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Perseverative error in schizophrenia: correlation with cortical blood flow by SPECT

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Introduction. Perseverative error (PE) is a core symptom of schizophrenia which has been proposed as a phenotypic marker of the illness. Moreover, hypofrontality observed in functional neuroimaging studies while executing a cognitive task has also been suggested as a characteristic sign of schizophrenia. We propose combining symptom and sign to demonstrate the existence of a regional cortical blood flow (RCBF) pattern associated to PE that might constitute a biological marker of schizophrenia.

Material and method. We used Single Photon Emission Computerized Tomography (SPECT), to study the RCBF associated to PE and to correct response (CR), during the execution of the Wisconsin Card Sorting Test (WCST), of 18 patients with schizophrenia and 13 controls. We focused on five well-defined bilateral brain regions, using the RCBF of the same regions at rest as a baseline.

Results. Patients made more PE than controls in the WCST. Among patients, we observed a correlation between PEs and right occipital RCBF. Among controls, we found a negative correlation between PEs and left temporal cortex RCBF and a positive correlation between CRs and left frontobasal and overall left frontal cortexes RCBF.

Conclusions. The severity of PE is associated to higher right parietal-occipital activity in patients with schizophrenia. CR in the WCST are associated to higher left frontal activity in controls but not in patients. Probably, there is a RCBF redistribution pattern related to the typical perseveration of schizophrenia which might constitute a phenotypic marker of the illness observable by functional neuroimaging techniques.

Key words:
Schizophrenia. Wisconsin Card Sorting Test. Perseveration. Prefrontal cortex. Neuroimage. Regional cortical blood flow.

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El error perseverativo en la esquizofrenia: correlación con el flujo sanguíneo cortical mediante SPECT

Introducción. El error perseverativo (*perseverative Error*, PE) es un síntoma característico de la esquizofrenia que ha sido propuesto como marcador fenotípico de la enfermedad. Junto a ello, la hipofrontalidad observada mediante neuroimagen funcional durante la ejecución de una prueba cognitiva ha sido igualmente sugerida como signo característico de la esquizofrenia. Nos proponemos combinar síntoma y signo para demostrar la existencia de un patrón de flujo sanguíneo cortical relativo (*relative cortical blood flow*, RCBF) asociado al PE, lo que podría constituir un marcador biológico de la esquizofrenia.

Material y métodos. Mediante tomografía computarizada por emisión de fotón único (SPECT) estudiamos el patrón de RCBF asociado al PE y a la respuesta correcta (*Correct Response*, CR) del Test de Ordenación de Cartas de Wisconsin (*Wisconsin Card Sorting Test*, WCST) en 18 pacientes con esquizofrenia y 13 controles. Nos centramos en cinco regiones cerebrales bien definidas bilateralmente, utilizando como línea de base el RCBF de dichas regiones en reposo.

Resultados. Los pacientes cometieron más PE que los controles en el WCST. En los pacientes observamos una correlación entre PE y RCBF de la corteza occipital derecha. En los controles encontramos una correlación negativa entre PE y RCBF de la corteza temporal izquierda y una correlación positiva entre CR y RCBF de las cortezas frontobasal izquierda y frontal global izquierda.

Conclusiones. La severidad del PE se asocia a una mayor actividad parietooccipital derecha en pacientes con esquizofrenia. La CR del WCST se asocia a mayor actividad frontal izquierda en controles, pero no en pacientes. Probablemente existe una redistribución del RCBF relacionada con la perseveración típica de la esquizofrenia, lo que podría constituir un marcador fenotípico de la enfermedad observable mediante técnicas de neuroimagen funcional.

Palabras clave:
Esquizofrenia. *Wisconsin Card Sorting* Test. Perseveración. Corteza prefrontal. Neuroimagen. Flujo sanguíneo cerebral regional.

INTRODUCTION

Most of the works currently published stress the combination of genetic and environmental factors in the etiology of schizophrenia[1,2]. The hypothesis of neurodevelopment proposes that small aggressions, occurring during intrauterine or perinatal stages, could motivate a shift in the normal process of neurological development that culminates later on in a psychotic picture[3-5]. These small brain lesions and consequent deviation of development could cause neuropsychological dysfunctions that represent phenotypic markers or indicators of vulnerability to schizophrenia[6-8], that could even be present in non-ill family members. The arrival of functional cerebral neuroimaging techniques provided the possibility of finding a neurological substrate of these possible cognitive disorders. In 1994, Catafau et al.[9] observed signs of hypofrontality and hypotemporality in patients with schizophrenia in at rest situation by SPECT. In 1997, Sabri et al.[10] proposed two types of hypofrontality characteristic of schizophrenia: one in which a reduced RCBF was seen in the prefrontal area in baseline conditions (at rest) and another that was characterized by a relative failure in the activation of the prefrontal cortex when executing a cognitive task (in comparison with at rest)[11]. In 1998, Parellada et al.[12] replicated this second type of hypofrontality in young patients not treated pharmacologically during an acute psychotic episode and observed a failure in the activation of the frontal regions during the performance of WCST, there not being any reduction in the frontal area flow at rest. On the other hand, Saoud et al, in 2000[13], found that both a group of patients with schizophrenia and their families had a greater proportion of PEs than the controls when doing a WCST. In 2001, Ismail et al.[14], trying to replicate the previous study, found that the PEs were more frequent only in the patient group.

