery and then leveled off without ever exceeding the base-line values. These results were confirmed in another group of 27 animals (ten left, nine right, and eight shams); there were no significant differences between these groups in food or water intake.

In the second series of experiments, spontaneous activity was measured by a different method, open field observation. Rats were placed in an opaque cylindrical container in one corner of a 90 by 90 cm open field that contained 15 by 15 cm grid markings. After 30 seconds, the open-end container was gently removed, and latency to leave the home corner, total number of grids crossed, rearings, and defecations were counted by two observers (*8*) during a 5-minute period. After two preoperative exposures to this open field environment, the rats, which were housed in the same type of cages as in the previous experiment, were randomly selected for either sham lesion ($N = 6$) or right ($N = 7$) or left ($N = 8$) hemispheric infarction. Although the groups showed no preoperative differences in activity levels, the group with right hemispheric infarctions was significantly more active 5 days after surgery than were those with sham operations or left middle cerebral artery infarction (Fig. 1B). This difference persisted until 17 days after surgery with the exception of one data point at 10 days. In animals with left hemispheric infarcts, activity did not increase above that of control animals or their own preoperative level.

The statistical significance of these differences in activity in the postoperative period was confirmed by nonparametric and parametric analysis. For example, at 12 days after surgery the distribution of animals with right hemispheric lesions that were more than 110 percent above base-line activity and those with left hemispheric lesions that were less than 110 percent of base line was significantly different from random for both running wheels ($\chi^2 = 12.9$, $P < .001$) and the open field ($\chi^2 = 9.7$, $P < .01$). The results of the parametric analysis by Student's $t$-test are shown in Fig. 1.

