

# Absence of activation in frontal structures during psychological testing of chronic schizophrenics

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**SYNOPSIS** The distribution of activity in the dominant hemisphere was measured with the regional cerebral blood flow (rCBF) technique in 27 chronic schizophrenics and 15 non-schizophrenic control subjects (alcoholics) at rest and during psychological testing. In the non-schizophrenics, an increase of rCBF was observed during the test in frontal regions. In the chronic schizophrenics, on the other hand, no or only a very limited increase was recorded. In postcentral structures the flow response during testing was, by and large, equal in the psychotics and the controls. The findings support the hypothesis advanced previously by the authors that in chronic schizophrenia there is defective transmission in the mediotthalamic frontocortical projection bundle. This defect also appears responsible for the abnormally low resting flow (activity) in the dominant hemisphere in chronic schizophrenia which we have described previously.

By means of regional cerebral blood flow (rCBF) measurements we have recently demonstrated that the resting brain activity (blood flow) in chronic schizophrenia has an abnormal distribution. Relative to the hemisphere mean, the activity is low in frontal regions and high in postcentral structures, as compared with non-schizophrenic subjects (Ingvar and Franzén, 1974a, b; Franzén and Ingvar, 1975). This abnormal distribution of function could be due to a defective transmission within the mediotthalamic frontocortical projection system (Skinner and Lindsley, 1973). Such a defect would give low activity in frontal parts of the brain and a relatively high activity in postcentral regions. This state was tentatively termed 'hypointentional' and 'hypergnostic', since the low activity frontally correlated with inactivity and autistic tendencies and the high activity postcentrally correlated with cognitive disturbance.

The present paper includes the results of rCBF measurements during mental activation in the above-mentioned investigation in patients with chronic schizophrenia. It will be shown that the chronic schizophrenics, especially those who were most deteriorated, in contrast with the controls,

did not show a flow (activity) increase frontally during psychological testing. This finding supports our hypothesis that in chronic schizophrenia there is a defect of some thalamocortical projection system which apparently plays a fundamental role in normal mentation.

## METHODS

The present results are based upon measurements of regional cerebral blood flow (rCBF) at rest and during psychological testing in 27 patients with chronic schizophrenia. The majority of the patients have been reported in detail in two previous communications (Ingvar and Franzén, 1974; Franzén and Ingvar, 1975). Briefly, two psychotic groups were investigated. One of them, the high score group, consisted of 13 older chronic patients (nine women and four men) aged  $66 \pm 6$  years with a very long period of hospitalization ( $42 \pm 7$  years). Their psychotic state was very advanced and, when rated with the Rockland-Pollin scale (Rockland and Pollin, 1965; *vide infra*), they got high total scores (total points, degree of psychosis, 73 to 89 points; zero representing normality). The other group, the low score group, consisted of patients with less advanced overt psychotic symptoms. It consisted of 10 younger psychotics (four women and 10 men, aged  $25 \pm 6$  years) and four

older men (aged  $66 \pm 4$  years). Their total scores ranged from 31 to 45 points.

All patients had had a normal premorbid intellectual equipment and were physically healthy apart from signs of mild hypertension in two cases. The EEG records were normal in most subjects; four subjects showed borderline EEG records with slight slowing. One case in the low score group showed occasional brief paroxysmal bilaterally synchronous spike-wave formations of low voltage.

Regional cerebral blood flow (rCBF) was measured in the dominant (left) hemisphere with the  $^{133}\text{Xenon}$  clearance method (Ingvar and Lassen, 1972; Ingvar and Franzén, 1974). Briefly, the uptake and subsequent clearance of the isotope, after injection into the cannulated internal carotid artery, was recorded by a 32 detector unit placed laterally of the patient's head. For each region measured, initial ( $f_{\text{init}}$ ) and 10 minute ( $f_{10}$ ) rCBF values, 'grey' and 'white' matter flow values ( $f_g$  and  $f_w$ ), as well as relative weights for the grey matter ( $g\%$ ) were obtained. Two studies (in some cases three or four) were made, the first at rest with the patient lying silent and supine, undisturbed by touch or verbal contact, in the laboratory and with a pad over the eyes.