Hoff and Kremen, in 2002[15], proposed that most of the patients with schizophrenia and many of their family members had some degree of involvement in their attentional, executive, verbal declarative memory and verbal fluency functions.

In the present work, we compare the characteristic profile of WCST execution of patients and controls. Subsequently, we analyze the possible association existing between the RCBF and results of WCST. That is, we have tried to find the RCBF pattern that was associated to correct answer and mistake, with special emphasis in the perseverative type error. This is probably the most specific of schizophrenia and has even been proposed as a risk marker of this disorder[3,7]. We include the analysis of non-prefrontal regions that could be involved in the network of cerebral circuits that is activated while performing an executive type cognitive task such as the WCST[16]. Our hypothesis was that there are differences between patients with schizophrenia and subjects without the disease, in regards to the characteristic patterns, both in the execution of the test[15] and of the RCBF of the regions involved in this execution and that not only the prefrontal area is included[17]. These differences could constitute a phenotypic marker of schizophrenia.

SUBJECTS, MATERIAL AND METHODS

Subjects

The inclusion criteria common to both groups were: have an age ranging from 18 to 60 years, not being in period of pregnancy or lactation, not having a previous history of substance dependence or abstinence, nor recent history of intoxication (last 6 months) and not having another disease at the time of the study. Both the patients and controls were enrolled voluntarily and without payment and the informed consent was signed by the participant in all the cases.

The patient group was made up of 18 right-handed subjects[18] (age: 25.61; SD: 6.18) who came to our unit for diagnostic study or treatment of a diagnosed picture of schizophrenia by two independent members of the medical team. Exclusion criteria in this group were considered to be having an intellectual quotient less than 85 on the Raven test (inferior to the percentile 15 approximately), for having possible difficulties in the understanding of the WCST, and having been diagnosed at some time of another mental disorder besides schizophrenia.

The control group was made up of 13 right-handed subjects (age: 27.92; SD: 6.95) without clear psychiatric disease at the time of the study and without psychiatric, neurological, personal or family background. They were enrolled among the staff of our site, excluding those who had an intellectual quotient inferior to 85 according to the Raven test (inferior to percentile 15 approximately), for the reasons presented in the previous paragraph.

At the time of the study, three patients were not receiving any antipsychotic treatment while 15 were receiving treatment with atypical antipsychotics: 8 with risperidone, 4 with olanzapine and 3 with clozapine. The mean admissions in acute psychiatric hospitalization units in the patients were 2.1 (SD: 2). No significant differences were found in the age of the two groups (tables 1 and 2).

Material

Diagnosis

To be accepted in the study, the patients should comply with the diagnostic criteria, both of the World Health Organization International Classification of Diseases (ICD-10) and of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) of the American Psychiatric Association. Evaluation was conducted by two independent members of the medical team who used a semistructured interview that included the diagnostic criteria of both clas-

Table 1 Description of the samples

Gender	Frequency	%
Controls		
Men	9	69.2
Women	4	30.8
Total	13	100
Patients		
Men	16	88.9
Woman	2	11.1
Total	18	100

	N	Min.	Max.	Mean	SD
Controls					
Age	13	22	46	27.92	6.95
Patients					
Age	18	18	41	25.61	6.18

sifications, besides the Spanish version of the Positive and Negative Syndromes Scale (PANSS)[19,20] and the Association for Methodology and Documentation in Psychiatry (AMPD) system[21-23].

SPECT

We used the SPECT to study functional neuroimaging. The images were obtained with gamma-camera (Siemens, Orbiter 75) equipped with an astigmatic collimator (Neurofocal, Siemens) after having injected the participants with perfusion tracer ^{99m}technetium hexamethyl propylene amine oxime (^{99m}Tc-HMPAO). The dose administered was 740-1,110 Mbq (13.32 MBq/Kg of weight) ^{99m}Tc-HMPAO injected intravenously.

