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Regional Cerebral Blood Flow and Lateralized Hemispheric Dysfunction in Depression

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Summary: Cerebral blood flow is known as an indicator of cerebral metabolism. Using the ^{133}Xenon inhalation method, we studied the regional cerebral blood flow (r-CBF) in patients with different subtypes of depression and in remission. A left frontal hypervascularization and a right posterior hypovascularization were found in major depressives, compared to normal subjects, minor depressives, and normothymic bipolar patients. These results tend to confirm the existence of cerebral dysfunction in both hemispheres in major depression, as reported by other authors using different techniques.

Several studies have reported lateralized hemispheric dysfunction in affective disorders (D'Elia and Perris, 1973; D'Elia and Perris, 1974; Flor-Henry, 1976; Gruzelier and Venables, 1979; Gruzelier and Flor-Henry, 1979). Recently, cerebral blood flow measurement has been used as an indicator of cerebral metabolism in psychiatry. This method has shown cerebral dysfunction in schizophrenia (Ingvar and Franzen, 1974; Jacquy *et al*, 1976; Ingvar, 1980), but few studies have been performed in the field of affective disorders, and their results are controversial (Mathew *et al*, 1980; Ingvar, 1981; Gustafson *et al*, 1981). For this reason, we have used the ^{133}Xenon inhalation method to measure the regional Cerebral Blood Flow (r-CBF) in patients with different subtypes of depression and in remission.

Methods

Four groups of subjects were selected according to the Research Diagnostic Criteria (Spitzer *et al*, 1975): (i) 16 patients (three men and 13 women; mean age±SD = 51.5±13.4 years) with the diagnosis of definite major depressive disorder; (ii) ten patients (three men and seven women; mean age±SD = 35.4±8.1 years) suffering from a minor depression; (iii) eight bipolar manic-depressive patients (two men and six women; mean age±SD = 50.6±11 years) studied in a normothymic phase; and (iv) 20 non-psychiatric healthy volunteers (eight men and 12 women; mean age±SD = 41±11 years) as a control group. Patients with dementia, migraine, epilepsy, alcoholism, drug addiction, or somatic disorders were excluded from this study through physical examination, EEG, CAT scan and laboratory tests.

All depressive patients were in-patients and underwent a medication wash-out period of at least 15 days, except for a benzodiazepine at low dosage (lorazepam, 2.5–7.5 mg/day; mean: 6.7±1,3 for the group of major depressives; mean: 6.6±1,4 for the group of minor depressives; no significant difference).

All manic-depressive patients in remission were treated with lithium carbonate (plasma levels: 0.8–1.4 mEq/1) on an out-patient basis, but did not receive any other psychotropic drug for at least one month before the study. The severity of depression was quantified by the Hamilton Rating Scale for Depression (Hamilton, 1960) on the day of the CBF measurement.

The ^{133}Xenon inhalation technique is non-invasive, reliable, and reproducible (Obrist *et al*, 1975; Meyer *et al*, 1978). ^{133}Xenon, a chemically inert and diffusible gas which emits gamma activity, is mixed with ambient air and inhaled through a face mask. After a one-minute period of inhalation, the decreasing activity of the isotope is monitored for ten minutes by 16 collimated probes, mounted in a helmet and applied to the scalp. The end-tidal ^{133}Xenon activity is also measured. The values of r-CBF are calculated by two compartmental analyses of the recorded curves, by a computer, during the ten-minute desaturation period. This analysis is based on the Fick principle, and the end-tidal ^{133}Xenon curves, recorded from the face mask, are used for correction of ^{133}Xenon recirculation to the brain. After obtaining informed consent, CBF was measured on a Baylor system, at rest (eyes open in a still dark room) under the same standard conditions for the four groups.

To calculate and interpret the results, we used the initial slope index 2.5 (ISI 2.5), which is the most

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TABLE I

Comparison between the groups of major depression (M), minor depression(M), normothymic bipolar patients (BP), and normal subjects (N). (Relative values of i.s.i. 2,5.)

