

CLOZAPINE VERSUS CLASSICAL ANTIPSYCHOTICS ON TREATING SCHIZOPHRENIA; USING SPECT AND PANSS

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Abstract: Many neuroimaging studies of schizophrenia have shown abnormalities in the frontal cortex, limbic system, basal ganglia, temporal and parietal lobes [1-10]. These findings are not specific or consistent enough to build up a coherent theory of the origin of the brain abnormality in schizophrenia. The present paper describes a state-of-the-art approach of SPECT to correlate neuropsychological evaluation; PANSS scores and different brain focal abnormalities of two groups of patients receiving Clozapine and classical antipsychotic treatments were observed. A total of 20 drug-free patients, actively psychotic schizophrenic were selected according to the DSM-IV criteria. Pre-Post-treatment was designed using PANSS and ^{99m}Tc - ECD-SPECT to assess regional Cerebral Blood Flow (rCBF). The results showed that after treatment, differences in PANSS scores were significant in both groups, with superior scores results from the Clozapine therapy. Results were supported by SPECT, which showed a greater improvement in the Clozapine group. Both positive and negative symptoms were improved with Clozapine as well. Before treatment, hypofrontality was the most common (85%) finding, whereas after treatment hypofrontality was mostly cleared. However, in some cases hyperfrontality was induced. Negative symptoms showed linkage to hypofrontality in both groups before and after treatment, and both positive and negative symptoms were improved more with Clozapine therapy than with classical treatment.

Abbreviations: rCBF = regional cerebral blood flow; SPECT = single photon emission computed tomography; PANSS = Positive and Negative Syndrome Scale; ^{99m}Tc -ECD = 99m -technetium ethyl cysteinatate dimer; DSM-IV = Diagnostic and statistical manual of mental disorders, 4th edition of the American psychiatric association.

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MAIN CLINICAL INTEREST: Schizophrenia, Mood and Eating disorders and brain mapping.

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1. Introduction

Schizophrenia is a chronic and disabling brain disease affecting around 24 million people worldwide and more than 2 million Americans in a given year. Approximately 1 percent of the population develops schizophrenia during their lifetime [8-11]. Risk factors include birth in cities, birth in winter and early spring, and viral infections in the mother during the second and third trimesters of gestation. A strong association between hypofrontality and negative symptoms of schizophrenia, as well as with antipsychotic treatment, has been reported. Some studies have reported that about half of the chronic cases of schizophrenia show hypofrontality at rest [11-13]. Studies have shown that individuals with schizophrenia, including those who have never been treated, have a reduced volume of gray matter in their brains, especially in the frontal and temporal lobes.[5,7] Patients with the worst brain tissue loss also have the worst symptoms, including hallucinations, delusions, psychosis and bizarre behavior [14-17]. Therefore, through early diagnosis and appropriate treatments we can make the illness less severe and more tolerable for the patients and their families.

Dopamine hypothesis, which posited that schizophrenia was caused by abnormalities in dopamine production and activity in the brain, was first proposed in the 1950s. The basis for the hypothesis was that the most widely used drugs for the treatment of schizophrenia block dopamine D2 receptors and signal transmissions by dopamine. These drugs function as antipsychotic medications and reduce delusion and hallucination. By contrast, drugs such as amphetamine reinforce signal transmissions by dopamine and induce schizophrenic symptoms such as delusion and hallucination. A large body of theory and evidence now holds that a failure to properly develop glutamate neurons is responsible for much of the pathology in schizophrenia. According to this hypothesis, schizophrenia is associated with increased activity in dopaminergic neurones [19].

Clozapine (Leponex) is the prototype of atypical antipsychotic drugs that are used to treat patients with schizophrenia who are unresponsive or intolerant to typical antipsychotics. It is effective in treating the positive and negative symptoms of schizophrenia. As demonstrated in this article, Clozapine is more effective in schizophrenia than older antipsychotics. It may also help reduce relapses, suicide and the need for hospitalization. Clozapine is characterized as *atypical* by its preferential binding to serotonin 5-HT₂ and dopamine D₄ receptors relative to dopamine D₂ receptors. Dopamine receptors involved in Clozapine therapy included D₄, D₂, serotonin type 2, norepinephrine, acetylcholine, and histamine [20-22].