Table 2 Age. Comparison of means between samples. No significant differences are observed in the age of both group

Age	Levene		Student's t test (*t*)			
	F	Sign.	T	Sign. (bilateral)	Mean of the difference	95% confidence Interval
	0.073	0.788	0.976	0.337	2.31	-2.53 7.16

WCST

To examine the executive function, we used the Wisconsin Card Sorting Test (WCST).

Method

SPECT procedure

Part of the procedure and the reference to the at rest and activation conditions have been explained in another publication of our group[24]. The tomography began 30 minutes after the intravenous injection of 20-30 mCi of ^{99m}Tc-HMPAO. A total of 128 images were obtained, at 10 seconds per image, in a matrix of 128 × 128, and with a pixel size of 3.3 mm (FWHM at approximately 8-10 mm)[25]. The tracer was injected after each subject has achieved 5 correct consecutive answers on the WCST, which indicated that they had understood the mechanics of the test execution. The test ended when the individual completed a total of 128 cards. The reconstruction process of the SPECT images included a Chang attenuation correction. Subsequently, the frontal-occipital line was defined as that which joined the inferior frontal pole with the inferior occipital pole in a middle sagittal cut. After this, two parallel cuts were made: one 6.6 mm and another 26.4 mm, above the mentioned frontal-occipital line. It was chosen for its reliability and due to the difficulty of defining the line commonly used as reference by SPECT, that is, that which joins the anterior commissure with the posterior one. In this way, five regions were defined bilaterally, according to Talairach and Tournoux's Stereotaxic Atlas[26]: frontobasal, temporal and occipital in the inferior level; prefrontal and parietal in the superior level (fig. 1).

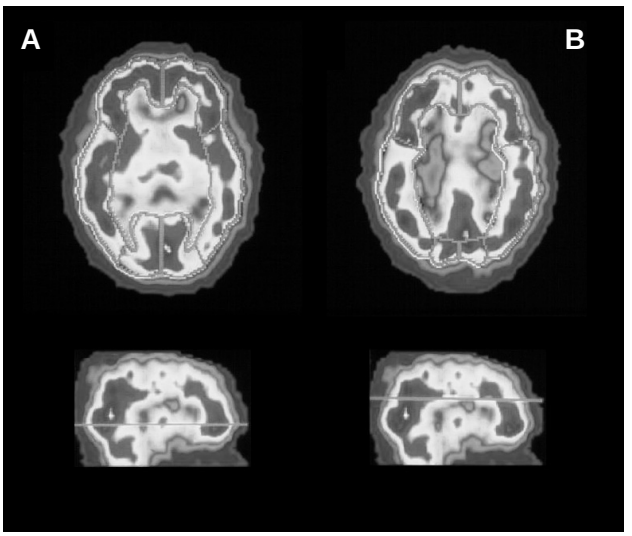

Figure 1 *Visual description of the brain regions chosen and the cuts made for the SPECT analysis.*

Table 3 Correct responses (CR) and perseverative errors (PE). Comparison of means between patient and control group

Student's *t* test	N	*t*	Sign. (bilateral)
Total CR			
Controls	13	0.128	0.899
Patients	18		
Mann-Whitney U test	**N**	**U**	**Sign. (bilateral)**
Total RC			
Controls	13	93,000	0.336
Patients	18		
Total PE			
Controls	13	47,500	0.005**
Patients	18		

The mean pixel count was found after three consecutive cuts of 1 pixel thickness in each region. The regional activity was normalized in relationship to the global activity of all the cerebral cortex to obtain the relative cortical blood flow (RCBF).

Evaluation of the WCST

Execution of the test was evaluated following the recommendations of the long version of the WCST Manual[27]. We paid special attention to the «correct-incorrect» and «perseverative-not perseverative» dimensions of the test. The total of correct answers (a measure that reflects the subject's capacity to perform changing tasks) was used as a parameter representative of the correct response (CR). During the execution of the WCST, we used a feedback system by the examiner, according to which each response was evaluated as correct or incorrect. The subjects than acted in consequence, and their perseverative dimension was scored depending on their type of subsequent answer. The total number of perseverative errors (PE) was used as measurement of perseveration, since it reflects the subject's difficulty to change the approach of a response when faced with the circumstance of a sudden appearance.

Statistical analysis

The results were analyzed with the SPSS program, version 10.0 for Windows. Adjustment to normal distribution was verified with the Shapiro-Wilk test.

Comparison between the PE of the patients and controls was performed with the Mann Whitney U test (table 3).

Possible association between responses and RCBF was studied with Spearman's correlation test (rS) or that of Pearson r based on the association of variables compared to normal distribution (tables 4 and 5).

