ARTIGO ORIGINAL

Cerebral perfusion and automated individual analysis using SPECT among an obsessive-compulsive population

Perfusão cerebral e análise individual automatizada utilizando SPECT em uma população com transtorno obsessivo-compulsivo

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ABSTRACT

Objective: To make individual assessments using automated quantification methodology in order to screen for perfusion abnormalities in cerebral SPECT examinations among a sample of subjects with OCD. **Methods:** Statistical parametric mapping (SPM) was used to compare 26 brain SPECT images from patients with OCD individually with an image bank of 32 normal subjects, using the statistical threshold of $p < 0.05$ (corrected for multiple comparisons at the level of individual voxels or clusters). The maps were analyzed, and regions presenting voxels that remained above this threshold were sought. **Results:** Six patients from a sample of 26 OCD images showed abnormalities at cluster or voxel level, considering the criteria described above, which represented 23.07%. However, seven images from the normal group of 32 were also indicated as cases of perfusional abnormality, representing 21.8% of the sample. **Conclusion:** The automated quantification method was not considered to be a useful tool for clinical practice, for analyses complementary to visual inspection.

Keywords
Brain SPECT, SPM, OCD, individual analysis.

RESUMO

Objetivo: *Avaliar uma amostra de pacientes com transtorno obsessivo-compulsivo (TOC), individualmente, empregando uma metodologia de quantificação automatizada para rastrear anormalidades de perfusão em exames de SPECT cerebral.* ***Métodos:*** *Foi utilizado o Statistical Parametric Mapping (SPM) para comparar 26 imagens de SPECT cerebral de pacientes com TOC, individualmente, com um banco de 32 imagens de voluntários normais, usando o limiar estatístico de $p < 0,05$ (corrigido para comparações múltiplas ao nível do voxel individual ou clusters). Os mapas foram analisados procurando por regiões que apresentassem voxels acima desse limiar.* ***Resultados:*** *Seis pacientes da amostra de 26 imagens com TOC mostraram anormalidades ao nível do cluster ou voxel, considerando os critérios descritos acima, os quais representaram 23,07%. Contudo, sete imagens do grupo de 32 voluntários normais também foram apontadas com anormalidades de perfusão, que representou 21,8% da amostra.* ***Conclusão:*** *O método de quantificação automatizada não foi considerado como uma ferramenta útil na prática clínica, como forma de análise complementar à inspeção visual.*

Palavras-chave
SPECT cerebral, TOC, SPM, análise individual.

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INTRODUCTION

The neurobiology of obsessive-compulsive disorder (OCD) has been widely investigated over the past decades. Functional neuroimaging studies using positron emission tomography (PET), single-photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) have sought to investigate the pathophysiology of OCD, and these have mainly implicated circuits involving fronto-subcortical connections. A series of published papers has indicated functional brain abnormalities in group comparisons of OCD patients relative to healthy controls, particularly involving the orbitofrontal cortex, anterior cingulate cortex, basal ganglia and thalamus[1-4]. Cortical regions such as the orbitofrontal cortex and the cingulate gyrus have been recognized to be heterogeneous among humans, with evidence of the existence of subregions that possibly perform specific roles in the pathophysiology of OCD[5,6].

Despite the great impact that neuroimaging studies have had with regard to elucidating the pathophysiology of the so-called functional psychiatric disorders such as major depressive disorder, OCD and psychoses, the results from such investigations have generally come from statistical comparisons of means from cerebral measurements, between groups of patients and normal controls. On the other hand, when brain functional images of any type are inspected individually, abnormalities are only detected in a certain proportion of patients with psychiatric disorders, and with considerable variability regarding the nature and cerebral location. In this respect, there has been a scarcity of systematic studies which suggest that such neuroimaging examinations could be useful for practical clinical diagnostic purposes in the individual evaluation of subjects with functional psychiatric disorders. This is in sharp contrast with the well-established practical applications for functional neuroimaging methods in the differential diagnosis of neurological diseases that presumably present well-defined cerebral pathological findings[7-9].