Introduction to brain imaging:

Functional brain imaging methods have been applied for studying schizophrenia. These methods include positron emission tomography (PET) [10], SPECT for studying CBF and neuroreceptors, and more recently, functional magnetic resonance imaging (fMRI) for measuring changes attributable to cerebral blood flow. In this article, the author reviews the application of brain SPECT in schizophrenia research; summarizes studies he has

conducted; and integrates them with our current understanding of brain function in schizophrenia.

Rotating camera: Scans have become more sensitive through the use of the rotating camera. Improvements in camera designs, collimator design and in reconstruction algorithms have substantially improved the quality of SPECT images using the Anger type gamma camera. SPECT images can be merged with MRI and CT, creating a single image that combines anatomy and physiology. Three dimensional surface and volume-rendered images add perspective and facilitate the localization and sizing of lesions. Systems should be capable of sequential image acquisition. The option to acquire multiple short studies back to back makes it possible to subsequently discard segments degraded by patient motion [3, 23, 26,28].

Supporting Software includes dynamic filters, multiple angle reconstructions, surface variable attenuation corrections, three dimensional/conventional /cross sectional displays. The computer then reconstructs 3-D images of the brain (figure1). With these brain maps, physicians are able to identify certain patterns of brain activity in different psychiatric and neurological problems. Basically, in a typical brain SPECT we are looking for an asymmetry and different activity levels and comparing it to what we know as a normal brain (figure2). A normal SPECT image reveals homogeneous and uniform tracer accumulation throughout the cerebral cortex, with the cerebellum being the area with the most intense activity [24, 26, 28].

2. Material and Method

This article analyzes a study conducted using a protocol approved by the committee at Tehran Psychiatric Institute, Iran Medical University and Rajai Hospital Research center, Tehran, Iran. Twenty random samples in an acute phase of schizophrenia (drug free and drug naive) were selected after a proposal study had been completed, according to DSM-IV from the different outpatient and inpatient clinics and teaching hospitals. Eleven men (ranging from 24-40 years) and 9 women (ranging from 18-40 years) were placed in 2 groups, the Clozapine and classical groups, according to the selected treatment. The mean duration of illness was 8.7 years, ranging from 1-19 years (Table 1). Two subjects were not cooperative for the second SPECT, so data from these two patients was not included. 88% of the classical and 90% of the Clozapine group suffered from delusion, while 88% of the classical and 54% of the Clozapine group showed hallucination. The control subjects were 12 healthy volunteers [8 men aged 34 ± 6.5 (S.D.) years, 4 women aged 33 ± 3.5 (S.D.) years]. Drug-washout was 3 months prior to the PANSS and SPECT scanning. Exclusive criteria: age less than 18 years, more than 65 years, neurological and general medical condition and pregnancy. The mean daily dosage for Clozapine: 300mg, and for classic: equal to 600 mg chlorpromazine.

SPECT Acquisition

The SPECT study was performed using a single-head rotating gamma camera (Sophycamera- SMV-DSX). 64-40 seconds frames were collected during a 360 degree

rotation in a 64x64 matrix with a zoom of two obtaining a 4.5 mm pixel size. Data acquisition was started 40 minutes after IV injection of 740 MBQ (20 mci) of ^{99m}Tc -ECD (Neurolite, Kavoshyar co.). As a clinical tool for rCBF evaluation by SPECT, ECD (ethyl cysteinyl dimmer) has recently been introduced. Results of rCBF in schizophrenia are considerably limited to the use of the older radiopharmaceuticals like ^{99m}Tc -HMPAO (Hexamethyl propylene amine oxide) and $\text{I}^{131}\text{-IMP}$ (Iodoamphetamine). Fewer data are available from rCBF studies in schizophrenia by ^{99m}Tc -ECD [23]. In general, ECD has several favorable characteristics:

- A.** Chemical stability lasting several hours after reconstitution,
- B.** Fast blood clearance,
- C.** High signal-to-noise ratio.

