Proc. Natl. Acad. Sci. USA
Vol. 84, pp. 561–563, January 1987
Medical Sciences

Left globus pallidus abnormality in never-medicated patients with schizophrenia

(cerebral blood flow/positron emission tomography)

TERRENCE S. EARLY*†, ERIC M. REIMAN*†, MARCUS E. RAICHLE†‡§¶, AND EDWARD L. SPITZNAGEL‖

*Department of Psychiatry; †McDonnell Center for Studies in Higher Brain Function; ‡Department of Neurology and Neurological Surgery; §Edward Mallinckrodt Institute of Radiology; and ‖Departments of Mathematics and Preventive Medicine (Divisions of Biostatistics and Health Care Research), Washington University School of Medicine, St. Louis, MO 63110

Communicated by Michael I. Posner, October 3, 1986

ABSTRACT **Schizophrenia is a severe psychiatric disorder characterized by onset in young adulthood, the occurrence of hallucinations and delusions, and the development of enduring psychosocial disability. The pathophysiology of this disorder remains unknown. Studies of cerebral blood flow and metabolism designed to identify brain abnormalities in schizophrenia have been limited by inadequate methods of anatomical localization and the possibility of persistent medication effects. We have now used positron emission tomography and a validated method of anatomical localization in an attempt to identify abnormalities of regional cerebral blood flow in newly diagnosed never-medicated patients with schizophrenia. An exploratory study of 5 patients and 10 normal control subjects identified abnormally high blood flow in the left globus pallidus of patients with schizophrenia. A replication study of 5 additional patients and 10 additional control subjects confirmed this finding. No other abnormalities were found.**

Studies of cerebral blood flow (1–9) and metabolism (10–17, 41) have attempted to identify regional abnormalities in patients with schizophrenia. Unfortunately, at least two methodological problems have contributed to inconsistent findings. One important problem is the localization of specific anatomical regions within images of blood flow and metabolism. This problem is attributable to the lack of precise anatomical landmarks within these physiological images. One strategy for anatomical localization identifies regions based on visual inspection of the image; however, this strategy is imprecise, unreliable, and subject to observer bias. Another strategy identifies regions based on comparisons between tomographic images of blood flow and metabolism and an atlas of the brain, such that all planes are parallel to a standard reference plane (e.g., a horizontal plane through the canthomeatal line); however, this strategy may be inaccurate because of the variability in the relationship of the brain to standard craniofacial landmarks. A third strategy compares tomographic images of blood flow and metabolism to a computerized tomography or magnetic resonance image obtained in the same plane; however, this strategy cannot distinguish adjacent regions of gray matter and is uncertain in its ability to provide reliable comparisons among different subjects. (See ref. 18 for a review of these issues.)

Another important problem is the physiological effect of antipsychotic medications on measurements of blood flow and metabolism. All but three previous studies (10, 17, 41) used patients with a history of antipsychotic drug use and withdrawal periods of less than a few weeks. Since the effects of antipsychotic drugs can last for many weeks [e.g., the inhibition of apomorphine-induced stereotopy (19)] or longer [e.g., tardive dyskinesia (20)], these studies cannot account for the possibility of persistent medication effects.

We have now used positron emission tomography and a validated method of anatomical localization (18) to identify abnormalities of regional cerebral blood flow in newly diagnosed never-medicated patients with schizophrenia.

SUBJECTS

Five patients (all males; mean age, 21 years; range, 18–26 years) and 10 normal control subjects (all males; mean age, 25 years; range, 20–31 years) were included in an exploratory study designed to generate hypotheses about regional abnormalities. Five additional patients (4 males and 1 female; mean age, 30 years; range, 23–32 years) and 10 additional control subjects (5 males and 5 females; mean age, 24 years; range, 21–25 years) were included in a replication study designed to test newly generated hypotheses. All of the patients satisfied DSM-III criteria (21) for schizophrenia, including a minimum duration of 6 months at either the time of study or the time of follow-up. They had never been exposed to psychotropic medication or hospitalized prior to the study. They denied a history of other psychiatric disorders or substance abuse and were physically well. The control subjects were unmedicated, denied a history of psychiatric disorders, and were medically well. All of the patients and control subjects were right-handed. (Patient histories will be described in a future report and are available upon request.)