In recent years, automated image analysis methods have been developed to allow voxelwise quantifications of findings in PET, SPECT and MRI studies. Classically, these methods have been used to make statistical comparisons of mean signal intensities in each voxel of the cerebral volume between groups of patients and normal controls, or alternatively, to compare images from the same group under two different conditions[10,11]. The possibility of using SPECT in association with some form of automated quantification for evaluating individual patients with functional psychiatric disorders is of great interest, but there have been few published papers using this approach. Nevertheless, automated voxel-based image analysis methods have been applied in case-by-case evaluations for investigating epileptic foci[12], for comparative assessments with visual analysis among patients with Alzheimer's disease, and even for assessments of normal subjects[13,14].

Conventional methods using regions-of-interest to quantify brain perfusion abnormalities are not appropriate for studying subregions within functionally heterogeneous brain structures of relevance to the pathophysiology of OCD, such as the orbitofrontal and anterior cingulate cortices. Thus, automated voxel-based quantification methods may afford a better strategy for assessing subtle and highly circumscribed changes in cerebral SPECT examinations in individual OCD cases. Hence, the aim of the present study was to evaluate whether the voxel-based statistical parametric mapping (SPM) approach might have a complementary role in investigating possible perfusional abnormalities among a group of patients with OCD (n = 26) assessed individually with SPECT. We predicted that the SPM-based approach could enable the detection of subtle brain perfusion abnormalities in a proportion of OCD patients, in a frequency greater than that found in the group of healthy control subjects (n = 32) evaluated with exactly the same imaging methods.

MATERIAL AND METHODS

A sample of 26 patients (15 males/11 females, 23 right-handed) fulfilling DMS-IV criteria for OCD[15] was selected. Their mean age was 32.1 years (SD 7.8). Eleven of the patients had never previously undergone any kind of treatment. Four patients agreed to remain free from medication for three weeks in order to undergo washout from previous treatments. The remaining patients had taken medications in the past, but had been free from all OCD treatments over the four-year period preceding the start of this study. The patients were recruited at the Institute of Psychiatry of Hospital das Clínicas, School of Medicine of the University of São Paulo (IPq-HC-FMUSP). All of the patients underwent a structured clinical interview in accordance with DSM-IV- Patient Edition (SCID-I/P)[16]. This group of OCD patients was recruited for a controlled study on cerebral SPECT and structural MRI[17]. The intensity of obsessive-compulsive symptoms was measured moments before performing the cerebral SPECT examination, with the Yale-Brown-Obsessive-Compulsive Scale[18] (mean = 26.8; SD = 5.9).

A control group of 32 normal volunteers, of mean age 32 years (SD = 9.6) and age range from 20 to 57 years, composed of 15 men and 17 women, was recruited at IPQ HC-FMUSP but also from social contacts. Before undergoing the SPECT examination, all the subjects in this control group had undergone a detailed assessment, including general medical anamnesis and the structured clinical interview for the DSM-IV diagnosis of psychiatric disorders (SCID[19]), in order to rule out any presence of neurological and/or psychiatric disorders. Moreover, these individuals had no signs of gross brain

abnormalities as assessed by structural magnetic resonance scans, visually inspected by two radiologists independently from each other. The study received institutional review board approval.

Protocol for acquisition and processing of cerebral SPECT images

The protocols used for acquisition and processing of cerebral SPECT data were the same for all subjects in the above groups. After venous puncture in a superficial vein of the arm, the individuals remained at rest for 20 minutes and then received a dose of 740 MBq of ^{99m}Tc-ECD. After a further 20 minutes, image acquisition was started. All the examinations were performed using a device with two detectors and high-resolution collimators (OPTIMA NX, General Electric, Milwaukee, USA). The images were acquired using the step-and-shoot method. A matrix of 128 X 128 was used, and 128 projections were acquired (20 seconds per projection).

The orbital-meatal line was used for reconstructing the SPECT images, which was done by using the filtered back-projection method with attenuation correction in accordance with Chang's algorithm ($\mu = 0.12$ cm^{-1}). All the images were reconstructed with pixels of 2.25 mm and a tenth-order Butterworth filter with Nyquist frequency of 0.57. Transverse sections through the reconstructed images were selected for the subsequent stages of the analysis.