The pre and post treatment SPECT results were differentiated from severe hypo (-3) to severe hyper (+3) perfusion (zero means normal scan). Pre and Post-treatment was designed using the PANSS and ^{99m}Tc - ECD-SPECT to assess regional Cerebral Blood Flow. Patients were assessed psychometrically both times the day before the scans with PANSS, a 33-item scale with 1 to 7 points (normal to extremely abnormal) for each item and sub-scores for 7 positive, 7 negative, and 16 global psychopathological symptoms: delusions, formal thought disorders, hallucinations, agitation, grandiosity, suspiciousness/persecution, and hostility (P1 to P7); blunted affect, emotional withdrawal, poor rapport, social passivity and apathy, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking (N1 to N7); and health concerns, anxiety, guilt, tension, mannerisms and posturing, depression, motor retardation, uncooperative behavior, unusual thought contents, disorientation, poor attention, lack of judgment and insight, avolition, poor impulse control, self-centeredness, and active social avoidance (G1 to G16)[18].

A brain CAT scan or MRI was performed on each subject before the SPECT, to rule out any pre-existing medical conditions and for parallel comparison with SPECT. As stated in *table 3*, ROIs (region of interest) were positioned in 8 canthomeatal slices in each side. For every ECD brain SPECT the subjects were seated in a quiet room with closed eyes, 15 minutes before the injection. Before the SPECT scanning, all subjects had an intravenous line established while they were lying down. Each subject received an intravenous injection of ^{99m}Tc -ECD, which crosses the blood-brain barrier on first pass, is rapidly taken up by neural cells, and is distributed in proportion to regional cerebral perfusion. Because ^{99m}Tc -ECD remains fixed in the cells after uptake, its distribution provides a picture of the pattern of brain perfusion immediately after administration. Therefore, the effect of sedation on measured rCBF should be negligible. Thirty minutes after the administration of ^{99m}Tc -ECD, each subject was given sedation in the amount of 10 mg Diazepam to decrease motion during scanning. Ten minutes after injection of Diazepam, SPECT scans were taken. Therefore, data acquisition started 40 minutes after ECD IV injection for each subject.

3. Results

Table 1 shows demographic and clinical characteristics of the above study. SPECT scans were interpreted independently by three nuclear physicians who were unaware of the patients' diagnoses. Intra-observer agreement ranged from 60 to 90%. PANSS scores also were evaluated by three researchers independently, and the agreement ranged from 75 to 95%. Before treatment there was no significant difference on the PANSS between the Clozapine and classical groups. We conducted Levene's test for equality of variances in PANSS; $F = 0.197$, $P = 0.662$ and t-test for independent samples (before any treatment); $t_{(pre)} = 2.50$, $t_{(post)} = 2.48$, was done to rule out possibility of bias in choosing the samples. In addition, statistical analysis ruled out the possibility of any baseline difference effects between the Clozapine and classical treatments.

The PANSS scores, pre and post treatment (*table 2*), were compared using t-tests for dependent samples (for ten subgroups). The Pearson's correlation coefficient was used between different SPECT areas and PANSS subgroups. All statistical tests were two-tailed with a 0.05 alpha level. Before treatment, the total classical PANSS score was 175 and after treatment it decreased to 111 ($P < 0.001$, $N = 9$); $t = -5.98$. Before treatment, the total PANSS score in the Clozapine group was 235, and after treatment it decreased to 123 ($P < 0.0001$, $N = 11$); $t = -7.83$. Results were supported by SPECT, which showed a greater improvement in the Clozapine group.

Table 3 shows the comparison of the mean values of relative perfusion in schizophrenic subjects pre and post treatment. The results show that the mean rCBF values of the schizophrenic patients were significantly lower than those of the control in all frontal, temporal, thalamus/basal ganglia, caudate and parietal regions. So, we selected the region of interest for correlation.

