Evaluation of SISCOM in routine regional cerebral blood flow alterations after clozapine, in schizophrenia

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Abstract

Subtraction ictal single photon emission tomography (SPET) co-registered to magnetic resonance imaging (SISCOM) is an ictal-interictal brain perfusion SPET subtraction method, developed for evaluation of brain perfusion changes applied for the identification of epileptic foci. *The aim* of this study was to test whether regional cerebral blood flow (rCBF) alterations due to clozapine in schizophrenic patients could also be detected with SISCOM. *We have studied* the brain perfusion SPET data obtained both before (pre-SPET) and 8 weeks after (post-SPET) clozapine treatment, in 20 patients with schizophrenia. These data were used for SISCOM processing. In order to identify any alterations in the perfusion pattern using SISCOM, pre- and post-SPET data were subtracted from each other. Activation maps were created and merged on either pre- or post-SPET images. Visual interpretation of brain perfusion SPET studies were performed and compared with SISCOM findings. *We found* that final SISCOM images and visual evaluation of pre- and post-SPET studies were well concordant in 17/20 patients. Discordance was observed in 3 patients. In 1 of these 3 patients alterations observed with SISCOM were confirmed as subtle changes on visual re-evaluation of the images. In the remaining 2 of these 3 patients, SISCOM did not confirm the changes observed by visual analysis. Additionally, SISCOM depicted perfusion alteration in occipital cortex in 5 patients. *In conclusion,* the algorithm of SISCOM seemed to be useful and complementary to visual evaluation, to assess rCBF changes due to clopazine in outpatient schizophrenic patients who had treatment refractoriness or intolerance of previous antipsychotics and to provide additional information when both pre- and post-SPET data were subtracted from each other.

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Introduction

Subtraction ictal single photon emission tomography (SPET) co-registered to magnetic resonance imaging (SISCOM) method has been mainly developed for the evaluation of epileptic foci in intractable partial epilepsy [1-4]. In this technique, interictal brain perfusion SPET images are subtracted from ictal SPET creating an activation map which is then overlapped on magnetic resonance imaging (MRI). The final image is used to optimally determine regions of altered activation during seizures.

Altered regional brain blood flow (rCBF) in the frontal cortex and basal ganglia in response to an atypical antipsychotic drug, clozapine (CP), has been reported in several studies in schizophrenic patients who were refractory to conventional antipsychotics [5-7]. Conventional antipyschotics, that mainly block dopamine D2 receptors are relatively effective in treating psychotic symptoms but can also produce problematic side effects including Parkinsonian/extrapyramidal symptoms and tardive dyskinesia [8, 9]. Clopazine acts on especially limbic dopaminergic receptors, primarily D4 receptors, therefore it does not induce extrapyramidal side effects and is also a partial agonist of 5-HT1A receptor improving negative cognitive symptoms. It has been shown that atypical antipsychotics increase cortical perfusion and decrease striatal and thalamic perfusion in responders [6, 7]. The effect of CP on rCBF was investigated in patients who had previously used risperidone in another study [10]. They showed that CP normalized the increased perfusion in the limbic system.

In this study, we aimed to test whether SISCOM technique, could be applied for the assessment of rCBF changes due to CP outpatient schizophrenic patients. We compared SISCOM findings with results of visual interpretation of brain perfusion SPET studies obtained before and after CP in schizophrenic patients.

Patients and methods

The brain perfusion SPET data which had been previously obtained both before (pre-SPET)

and 8 weeks after (post-SPET) the initiation of CP treatment, of 20 patients with schizophrenia (9 male, 11 female; age range: 19-58yr; median: 28yr) have been used for SISCOM processing. The mean CP dose during the 8 weeks was 390.48±109.11mg/day. The patients were outpatients with Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria [8, 9] for schizophrenia. One of major diagnostic systems for schizophrenia is DSM-IV and in common use for schizophrenia currently. This system defines symptoms and characteristic impairments of schizophrenia and has improved the reliability of diagnostic assessments over more subjectively based approaches. All patients had paranoid subtype of schizophrenia and had a history of using multiple typical and atypical antipsychotics. Initiation of CP was decided because of treatment refractoriness of the patients or intolerance of previous antipsychotics by their treating psychiatrists and they did not take other drugs together with CP. Previous antipsychotics were terminated 1-72 months before CP initiation. Exclusion criteria were alcohol or drug abuse/dependency, chronic use of any other medication and any major medical or neurological disorder. The mean duration of the illness was 8.14±6.6yr.