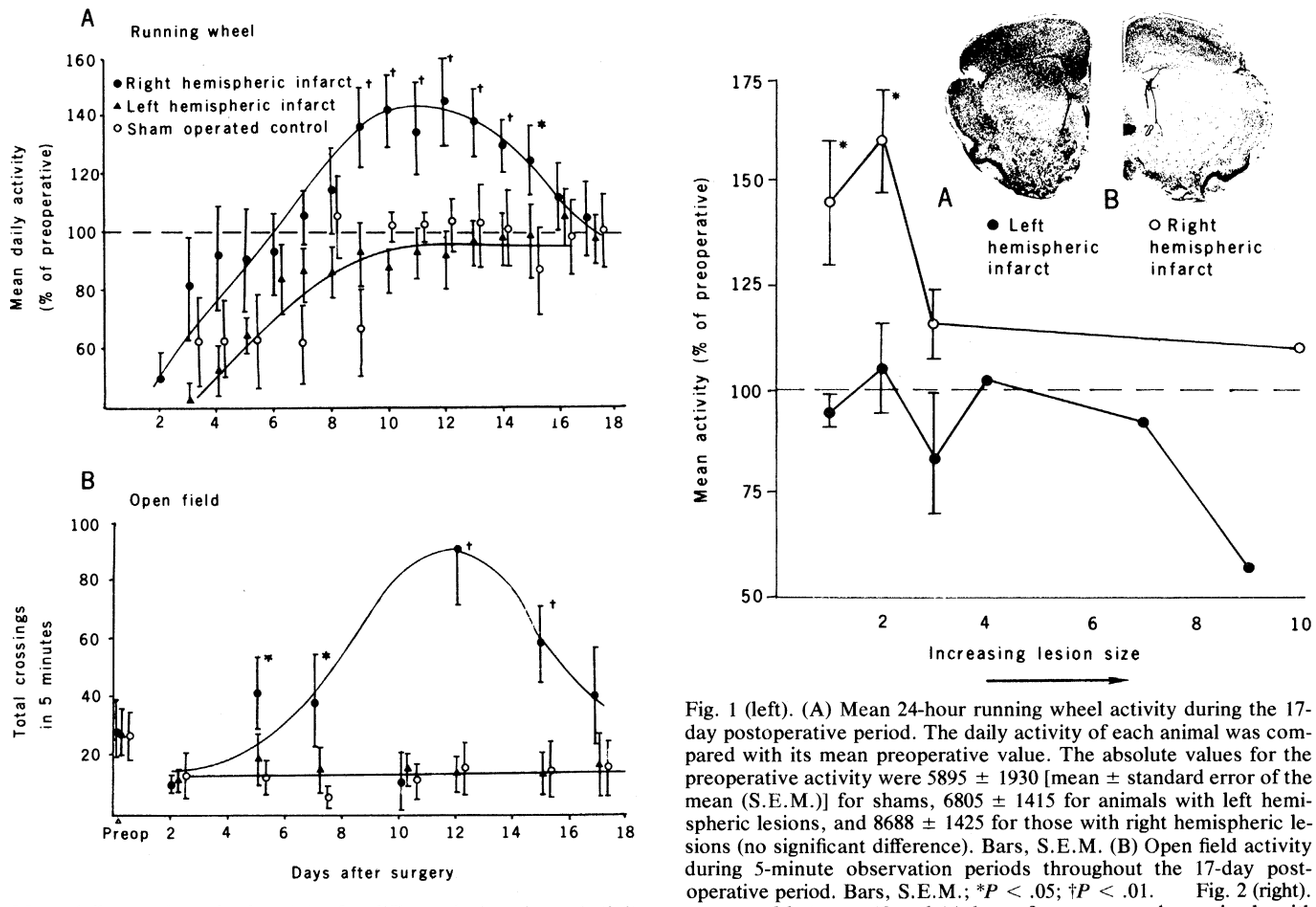


Fig. 1 (left). (A) Mean 24-hour running wheel activity during the 17-day postoperative period. The daily activity of each animal was compared with its mean preoperative value. The absolute values for the preoperative activity were 5895 ± 1930 [mean ± standard error of the mean (S.E.M.)] for shams, 6805 ± 1415 for animals with left hemispheric lesions, and 8688 ± 1425 for those with right hemispheric lesions (no significant difference). Bars, S.E.M. (B) Open field activity during 5-minute observation periods throughout the 17-day postoperative period. Bars, S.E.M.; $*P < .05$; $\dagger P < .01$. Fig. 2 (right). Mean daily running wheel activity for different lesion sizes. Activity was averaged between 10 and 14 days after surgery when animals with right hemispheric lesions were maximally active. All lesion sizes were estimated by two independent observers on a scale of 1 to 10 at 3 weeks after surgery (*8*). Bars, S.E.M.; $*P < .05$. (A) A 25-$\mu$m coronal section (toluidine blue stain) viewed from posterior to anterior of the left hemisphere. The lesion (size 2) extends through the cortex but not below the fibers of the internal capsule. Bar in upper left, 2 mm. (B) A 25-$\mu$m toluidine blue-stained section of right hemisphere with lesion (size 2). The right and left hemispheric lesions are comparable in size and location.

At 5 or 14 days after surgery, rats were killed and their brains quickly removed, dissected over ice, and stored in a nitrogen freezer. The brains were dissected into ipsilateral and contralateral samples of lesioned cortex, uninjured posterior cortex, locus coeruleus, and substantia nigra. The radioenzyme assay, which measured both NE and dopamine (DA) (*9*), revealed that by 5 days after surgery right hemispheric infarction led to significant depletions of NE in the lesioned cortex, posterior cortex, and locus coeruleus, and of DA in the substantia nigra (Table 1). These data which corroborate earlier results (*1*) indicate the profound effect of right hemispheric infarction on brain catecholamine concentrations. In contrast, left hemispheric infarction had no significant effects on catecholamine concentrations 5 (*10*) or 14 days after surgery in any brain region studied (Table 1).

Table 1. Brain catecholamine concentrations following middle cerebral artery ligation. All values are means ± standard error of mean.