Table 1: Demographic and clinical characteristics of the study:

	<i>Clozapine (11)</i> <i>Mean ± SD</i>	<i>Classic (9)</i> <i>Mean ± SD</i>
Gender	63% M 36% F	55% M 44% F
Job	36% E 63% U	44% E 55% U
Age	29.18 Y ± 6.30	30.9 ± 8.72
No. of hospitalizations	3.7 T ± 2.5	2.1 ± 2.0
Duration of disease	9.7 Y ± 3.1	8.6 ± 3.7
Duration of treatment	6.6 mon ± 4.0	7.7 ± 4.6
Suicide	9%	22%
OCD	27%	22%
Family history	45%	55%
ECT history	18%	22%
Smoking	27%	55%
Marriage	0%	44%

M: male, F: female, E: employed, U: unemployed, Y: year, T: times, Mon: month.

Table 2: Mean PANSS scores pre-post treatment in different groups:

PANSS scores	Clozapine (11)				Classic (9)			
	PreTx ± SD	PostTx± SD	t	p	Pre Tx ± SD	PostTx ± SD	t	p
Positive	34±8.81	17±3.76	-7.71	.0001	24.4 ±7.8	14.11 ±3.78	-4.83	.001
Negative	34.45± 8.8	18.45±5.62	-7.34	.0001	24.2 ±7.9	16 ± 4.5	-5.07	.001
Composite(P-N)	-0.36±6.96	-4 ±2.36	-1.58	.145	0.22± 7.82	-1.77±4.63	-1.10	.303
General Psychopath.	64.27± 16.17	32.16±11.1	-6.96	.0001	50.6± 16.5	33.3±11.16	-5.47	.001
Anergia	31.87± 5.64	9.27 ±2.72	---	---	12.11 ±5.46	7.77±2.81	---	---
Thought disturbance	18.72± 3.46	9.63 ±2.57	---	---	12.7 ± 5.2	9± 2.54	---	---
Activation	11.9 ±3.35	6 ±1.34	---	---	8.55 ±3.12	5.33± 2	---	---
Paranoid bellig.	14.18± 3.54	7.27 ±1.27	---	---	9.33 ±3.55	5.55± 1.5	---	---
Depression	14.63 ±3.26	8.18± 1.83	-6.27	.0001	13.11± 4.01	8.55±3.24	-4.90	.001
Supplemental	25.45± 6.28	12.18± 1.99	---	---	19.4 ±5.87	12±4.12	---	---

Table 3: comparison of means in different brain regions:

	Right	T	P	Right	T	P	Left	T	P	Left	T	P
	Pre Tx ± SD			Post Tx ± SD			Pre Tx ± SD			Post Tx ± SD		
Sup. frontal	-1.07±.93	-	.000	.50±.659	-3.71	.001	.73±1.00	3.71	.001	-.33±.56	-	.008
Inf. frontal	-.538±.98	-	.010	.25±.442	-2.76	.011	.65±.845	3.94	.001	.166±.38	-	.043
temporal	.576±1.20	2.44	.022	.166±.48	1.696	.103	.38±.752	2.6	.015	.20±.588	1.73	.096
Post. parietal	-1.3±1.12	-5.93	.00	-.70±.80	-4.3	.00	-	-	.000	-	-4.0	.001
Ant. parietal	-.69±.97	-	.001	.458±.83	-2.69	.013	1.1±1.10	5.13	.002	.666±.81	-	.057
caudate	-3.85E- 02±.527	-3.72	.713	-4.17E- 02±.204	-1.00	.328	.69±1.04	3.36	.000	-.20±.50	2.00	1.00
Thalamus/Basal Ganglia	-.15±.73	-1.07	.29	-.20±.50	-2.0	.057	-.19±.80	-	.232	.000	.000	1.000

The Cerebellum had no significant changes before and after treatments. The occipital region only showed some non-significant changes.

Table 4: Severity index was calculated as; degree of severity x number of hypo/hyper-intense areas in different brain regions.