RESULTS

- Patients committed more PE than controls ($p = 0.005$) (table 3).
- No significant differences were found between CR of patients and controls (table 3).
- We observed a marked correlation (r: 0.65; $p = 0.004$) in patients between PE and right occipital RCBF in activation (table 4).
- In controls, PE negatively correlated in a moderate way with left temporal RCBF in activation (r: –0.57; $p = 0.042$) (table 4) and right temporal RCBF at rest (r: –0.66; $p = 0.014$) (table 5).
- In controls, the CR moderately correlated with RCBF of the left frontobasal area, at rest (r: 0.58; $p = 0.039$) (table 5), and sharply with the RCBF of the left frontobasal region (r: 0.87; $p < 0.0001$) and left global frontal region (r: 0.64; $p = 0.017$), in activation (table 5). Furthermore, the CR inversely correlated significantly with right parietal region RCBF in activation (r: –0.80; $p = 0.001$) (table 4).

DISCUSSION

In the semiological organization of schizophrenia, perseverative error constitutes one of the fundamental and most specific symptoms of the disease[28,29].

In the present work, we postulate that this perseverative error typical of schizophrenia could be related with small brain lesions that affect the connection between the different regions and that, therefore, it would be associated to a cerebral perfusion pattern different from that of the subjects without the disease[6]. We based this on previous works that suggested the presence of minimum cerebral lesions that do not cause epilepsy or mental retardation but that are sufficient to cause neuropsychological dysfunctions in the onset of the adult age[4,12,30]. Specific symptoms that had a neurological correlate with certain profiles of the RCBF could be derived from these dysfunctions[14]. Thus, we initially proposed to demonstrate that the patient group committed significantly more perseverative errors than the control group in order to then seek a coherent association between these perseverative errors and their functional neuroimage. It also seems interesting to us to study the RCBF pattern that is associated to the PEs in subjects without schizophrenia. Finally, we want to verify if the RCBF pattern associated to the CR in the controls differed from that observed in patients, which would suggest a different distribution in the activity of the regions involved in the execution of the same cognitive task.

Table 4 Correlation between RCBF and CR/PE in activation (performing the WCST) between patients and controls

Activation (WCST)	Controls (n =13)				Patients (n = 18)			
	Total correct responses (CR)		Total perseverative errors (PE)		Total correct responses (CR)		Total perseverative errors (PE)	
	Pearson correlation		Spearman correlation		Pearson correlation		Spearman correlation	
Regions	r	Sign. (p)	Rho	Sign. (p)	r	Sign. (p)	Rho	Sign. (p)
Right frontobasal	0.49	0.086	0.03	0.932	0.24	0.346	–0.38	0.116
Left frontobasal	0.87	0.000**	0.16	0.594	0.15	0.544	–0.25	0.319
Right prefrontal	0.05	0.869	0.41	0.159	0.23	0.358	0.15	0.550
Left prefrontal	0.20	0.515	–0.13	0.672	0.10	0.677	–0.22	0.385
Right temporal	0.12	0.693	–0.14	0.659	0.14	0.570	–0.09	0.723
Left temporal	0.44	0.130	–0.57	0.042*	0.04	0.874	0.04	0.874
Right parietal	–0.80	0.001**	0.20	0.502	–0.18	0.485	0.42	0.082
Left parietal	–0.50	0.083	–0.19	0.538	–0.35	0.155	0.03	0.916
Right occipital	0.08	0.797	0.23	0.450	–0.09	0.721	0.28	0.257
Left occipital	–0.11	0.717	0.28	0.355	–0.43	0.072	0.65	0.004**
Right total frontal (RFB+RPF)	0.35	0.239	0.23	0.439	0.30	0.218	–0.33	0.186
Left total frontal (LFB+LPF)	0.64	0.017*	0.10	0.739	0.28	0.26	–0.43	0.075

RFB: right frontal basal; RPF: right prefrontal; LFB: left frontal basal; LPF: left prefrontal.

The PE were significantly more frequent in patients than in controls

Perseveration has been suggested as a central symptom of schizophrenia[1,2]. Our work shows that the perseverative responses characterize the group of patients with disease and differentiates them from the healthy subjects.

Perseverative errors (PE)

In the patients

In our work, the PE of the patients were associated to the activity of the right occipital cortex. The right occipital and parietal cortexes are associated to functions related with space and attention. Its activation seems to be related with the selective attention towards a specific stimulus without paying attention to the context, which leads us to think that the patient's ability to disconnect from a specific stimulus and change to another may be deteriorated, which could be translated into perseveration. In the present study, we observe two significant facts in relationship with perseveration: that the patient group does not succeed in increasing the RCBF of the left frontal area during execution of WCST (related with inhibition of perseveration), which does occur in the control group. On the other hand, that this group has an elevated activity in the right occipital area and even in the right parietal one, in activation (Spearman r: 0.420; p = 0.082). These facts suggest, on the one hand, some incapacity to inhibit perseveration and on the other, as we previously commented, an exaggerated tendency to maintain attention on a specific stimulus in spite of being told that it is not the correct one.