Brain perfusion

SPECT data Pre-SPET was obtained before CP as follows: Seven hundred and forty MBq of ^{99m}Tc hexamethyl proplene amine oxime (^{99m}Tc-HMPAO) were injected intravenously while the patient was sitting, in a room with dim lighting. Twenty minutes after the radiopharmaceutical administration, SPET imaging was performed with a dual-headed rotating gamma camera (Siemens, E-CAM, USA) equipped with a high resolution, parallelhole collimator. During a 360^{o} rotation in 128X128 matrix, 128X40sec frames were obtained. Reconstruction was performed parallel to the orbito-meatal line using filtered back projection; Butterworth filter (cut-off: 0.28, order: 10) and attenuation correction were applied using Chang's method (attenuation coefficient: 0.12cm^{-1}) [11].

Post-SPET study was performed after 8 weeks of CP treatment as described in the pre-SPET study. The algorithm of SISCOM was performed using, Analyze 6.0 which is a commercial, licensed software package (Biomedical Imaging Resource, Mayo Foundation, U.S.A.). Pre- and post-SPET processed data were transferred in DICOM format and loaded into Analyze workspace. Registration of pre- and post-SPET were performed. During registration process, scatter and non-interest regions were eliminated using the threshold values. Radioactivity uptake level was automatically normalized choosing two standard deviations in the "activation level" option menu. Both pre- and post-SPET were subtracted from each other to study the effect of CP on rCBF. Final images were created as an activation map and merged on either pre- or post-SPET images. Cortical, subcortical and cerebellar brain perfusion in pre- and post-SPET images were evaluated visually by 3 nuclear medicine physicians blindly (ELE, BVS, BE). Side-by-side visual interpretation of brain perfusion SPET studies was compared with SISCOM findings.

Results

The summary of results of the visual interpretation of pre-, post-SPET and the SISCOM findings in Groups 1 and 2 are shown in Table 1.

Table 1. *Comparison of the visual analysis and the SISCOM findings*

Patient No (Response)	Visual interpretation		SISCOM
	Pre-SPET (rCBF)	Post-SPET (rCBF)	
Group 1			
1 (NR)	Normal	Bilateral basal ganglia (increased)	Post-Pre= Positive
2 (NR)	Frontal cortex (decreased)	Frontal cortex (normal)	Post-Pre= Positive
3 (R)	Normal	Right basal ganglia (increased)	Post-Pre=Positive
4 (R)	»	Normal	Post-Pre=Positive (Frontal cortex) (Right basal ganglia)
5 (NR)	»	Left basal ganglia (increased)	Post-Pre= Positive
6 (R)	Bilateral basal ganglia & right thalamus (increased)	Normal	Pre-Post=Positive
7 (NR)	Left frontal cortex (decreased)	Frontal cortex (normal)	Post-Pre=Positive
8 (R)	Normal	Bilateral basal ganglia (decreased)	Pre-Post=Positive
9 (NR)	»	Frontal cortex (increased)	Post-Pre=Positive
10 (NR)	Right basal ganglia (decreased)	Right basal ganglia (normal)	Post-Pre=Positive
11 (R)	Normal	Right basal ganglia (increased)	Post-Pre=Positive
12 (R)	Frontal cortex (increased) Left basal ganglia (increased)	Frontal cortex (normal)	Pre-Post=Positive
Group 2			
13 (NR)	Normal	Normal	Post-Pre= ND. Pre-Post= ND.
14 (R)	»	»	Post-Pre= ND. Pre-Post= ND.
15 (R)	»	»	Post-Pre= ND. Pre-Post= ND.
16 (R)	»	»	Post-Pre= ND. Pre-Post= ND.
17 (NR)	Right frontal cortex (decreased)	Right frontal cortex (decreased)	Post-Pre= ND. Pre-Post= ND.
18 (NR)	Left basal ganglia (decreased)	Left basal ganglia (decreased)	Post-Pre= ND. Pre-Post= ND.
19 (NR)	Left frontal cortex (decreased)	Left frontal cortex (normal) Bilateral basal ganglia (decreased)	Post-Pre= ND. Pre-Post= ND.
20 (NR)	Left basal ganglia (decreased)	Left basal ganglia (normal)	Post-Pre= ND. Pre-Post= ND.