METHOD

Studies were performed with the PETT VI system (22, 23), which simultaneously records data from seven parallel slices with a center-to-center separation of 14.4 mm. Studies had an in-plane resolution of 12.4–14.7 mm and a transverse resolution of 9.7–20.5 mm (22, 23). Regional blood flow was measured using an intravenous bolus injection of $H_2{}^{15}O$, a 40-sec emission scan, and a modification of the Kety autoradiographic model developed and validated in our laboratory (24, 25). During the scans, the subjects lay quietly with their eyes closed and received minimal sensory stimulation. Their heads were stabilized with a thermally molded plastic facial mask (22) to prevent movement during the study.

Regions of interest were selected from a stereotactic atlas of the brain (26) and identified in the positron emission tomography image using an anatomical localization method developed and validated in our laboratory (18). Data from these regions were recorded independent of the visual inspection of the image and were thus free from observer bias. This method permits regional comparisons among different subjects and different laboratories.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

¶To whom reprint requests should be addressed at: Washington University School of Medicine, Campus Box 8131, St. Louis, MO 63110.

In the exploratory study, whole brain, hemisphere, and regional blood flow were computed from the data in all subjects. Whole brain and hemisphere measurements were calculated according to a strategy developed in our laboratory (27). Regions for whole brain measurements measured 13.5 × 13.5 mm in the plane of the slice.

Local measurements were obtained bilaterally in 16 areas of the brain. The regions and their stereotactic atlas coordinates are listed in Table 1. Regions for local measurements measured 13.5 × 13.5 mm in the plane of the slice. Regional data were converted to ratios of regional/whole brain blood flow and ratios of left/right regional blood flow to permit comparisons independent of between-subject variations in absolute blood flow measurements.

Data from the exploratory study were analyzed using multiple *t* tests. Based on the results of this exploratory study, described below, a replication study was performed to test the newly generated hypothesis that patients with schizophrenia have abnormally high blood flow in the left globus pallidus. The ratios of left globus pallidus to whole brain blood flow were analyzed for the additional patients and control subjects using a separate *t* test. The ratios of regional/whole brain blood flow for each of the frontal regions were also analyzed for the additional patients and control subjects using *t* tests.

After separate analyses of the exploratory and replication studies, ratios of left globus pallidus/whole brain blood flow for the 10 patients and 20 control subjects were combined and then compared using an analysis of covariance that accounted for the effects of age, sex, and race.

RESULTS

The exploratory study identified an abnormally high ratio of left globus pallidus/whole brain blood flow in the patients with schizophrenia ($P = 0.0056$). No other abnormalities were found.

The replication study confirmed the finding of an abnormally high ratio of left globus pallidus/whole brain blood flow in the patients with schizophrenia ($P = 0.0012$). As before, this study failed to suggest abnormally low ratios of frontal/whole brain blood flow in the patients with schizophrenia.

Consistent with these results, the combined study demonstrated an abnormally high ratio of left globus pallidus/whole brain in the patients with schizophrenia ($P = 0.00011$; Fig. 1).

Table 1. Location of selected cerebral regions in a stereotactic atlas

	x, cm	*y*, cm	*z*, cm
Basal ganglia			
Globus pallidus	±1.6	1.0	0.0
Caudate	±1.0	2.5	0.8
Putamen	±2.3	1.5	0.3
Frontal regions			
Dorsolateral prefrontal cortex (anterior inferior)	±4.2	0.9	4.2
Dorsolateral prefrontal cortex (anterior superior)	±1.8	3.0	5.0
Dorsolateral prefrontal cortex (posterior)	±3.6	2.0	5.0
Medial frontal pole	±0.9	6.5	0.0
Lateral frontal pole	±2.6	5.3	0.9
Mesial precentral gyrus	±1.0	−0.5	5.0
Orbito-insular gyri	±3.4	2.7	0.7
Limbic structures			
Anterior cingulate gyrus	±0.7	4.0	2.0
Parahippocampal gyrus	±2.3	−2.3	−0.3
Amygdala	±2.3	0.9	−1.7
Hypothalamus	±0.7	0.8	−0.5
Other structures			
Medial thalamus	±0.8	0.0	1.3
Inferior parietal lobule	±3.0	−3.8	4.0

x, Lateral distance to the left (positive) or to the right (negative) of the center of the brain slice containing the region of interest. *y*, Distance anterior (positive) or posterior (negative) to the center of the brain slice containing the region of interest. *z*, Vertical distance of the brain slice containing the region of interest above (positive) or below (negative) a horizontal plane through the anterior and posterior commissures.