| Brain region | Control ($N$ = 16) (pg/mg) | Cerebral infarction (% of control) | | |
|---|---|---|---|---|
| | | Right hemisphere 5 days ($N$ = 10) | Left hemisphere 5 days ($N$ = 10) | Left hemisphere 14 days ($N$ = 6) |
| | | *Norepinephrine* | | |
| Lesioned cortex | 310 ± 16 | | | |
| Ipsilateral | | 70 ± 6* | 93 ± 10 | 94 ± 14 |
| Contralateral | | 83 ± 7 | 98 ± 9 | 117 ± 10 |
| Posterior cortex | 263 ± 18 | | | |
| Ipsilateral | | 72 ± 7* | 103 ± 5 | 92 ± 8 |
| Contralateral | | 89 ± 6 | 113 ± 7 | 96 ± 14 |
| Locus coeruleus | 440 ± 11 | | | |
| Ipsilateral | | 75 ± 8† | 93 ± 20 | 143 ± 37 |
| Contralateral | | 111 ± 12 | 86 ± 9 | 125 ± 19 |
| | | *Dopamine* | | |
| Substantia nigra | 910 ± 83 | | | |
| Ipsilateral | | 83 ± 10† | 96 ± 5 | 116 ± 8 |
| Contralateral | | 97 ± 9 | 82 ± 14 | 82 ± 7 |

*$P < .02$. †$P < .05$.

Histological examination of toluidine blue–stained sections periodically sampled between the lesion site and the locus coeruleus revealed that the only neuronal damage was limited to the cerebral cortex of either the right or left hemisphere. The lesion in either hemisphere had a similar appearance: it was generally circular when viewed from above and was in the frontoparietal cortex lateral to the cingulate cortex and above the rhinal fissure at about where the ligature was tied. The lesion varied in diameter from 1 to 5 mm but never extended below the white matter of the internal capsule (Fig. 2). Using a 1 to 10 rating scale (small to large), two observers rated the lesion size on the gross brain (*8*). At 35 days after surgery, the mean size of 21 left hemispheric infarcts was 3.9 ± 0.7 (standard error of mean) and that of right hemispheric infarcts, 3.3 ± 0.9 (not significantly different). At 5 days after surgery, sizes were 2.4 ± 0.4 for right infarcts and 2.6 ± 0.2 for left infarcts.

Since lesion size varied slightly from animal to animal, mean running wheel activity during the 5-day period from 10 to 14 days after surgery were compared for animals with similarly sized lesions (Fig. 2). Although numbers in each group were small, the animals with lesions on the right tended to be more active than those with lesions on the left for all infarct sizes.

These studies demonstrated differential behavioral and biochemical effect of right versus left hemispheric infarction. That is, animals with right hemispheric infarction showed a transient period of postoperative hyperactivity (as measured by running wheel or open field testing) and widespread depletions of catecholamines while animals with left hemispheric infarction were neither hyperactive nor depleted of catecholamines. Our study suggests that there was a generalized increase in activity after lesions of the right but not the left cerebral hemisphere. In contrast, specific behavioral deficits such as motor-sensory loss are localized to the contralateral cerebral hemisphere (*11*). In addition, animals with left hemispheric lesions did not appear to be ill or nonspecifically injured in a way that might suppress their activity; they ate and drank as much as controls and in the open field they moved normally with no evidence of hemiparesis or other neurological disability. Hyperactivity after right but not left hemispheric cortical injury in rats has been reported by Denenberg *et al.* (*12*). However, their methodology was quite different from ours; one entire hemisphere was ablated and thus the lesion was neither focal nor ischemic, and only open field activity was observed. The biochemical findings in the present study are supported by the work of Oke *et al.* (*5*), who reported lateralization of the subcortical catecholamine pathways in humans.

There are several reasons why I believe the right and left lesions described here are comparable. (i) The surgical approach on both sides was identical. (ii) The location of the lesion on the gross brain was symmetrical for the two groups. (iii) Mean lesion sizes for the two groups were not significantly different. (iv) Histological examination of the brain revealed no differential pathology related to side. Also, when the behavioral data were grouped by lesion size (Fig. 2), for the two smallest lesion sizes the animals with right infarcts were significantly more active than those with lesions on the left.