The second study was carried out during mental activation which was principally of the following types:

1. In the high score group, in which the patients were extremely autistic and uncooperative, only a simple picture test could be used consisting of illustrations from a weekly magazine. Such a test in normal subjects gives rise to an increase of rCBF in occipital and frontal regions. The patients were asked to name the objects in the pictures pointed at. Several of the patients could hardly be activated at all and gave only muttering monosyllabic answers in spite of the very encouraging attitude of the examiner. Other patients, however, answered more clearly though never without prodding. As a consequence of the state of these patients, a strictly uniform testing procedure could not be applied.

2. The low score patients were tested with a reasoning test (Raven's Progressive Matrices; Raven, 1938), in which a printed pattern with a defect is shown. The patient is asked to select from six samples the pattern which fits into the defect.

As control subjects 15 psychometrically normal, male chronic alcoholics (age  $46 \pm 5$  years) were used who were also studied with the rCBF technique at rest and during mental activation (Risberg and Ingvar, 1973). Ten subjects were tested with an auditory digit-span-backward-test and nine with Raven's Matrices (four subjects were tested with both methods).

The psychiatric state of the schizophrenics was, as mentioned above, scored with the aid of the Rockland-Pollin scale (Rockland and Pollin, 1965; Ingvar and Franzén, 1974a, b). It consists of 16 items grouped under three general categories: (1) behaviour (general appearance and manner); (2) affectivity (affect and mood); and (3) cognition (content of thoughts and thought processes). For most items, there is a positive-negative continuum with zero corresponding to normality. The degree of pathology is denoted by a negative or positive figure relative to normality. Individual totals within the three categories indicate where the major portion of the patient's psychopathology is to be found. By summarizing the scores from all three categories, a total score is obtained, which gives an index of the degree of psychosis.

All patients were studied with their routine pharmacological treatment, mainly consisting of neuroleptics (Franzén and Ingvar, 1975). In the high score group, most patients had small doses mainly of butyrophenone derivatives. One patient in this group was drug free. In the low score group, phenothiazines with a piperazine chain were used to a greater extent and the dosages were as a rule larger. Some of the control subjects (alcoholics studied in a 'dry' phase) were on small doses of neuroleptics or sedatives.

For the comparison of the resting flow values with those during activation, mean hemisphere values were used. Special emphasis was laid upon the mean grey matter flow in frontal and post-central regions. The mean frontal flow was calculated from four to seven separate regions (number varying dependent upon how many detectors covered the region) precentrally and the mean postcentral flow from a corresponding number of regions in occipitoparietal parts (see Table 3). In addition, flow changes of the white matter flow ( $f_w$ ) covering the basal ganglia (Ingvar, Rosén, and Elmqvist, in preparation) were especially analysed.

## RESULTS

MEAN HEMISPHERE RCBF PARAMETERS AT REST AND DURING TESTING In Table 1 the hemisphere mean rCBF parameters at rest are given for the different subgroups investigated. There was no significant difference between the groups, except for the flow parameter  $g\%$  (the relative weight of the grey matter), which was slightly lower in the high score group as compared with the controls. The other flow parameters, especially the  $f_{\text{init}}$  values were, in fact, somewhat but not significantly higher in the psychotic groups than in the control subjects.