DISCUSSION

Although the majority of studies involving chronic previously treated patients have identified "hypofrontality" (1–4, 8, 9, 11, 13–16) (i.e., an abnormally low ratio of frontal/whole brain or frontal/nonfrontal blood flow and metabolism) in patients with schizophrenia, this study, as well as three others (10, 17, 41) involving acute never-medicated patients, has been unable to confirm this finding. Furthermore, several studies have shown a reduction in the ratio of frontal/nonfrontal blood flow and metabolism after administration of antipsychotic medications (12, 15, 16). Based on these findings, we postulate that hypofrontality reflects a long-lasting effect of antipsychotic medication rather than the pathophysiology of schizophrenia. The role, if any, of additional factors in the development of hypofrontality (e.g., chronicity of illness or the patients' cognitive–emotional–behavioral state) remains to be determined.

This study demonstrated abnormally high blood flow in the left globus pallidus of never-medicated patients with schizophrenia. The failure of previous radiotracer studies to detect this abnormality can be explained. Nontomographic measurements of regional blood flow preferentially sample from the cerebral cortex, completely missing subcortical structures such as the globus pallidus. Previous positron emission tomography studies did not use anatomical localization strategies that permit accurate isolation of the globus pallidus. The method of anatomical localization used in our laboratory was critical to the success of this study.

The identification of a left-sided abnormality in this study is consistent with numerous studies that have suggested left hemispheric dysfunction in patients with schizophrenia. These studies used such diverse measures as electroencephalography, evoked potentials, auditory thresholds, ear ad-

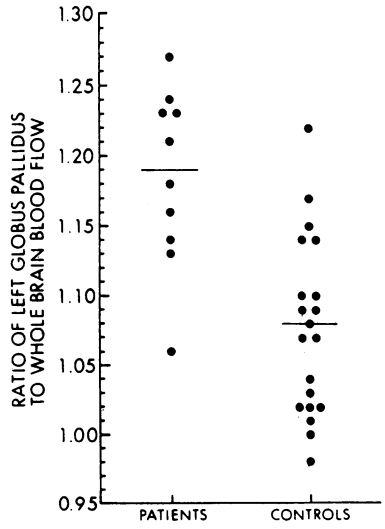

FIG. 1. The ratio of left globus pallidus/whole brain blood flow in 10 never-medicated patients with schizophrenia and 20 normal control subjects. The mean for each group is indicated by a horizontal line.

vantages in dichotic listening, dichotic shadowing, handedness, performance on psychometric tests, signs from computerized tomography, and hemispheric blood flow (6, 7, 28–31).

The finding of a specific abnormality in the basal ganglia of patients with schizophrenia is of special interest because of the recent suggestion that the basal ganglia may be involved in complex behavioral functions (32, 33). The globus pallidus and other structures in the basal ganglia are well recognized to affect motor functions. However, it also has been postulated that these structures affect cognitive functions, based on their afferent and efferent connections (32). Unfortunately, the resolution of the imaging device used in this study does not permit us to distinguish between ventral pallidum—which receives projections from limbic striatum, sends projections to limbic and frontal regions, and has been postulated to affect cognitive functions—and dorsal pallidum—which receives projections from nonlimbic striatum, sends projections to motor cortex, and is thought to affect motor function (32, 33).

Since there is a close coupling of regional blood flow and neuronal activity (34, 35), the abnormality in the left globus pallidus could reflect increased neuronal activity. Experimental studies in animals indicate that such increases reflect increased activity in terminal fields that innervate a region rather than the cell bodies that arise there (36, 37). Projections to the left globus pallidus arise in the left caudate, putamen, subthalamic nucleus, and nucleus accumbens (38). One of these structures, the nucleus accumbens, has been postulated to have a role in the pathophysiology of schizophrenia and in the therapeutic action of antipsychotic medications (39, 40).