The low activity of the left prefrontal area supposes greater ease of distraction, changing from one activity to another according to the novelty of each stimulus, more than following a previously designed plan, with lack of foresight and ambition. This could explain the difficulties of the patients to maintain the criteria that are being given on initiating the WCST, after a few minutes. On the other hand, once a criterion has been established and attention maintained on it, they find it difficult to change to another criteria, even though they are informed that the previous one was erroneous (elevated activity in the right occipital-parietal area).

In the controls

When a healthy subject perseveres (in our study, committing PE), the left temporal region shows a decrease in its activity in relationship to at rest[17]. This could explain difficulties in the planning of a complete task such as the WCST.

Table 5 Correlations between RCBF and CR/PE at rest, both in patients and in controls

Rest	Controls (n =13)				Patients (n = 18)			
	Total correct responses (CR)		Total perseverative errors (PE)		Total correct responses (CR)		Total perseverative errors (PE)	
	Pearson correlation		Spearman correlation		Pearson correlation		Spearman correlation	
Regions	r	Sign. (p)	Rho	Sign. (p)	r	Sign. (p)	Rho	Sign. (p)
Right frontobasal	0.55	0.054	0.05	0.879	0.04	0.876	–0.15	0.559
Left frontobasal	0.58	0.039*	0.07	0.822	-0.07	0.788	–0.16	0.512
Right prefrontal	–0.23	0.456	0.24	0.423	0.12	0.640	–0.11	0.668
Left prefrontal	0.10	0.740	0.53	0.065	0.03	0.918	–0.07	0.794
Right temporal	0.39	0.183	–0.66	0.014*	0.24	0.344	–0.16	0.515
Left temporal	–0.17	0.568	–0.34	0.255	–0.18	0.473	0.36	0.144
Right parietal	–0.51	0.077	–0.08	0.794	0.23	0.352	–0.06	0.804
Left parietal	–0.27	0.370	–0.14	0.646	–0.27	0.271	0.26	0.289
Right occipital	–0.07	0.816	0.23	0.456	0.10	0.690	–0.05	0.829
Left occipital	–0.19	0.539	0.17	0.575	–0.10	0.691	0.44	0.066
Right total frontal (RFB+RPF)	0.37	0.214	0.04	0.893	0.07	0.774	–0.13	0.601
Left total frontal (LFB+LPF)	0.48	0.099	0.23	0.456	–0.03	0.913	–0.14	0.590

RFB: right frontal basal; RPF: right prefrontal; LFB: left frontal basal; LPF: left prefrontal.

Correct responses (CR)

We found no significant differences between the CR of the patients and controls. In this study, the CR of the controls are associated to an increase in activity of the left frontobasal cortex. Studies prior to ours had already observed that an increase in activity of this brain region was involved in the inhibition of perseverative behaviors: «Persons with lesions in the orbital cortex persevere in their behavior and show a decreased capacity to reach adequate strategies in response to changing tasks»[31]. This area is also classically associated to affective and emotional aspects of the setting and the failure when increasing activity during performance of the WCST could be a reflection of emotional blunting of patients with schizophrenia.

The model of hypofrontality defined by Sabri et al. in 1997[10] as the incapacity of patients to increase frontal cortex activity during the execution of WCST is clearly seen in our study. Although the prefrontal area is the region most specifically involved in the performance of cognitive tasks[32], we have not found the expected increase in the activity of this area during CRs in subjects without disease. However, we do observe the association of CR to an increase of left global frontal cortex RCBF (that includes frontobasal and prefrontal) of controls in activation. The left frontal and temporal cortexes are involved in planning and monitoring processes[31] of behavior. In a complex task as the correct execution of WCST, that requires adequate planning and monitoring, it is expected that the frontal area increases its activity in subjects without the disease[33], as occurs in the controls of our study. The CRs of the controls were associated to low activity of the right parietal region in contrast with the typical pattern of patients when they commit PE.

Global differences between controls and patients during the performance of WCST

During the performance of the WCST, the controls preferentially involved the left half of their brain, both in CR (left frontobasal cortex) and on committing PE (inverse correlation with left temporal cortex RCBF). On the contrary, when they committed PE, the patients mainly increased RCBF of the right half of their brain (right occipital cortex). This fact could be related with hand preference and atypical lateralization processes observed in schizophrenia. Future studies should study this circumstance in greater depth. This would clarify the network of brain connections involved in the processes that occur in these patients[34] and that seem to differ from those that occur in subjects without the disease.