Brain regions	Clozapine (11)		Classic (9)	
	Pre-Tx	Post-Tx	Pre-Tx	Post-Tx
Superior Frontal*	-5.16; 0	-2.5; 0.5	-2.75; 0	-2.5; 0
Inferior Frontal	-4.5; 0.66	-2.0; 0	-1.5; 0	-2.0; 0
Temporal	-1.1; 4.03	-1.0; 4.33	-0.5; 4.33	0; 1.0
Posterior parietal	-5.75; 0	-4.0; 0	-4.5; 0	-2.75; 0
Anterior parietal*	-6.66; 0	-3.0; 0	-3.33; 0	-3.25; 0
Caudate*	-0.42; 2.71	-0.1; 0.5	-0.5; 0.5	-2.0; 0.5
Thalamus/basal ganglia	-1.33; 1.2	0; 1.0	-1.0; 1.0	-1.0; 1.0

Negative numbers mean decrease of rCBF and positive numbers mean increase in rCBF.

* Means of severity show the most changes in these regions, particularly in the Clozapine group.

Table 5: Correlation between psychological symptoms and region of interest before and after treatment; only coefficients with $r \geq .50$ / $r \leq -.50$ are shown (n= 20), $p < 0.05$.

Brain Regions	PANSS Positive		Negative		Composite (P-N)		General Psychopath.		Anergia		Thought disturbance		Paranoid bellig		Depression	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Sup. frontal		*LT -.75		LT -		RT .59		LT -.53				*LT -.71		*LT -.68		RT -.55
temporal														LT .50		
Post. parietal				RT -						RT -.50						
Ant. parietal	LT -			.51						LT -.53						
caudate						RT .51										
Thalamus/Basal Ganglia		LT .55										LT .55				

Inferior frontal and cerebellum have no significant correlation with PANSS scores.

*Only bold numbers (first row) in superior frontal had $r < -0.60$, $p < 0.01$.

Table 4 shows the severity index of pre-post treatment in both groups. The results show the superiority of clozapine to classical treatment in schizophrenia, particularly in Superior frontal, anterior and posterior parietal and caudate, which show the most changes in the Clozapine group.

In table5, the findings show only significant correlations ($r > .50$, $r \leq -.50$), $p < 0.05$. The most common abnormality in the schizophrenic brain SPECT was shown to be a decreased rCBF in the superior frontal region, which was cleared mostly by the Clozapine therapy.

At this step all PANSS subgroups were related to the brain regions, and this showed the correlation between positive symptoms with the left thalamus/basal ganglia, left anterior parietal and left superior frontal after treatment in both groups. For negative symptoms correlations were seen in the left temporal, right post parietal, right thalamus/ basal ganglia before treatment and with the left superior frontal after treatment in both groups, but as the findings show, the correlation was only significant with two of them (table5). The composite (positive-negative) subgroup correlation was significant with the right caudate before and with the right superior frontal after both treatments. General psychopathology correlation was only significant with one region in post treatment: the left superior frontal. And for Anergia it was significant in bilateral post parietal regions in both groups. Paranoia correlated significantly with two brain regions: the left temporal before and the left superior frontal after both treatments. For depression the correlation was significant only with one region: the right superior frontal in post-treatment in both groups.

Incidentally there was a strong correlation ($p < 0.01$) between the right temporal and right anterior parietal, and also between the right caudate and right thalamus / basal ganglia. In addition, based on our study, positive symptoms have a strong correlation with paranoia, thought disturbance and less with negative symptoms; whereas, negative symptoms have a strong correlation with activation ($P < .007$) and less with paranoia ($P < .011$).

4. Discussion

First, PANSS score differences (pre-post treatment) were significant in both the classical and Clozapine groups and for all subgroups, except for the composite subgroup, which was positive-negative. Therefore, both treatments have their benefits for schizophrenia. Some studies have reported that the efficacy of Clozapine is clinically significant on the negative symptomatology but is delayed compared to the efficacy on the other dimensions of symptomatology evaluated using the PANSS [3,20,22,25,26]. Based on these studies, both positive and negative symptoms seem to be improved with Clozapine. In addition, some studies have shown that negative symptoms improve in direct relation to positive symptoms in schizophrenia after Clozapine therapy [25,26]. Based on our study, positive symptoms have the strongest correlation with paranoia and thought disturbance and then with negative symptoms, whereas negative symptoms have a strong correlation with activation and less with paranoia. In other words, positive symptom improvement means less paranoia and more cooperativeness. And negative symptom improvement shows more activity and cooperativeness, and less paranoia as well.