This study does not preclude the existence of other regional abnormalities in patients with schizophrenia. Due to the problems imposed by multiple comparisons on statistical analysis, numerous regional comparisons were restricted to the exploratory phase of the study, which involved a small number of subjects. Furthermore, analysis of regions which are very close to the ventricles and lateral surfaces of the brain may be confounded by the effects of partial volume averaging. However, these limitations are unrelated to the robust finding of a globus pallidus abnormality in newly diagnosed never-medicated patients with schizophrenia.

The relationships between the left globus pallidus abnormality and other aspects of schizophrenia, such as the patient's cognitive–emotional–behavioral state, familial transmission, response to treatment, and prognosis were not addressed in this study. Such relationships will be important to establish.

This research was supported by National Institutes of Health Grant HL13851 from the National Heart, Lung and Blood Institute, Health and Human Services; Physician Scientist Award MY-00615 from the National Institute of Mental Health (E.M.R.); and the McDonnell Center for Studies in Higher Brain Function.

1. Ingvar, D. & Franzen, G. (1974) *Acta Psychiatr. Scand.* **50,** 425–462.
2. Franzen, G. & Ingvar, D. (1975) *J. Neurol. Neurosurg. Psychiatry* **38,** 1027–1032.
3. Ingvar, D. & Franzen, G. (1974) *Lancet* **ii,** 1484–1486.
4. Ariel, R., Golden, C., Berg, R., Quaife, M., Dirksen, J., Forsell, T., Wilson, J. & Graber, B. (1983) *Arch. Gen. Psychiatry* **40,** 258–263.
5. Mathew, R., Duncan, G., Weinman, M. & Barr, D. (1982) *Arch. Gen. Psychiatry* **39,** 1121–1124.
6. Gur, R., Skolnick, B., Gur, R., Caroff, S., Rieger, W., Obrist, W., Younkin, D. & Reivich, M. (1983) *Arch. Gen. Psychiatry* **40,** 1250–1254.
7. Gur, R. E., Gur, R. C., Skolnick, B., Caroff, S., Obrist, W., Resnick, S. & Reivich, M. (1985) *Arch. Gen. Psychiatry* **42,** 329–334.
8. Weinberger, D., Berman, K. & Zec, R. (1986) *Arch. Gen. Psychiatry* **43,** 114–124.
9. Berman, K., Zec, R. & Weinberger, D. (1986) *Arch. Gen. Psychiatry* **43,** 126–135.
10. Sheppard, G., Gruzelier, J., Manchanda, R., Hirsch, S., Wise, R., Frackowiak, R. & Jones, T. (1983) *Lancet* **ii,** 1448–1452.
11. Farkas, T., Wolf, A., Jaeger, J., Brodie, J., Christman, D. & Fowler, J. (1984) *Arch. Gen. Psychiatry* **41,** 293–300.
12. Widen, L., Blomquist, G., Greitz, T., Litton, J., Bergstrom, M., Ehrin, E., Ericson, K., Eriksson, L., Ingvar, D., Johansson, L., Nilsson, J., Stone-Elander, S., Sedvall, G., Wiesel, F. & Wiik, G. (1983) *Am. J. Neuroradiol.* **4,** 550–552.
13. Buchsbaum, M., Ingvar, D., Kessler, R., Waters, R., Cappelletti, J., van Kammen, D., King, C., Johnson, J., Manning, R., Flynn, R., Mann, L., Bunney, W. & Sokoloff, L. (1982) *Arch. Gen. Psychiatry* **39,** 251–259.
14. Buchsbaum, M., DeLisi, L., Holcomb, H., Cappelletti, J., King, C., Johnson, J., Hazlett, E., Dowling-Zimmerman, S., Post, R., Morihisa, J., Carpenter, W., Cohen, R., Pickar, D., Weinberger, D., Margolin, R. & Kessler, R. (1984) *Arch. Gen. Psychiatry* **41,** 1159–1166.