NR: non-responsive, R: responsive, Pre: Baseline brain perfusion SPET; Post: Brain perfusion SPET after 8 weeks of clozapine treatment, ND: No difference

Group 1: In this group of patients SISCOM indicated positive findings as rCBF alterations. In 12 patients no: 1-12, final images obtained from either pre-post or post-pre SPET indicated alterations of rCBF mostly in the frontal cortex, the basal ganglia or both. In 11 of these patients visual interpretation of the SPET studies were in concordance with SISCOM findings. In 1 patient (no: 4), initially no rCBF alteration was observed on visual interpretation while SISCOM indicated rCBF alterations (Table 1) and SISCOM findings led to the re-evaluation of the spet studies and visual interpretation of spet was modified.

Group 2: In this group of patients SISCOM showed no difference in rCBF between pre- and post-SPET findings. In 4 patients (no: 13-16) both SISCOM images and visual interpretation showed no alterations in rCBF and in 2 patients (no: 17 and 18) visual analysis showed persistant rcbf decreases and SISCOM displayed no difference accordingly. In 2 patients (no: 19 and 20), SISCOM findings did not show the alterations observed with visual evaluation (Table 1).

Overall SISCOM findings and visual evaluation of pre- and post-SPET studies were concordant in 17 patients no: 1-3 and 5-18 (Fig. 1-5). Additionally, SISCOM images depicted alterations of rCBF in the occipital cortex in 5 patients no: 3, 6, 10-12 (Fig. 1, 3, 5).

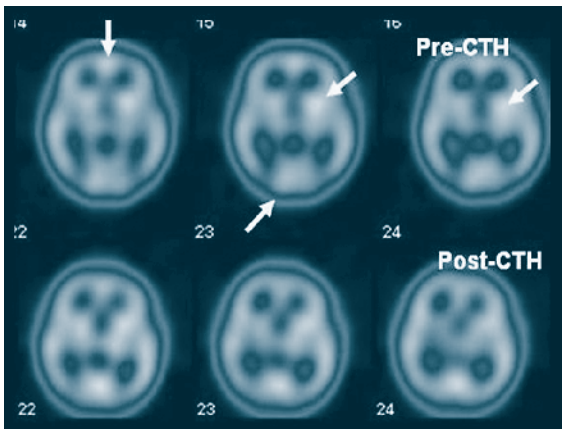

Figure 1a and 1b. a) Visual evaluation: rCBF is higher in the frontal lobe, left basal ganglia, right occipital lobe (arrows) on pre-SPET when compared to post-SPET performed after 8 weeks of clozapine treatment (patient no. 12). b) Images by SISCOM algorithm of the same patient: Activation map indicates the final SISCOM image when post-SPET is subtracted from pre-SPET. The rCBF alterations on the frontal lobe, left basal ganglia and right occipital lobe are presented with arrows. Findings are well concordant with visual evaluation. The merged image shows the final SISCOM image which is superimposed on post-SPET data.