In our study, difference means of PANSS subgroups were more significant in the Clozapine group than the Classical group, which showed in decreasing order: general psychopathology, anergia, positive and negative symptoms, in compare with the classic group, which was in decreasing order; general psychopathology, positive and negative symptoms. This finding shows the priority of positive symptom improvement to negative symptom by both treatments.

Second, Corresponding with the widespread literature that frontal hypo-perfusion is the most consistent finding in the resting state of chronic schizophrenia [10-13,27], the most common finding in our study was a decrease of perfusion, mostly (85%) in the superior frontal region (17 out of 20 cases). Although some researchers have pointed out that frontal hypo-perfusion might be associated by chronicity of illness or long-term anti-psychotic treatment or even the aging process, most studies have shown a reduced frontal cerebral blood flow in drug-naïve patients. Thus, decrease of frontal perfusion can be an existing finding before any clinical manifestation of schizophrenia.

Third, in our study, we found a significant negative correlation between negative symptoms and hypofrontality in both groups, especially in the left superior frontal (table 5). This relationship between negative symptoms and frontal hypo-perfusion has been supported by many other studies [12,13]. However, there is another argument that in the first-episode of schizophrenia, and in the acute phase, hyper perfusion in the frontal and temporal region is dominant, unlike the chronic phase which exhibits hypo-perfusion. At any rate, such hypo-perfusion correlates positively with some acute schizophrenic symptoms and with their severity [6,12].

Fourth, in the temporal region there was an increased perfusion and mostly in the left side with the Clozapine therapy, but not with the classical treatment. This pattern is usually seen in hallucinatory states [1,11,14,15], but here under antipsychotic treatments and the resulting PANSS scores improvement, this finding may demonstrate an over-

reaction to Clozapine therapy, not a hallucinatory state. Future studies will help us understand more about this reaction.

Fifth, contrary to our expectation, based on passed studies, a significant increased rCBF was observed in the thalamus, particularly with Clozapine treatment. This can be due to Clozapine's effect on the thalamus by dopaminergic receptors, which is less with the classical treatment. It may explain some higher efficacy of Clozapine to the classical treatment, especially on refractory schizophrenia.

In conclusion, based on our study and past studies, schizophrenia can affect different brain regions, from the frontal, temporal, parietal to the thalamus and basal ganglia. Some studies show hypo-perfusion, others hyper-perfusion. This variety and inconsistency in results may explain the real nature of this illness, which is diversity of causes involved in different levels in this illness. However, our study by using ^{99m}Tc -ECD-SPECT and PANSS has shown the superiority of Clozapine to classical anti-psychotics in treating schizophrenia in both positive and negative symptoms.