	M-N	m-N	BP-N	M-m	M-BP
Left frontal ratio	6.78*	2.24	−1.91	4.54	8.69**
Right frontal ratio	−3.03	1.02	−1.15	−4.50*	−1.88
Left posterior ratio	−0.22	1.72	−0.40	−1.94	0.18
Right posterior ratio	−4.69*	−0.47	1.68	−4.22*	−6.37**
Hemispheric ratio* (Left/Right)	6.45	1.45	1.45	5	5

Level of significance: * = P <0.05
** = P <0.01

TABLE II

Analysis of variance comparing the groups of normal subjects (N), normothymic bipolar patients (BP), minor depressives (m) and major depressives (M).

	N+m+BP	N+m+BP+M	m+BP+M
Left frontal region (L.F.)	F : 0.82 (2–35)	F : 3.59* (3–50)	F : 5.36** (2–31)
Right frontal region (R.F.)	F : 0.31 (2–35)	F : 1.13 (3–50)	F : 1.49 (2–31)
Left posterior region (L.P.)	F : 0.63 (2–35)	F : 0.47 (3–50)	F : 0.72 (2–31)
Right posteroir region (R.P.)	F : 0.28 (2–35)	F : 2.65 (3–50)	F : 5.22* (2–31)
Hemispheric ratio (left/right)	F : 0.15 (2–35)	F : 1.88 (3–50)	F : 1.42 (2–31)

* P <.05; ** P <.01

reliable one in this technique (Prohovnik *et al*, 1980). To avoid non-specific effects on the absolute values of CBF—age, pCO_2 variations, vigilance or anxiety (Lassen *et al*, 1977)—we expressed each value as a relative one, compared with the global cerebral blood flow of the patient, as used in previous studies (Jacquy *et al*, 1976). The four anterior and three posterior probes of each hemisphere were grouped so as to study the frontal and posterior (parieto-temporo-occipital) regions. The different values were then compared, using Student's *t* test and an analysis of variance.

To test the possible effect of age on relative values of r-CBF, we calculated the correlation coefficient between age and the relative values of ISI 2.5 for each region, in the group of 20 healthy volunteers (range: 25–64 years).

Results

The mean score (±SD) on the Hamilton Rating Scale for Depression was 27.5±6.6 for the group of major depressives and 20.8±3.8 for minor depressives. Table I shows the main results of this study (detailed data available on request): the comparison between the different groups for frontal and posterior ratios of each hemisphere to the global cerebral blood flow, and for the hemispheric ratio (left/right).

A significant left frontal hypervascularization (P <0.05) was observed in the group of major depressives, when compared to normal controls and to normothymic bipolar patients. This left frontal hypervascularization was not found either in patients with minor depressives disorders nor in normothymic bipolar patients. A significant (P <0.05) hypovascularization of the right posterior region is present in the group of major depressives, as compared to normals, minor depressives, and normothymic bipolar patients. The results are confirmed by the analysis of variance shown in Table II.

These differences are also illustrated in Figs 1 and 2.

The most significant disturbance found in major depressives, when compared to normal subjects and to normothymic bipolar patients, was in the left superior frontal area (P <0.01). The hemispheric ratio values seem to indicate that there is no significant hemispheric asymmetry in any of the groups studied. Nevertheless, the hemispheric ratio (left/right) is rather high in

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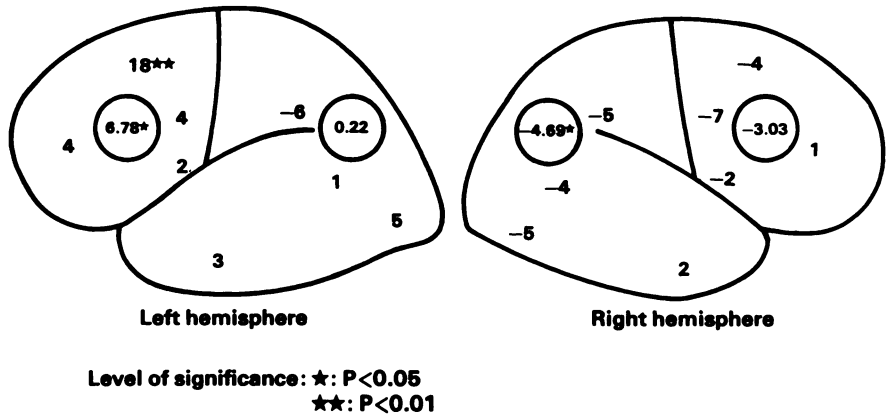


FIG 1.—Difference between the group of major depression and the control group of normal subjects (Relatives values of i.s.i. 2,5.)