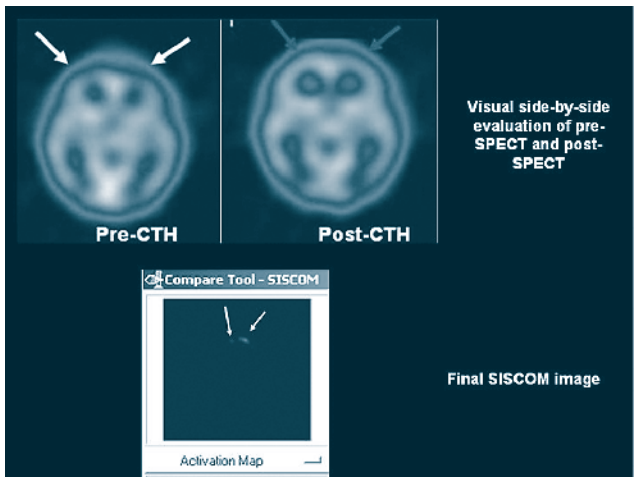

Figure 2. Visual evaluation of pre-SPET and post-SPET of patient no. 2. White arrows display hypoperfusion in the bilateral frontal lobes on pre-SPET and gray arrows show normalisation of perfusion in the frontal lobe after clozapine on post-SPET. Final SISCOM image as activation map, when pre-SPET is subtracted from post-SPET is displayed. This figure confirms the rCBF increase in the frontal lobes after clozapine (arrows).

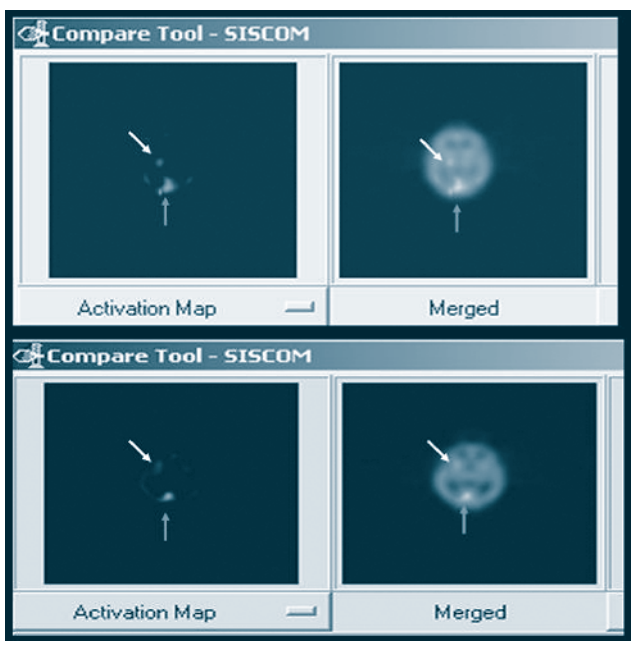

Figure 3. Images by SISCOM algorithm show rCBF alterations due to clozapine treatment in the right basal ganglia in 2 different patients no. 3 and 11 (white arrows). SISCOM depicted increased occipital rCBF due to visual activations of the patients during the injection of the radiopharmaceutical in one of the brain SPET studies (gray arrows).

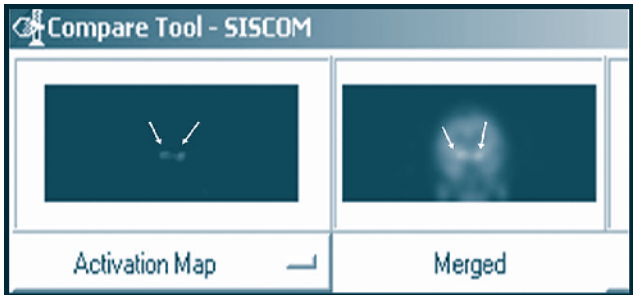

Figure 4. Coronal SISCOM images indicate rCBF difference in bilateral basal ganglia in another patient no. 1 due to clozapine treatment (arrows).

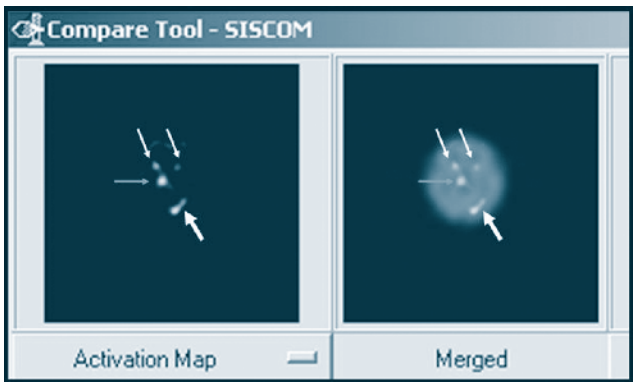

Figure 5. Images by SISCOM algorithm in patient no. 6 rCBF alterations in bilateral basal ganglia (white arrows), right thalamus (gray arrow). Thick arrow shows the increased occipital rCBF due to visual activation in the patient.

