Negative and Positive Symptoms: In Relation to Regional Cerebral Blood Flow in Drug-Free Schizophrenic Patients*

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SUMMARY:
NEGATIVE AND POSITIVE SYMPTOMS: IN RELATION TO REGIONAL CEREBRAL BLOOD FLOW IN DRUG-FREE SCHIZOPHRENIC PATIENTS

Objective: Although most of the functional neuroimaging studies in schizophrenic patients have supported the hypothesis of frontal hypoperfusion, there are some studies which indicates that the perfusion of some other cortical regions are also affected. In this study, we aimed to investigate whether negative and positive symptoms of schizophrenia were related to abnormal blood perfusion in different cerebral areas. **Method:** Twenty drug-free patients (14 male, 6 female) who fully met DSM-IV criteria for schizophrenia and 17 age and sex matched healthy volunteers (12 male, 5 female) were included in the study. Symptoms of the patients were assessed by PANSS (Positive and Negative Symptom Scale) and regional CBF images were obtained by SPECT using ^{99m}Tc-HMPAO as a radiopharmaceutical. **Results:** We found frontal and temporal hypoperfusion in schizophrenic patients compared to the controls. As assessed with PANSS, ideas of grandiosity were correlated positively with the left temporal and parietal cortical perfusion values, and suspiciousness/persecution ideas were correlated negatively with all frontal and right temporoparietal rCBF values. There were negative correlation between emotional withdrawal scores and bilateral temporal rCBF values. We did not find any relation between reduced frontal perfusion and negative symptoms. **Conclusion:** Our results support the hypothesis that brain perfusion is reduced in frontal and temporal regions of schizophrenic patients. Furthermore, different positive and negative symptoms seem to originate from different brain areas, such as frontal, temporal and parietal regions.

Key words: *schizophrenia, SPECT, positive symptoms, negative symptoms*

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ÖZET:
İLAÇSIZ ŞİZOFRENİ HASTALARINDA NEGATİF VE POZİTİF BELİRTİLERİN BÖLGESEL BEYİN KAN AKIMI İLE İLİŞKİSİ

Amaç: Şizofreni hastalarında yapılan fonksiyonel beyin görüntüleme çalışmalarının çoğu frontal hipoperfüzyon hipotezini desteklemekle birlikte, diğer kortikal bölgelerin perfüzyonunda değişiklikler olduğunu bildiren çalışmalar da vardır. Bu çalışmada şizofreninin negatif ve pozitif belirtilerinin farklı beyin bölgelerindeki kan akımı anormallikleri ile ilişkisinin araştırılması amaçlanmıştır. **Yöntem:** Çalışmaya DSM-IV şizofreni tanı kriterlerini karşılayan 20 hasta (14 erkek, 6 kadın) ve yaş ve cinsiyet bakımından karşılaştırılmış 17 sağlıklı denek (12 erkek, 5 kadın) dahil edildi. Hastaların semptomları PANSS (Pozitif ve Negatif Semptom Skalası) ile değerlendirildi ve Tc^{99m}-HMPAO kullanılarak SPECT çekimleri yapıldı. **Bulgular:** Şizofreni hastalarının kontrollere göre frontal ve temporal hipoperfüzyon gösterdikleri bulundu. PANSS ile değerlendirildiğinde, büyüklük fikirleri ile sol temporal ve parietal bölge kan akımı değerleri arasında pozitif bir ilişki, şüphecilik-kötülük görme skorları ile tüm frontal bölgeler ve sağ temporoparietal bölge kan akımı değerleri arasında negatif bir ilişki olduğu gözlendi. Emosyonel çekilme semptomu ile bilateral temporal kan akımı değerleri arasında negatif bir ilişki vardı. Negatif semptomlarla frontal kan akımı arasında herhangi bir ilişki tespit edilemedi. **Tartışma:** Çalışmanın sonuçları şizofreni hastalarında frontal ve temporal bölgelerdeki kan akımının azalmış olduğu hipotezini desteklemektedir. Ayrıca farklı pozitif ve negatif semptomlar beynin farklı bölgelerindeki anormalliklerle ilişkili gibi görünmektedir.

Anahtar sözcükler: *şizofreni, SPECT, pozitif belirtiler, negatif belirtiler*

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INTRODUCTION

Since Ingvar and Franzén first demonstrated an abnormality of blood flow in the left hemispheres of schizophrenic patients (1), many functional neuroimaging studies have suggested abnormalities at frontal cortex, temporal and limbic regions, parietal lobes and basal ganglia (2-10). Although one of the most repeating findings in these studies is hypofrontality, there are also some conflicting studies that we-

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re not able to replicate this finding or have found hyperfrontality (5,9,11-14).

