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IS THERE A CORTICAL BLOOD FLOW REDISTRIBUTION PATTERN RELATED WITH PERSEVERATIVE ERROR IN SCHIZOPHRENIA?

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SUMMARY

Background: *We studied relative cortical blood flow (relCBF) patterns associated to correct performance (CP) and perseverative error (PE) during Wisconsin Card Sorting Test (WCST) execution, in controls and patients with schizophrenia.*

Subjects and methods: *relCBF (regional cortical blood flow (rCBF) / whole cortex blood flow) of 10 well defined cortical regions was measured in 18 patients with schizophrenia and 13 healthy controls by a Technetium – 99 – HMPAO – SPECT, at rest and while they performed WCST.*

Results: *Patients made significantly more PE than controls during WCST performance. In patients, we found a significant correlation between PE and relCBF in right occipital cortex. In controls, we found a significant correlation between CP and relCBF of several cortical regions during WCST execution: left orbitofrontal cortex and left global frontal cortex positively and parietal bilateral cortex negatively. PE was inversely correlated with relCBF in left temporal cortex.*

Conclusions: *Successful WCST performance is associated to a high left frontal activity in controls but not in patients. The severity of PE during WCST performance is associated to a low left frontal-temporal activity in controls and to a high right parietal-occipital activity in schizophrenia. This may represent a cortical activity redistribution pattern related to perseveration in schizophrenia.*

Key words: *schizophrenia - Wisconsin Card Sorting Test – SPECT – perseveration - prefrontal cortex*

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INTRODUCTION

Most current reports show the role of genetic and environmental etiologic factors in schizophrenia (Egan et al. 2001, Allin & Murray 2002). The neurodevelopmental hypothesis proposes that subtle in-utero or perinatal brain insults may initiate an altered developmental process that eventually culminates in the onset of psychosis. (Allin & Murray 2002) Brain lesions may cause neuropsychological dysfunctions that could represent phenotypic markers or indicators of vulnerability to the disorder in schizophrenia (Franke et al. 1992), which could be present even in the non psychotic relatives. Patients with schizophrenia and many of their relatives have impairment in attentional, executive, verbal declarative memory and verbal fluency functions (Hoff & Kremen 2002). Saoud et al. (2000) found that both probands with schizophrenia and siblings had a greater percentage of PE than controls on WCST. Ismail et al. (2001) found that PE were more frequent only in the patients group. Sabri et al. (1997) reported two forms of hypofrontality in schizophrenia: a reduced prefrontal blood flow at rest; and a relative failure in prefrontal cortex activation (relative to rest) when performing cognitive tasks. Catafau et al. (1994), found hypofrontality and hypotemporality at rest in patients with schizophrenia, and Parellada et al. (1998) reported hypofrontality in young acute unmedicated patients resulting in failure to activate frontal regions during cognition without a baseline reduction in frontal activity.

We analyze whether PE were more frequent in patients with schizophrenia than in controls during

WCST performance. We studied the rel-CBF patterns, at rest and during WCST, associated to perseveration in schizophrenia and to successful execution in normality and schizophrenia. We include analysis of non-prefrontal regions which may play a role in the complex network activated during WCST (Berman 1995, Tien et al. 1998). Differences might be found in patients because of the probably abnormal rel-CBF distribution pattern that could represent a phenotypic marker in schizophrenia (Hoff & Kremen 2002).

A recent meta-analysis supports resting hypofrontality in schizophrenia. Although task-activated hypofrontality is also supported, there is little from voxel-based studies to suggest that this is associated with an altered pattern of regional functional architecture (Hill et al. 2004).

In our view, cerebral blood flow WCST activation patterns in schizophrenia may represent more specifically the working memory failure of schizophrenia. In other words, cerebral blood flow WCST activation studies in schizophrenia should investigate the presence of CBF changes associated with especifical neuropsychological working memory deficits, rather than testing for quantitative changes (hypoactivation). Schizophrenia patients tend to more perseverative and non-perseverative errors on the WCST than healthy controls (Li 2004).

The goal of this study was to test if correct (CP) and perseverative errors (PE) during WCST performance is associated with specific patterns of regional cerebral blood flow in schizophrenia in comparison with healthy subjects. For this purpose we conduct a correlation analysis between PE and CP scores and cerebral blood flow.