TABLE 1

MEAN HEMISPHERE RCBF VARIABLES (AT REST) IN TWO GROUPS OF CHRONIC SCHIZOPHRENICS: HIGH SCORE AND LOW SCORE PSYCHOTIC GROUP AND NON-PSYCHOTIC CONTROL GROUP

	Subjects	No.	Age (yr)	$f_{init}$	$f_{10}$	$f_g$	$f_w$	$g\%$
A	High score psychotics	13	66	53.1 (8.2)	45.8 (5.6)	72.0 (9.5)	18.9 (3.5)	47.1 (2.4)
B	Low score psychotics	14	35	54.4 (13.4)	48.4 (8.6)	75.4 (16.4)	19.1 (3.9)	49.4 (3.5)
C	Control group	15	46	47.4 (6.6)	44.4 (4.3)	66.8 (10.1)	19.5 (3.0)	50.2 (3.9)
A/B			<i>t</i>	0.31	0.93	0.64	0.17	1.91
A/C			<i>t</i>	2.03	0.75	1.38	0.48	2.46*
B/C			<i>t</i>	1.82	1.61	1.66	0.28	0.55

\*  $P < .05$ .

The abbreviations are:  $f_{init}$  = 'initial flow' calculated from the first minute of the clearance curves.  $f_{10}$  = regional 10 minute flow.  $f_g$ ,  $f_w$  = flow values for the grey and white matter; Flows in ml/100g/min.  $g\%$  = relative grey matter in %. SD in parentheses. Student's *t* test. Note the similarity of the values in the three groups.

In Table 2 the changes in the hemisphere mean rCBF parameters during the tests are given for the three patient groups. Apart from significant decreases in  $f_w$  (*t* values 5.37 and 3.97 for the high and low score groups, respectively), the two groups of schizophrenics did not show any significant changes of the different parameters. In contrast, the controls increased for  $f_{init}$  (*t* value 8.67),  $f_{10}$  (*t* value 4.64), and  $f_g$  (*t* value 4.15), which were all significant at the 1% level. The absence of a flow response to mental activation in the psychotic groups, most pronounced in

the high score group, differed significantly from the distinct flow changes in the control group.

TABLE 2

CHANGES IN RCBF PARAMETERS DURING PSYCHOLOGICAL TESTING IN TWO GROUPS OF SCHIZOPHRENIC PATIENTS (HIGH SCORE AND LOW SCORE PSYCHOTIC GROUP) AND CONTROL GROUP

	Subjects	No.	$f_{init}$	$f_{10}$	$f_g$	$f_w$	$g\%$
A	High score psychotics	12	0.8 (3.8)	1.3 (2.1)	2.2 (4.5)	-2.0* (1.1)	-1.4 (2.6)
B	Low score psychotics	10	2.3 (6.2)	1.6 (4.9)	1.7 (8.4)	-1.1* (0.9)	-1.6 (2.7)
C	Controls	15	5.6* (2.5)	3.8* (3.2)	10.3* (9.3)	-0.9† (1.4)	-2.8† (3.5)
	F		4.61†	1.89	4.40	2.41	0.70
A/C	<i>t</i>		2.96*	1.57	2.36†	2.12†	1.04
B/C	<i>t</i>		1.88	1.65	2.59†	0.35	0.95

\*  $P < 0.01$  †  $P < 0.05$

Abbreviations as in Table 1. Flow values are given in ml/100 g/min.

FRONTAL AND POSTCENTRAL BLOOD FLOW AT REST AND DURING MENTAL ACTIVATION In Table 3 the mean frontal and postcentral flows at rest are given for the different groups of subjects. There were no statistically significant differences in the resting levels of the frontal flow between the groups but the postcentral flow was in the psychotic groups considerably (in part significantly) higher than that in the control groups (Ingvar and Franzén, 1974).

At mental activation (note that the testing procedures were different between the groups), none of the two psychotic patient groups changed significantly, either in frontal regions or postcentrally. In most of the high score patients there was, in fact, instead of an increase, a slight decrease (NS) in the frontal flow. In the non-psychotic control groups, on the other hand, mental activation caused a distinct significant flow increase both postcentrally and, especially, in frontal regions.