Discussion

The algorithm of SISCOM has been proposed as a recently developed neuroimaging method for the localization of epileptic foci [1, 12, 13] and for right and left temporal seizures [14]. In SISCOM algorithm, masks for both ictal and interictal SPET images were created by tresholding and brain contours were overlapped using surface-based registering. Mean pixel intensities of both ictal and interictal studies were normalized to a constant value. The normalized interictal image was subtracted from the normalized ictal image where changes in two standard deviations showed significant activation pixels. This activation map, created from the subtraction of these two images can be superimposed to either MRI or interictal SPET image. The final image has been considered a useful tool for the identification of the epileptogenic zone in patients with drug-resistant temporal and extratemporal lobe epilepsy [15]. Others have studied SISCOM technique in localizing seizure foci in specific forms of epilepsy such as in polymicroglia syndromes [16], periSylvian syndrome [17], musicogenic epilepsy [18] or gelastic seizures [19]. Therefore, studies with SISCOM mainly investigate the various kinds of epilepsy.

A study like the present one, comparing pre- post-SPET rCBF after CP in outpatient paranoid schizophrenic patients using siscom algorithm has not been published before. To our knowledge, SISCOM has been applied for the SPET studies of only one patient with Tourette syndrome [20]. In our study, final SISCOM findings and visual evaluation of pre and post-SPET studies were well concordant in most (17/20) of our patients indicating that SISCOM findings were supplementary to visual interpretation for rCBF changes mainly in the frontal cortex and basal ganglia.

Additional alterations of rCBF were depicted by SISCOM in the occipital cortex in 5 patients. Increased perfusion in occipital/occipito-temporal regions due to CP action was reported in the literature [10]. In 2 of our patients (no: 6 and 12) occipital hyperperfusion was observed with SISCOM on pre-post SPET subtraction and in 3 (no: 3, 10, 11) during post-pre SPET subtraction. To our opinion these do not contribute to a specific perfusion pattern which might be attributed to CP action. Therefore, we believe that this finding might be due to visual stimulation of these patients during injection of the radiopharmaceutical in one of the SPET sessions. The algorithm of SISCOM may have the potential to show unexpected functional alterations or incidental findings in rCBF SPET studies and might better support the diagnosis.

The algorithm of SISCOM is designed in order to emphasize perfusion changes in epilepsy, especially the hyperperfusion which evolves during ictal state. On the other hand, in psychiatric applications perfusion patterns and alterations might be quite different such as an increase, decrease or normalization in perfusion of different brain regions according to the acting mechanisms of the drugs used. In order to scrutinize and verify faint perfusion changes and to display a drug specific perfusion pattern we subtracted both pre- and post-SPET data from each other using SISCOM algorithm in our study. The algorithm of SISCOM showed areas of perfusion alteration. Either when pre-SPET was subtracted from post-SPET or when post-SPET was subtracted from pre-SPET (Group 1, Table 1). SISCOM findings were concordant with the perfusion changes in frontal cortex, basal ganglia, and thalamus observed by visual inspection and supported the hypothesis that CP, an atypical antipsychotic may act through an alteration in fronto-striato/thalamic circuitry [5-7]. Moreover, SISCOM displayed some incidental findings like increased perfusion in occipital lobes and increased the detectability of subtle perfusion alterations.

A limitation of this study is the lack of a control group which was not possible because of ethical reasons. However, we believe that changes detected by SISCOM or by visual inspection between two consecutive scans indicate true significant findings other than test-retest variability or image noise. Because, neither minimal nor significant rCBF alteration in the regions of the brain other than frontal cortex, basal ganglia, thalamus and occipital cortex, was observed by SISCOM or visual inspection.

In conclusion, our study suggests that the algorithm of SISCOM seems to be useful to evaluate and increase the detectability of the rCBF changes due to CP in outpatient paranoid schizophrenic patients and to provide additional information. Both pre- and post-SPET data should be subtracted from each other in order to better study the effect of CP treatment on rCBF in these patients.

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