About twenty years ago, several authors proposed that schizophrenia comprises (at least partly) positive and negative syndromes (15). Clinical assessment by means of PANSS (Positive and Negative Syndrome Scale) yields separate scores along a positive syndrome scale, negative syndrome scale, composite index, and general psychopathology scale (16). Though not all, in many studies, negative symptoms are found to be strongly associated with decreased frontal cortical blood flow (4,5,7-20). Some authors have argued that this hypofrontality may be related to the duration of the disease and long-term neuroleptic treatment. To overcome this issue, some studies have been planned on drug-naive and first-episode schizophrenic patients and it has been found that decreased frontal cortical blood flow is present at the onset of the illness (4,11,14,18,19).

It is assumed that different negative and positive symptoms arise from different brain areas. Liddle et al found negative correlation between rCBF of the left prefrontal and left superior parietal association cortices and psychomotor poverty (21). Reality distortion was also found to be related with rCBF of left temporofrontal region in the same study. Rubin et al found that formal thought disorders were correlated positively with rCBF in prefrontal and temporal cortex (17). In a recent study, Erkwoh et al showed a correlation between formal thought disorder, ideas of grandiosity and left hemispheric cortical blood flow (18). In the present study, we aimed to compare the rCBF values of drug-free schizophrenic patients with those of control subjects, and to evaluate the relationship between rCBF values and negative/positive symptoms of schizophrenia.

METHOD

Subjects

Twenty right-handed patients (14 males, 6 females) who fully met DSM-IV criteria for schizophrenia were included in the study. Thirteen of them had paranoid and the others had undifferentiated subtype of schizophrenia. Their mean age±SD was 30.1± 8.08 years (range: 18-36), the mean±SD age at onset was 27.7 ± 10.26 years, and the mean±SD duration of illness was 89.4±54.14 months. Control group consisted of 17 age-and sex-matched right-handed healthy volunteers (mean±SD age: 30.29±8.00, range: 20-37; 12 male, 5 female).

All subjects underwent a structural brain imaging examination with CT. In the patient group, the inclusion criteria were the absence of organic brain disorder, alcohol or drug abuse, pregnancy or any physical illness as assessed on the basis of personal history, clinical examination and laboratory data including complete blood count, serum electrolyte assay, liver function tests, thyroidal function tests, urine analysis, serological tests for hepatitis and HIV, electrocardiography and electroencephalography. All of the patients were inpatients and drug-washout period was 2 weeks prior to the SPECT scanning.

Symptoms of patients were assessed on the day of the SPECT examination with the PANSS (Positive and Negative Symptom Scale), CGI (Clinical Global Impression) and ESRS (Extrapyramidal Symptom Rating Scale) to analyse possible relationships between rCBF pattern and concurrent symptom state while they were drug-free. The study protocol was approved by the ethics committee of our hospital, and the patients gave their written informed consent.

SPECT scanning procedure

All subjects were studied in the supine resting position with closed eyes in a silent and darkened room from approximately 09.00 to 11.00 a.m. No extreme anxiety rating was noted during the SPECT study. The SPECT scans were coded with random numbers and evaluated by the same nuclear medicine specialist without having any knowledge of the clinical data.

Regional CBF images were obtained by SPECT using Tc-^{99m} HMPAO (Ceretec, Amersham, International plc, UK) as a radiotracer prepared according to the manufacturer's instructions and it was injectedto the subject within 10 minutes after labelling. The SPECT study was performed 20 minutes after injection of 370-550 MBq Of ^{99m} Tc-HMPAO with 360° rotating single-head gamma camera system (Toshiba GCA 602 A/SA, Japan) equipped with a low-energy all-purpose collimator interfaced to a Toshiba computer system. Each subject's head was held in a plastic holder while scanning to minimize head movements. Data were obtained in 64X64 matrices through 360° rotation at 6° intervals for 30 s per arc interval. No zoom was used, and the corresponding pixel size was 5.5 mm. Reconstruction was performed by filtered back-projection using a Butterworth filter

(cut-off frequency=0.25, power factor=8). Slice thickness was 1 pixel, and no attenuation or scatter correction was done. The images were reoriented to obtain transaxial slices parallel to the orbitomeatal (OM) line. The transaxial slices were approximately 33 mm, 49.5 mm and 66 mm above the orbitomeatal plane (Fig. 1) (22). These regions were chosen based on the neuroanatomic cross-sections illustrated in an atlas depicting the relevant slice levels (23). On the transaxial slices, hemisphere contours were drawn using semiautomated technique to describe the region of the whole brain cortex (W). Rectangular regions of interest (ROI) by 5X5 pixel were set on SPECT images in the upper and lower frontal, temporal, parietal and occipital regions, and cerebellar hemispheres (Fig. 2) (24).