Compared with the controls, the high score psychotic patients showed significantly less frontal flow response at mental activation, but postcentrally the flow increases were of a similar magnitude. The same tendency for a diminished flow response frontally was found in the low

TABLE 3

RESTING BLOOD FLOW IN FRONTAL AND POSTCENTRAL REGIONS AND CHANGES DURING PSYCHOLOGICAL TESTING IN FOUR GROUPS OF PATIENTS (TWO PSYCHOTIC AND TWO CONTROL GROUPS)

Subjects	No.	Frontal flow		Postcentral flow	
		Mean flow at rest	Flow change during test	Mean flow at test	Flow change during test
A High score psychotics (Picture test)	11	53.2 (9.8)	-1.4 (5.1)	53.9 (10.1)	5.1 (10.6)
B Low score psychotics (Reasoning test)	10	59.1 (14.6)	0.9 (7.7)	54.9 (13.5)	2.1 (6.4)
C I Controls I (Digit-span-backward-test)	9	49.0 (4.8)	9.0* (4.7)	45.3 (3.4)	5.8* (4.0)
C II Controls II (Reasoning test)	10	49.7 (8.7)	4.8* (2.9)	45.5 (7.4)	5.6* (4.1)
A/C I	<i>t</i>	1.18	4.69*	2.44†	0.19
A/C II	<i>t</i>	0.89	3.36*	2.21†	0.14
B/C I	<i>t</i>	2.00	2.72†	2.08†	1.49
B/C II	<i>t</i>	1.82	1.49	2.00	1.45

\*  $P < 0.01$ . †  $P < 0.05$ .

The flow values are calculated on mean  $f_{int}$ —values from four to seven detector areas frontally and postcentrally respectively. Flow values are given in ml/100g/min. SD in parentheses. For reasons explained in the text the testing procedures were not fully uniform. Student's *t* test.

score psychotics, but for identical testing procedure (reasoning test) the difference was not statistically significant.

RELATIONS OF DIFFERENT BLOOD FLOW PARAMETERS TO RATED MENTAL CONDITION OF PATIENTS As to flow distribution in the high score group, overt-productive symptoms of psychosis (number of positive R.P. points) showed a distinct positive correlation with the blood flow level in postcentral regions ( $r = .701$ ,  $P < .01$ ; Ingvar and Franzén, 1974); moreover, these rated positive symptoms emanated mainly from the cognition category of the scale used (cognition *vs* postcentral blood flow  $r = .635$ ,  $P < .05$ ). This implies that the higher the blood flow postcentrally the more marked was the cognitive disturbance.

In precentral regions the blood flow levels correlated significantly with increasing symptoms of inactivity ( $r = .588$ ,  $P < .05$ )—that is, the lower the blood flow in frontal regions the more inactive, autistic, and withdrawn was the patient.

We also explored whether there was any connection between the flow response to mental activation and the degree of psychosis. In the high score group there was a positive correlation between symptoms of inactivity and changes in

the frontal blood flow upon testing ( $r = .613$ ,  $P < .05$ ). This implies that the frontal flow decrease was less marked the more marked the symptoms of inactivity.

In postcentral regions there was in the high score group a tendency to less flow response on activation with increasing cognitive disturbance ( $r = .521$ , NS).

In the low score group no significant correlations were found between rest and test flow values and the psychiatric rating.

BLOOD FLOW OVER BASAL GANGLIA We also analysed the white matter flow,  $f_w$ , in a central region recorded from two to three detector fields over the basal ganglia. Normally this region shows  $f_w$ -values which are about 10–20% above the hemisphere mean  $f_w$  (Ingvar, Rosén, and Elmqvist, in preparation).

Also within this region some interesting findings were made in the high score group psychotic patients. Thus, while the  $f_w$ -level over the basal ganglia in the control subjects and the low score psychotic patients varied in the same direction at rest and during testing as the mean flows in frontal and postcentral regions, it did not do so in the high score group. Furthermore, the resting

$f_w$  over the basal ganglia correlated with the rated level of emotion and the change in  $f_w$  in this region during testing also correlated with the rate of disturbed cognition.

It is difficult to interpret these findings fully. They indicate, however, that the abnormalities in cerebral flow (activity) distribution which exist in chronic schizophrenia pertain not only to the grey matter tissue compartment but also to tissue regions included in the white matter compartment.