Generation of individualized statistical parametric maps showing rCBF abnormalities

Individualized statistical parametric maps for each subject were produced using the SPM program, version 1999, executed in MATLAB 4.2. Firstly, SPECT images of all patients with OCD and controls were spatially normalized, with linear 12-point affine transformations, to an anatomical *template* provided by the SPM program, which approximates the stereotaxic space of the Talairach-Tournoux atlas[20]. Subsequently, images were re-sliced using bi-linear interpolation to a final voxel size of 2x2x2 mm^3, and smoothed with an isotropic Gaussian filter (12 mm full-width at half maximum) in order to improve the signal-to-noise ratio and to reduce errors attributed to inter-individual variations in gyral and sulcal anatomy. For each of the subjects with obsessive-compulsive disorder (n = 26), a voxel-by-voxel t-test map was obtained by comparison against the pool of controls (n = 32). With the purpose of accounting for inter-individual differences in overall cerebral blood flow, the regional ^{99m}Tc-ECD uptake was standardized to the mean overall uptake using proportional scaling. The measure of total brain radioactive uptake was obtained automatically by the SPM program, given by the mean counts of all voxels included in the SPECT volume of each subject, after the spatial transformations described above. In order to reduce the number of statistical comparisons, only voxels with signal intensities above 50% of the mean overall value were entered in each analysis. The individualized SPM{t} maps for each subject were transformed to the unit's normal distribution (Z scores), thresholded at 3.09 (corresponding to $p < 0.001$, uncorrected for multiple comparisons), and displayed as statistical parametric maps into standard space. The same procedure was carried out to provide individualized statistical parametric maps of rCBF abnormalities for the control subjects, by comparing each control individual against the remaining thirty-one subjects.

Clusters of rCBF abnormalities in the individualized maps were then examined in terms of size (k) and peak height (u), and were considered significant only if retaining statistical significance after correction for multiple comparisons based on Gaussian random field theory ($p < 0.05$), either at the level of individual voxel height or at the level of clusters[21].

RESULTS

Table 1 shows the results from the SPM maps relating to the individual comparisons of each of the 26 patients with OCD against the pool of healthy controls, with voxels that were screened at the significance threshold of $p < 0.05$, corrected for multiple comparisons. Significant abnormalities due to hypoperfusion were found in one patient at voxel level and in another subject at the cluster level; with regard to hyperperfusion, there were three patients with significant findings at the voxel level and one subject at cluster level (Figure 1). Thus among the 26 images analyzed, only six cases showed abnormalities, i.e. 23.07% of the full sample. Such abnormalities were considerably variable in their location, involving the frontal, temporal and occipital cortices (Table 1).

Among the 32 images from healthy controls analyzed for hypoperfusion, two abnormal examinations were found at voxel level and two at cluster level, of which one presented significance at both levels, i.e. three healthy subjects with abnormalities (Table 2). The abnormalities were located in the right occipital cortex and right inferior frontal cortex (Figure 2). In evaluating the presence of hyperperfusion, two examinations with voxels above the threshold were found at voxel level, and four at cluster level. However, one examination at voxel level and another at cluster level had already been described with hypoperfusion contrast. Thus, four subjects were deemed to present perfusion abnormalities, thus total seven healthy subjects (21.8%) with abnormal examinations considering both contrasts.

Table 3 shows the severity of symptoms with measures of compulsion, obsession and Y-BOCS for the group of six OCD patients as described in table 1. It can be noticed that in this sub-group the Y-BOCS scores ranged 25-34 (mean 28,7), compulsion 12-17 (mean 14) and obsession 11-17 (mean 14,7).