Figure 1. Schematic illustration of transaxial SPECT slices which are parallel to the orbitomeatal line

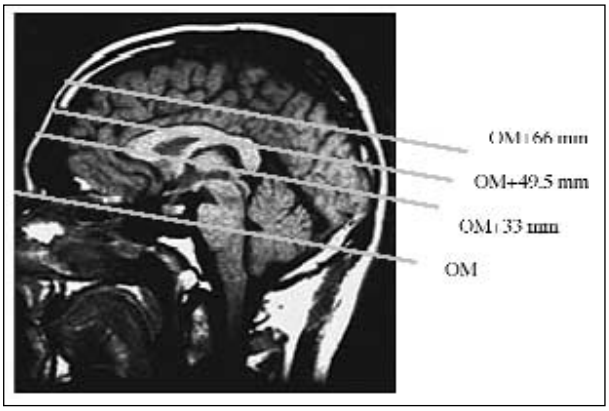
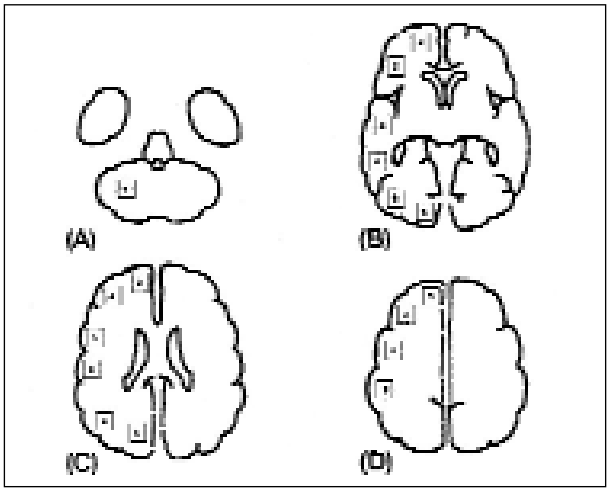


Figure 2. ROIs in each brain slices
A: OM (orbitomeatal line) B: OM+33 mm
C: OM+49.5 mm D: OM+66 mm
1: Cerebellum 2: Low frontal cortex 3: High frontal cortex 4: Temporal cortex 5: Parietal cortex
6: Occipital cortex



The SPECT imaging data were evaluated by semiquantitative analysis. Cerebellar ratio method was used as reference values to determine the indices of relative perfusion in the form of ratios (i.e., indices of relative perfusion were the ratio of averaged counts for each anatomical subdivision to the average counts of cerebellar hemispheres) (19).

Statistical analysis

The Student's t test for independent samples was applied between the patient and control groups. Pearson's correlation coefficient was used between rCBF and general characteristics or clinical symptoms. All statistical tests were two-tailed, with a 0.05 alpha level.

RESULTS

Demographic and clinical characteristics of the groups are shown in table 1. Table 2 shows mean PANSS scores. Table 3 shows the comparison of the mean values relative perfusion in schizophrenic and normal subjects. The mean rCBF values of the schizophrenic patients were significantly lower than those of the controls in all frontal and temporal regions and in the left parietal region.

Table 1. Demographic and clinical characteristics of the patient and control groups.

	Controls (n=17) Mean±SD	Patients (n=20) Mean ± SD	Comparison t	p
Age (years)	30.29 ± 8.00	30.10 ± 8.08	0.073	n.s.
Gender	12M: 5F	14M: 6F	-	-
Age at onset (years)	-	24.70 ± 10.26	-	-
Duration of illness (months)	-	89.40 ± 54.15	-	-
Total PANSS score	-	41.90 ± 11.40	-	-
Positive PANSS score	-	15.05 ± 6.37	-	-
Negative PANSS score	-	9.55 ± 2.94	-	-
CGI	-	4.50 ± 0.51	-	-
ESRS	-	14 ± 1.51	-	-