SUBJECTS AND METHODS

Written informed consent was obtained from the subjects or their legal guardians. We studied 18 right-handed patients (Annet 1974) who met DSM-IV and ICD-10 criteria for schizophrenia and 13 right-handed healthy controls (see Table 1). For diagnostic evaluation, we used a semi-structured investigator-based interview that included DSM-IV criteria, the AMDP system (AMDP 1997) and the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al. 1987). At the time of the study, 3 patients were antipsychotic-naive and 15 were on stable treatment with an atypical antipsychotics (8 with risperidone, 4 with olanzapine, and 3 with clozapine). The mean number of hospitalizations in patients was 2.1 (S.D.: 2.0). In the previous six months, no subject presented history of drug or alcohol abuse and none presented history of medical illness, and there was no comorbid mental disorder. In the control group there was no personal psychiatric history. All participants had an I.Q. over 85 according to Raven´s test.

Table 1. Characteristics of healthy subjects and schizophrenia patients

HEALTHY SUBJECTS					
GENDER		FREQ.		%	
Male		9		69.2	
Female		4		30.8	
Total		13		100	
SCHIZOPHRENIA PATIENTS					
GENDER		FREQ.		%	
Male		16		88.9	
Female		2		11.1	
Total		18		100	
HEALTHY SUBJECTS					
	N	Min.	Max.	Mean	S.D.
Age	13	22	46	27,92	6,95
SCHIZOPHRENIA PATIENTS					
	N	Mín.	Max.	Mean	S. D.
Age	18	18	41	25,61	6,18

SPECT procedure

We used a similar SPECT procedure described previously (Catafau et al 1998; Parellada et al 1994). Each subject was scanned in two SPECT sessions performed within 24 hours, measuring relative cerebral blood flow (relCBF) at rest and during WCST by means of 99mTc- HMPAO. During the baseline resting condition, subjects were instructed to lie quietly listening to the background noise and fixate on the roof of a dimly lighted room.

During the WCST performance condition subjects were following manual recommendations. The tracer was injected after the subjects had consecutively matched 5 cards of the WCST correctly (indicating that they were engaged with the WCST), continuing the test until a total of 128 cards had been completed.

The scans were performed in a single-detector rotating camera (Orbiter 75, Siemens) equipped with an astigmatic focused collimator (Neurofocal, Siemens). Scan acquisition started 30 minutes after

intravenous injection of 20-30 mCi of 99mTc-HMPAO. One hundred twenty-eight images were collected at 10 sec per image on a 128x128 matrix, and a 3.3 mm pixel size was obtained (FWHM around 8-10 mm) (Richter et al. 1992). The tracer was injected after the subjects had consecutively matched five cards of WCST correctly (indicating that they were engaged with the WCST), and the test was continued until the subjects had completed 128 cards. After SPECT reconstruction, which included Chang attenuation correction, transaxial slices parallel to the fronto-occipital line were obtained. The fronto-occipital line was defined as a line going from the inferior frontal pole to the inferior occipital pole in a medial sagittal slice. This line was chosen because of its reproducibility, and the lack of SPECT resolution to delineate the more common stereotactic reference line through the anterior commissure to the posterior commissure. Five cortical regions were bilaterally defined according to stereotactic atlas of Talairach and Tournoux (1988): frontobasal, temporal, and occipital at an inferior level (6.6 mm above the fronto-occipital line) (see figure A); and prefrontal and parietal at a superior level (26.4 mm above fronto-occipital line) (see figure B). We obtained mean counts per pixel over three consecutive slices per region (1 pixel slice thickness). Regional activity was normalized to the whole-cortex region in order to obtain relCBF.