Table 1. rCBF findings of hypoperfusion and hyperperfusion in OCD group evaluated using SPM

Age	Hypoperfusion					Hyperperfusion				
	Z max	ρ voxel level	ρ cluster level	No. of voxels	Location	Z max	ρ voxel level	ρ cluster level	No. of voxels	Location
32		Zero Vx				**4.86**	**0.02**	**0.09**	**199**	**Left posterior occipital**
34	3.71	0.714	0.940	18		**5.03**	**0.009**	**0.000**	**1,813**	**Right superior temporal**
28		Zero Vx				**4.36**	**0.131**	**0.004**	**467**	**Left cerebellum**
24	**4.47**	**0.08**	**0.008**	**409**	**Right inferior frontal**	3.66	0.762	0.792	40	
32		Zero Vx				**4.61**	**0.05**	**0.01**	**343**	**Left temporal**
38	**5.62**	**0.001**	**0.028**	**300**	**Left medial frontal**	**4.50**	**0.07**	**0.207**	**144**	**Left cerebellum**

Z max: Z score attained; p voxel level: significance level at voxel level; p cluster level: significance level at cluster level.

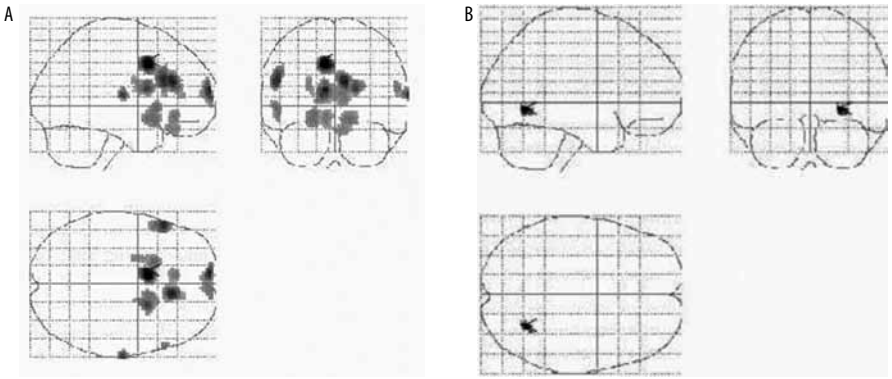

Figure 1. (A-B) Individual SPM maps of 38(A) and 55(B) years OCD patients. Y-BOCS score were 26 and 24, respectively. SPM maps (A) showed hypoperfusion in the inferior frontal cortex and anterior cingulate gyrus which were significant after correction for multiple comparison with $p < 0.02$ and 0.01; SPM map in (B) shows a small group of voxels, not significant.

Table 2. rCBF findings of hypoperfusion and hyperperfusion in normal volunteers evaluated using SPM

age	Hypoperfusion					Hyperperfusion				
	Z max	ρ voxel level	ρ cluster level	No. of voxels	Location	Z max	ρ voxel level	ρ cluster level	No. of voxels	Location
26	**4.80**	**0.02**	**0.001**	**615**	**Right Occipital**		Zero Vx			
38	3.61	0.813	0.815	37		**4.15**	**0.05**	**0.001**	**665**	**Left inferior frontal**
41	**4.12**	**0.28**	**0.01**	**348**	**Left ventricle**		Zero Vx			
47	**5.02**	**0.01**	**0.000**	**791**	**Right inferior frontal**	**5.03**	**0.004**	**0.029**	**284**	**Anterior cingulate**
22		Zero Vx				**4.21**	**0.219**	**0.05**	**249**	**Left medial frontal**
20	3.71	0.723	0.617	62		**4.39**	**0.124**	**0.029**	**290**	**Right superior frontal**
32	**3.83**	**0.574**	**0.04**	**272**	**Left ventricle**	3.91	0.493			

Z max: Z score attained; p voxel level: significance level at voxel level; p cluster level: significance level at cluster level.

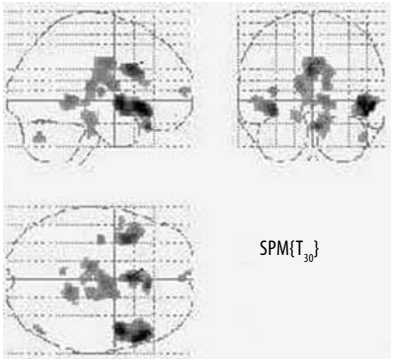

Figure 2. Individual SPM maps of 47 years old healthy volunteer. SPM map shows hypoperfusion in the inferior frontal cortex significant after correction for multiple comparison with $p < 0.01$.