15. DeLisi, L., Holcomb, H., Cohen, R., Pickar, D., Carpenter, W., Morihisa, J., King, C., Kessler, R. & Buchsbaum, M. (1985) *J. Cereb. Blood Flow Metab.* **5,** 201–206.
16. Wolkin, A., Jaeger, J., Brodie, J., Wolf, A., Fowler, J., Rotrosen, J., Gomez-Mont, F. & Cancro, R. (1985) *Am. J. Psychiatry* **142,** 564–571.
17. Garnett, E. S., Nahmias, C., Firnau, G. & Cleghorn, J. (1985) *J. Cereb. Blood Flow Metab.* Suppl. 1, **5,** S220.
18. Fox, P., Perlmutter, J. & Raichle, M. (1985) *J. Comput. Assist. Tomogr.* **9(1),** 141–153.
19. Campbell, A., Baldessarini, R., Teicher, M. & Kula, N. (1985) *Psychopharmacology* **87,** 161–166.
20. Task Force on Late Neurological Effects of Antipsychotic Drugs (1980) *Am. J. Psychiatry* **137,** 1163–1172.
21. *Diagnostic and Statistical Manual Vol. 3* (1980) (Am. Psychiatric Assoc., Washington, DC).
22. Ter-Pogossian, M., Ficke, D., Hood, J., Yamamoto, M. & Mullani, N. (1982) *J. Comput. Assist. Tomogr.* **6,** 125–133.
23. Yamamoto, M., Ficke, D. & Ter-Pogossian, M. (1982) *IEEE Trans. Nucl. Sci.* **NS29,** 529–533.
24. Raichle, M., Martin, W., Herscovitch, P., Mintun, M. & Markham, J. (1983) *J. Nucl. Med.* **24,** 790–798.
25. Herscovitch, P., Markham, J. & Raichle, M. (1983) *J. Nucl. Med.* **24,** 782–789.
26. Talaraich, J. & Szilkz, G., eds. (1967) *Atlas D-Anatomie Stereotaxique du Telencephale* (Masson, Paris).
27. Perlmutter, J., Herscovitch, P., Powers, W., Fox, P. & Raichle, M. (1985) *J. Cereb. Blood Flow Metab.* **5,** 476–478.
28. Gruzelier, J. D. (1985) in *Handbook of Clinical Neurology,* ed. Frederiks, J. A. M. (Elsevier, New York), Vol. 2 (46), pp. 481–521.
29. Newlin, D., Carpenter, B. & Golden, C. (1981) *Biol. Psychiatry* **16,** 561–582.
30. Davidson, K. & Bagley, C. (1969) *Current Problems in Neuropsychiatry* (Headley, Ashford, Kent), pp. 113–184.
31. Nasrallah, H. (1982) *Schizophrenia as a Brain Disease,* eds. Henn, F. & Nasrallah, H. (Oxford, New York).
32. Nauta, W. H. (1986) in *The Limbic System: Functional Organization and Clinical Disorders,* eds. Doane, B. K. & Livingston, K. F. (Raven, New York), pp. 43–54.
33. Heimer, L., Switzer, R. D. & Van Hoesen, G. W. (1982) *Trends Neurosci.* **5,** 83–87.
34. Raichle, M., Grubb, R., Gado, M., Eichling, J. & Ter-Pogossian, M. (1976) *Arch. Neurol.* **33,** 523–526.
35. Fox, P. R. & Raichle, M. (1986) *Proc. Natl. Acad. Sci. USA* **83,** 1140–1144.
36. Schwartz, W., Smith, C., Davidson, L., Savaki, H., Sokoloff, L., Mata, M., Fink, P. J. & Gainer, H. (1979) *Science* **205,** 723–725.
37. Perlmutter, J. & Raichle, M. (1985) *Neurology* **35,** 1127–1134.
38. Dray, A. (1980) *Prog. Neurobiol.* **14,** 221–335.
39. Stevens, J. (1973) *Arch. Gen. Psychiatry* **29,** 177–189.
40. Crow, T., Deakin, J. & Longden, A. (1977) *Psychol. Med.* **7,** 213–221.
41. Volkow, N. D., Brodie, J. D., Wolf, A. P., Angrist, B., Russell, J. & Cancro, R. (1986) *J. Neurol. Neurosurg. Psychiatry* **49,** 1199–1202.