Finding a generalized behavioral and biochemical disturbance which can be elicited by lesions of one cerebral hemisphere but not the other strongly suggests that there is an underlying anatomical or physiological asymmetry in the brain. We have proposed that catecholaminergic pathways, particularly noradrenergic ones, may be involved in the transient period of postinfarction hyperactivity (*4*) and that changes from intracellular manufacture of catecholamines to protein for regeneration and sprouting (*13*) may explain the development and disappearance of hyperactivity. However, these findings do not necessarily mean that the catecholaminergic pathways are anatomically or functionally asymmetrical. If the postischemic changes in catecholamine concentrations are the result of retrograde reactions within the catecholaminergic neurons, this would suggest that the NE- and DA-containing pathways are anatomically or physiologically different on the two sides of the brain. However, if the postoperative changes in catecholamine concentrations are the results of a feedback loop involving noncatecholaminergic neurons, then these feedback neurons could be physiologically or anatomically asymmetrical. Recent evidence in both humans and rats (*5, 6*) has suggested that the subcortical catecholaminergic pathways may be asymmetrical. Since ascending subcortical catecholaminergic pathways arborize within the cerebral

cortex (*14*), asymmetries within these pathways could cause lesions of the right hemisphere to affect catecholaminergic neurons differently from identical lesions of the left hemisphere. Although Glick *et al.* found asymmetry in the rat nigrostriatal pathway, the side with greater DA concentration varied among animals. In addition they found no asymmetry in forebrain NE (*6*).

In previous studies we have suggested that post-stroke emotional changes in humans, such as apathy and depression, may be the psychological manifestation of the changes occurring within the catecholaminergic neurons (*1–4*). Our current results suggest that emotional lateralization following brain injury may also be the psychological consequence of the asymmetrical response of catecholaminergic neurons to cortical injury.

ROBERT G. ROBINSON
*Department of Psychiatry and Behavioral Science, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205*

### References and Notes

1. R. G. Robinson, W. J. Shoemaker, M. Schlumpf, T. Valk, F. E. Bloom, *Nature (London)* **255**, 332 (1975).
2. R. G. Robinson, F. E. Bloom, E. L. F. Battenberg, *Brain Res.* **132**, 259 (1977).
3. R. G. Robinson and F. E. Bloom, *J Comp. Physiol. Psychol.* **92**, 969 (1978).
4. ———, *Biol. Psychiatry* **12**, 669 (1977); in *Cerebrovascular Diseases*, P. Scheinberg, Ed. (Raven, New York, 1976), p. 199; F. W. Bloom, S. Algeri, A. Groppetti, A. Revuelta, E. Costa, *Science* **166**, 1284 (1969).
5. A. Oke, R. Keller, I. Mefford, R. N. Adams, *Science* **200**, 1411 (1978).
6. S. D. Glick, T. P. Jerussi, B. Zimmerberg, in *Lateralization in the Nervous System*, S. Harnad *et al.*, Eds. (Academic Press, New York, 1977), p. 213.
7. The cages, designed by C. P. Richter, consisted of a stationary 8 by 13 by 28 cm wire mesh compartment and a wire mesh running wheel 34 cm in diameter. The friction of rotation for each wheel was checked periodically to ensure uniform conditions [C. P. Richter and G. H. Wang, *J. Lab. Clin. Med.* **12**, 289 (1926)].
8. The Interrater correlation coefficient for reliability of the total number of grid crossings during a 5-minute period was 0.99 for all rats; that for reliability for lesion size was 0.96. One of the raters was unaware of the behavioral findings at the time of testing.
9. J. T. Coyle and D. Henry, *J. Neurochem.* **21**, 61 (1973).
10. R. G. Robinson and J. T. Coyle, *Life Sci.* **24**, 943 (1979).
11. C. N. Woolsey, in *Biological and Biochemical Bases of Behavior*, H. F. Harlow and C. N. Woolsey, Eds. (Univ. of Wisconsin Press, Madison, 1958); W. Penfield and E. Boldrey, *Brain* **60**, 389 (1937).
12. V. H. Denenberg, J. Garbanati, G. Sherman, D. A. Yutzey, R. Kaplan, *Science* **201**, 1150 (1978).
13. D. J. Reis, R. A. Ross, G. Gilad, T. H. Joh, *Neuronal Plasticity* (Raven, New York, 1978), pp. 197–226.
14. V. M Pickel, M. Segal, F. E. Bloom, *J. Comp. Neurol.* **155**, 15 (1974); U. Ungerstedt, *Acta Physiol. Scand. Suppl.* **367**, 1 (1971); P. C. Emson and G. F. Koob, *Brain Res.* **142**, 249 (1978); O. Lindvall *et al.*, *ibid.* **81**, 325 (1974).
15. Supported in part by NIH grants MH 32902, RR-5378, and MH 26654. I thank J. T. Coyle for doing the biochemical assays, P. R. McHugh, J. B. Wirth, and E. M. Stricker for their reviews of the manuscript, and C. Commander for secretarial assistance.