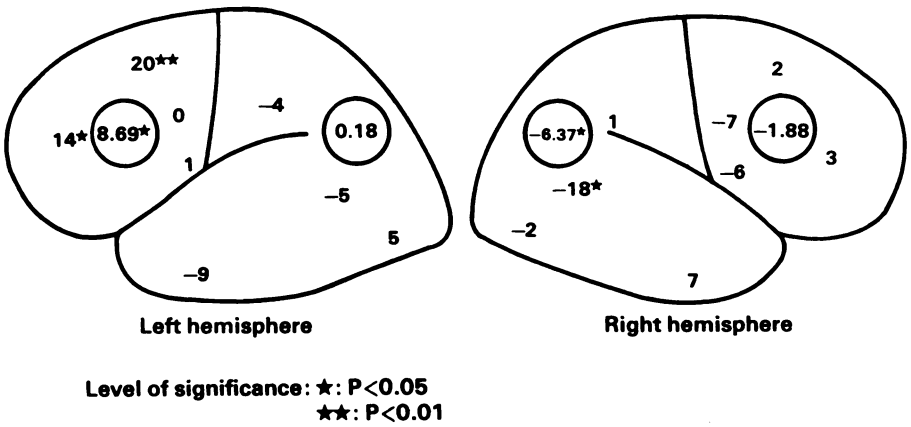


FIG 2.—Difference between the group of major depression and the group of normothymic bipolar patients (Relative values of i.s.i. 2,5.)

the major depressives, showing a trend to abnormal lateralization. In the 20 controls, no correlation was found between age and the regional relative values used in this study (L.F.: r = 0.35; R.F.: r = 0.19; L.P.: r = 0.06; R.P.: r = 0.12; all values of r = not significant).

Discussion

Most previous studies, using different techniques, reported lateralized cerebral dysfunction in major depression, mainly in the right hemisphere (Flor-Henry, 1976; Gruzelier and Venables, 1974; Myslobodsky and Horesh, 1978) but not constantly so (D'Elia and Perris, 1973; D'Elia and Perris, 1974). The results of previous CBF studies in depression are controversial, Gustafson *et al* (1981) and Ingvar (1981) having found normal CBF in depressed patients, while Mathew *et al* (1980) found significantly low values of CBF in the left hemisphere of depressed patients. These different results could be explained at least partially by methodological problems and by the use of different diagnostic criteria for selecting the patients. Because absolute values of CBF may be influenced by non-specific factors like age, vigilance, anxiety or pCO_2 variations, in our study, we used relative values of ISI 2.5 to control for such factors, which could interfere with biological phenomena.

Considering the results of several studies on the effect of aging on regional cerebral blood flow and metabolism, (Melamed *et al*, 1980; Kuhl *et al*, 1982) as well as our own results (no influence of age on the relative values used in this study), the differences of

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CBF between the different groups cannot be explained by an age effect.

The main finding of this study is the observation of a left frontal hypervascularization and of a right posterior hypovascularization in patients with major depressive disorder. This disturbance seems to be state-dependent rather than trait-dependent because it is not found in bipolar patients in remission.

Furthermore, the differences of CBF cannot be explained by the use of lorazepam because this medication was administered to major and minor depressives in equal amounts. The dysfunction found in both hemispheres in our study is consistent with the observation of Perris and Monakhov (1979), who reported bilateral hemispheric dysfunction correlated with depressive symptomatology, using systemic structural analysis of the EEG.

In conclusion, these results tend to confirm the existence of distinct sub-types of depression, the major depressive episodes being related to a bilateral but asymmetrical cerebral dysfunction. These findings need further confirmation, however, in well defined genetic sub-types of depression, before and after biological treatment.

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