Methodological limitations

This study has several methodological limitations that we present in the following:

- Due to the limited anatomic definition of SPECT, it would have been better to have used other cerebral neuroimaging methods such as PET or fMRI, which we did not have at the time of the study[35]. However, most of the works published up to now in relationship with this subject, whose results have inspired us and which we have aspired to replicate in some case, had been done with brain SPECT[9-12]. Considering these limitations, we selected anatomical regions having a clear functional significance and that could be easily defined in the SPECT image.
- In our study, there was a significant proportion of patients who received or had received at some time treatment with atypical antipsychotics. This circumstance is determined by the real, practical and ethical difficulty that exists to find patients with a psychotic picture who agree to voluntarily participate in a study without having been previously administered medication.

  Previous studies have demonstrated that treatment with risperidone and clozapine in patients with schizophrenia may cause variations in cortical perfusion of the temporal and frontal areas, in at rest situations[16,34]. Furthermore, patients with schizophrenia may improve their initial performances in the WCST after having been treated with atypical antipsychotics[36]. This could have an affect on their RCBF patterns. Along this line, small improvements of the long term perseveration symptom have been described after an antipsychotic treatment[37]. On the other hand, the new antipsychotics seem to have a minimum effect on the negative symptoms of the disease[38,39].

  In our study, it is possible that treatment with atypical antipsychotics would influence better performance on the WCST by the patients. In fact, we only find significant differences between patients and controls in the frequency of perseverative errors. This, due to the characteristics of the disease, was to be expected and constitutes a qualitative difference more than a difference in global performance. If this were so, we could suppose that the differences would have been even clearer without treatment. Clozapine has shown its capacity to compare the responses of the patients in neurocognitive tests to those of the controls, demonstrating a greater negative priming effect in the former than in the untreated patients or those in treatment with classical antipsychotics[40,41]. This would even give greater weight to the differences that our group has found.

  The fact of using relative values of RCBF would reduce the possible effect of the medication on the RCBF patterns since the comparisons are of each subject with him/herself.

  Our patients showed significantly more perseverative errors. Based on this data, we have tried to find the neurophysiological correlate of the blood flow of said symptom, that was even present in patients who were being treated with an atypical antipsychotic. The next studies should consider if treatment with this type of drugs can modify the RCBF patterns, and if this is so, if this modification would involve a reduction of the patterns associated to the PEs and/or an improvement in the CR patterns.

- In previous studies conducted in this field, the factor of multiple comparisons which due to their own nature entail functional neuroimaging studies were not taken into account. To approach this possible problem, some investigators have proposed Bonferroni's adjustment. The possible use of this adjustment poses pros and cons in the neuroimaging works, which is why it was discussed in the design of our study. Finally, we decided not to use Bonferroni's adjustment in the statistical analysis, basing this decision on previous articles that suggest that this method may become harmful because it could eliminate real activations in a human model as it is too strict. We consider that applying the adjustment would have been a greater limitation because functional neuroimaging works require many statistical tests and its application could generate many false positives and false negatives. This would deprive us of coherent findings and valuable clinical significance[42,43]. These authors consider that the best way to approach the difficulty of multiple comparisons is a detailed description of the paradigm and the statistical significance used, reasons with clarity why it is used and supplying a coherent explanation of the expected results[44]. Our analysis is based on the clinical experience and findings of previous studies. Our work objectives and hypothesis have been clearly defined, so that we consider that the results obtained constitute a significant contribution, having clear scientific significance, in spite of the difficultly avoidable methodological limitations. This, nonetheless, should be explained by the authors and considered by the readers when interpreting the results. These results can, and in my humble opinion should, constitute an advisable reference for future investigations and supply new pathways to the study of psychopathology of schizophrenia.

CONCLUSIONS

Patients with schizophrenia commit more PE than subjects without the disease. Perseveration is a differential and specific characteristic of this disease. The PE of the patients have a specific functional neurological correlate, characte-

rized by right lateralization (different from that of patients without the disease), with caudal brain region predominance (parieto-occipital). The non-committing of these errors could be related with attentional processes whose substrate would be the most rostral and left areas of the brain in healthy subjects (especially the frontobasal region). This capacity could be affected in subjects with schizophrenia, which would increase their perseveration.

These findings could be reflecting a redistribution of cortical activity related with perseveration in schizophrenia. This characteristic pattern could be used as a marker of the phenoytpe characteristic of schizophrenia and would be easily detectable through a correlation between the data of a semiquantitative study by SPECT and those obtained in the execution of a WCST.