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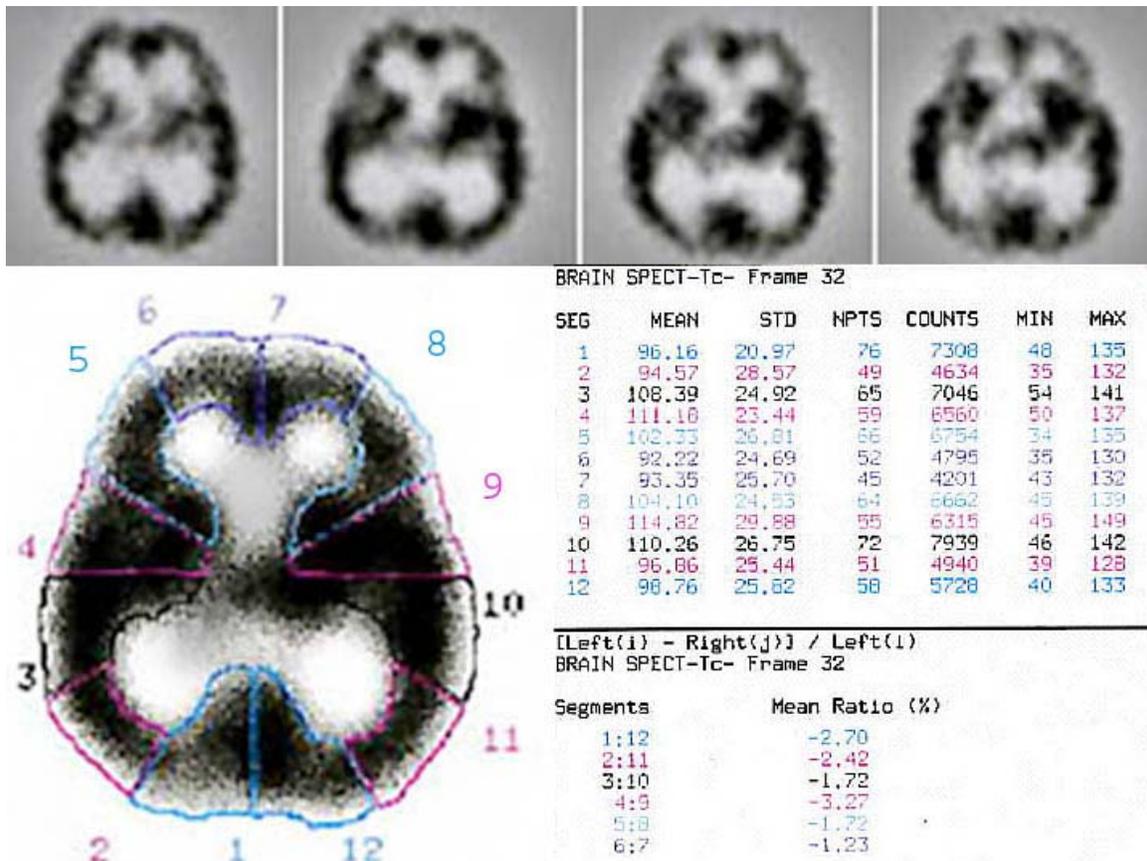


Figure 1: Quantification of regional involvement in schizophrenia; a sample of ^{99m}Tc -ECD-Brain SPECT data analysis in a schizophrenic patient. Data was processed by a DSX computer vision (revision-7.0) and picture reconstruction was performed by using Butterworth filter with automatic attenuation correction. Single-photon-emission-computed-tomography, as its name might suggest, relies heavily on computers to acquire, process and display the SPECT image. As image processing software and hardware become smaller, faster and just "better", SPECT will adapt and incorporate those advances it can use. It is hoped that improvements in parallel processing and computer architectures will make Bayesian reconstruction faster and take less computer memory, and thus make it more attractive for potential use in the clinic.