M: male F: female n.s: non significant PANSS: Positive and Negative Symptom Scale BPRS: Brief Psychiatric Rating Scale CGI: Clinical Global Impression ESRS: Extrapyramidal Symptom Scale

Table 2. Mean PANSS scores in schizophrenic patients

Items in PANSS	Scores Mean±SD
Positive	
Delusions	3.06 ± 1.16
Formal thought disorders	1.92 ± 1.01
Hallucinations	2.35 ± 1.30
Agitation	1.15 ± 1.11
Ideas of grandiosity	1.82 ± 1.24
Suspiciousness / Persecution	2.50 ± 1.56
Hostility	1.97 ± 1.27
Negative	
Blunted affect	3.22 ± 0.74
Emotional withdrawal	3.15 ± 0.89
Lack of affective contact	2.40 ± 0.73
Social withdrawal	2.97 ± 0.75
Difficulties abstract thinking	2.97 ± 0.97
Lack of spontaneity	1.60 ± 0.77
Stereotyped thoughts	2.55 ± 0.75

Table 3. Comparison of mean relative perfusion in schizophrenic and normal subjects

	CBF VALUES** Controls	Patients	Comparison	
Regions	(n=17) Mean ± SD	(n=20) Mean ± SD	t	p
Left high frontal	0.93 ± 0.02	0.90 ± 0.04	2.46	0.019*
Right high frontal	0.94 ± 0.03	0.89 ± 0.05	3.34	0.002*
Left low frontal	0.95 ± 0.02	0.91 ± 0.05	2.94	0.006*
Right low frontal	0.95 ± 0.02	0.90 ± 0.06	2.94	0.006*
Left parietal	0.97 ± 0.03	0.94 ±0.05	2.09	0.044*
Right parietal	0.96 ± 0.03	0.94 ± 0.06	1.10	0.277
Left temporal	1.03 ± 0.03	0.98 ± 0.06	2.32	0.026*
Right temporal	1.01 ± 0.04	0.97 ± 0.07	2.42	0.020*
Left occipital	0.99 ± 0.04	0.99 ± 0.08	0.05	0.960
Right occipital	1.00 ± 0.04	1.15 ± 0.68	0.90	0.372

* Statistically significant ** Values represent regions of interest/cerebellar ratio On the basis of correlational analysis of symptoms and ROIs, two positive and one negative symptom were related to rCBF values. Ideas of grandiosity were correlated positively with the left temporal ($r=0.45$, $p<0.05$) and parietal ($r=0.45$, $p<0.05$) cortical rCBF. Suspiciousness/persecution ideas were correlated negatively with bilateral high ($r=-0.52$, $p<0.05$; $r=-0.51$, $p<0.05$ respectively) and low frontal ($r=-0.53$, $p<0.05$; $r=-0.60$, $p<0.01$ respectively) cortical rCBF, as well as right parietal ($r=-0.45$, $p<0.05$) and temporal ($r=-0.45$, $p<0.05$) cortical rCBF. Emotional withdrawal was negatively correlated with the bilateral temporal cortical rCBF ($r=-0.45$, $p<0.05$; $r=-0.61$, $p<0.01$). There were negative but statistically non-signifiant correlations between rCBF values and ESRS, PANSS total, negative and positive scores.

DISCUSSION

Our sample size of 20 schizophrenic inpatients is large enough to allow comparing with research in this area. This study of drug-free schizophrenic patients in the active phase of the disease yielded two major findings.

First, our data shows lower mean rCBF values in all frontal and temporal regions and the left parietal region in schizophrenics compared with the controls. As far as hypofrontality is concerned, there may be a parallel to widespread literature that frontal hypoperfusion is the most consistent finding in resting state of chronic schizophrenia (3,8,11-14). Our results are in accordance with these earlier reports. The term resting state is correct for our study design in the sense of not performing any activation task. Thus, all differences found in rCBF values of patients can be attributed to psychopathological features of schizophrenia and contribute to an understanding of the pathophysiological basis of the illness. Although some researchers pointed out that frontal hypoperfusion might be associated by chronicity of illness, long-term antipsychotic treatment or the aging process, in the recent studies, reduced frontal cerebral blood flow was measured in the drug-naive patients (4,11,14,18,19). Therefore, frontal hypoperfusion can be seen as a finding existing before clinical manifestation of the illness. Since our patients were drug-free for at least two weeks and there was no correlation between age, duration of illness and rCBF in frontal regions, our results appear to suggest that frontal hypoperfusion is a primary deficit in schizophrenia rather than secondary to other factors.
We found reduced cerebral blood flow in temporal regions in common with some other studies (7,8,14). Although particularly left temporal lobe pathologies were underscored in schizophrenics (20,21), we did not show any difference between left-right regional blood flow.