REFERENCES

1. Egan MF, Hyde TM, Bonomo JB, Mattay VS, Bigelow LB, Goldberg TE, et al. Relative risk of neurological signs in siblings of patients with schizophrenia. Am J Psychiatry 2001;158:1827-34.
2. Egan MF, Goldberg TE, Gscheidle T, Weirich M, Rawlings R, Hyde TM, et al. Relative risk for cognitive impairments in siblings of patients with schizophrenia. Biol Psychiatry 2001;50:98-107.
3. Fearon P, O'Connell P, Frangou S, Aquino P, Nosarti C, Allin M, et al. Brain volumes in adult survivors of very low birth weight: a sibling-controlled study. Pediatrics 2004;114:367-71.
4. Allin M, Henderson M, Suckling J, Nosarti C, Rushe T, Fearon P, et al. Effects of very low birthweight on brain structure in adulthood. Develop Med Child Neurol 2004;46: 46-53.
5. Allin M, Matsumoto H, Santhouse AM, Nosarti C, AlAsady MH, Stewart AL, et al. Cognitive and motor function and the size of the cerebellum in adolescents born very pre-term. Brain 2001; 124:60-6.
6. Meyer-Lindenberg A, Poline JB, Kohn PD, Holt JL, Egan MF, Weinberger DR, et al. Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. Am J Psychiatry 2001;158:1809-17.
7. Maier W, Franke P, Hain C, Kopp B, Rist F. Neuropsychological indicators of the vulnerability to schizophrenia. Prog Neuro-Psychopharmacol Biol Psychiatry 1992; 16:703-15.
8. Franke P, Maier W, Hain C, Klingler T. Wisconsin Card Sorting Test: an indicator of vulnerability to schizophrenia? Schizophr Res 1992;6:243-9.
9. Catafau AM, Parellada E, Lomeña F, et al. Prefrontal and temporal blood flow in schizophrenia: resting and activation technetium-99m-HMPAO SPECT patterns in young neuroleptic-naive patients with acute disease. J Nucl Med 1994;35:935-41.
10. Sabri O. Erkwoh R. Schreckenberger M. Owega A. Sass H. Buell U. Correlation of positive symptoms exclusively to hyperperfusion or hypoperfusion of cerebral cortex in never-treated schizophrenics. Lancet 1997;349:1735-9.
11. Ortuño F, Moreno-Íñiguez M, Millán M, Soutullo CA, Bonelli RM. Cortical blood flow during rest and Wisconsin Card Sorting Test Performance in Schizophrenia. Accepted in December 2, 2005 for publication in Wien Med Wochenschr.
12. Parellada E, Catafau AM, Bernardo M, et al. Prefrontal dysfunction in young acute neuroleptic-naive schizophrenic patients: a resting and activation SPECT study. Psychiatry Res 1994;55: 131-9.
13. Saoud M, d'Amato T, Gutknecht C, Triboulet P, Bertaud JP, Marie-Cardine M, et al. Neuropsychological deficit in siblings discordant for schizophrenia. Schizophr Bull 2000;26:893-902.
14. Ismail B, Cantor-Graae E, McNeil TF. Neurodevelopmental origins of tardivelike dyskinesia in schizophrenia patients and their siblings. Schizophr Bull 2001;27:629-41.
15. Hoff y Kremen. Is there a cognitive phenotype for schizophrenia: the nature and course of the disturbance in cognition? Curr Opin Psychiatry 2002;15:43-8.
16. Berman I, Merson A, Sison C, et al. Regional cerebral blood flow changes associated with risperidone treatment in elderly schizophrenia patients: a pilot study. Psychopharmacol Bull 1996;32:95-100.
17. Tien AY, Schlaepfer TE, Orr W, Pearlson GD. SPECT brain blood flow changes with continuous ligand infusion during previously learned WCST performance. Psychiatry Res 1998;82:47-52.
18. Annet M. A classification of hand preference by association analysis. Br J Psychology 1974;61;303-21.
19. Kay SR, Opler LA, Fiszbein A. The Positive and Negative Syndrome Scale (PANSS). Rating Manual. Soc Behav Sci Docum 1984;17;28-9.
20. Peralta V, Cuesta MJ. Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. Psychiatry Res 1994;53:31-40.
21. Winterer G, Dorn H, Herrmann WM, Gallhofer B, Bauer U, Hegerl U, et al. The AMDP modules I-IV: recommendations for a standardized acquisition of EEG data in psychiatry. Association for Methodology and Documentation in Psychiatry. Neuropsychobiology 1997;36:100-6.
22. López-Ibor JJ. El sistema AMDP. Protocolo de la Asociación para la Metodología y Documentación en Psiquiatría. Madrid: Garsi, 1980.
23. Sánchez Blanque A, Bobon D, Lozano Soriano I, Lusilla Palacios P. Spanish Adaptation and Validation of an Anxiety Scale derived from the AMDP (AMDP-AT) System: Adaptation and Convergent Validity. Actas Luso Esp Neurol Psiquiatr Cienc Afin 1989;17:139-9.
24. Moreno-Íñiguez M, Ortuño F, Bonelli R, Arbizu J, Millán M, Soutullo C, et al. Estudio del flujo sanguíneo cerebral regional (FJCR) mediante SPECT en reposo y activación con el Test de Clasificación de Tarjetas de Wisconsin (WCST) en pacientes con esquizofrenia sin tratamiento o tratados con neurolépticos atípicos. Actas Esp Psiquiatr 2005;33:343-51.
25. Moore SC, Kouris K, Cullum I. Collimator design for single photon emission tomography. Eur J Nucl Med 1992;19:138-50.
26. Talairach y Tournoux. Co-planar stereotaxic atlas of human brain 2. Thieme 1998.
27. Heaton RK. Wisconsin Card Sorting Test Manual. PAR, Psychological Assessments Resources, Inc, 1993.
28. López-Ibor MI, López-Ibor JJ Jr, Ayuso-Gutiérrez JL. Neuroimagen y síntomas fundamentales en esquizofrenia. Actas Luso Esp Neurol Psiquiatr Cienc Afin 1996; 1:25-8.
29. López-Ibor MI, López-Ibor JJ, Ayuso Gutiérrez JL. Neuroimaging and basic symptoms of schizophrenia. Actas Esp Psiquiatr 2000; 28:1-4.
30. Bergsneider M, Hovda DA, McArthur DL, Etchepare M, Huang SC, Sehati N, et al. Metabolic recovery following human traumatic brain injury based on FDG-PET: time course and relationship to neurological disability. J Head Trauma Rehab 2001;16:135-48.