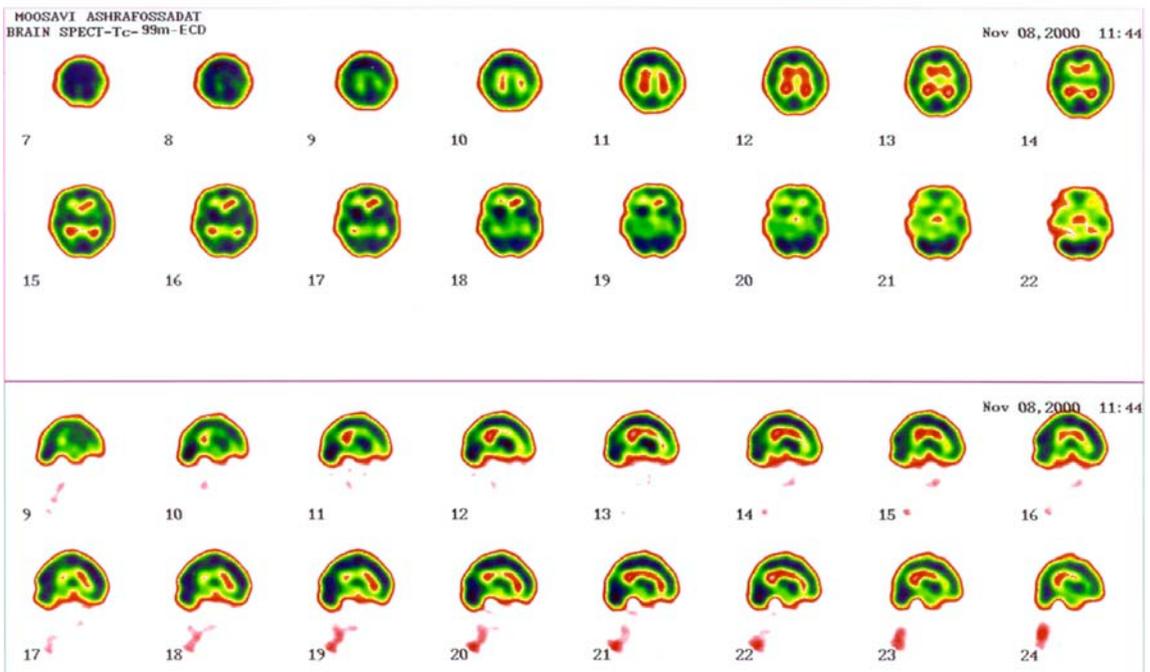
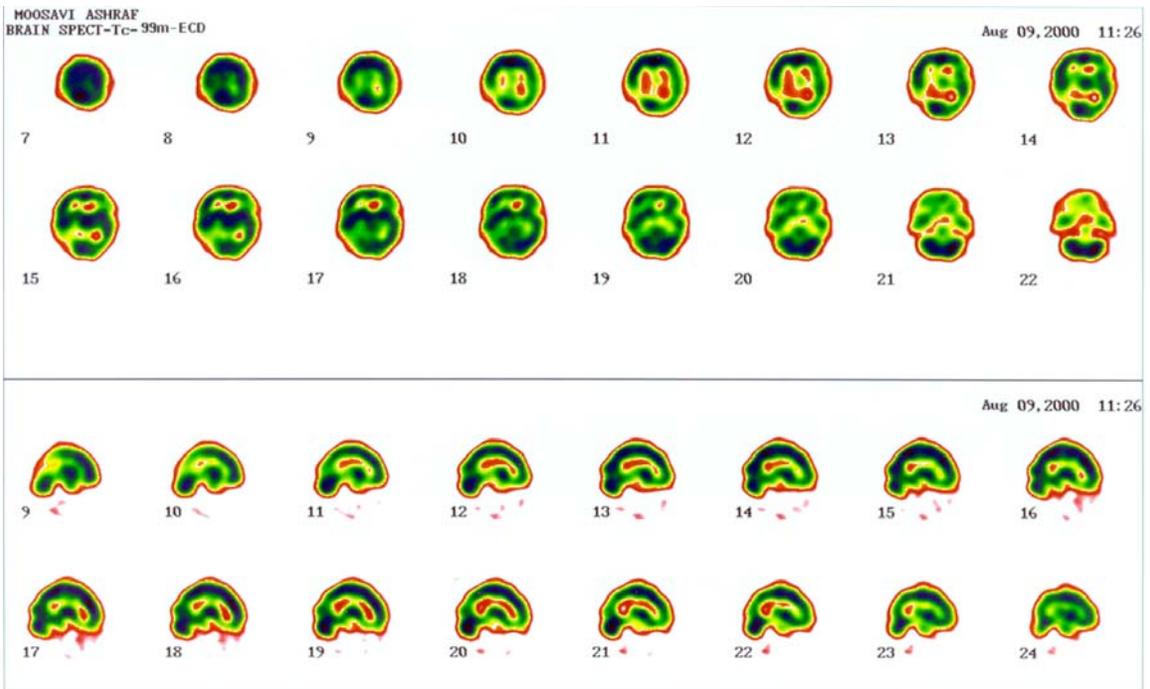


Figure 2: SPECT by ^{99m}Tc -ECD in a 39 year-old drug naïve schizophrenia, pre (up) and post (down) treatment with Clozapine. A severe hypo-perfusion in right occiputo-posteroparietal (upper transverse cuts # 9-15) has been nearly removed after 3 months of consistent treatment.