5 September 1978; revised 26 April 1979

## Differences in Neural Organization Between Individuals with Inverted and Noninverted Handwriting Postures

Abstract. *Levy's hypothesis that movements of the distal musculature are controlled by ipsilateral motor projections in subjects with inverted writing posture was tested in a reaction-time experiment with lateralized auditory, tactual, and visual stimulation. Subjects were required to depress a response key with the left or right index finger when they detected a stimulus in either the left or right sensory field. Writers with noninverted posture responded quickest to stimuli on the same side as the responding hand in all modalities tested, whereas inverted writers showed this pattern only in auditory and tactual modalities. In the visual modality, they responded quickest to stimuli on the side opposite the responding hand. Because Levy's hypothesis predicts the latter effect in all modalities for inverted writers, it is challenged by our results, which suggest that inverted writers may be characterized by anomalous visual or visuomotor organization.*

The relation between handedness and cerebral dominance would be relatively simple if there were no left-handers. Whereas more than 95 percent of right-handers are left hemisphere–dominant for language, only 60 to 70 percent of left-handers show this pattern, the remainder being divided into those who have language represented bilaterally and those who have it on the right (*1*). Attempts to predict cerebral dominance in left-handers on the basis of such factors as familial handedness and strength of handedness have not been entirely successful, which indicates that relation among these factors and cerebral dominance in left-handers is not well understood (*1, 2*). It has been proposed, however, that hand posture during writing may provide the best index of cerebral dominance in both left- and right-handers (*3*).

Most individuals assume one of two postures during writing; noninverted, with the hand below the line of writing and the pen pointing to the top of the page; or inverted, with hand above the line of writing and the pen pointing downward giving the hand a hooked appearance. According to a model proposed by Levy (*3*), hemispheric motor projections, such as the pyramidal tracts, that control fine movements of the distal musculature are primarily contralateral in noninverted writers and ipsilateral in inverted writers. Consequently, the language-dominant hemisphere is on the same side as the writing hand in inverted writers and on the opposite side in noninverted writers. The ideas regarding hemispheric motor control, and the predictions that follow from it, are derived, in part, from a genetic model of handedness and cerebral dominance (*4*). It states that cerebral dominance is determined by one gene and handedness is determined indirectly by a second gene that specifies whether the dominant hand will be ipsilateral or contralateral to the language-dominant hemisphere.

Levy and Reid (*5*) found that the pattern of hemispheric specialization as reflected in the performance of normal people on tachistoscopic laterality tests was in accordance with the model. In identifying unilaterally presented nonsense syllables, noninverted writers favored the visual field on the same side as the writing hand, thereby implicating the hemisphere contralateral to it as the dominant one for language. Inverted writers showed the opposite pattern of results, except for diminished perceptual (and presumably hemispheric) asymmetries, which suggests that in this population speech is relatively bilaterally represented (*1*).

Not all attempts to verify this hypothesis were as successful. A number of investigators (*6–8*) using a variety of techniques, including tachistoscopic ones, to assess cerebral dominance either found no relation between hand posture and speech lateralization or a weak correlation. Rather than attempt to assess language lateralization yet another time, we decided to test that aspect of the model that deals with hemispheric control of the distal musculature. This problem is central both to the model on hand posture during writing and cerebral organization and to the genetic model (*4*) of handedness and cerebral dominance. In addition, there was no direct empirical evidence on the validity of the assertion that fine motor movements are controlled by the ipsilateral hemisphere in inverted writers or, for that matter, in anyone. This notion is so contrary to widely held views of structural and functional neuroanatomy (*9*) that any evidence in its favor would have far-reaching implications on our ideas of the organization of the nervous system. Negative evidence, on the other hand,


0036-8075/79/0817-0710$00.50/0 