31. Drevets WC. Neuroimaging and neuropathological studies of depression: implication for the cognitive emotional features of mood disorders. Curr Opin Neurobiol 2001; 11:240-9.
32. Estévez A, Calvo MG. Working memory capacity and time course of predictive inferences. Memory 2000;8:51-61.
33. Volz HP, Rzanny R, Rossger G, Hubner G, Kreitschmann-Andermahr I, Kaiser WA, et al. Phosphorus magnetic resonance spectroscopy of the dorsolateral prefrontal region in schizophrenics-a study including 50 patients and 36 controls. Biol Psychiatry 1998;44:399-404.
34. Satz P, Green MF. Atypical handedness in schizophrenia: some methodological and theoretical issues. Schizophr Bull 1999;25:63-78.
35. Ortiz T, Fernández A, Maestu F, Martínez E, López-Ibor JJ Jr. Aplicaciones de la magnetoencefalografía en el estudio de la esquizofrenia. Actas Luso Esp Neurol Psiquiatr Cienc Afin 1999;27:259-63.
36. Molina-Rodríguez-V, Montz-Andree-R, Pérez-Castejon-MJ. SPECT study of regional cerebral perfusion in neuroleptic-resistant schizophrenic patients who responded or did not respond to clozapine. Am J Psychiatry 1996;153:1343-6.
37. Meltzer D. Perspective and the measurement of costs and benefits for cost-effectiveness analysis in schizophrenia. J Clin Psychiatry 1999;60 (Suppl. 3):32-7.
38. Rossi-A, Mancini-F, Stratta-P. Risperidone, negative symptoms and cognitive deficit in schizophrenia: an open study. Acta Psychiatr Scand 1997;95:40-3.
39. Perkins D, Lieberman J, Gu H, Tohen M, McEvoy J, Green A, et al. HGDH Research Group. Predictors of antipsychotic treatment response in patients with first-episode schizophrenia, schizoaffective and schizophreniform disorders. Br J Psychiatry 2004; 185:18-24.
40. McQueen GM, Galway T, Goldberg JO, Tipper P. Impaired distractor inhibition in patients with schizophrenia on a negative priming task. Psycholog Med 2003;33;121-9.
41. Green M. Recent studies of the neurocognitive effects of second generation antipsychotic medications. Curr Opin Psychiatry 2002;15:25-9.
42. Huettel SA, Obembe OO, Song AW, Woldorff MG. The BOLD fMRI refractory effect is specific to stimulus attributes: evidence from a visual motion paradigm. Neuroimage 2004;23: 402-8.
43. Huettel SA, Song AW, McCarthy G. Functional Magnetic Resonance Imaging. Sinauer Ass, 2004.
44. Perneger TV. What's wrong with Bonferroni adjustments. BMJ 1998;316:1236-8.