**INFLUENCE OF PSYCHOTROPIC DRUGS AND AGE OF SUBJECTS** Pharmacological treatment was not found to have any substantial influence upon the relations reported above (Franzén and Ingvar, 1975). It was also found that age could not have influenced the findings significantly. On the contrary, statistical elimination of the age by partial correlations strengthened some of the correlations between psychiatric state and the frontal or postcentral flow level—for instance, the relation between increasing symptoms of inactivity and reduced resting frontal flow (from 0.588 to 0.731) in the high score psychotic group.

#### DISCUSSION

In our previous papers (Ingvar and Franzén, 1974a, b; Franzén and Ingvar, 1975) we have considered in detail technical aspects of the regional cerebral flow method and also presented the evidence that rCBF measurements may be used to measure the functional level of activity in different parts of the brain.

Franzén and Ingvar (1975) concluded that there is no reason to believe that the abnormal resting flow (activity) distribution in chronic schizophrenia is caused by age factors or by neuroleptic medication, but that the abnormal rCBF distribution is a specific feature in chronic schizophrenia. This conclusion is supported by the fact that the low frontal blood flows correlated with autism, inactivity, and indifference, while the high postcentral flows correlated with the severity of the cognitive disturbance.

The main result of the present study is the demonstration that psychological testing or mental activation in the psychotic patients gave rise to a much less pronounced increase—or even a decrease in some highly deteriorated cases—of

blood flow (activity) in frontal regions than in normal subjects. The difference was much less pronounced in postcentral structures and the flow increase here was in general of the same size in the schizophrenics and in the control subjects.

It is difficult to state whether the difference found in flow response to psychological testing between the schizophrenics and the reference groups could have been due to neuroleptic medication. Since medication was found to exert only limited effects upon the resting rCBF distribution, it appears unlikely that this factor could explain the differences between the groups during testing.

Admittedly, great difficulties beset the testing of psychological function of highly deteriorated chronic schizophrenics. We are fully aware of the fact that completely identical testing conditions could not be used for the reference groups and for the schizophrenics. In the high score group a most intense verbal encouragement had to be used in order to get any answer at all from most of the patients. In the other psychotic patients a good or fair collaboration was obtained, with prompt though never enthusiastic answers.

The different procedures might have influenced the differences in testing response between the groups (Ingvar, 1975). However, in the present study we have purposely not considered subtle regional changes in the rCBF landscape but dealt only with the mean flow in larger parts of the brain such as the frontal and postcentral regions. Such extensive areas are not easily influenced by incidental occurrences. Some information may have been lost by this method, but at the same time the risk of overinterpretation has diminished.

The lack of activation of frontal structures during psychological testing in chronic schizophrenics fits well with our hypothesis that this disorder implies not only a low resting activity in frontal structures, but also an inability to activate these structures. The results thus support the notion that in chronic schizophrenia a transmission failure might be present in a projection system activating the frontal granular cortex. We have proposed that the frontocortical mediothalamic projection bundle, which ascends *via* the anterior thalamic peduncle (Skinner and Lindsley, 1973), might be a likely candidate.

In accordance with this hypothesis, there should not be any limited access to postcentral

structures in chronic schizophrenia. On the contrary, the postulated transmission defect should cause a 'disinhibition' of afferent pathways, possibly related to the well-known perceptual abnormalities in schizophrenia (Chapman, 1966; Bowers and Freedman, 1966; Broen, 1968). In fact, the resting flow (activity) level in post-central regions was significantly higher in the psychotic patients as compared with the controls. The response to the testing procedures was, however, in the main, of equal size. The behaviour of the postcentral regions during mental activation in chronic schizophrenia thus appears also to fit well into our hypothesis, which implies a normal or supernormal reception of sensory messages in postcentral structures leading to overinclusion phenomena ('hypergnosis'; Franzén and Ingvar, 1975), and a defective translation of these messages into behavioural programmes in frontal structures.

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