Secondly, we found that different positive and negative symptoms were correlated with rCBF of different brain areas. Even though we did not find any correlation between delusions and rCBF, we observed a positive relation between ideas of grandiosity and left temporal and parietal regions' perfusion. Grandiosity lies on the spectrum of delusional ideas and can be seen as a factor that contributed to reality distortion. This finding seems to be in line with Liddle's earlier study in which he observed a relation between reality distortion and increased left temporal blood flow and argued that reality distortion stemmed from dysfunction of the medial temporal lobe in schizophrenia (21). But there are also some inconsistent results in terms of this issue. Erkwoh et al (14) found that ideas of grandiosity were correlated positively with rCBF in the bilateral frontal and right temporal regions but in another study of the same group (18), they were correlated positively with left frontotemporal and bilateral parietal regions' perfusions.

We found suspiciousness-persecution scores were negatively correlated with blood flow of all frontal regions and right temporoparietal region. If suspiciousness-persecution is a reality distortion factor and a positive symptom, this result is unexpected for us and inconsistent with Liddle's findings (21). However, Sabri et al's results concerning with suspiciousness–persecution were partly similar to ours (25). They found a negative correlation between suspiciousness and frontal and temporal region, too. But Sabri et al found this clinical feature to be correlated with left temporal blood flow in contrast to our result which is decreased blood flow in right temporal region. Some other SPECT studies also found a correlation decreased left temporal lobe blood flow and positive symptoms (26). Thus, our result which links right temporal lobe blood flow with suspiciousness symptom can be considered to be inconsistent with above-cited earlier studies. Nevertheless, given the results of the present study and Sabri et al's (25), suspiciousness and persecution seem to be related with a more spread brain pathology that includes frontal, temporal and parietal regions.

In schizophrenia, frontal hypoperfusion is suspected to relate causally to negative symptoms (4,12,13,20,27). However, on the contrary to our prediction in the beginning, we did not find a correlation between any negative symptoms and frontal rCBF values. Additionally, we did not find a relationship between sum score of all negative symptoms and frontal hypoperfusion in schizophrenics, in agreement with some other studies (14,18,19) but in contrast to many studies (4,5,12,13,27). On the other hand, there are some studies reporting a correlation between negative symptoms and hyperperfusion of frontal lobes (17,28). Therefore, it can be suggested that not all patients with negative symptoms may have a frontal hypoperfusion.

Moreover, concerning the relation of negative symptoms with hypoperfusion, among all negative symptoms we found only emotional withdrawal to be associated with diminished bilateral temporal blood flow. Erkwoh et al and Sabri et al also found temporal hypoperfusion-emotional withdrawal relationship (18,25). In general, given the implications that the negative symptoms such as emotional withdrawal, poverty of speech are connected with frontal lobes, and the positive symptoms such as hallucinations and delusions are connected with temporal lobes, our results are inconsistent with this impression (4,17,20,29,30). On the other hand, schizophrenia is not a completely understood disease, and evolving of symptoms should not be simplified in this manner, if it is taken into account complex interconnected structure of the brain. Indeed, in the literature, there are some studies that found correlation between negative symptoms and perfusion of temporal lobes in common with us (31,32). These findings are consistent with suggestions of a temporolimbic prefrontal network abnormality in schizophrenia.

One of the limitations of the present study may be the use of cerebellum as a reference point. The cerebellum may be invoked in attentional processes that are impaired in some patients with schizophrenia, and recently it has been reported some cerebellar blood flow changes in schizophrenics, especially during the activation tasks (13,33). But in our study, schizophrenic patients and control subjects were scanned under standard resting conditions without attentional manipulations or cognitive tasks.

Additionally, a washout period of two weeks might not be enough to remove the drugs of the body. However, for ethical reasons, we could not keep the patients antipsychotic-free for more than 2 weeks.

In conclusion, our results display that different positive and negative symptoms are accompanied by different rCBF changes in frontal, temporal and parietal lobes: some induce hyperperfusion, others hypoperfusion. This may explain inconsistencies of perfusion pattern results in rCBF studies in schizophrenia. These results also suggest that different symptoms of illness may be related to different regions of the brain, and schizophrenia may be an illness that affects more regions of the brain than estimated.

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