Table 3. Severity of symptoms in OCD patients

Age	Comp.	Obs.	Y-BOCS
32	13	16	29
34	12	15	27
28	17	17	34
24	15	16	31
32	12	13	25
38	15	11	26

Comp.: compulsion; Obs.: obsession;

Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

DISCUSSION

A group of patients with OCD was evaluated with the aim of measuring the efficiency of automated, SPM-based quantifications for detecting brain perfusional abnormalities individually, as assessed with SPECT[22]. Even considering the examinations with abnormalities that reached statistical significance either at the voxel level or at the cluster level, the number of patients whose abnormalities were mapped out and correlated with the diagnosis of OCD was very small. Moreover, contrary to our prediction, similar numbers of abnormal results were found in both the OCD and control groups. These results indicate that the evaluation of threshold perfusion changes using an automated voxelwise analysis method is not clinically useful and does not add anything to the routine clinical evaluation.

Despite this, it's important to note that OCD patients showed a wide spectrum of severity of symptoms with Y-BOCS mean 26,77 ± 5,89, ranging 16-36. The majority (53%) of patients diagnosed with OCD were categorized as serious, while a smaller portion was identified as moderate or extreme as to severity of symptoms. In this sample eight patients met DMS-IV criteria for major depressive episode and 10 met criteria for other anxiety disorders such as phobias and generalized anxiety disorder.

Moreover, all the healthy subjects recruited to the control group had undergone an assessment, which included a general medical anamnesis and the structured clinical interview for the DSM-IV diagnosis of psychiatric disorders. They also underwent structural magnetic resonance scan, that visually did not show any abnormality.

At this point it's important to take into account that single subject analysis is a very interesting tool for clinical practice and it has been successfully applied to neurological disorders characterized by precise regional deficit in brain function[14,20]. On the contrary, OCD is a really heterogeneous psychiatric disease where functional abnormalities are difficult to detect in resting condition and particularly at single subject level[21].

Based on these results, we concluded that SPM-based analyses of individual cases could be a valuable complementary tool within routine clinical practice for the assessment of brain abnormalities in SPECT datasets of patients with neurological conditions. Our present results, using exactly the same methods, indicate that the same clinical applicability cannot be reached for the diagnostic evaluation of patients with OCD.

However, caution is warranted in the evaluation of the present negative results for a number of reasons. Firstly, the low anatomical resolution of SPECT has to be born in mind, along with inter-individual differences in anatomy and metabolism and mood variations at the time of administering the radiopharmaceutical, thus leading to increased variability of brain perfusion patterns in both groups. Also, although the diagnoses of OCD were based on widely validate diagnostic criteria (DSM-IV), OCD is characterized by heterogeneity in its clinical presentation, and this may also add variability to rCBF patterns as assessed by SPECT.

Finally, it should be noted that the construction of individual statistical maps using SPM is not the only methodological strategy for using automated methods to analyze cerebral SPECT data in clinical practice. For instance, alternative analysis methods have been developed to support the diagnosis of neuropsychiatric conditions, enabling fully automated categorization of individual structural or functional brain images based on machine-learning techniques, such as support vector machines (SVMs)[23,24]. Recent studies have demonstrated the reliability and validity of SVM-based techniques, as well as their good diagnostic performance in discriminating, for instance, between Alzheimer's disease patients and healthy control individuals[24]. Therefore, replication of the current negative results are warranted using SVM-based methods, with the aim of studying whether these more sophisticated forms of analysis might lead to similar results or, instead, show greater promise for clinical applications for automated evaluations of rCBF SPECT data from OCD subjects. For the time being, we conclude that automated, SPM-based voxelwise analysis methods have very limited appli-

cability in clinical practice to aid in the diagnostic evaluation of OCD patients.

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