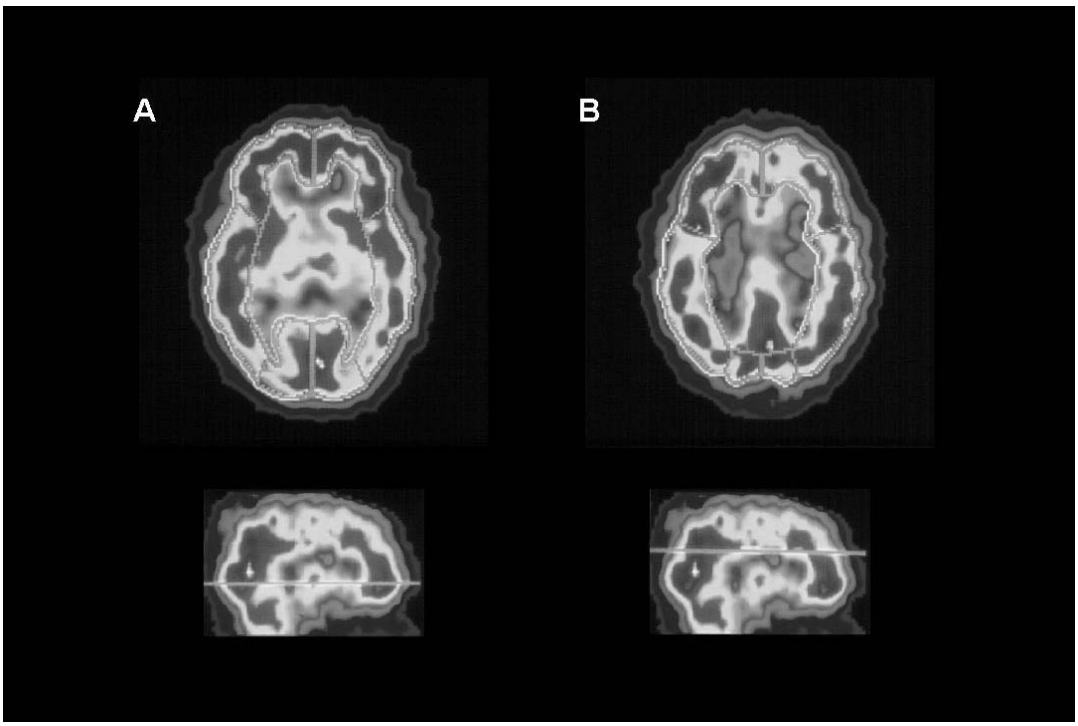

Figure 1. Cortical regions of interest selected for relCBF analysis: frontobasal, temporal, and occipital at an inferior level (6.6 mm above the fronto-occipital line) (figure A); and prefrontal and parietal at a superior level (26.4 mm above fronto-occipital line) (figure B)

WCST scores

Test performance was scored following WCST manual's recommendations (long-manual version, Heaton et al. 1993). We examined correct-incorrect and perseverative-non perseverative responses of WCST. Total correct responses (a measure that reflects the ability of executing changing tasks) were used as statistical parameter of CP. The total number of PE (a parameter of the difficulty to shift a cognitive set) was used as measure of perseveration.

Statistical analysis

All the results were statistically analyzed by SPSS version 10.0 for windows. Normality was assessed by Shapiro-Wilk´s test. Because PE (total frequency) values did not show a normal distribution (see table 2), comparison of mean PE between controls and patients was made by Mann-Whitney U-test whereas association to relCBF was studied by Spearman (Rho) correlation-test. Other correlations were assessed by Pearson (r) correlation-test.

Table 2. Mean comparison of CP and PE between controls and schizophrenia patients

STUDENT t TEST		N	t	Sign. (two tailed)
Total correct responses	Healthy subjects	13	0.128	0.899
	Schizophrenia patients	18		
MANN-WHITNEY U-TEST		N	U	Sign. (two-tailed)
Total correct responses	Healthy subjects	13	93.000	0.336
	Schizophrenia patients	18		
Total perseverative errors	Healthy subjects	13	47.500	0.005**
	Schizophrenia patients	18		

Table 3. Correlation between relCBF and CP/PE at rest

AT REST	HEALTHY SUBJECTS (N=13)				SCHIZOPHRENIA PATIENTS (N=18)			
	Total correct responses (CP)		Total number of perseverative errors (PE)		Total correct responses (CP)		Total number of 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 Fronto-basal	0.55	0.054	0.05	0.879	0.04	0.876	-0.15	0.559
Left Fronto-basal	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
Total Right Frontal (RFB+RPF)	0.37	0.214	0.04	0.893	0.07	0.774	-0.13	0.601
Total Left Frontal (LFB+LPF)	0.48	0.099	0.23	0.456	-0.03	0.913	-0.14	0.590

RESULTS

Total number of PE was significantly higher in patients than in controls (p=0.005) whereas total number of correct performance did not differ significantly (see table 2).

Correlations during WCST performance (Table 4)

In controls, correct performance (CP) correlated positively with left fronto-basal rCBF (r: 0.87; p<0.0001), total left frontal areas (r:0.64; p= 0.017) and also with right fronto- basal (r:0.49; p= 0.086) and negatively with right parietal (r: -0.80; p=0.001) and left parietal (r:-0.50; p=0.083). Perseverative errors (PE) correlated negatively with left temporal area (r: –0.57; p=0.042).

In patients CP correlated negatively with, right occipital area (r: -0.43 p=0.072).

PE correlated negatively with total left frontal (r: -0.43; p=0.075), and positively with right occipital (r: 0.65; p=0.004) and right parietal (r: 0.42; p=0.082).

Correlations at rest (table 3)

In controls CP correlated positively with right fronto-basal (r: 0.55, p=0.054), left fronto-basal (r: 0.58; p=0.039) areas and negatively with right temporal (r: -0.66, p=0.014), right parietal (r: -0.51, p= 0.077). PE correlated positively with left prefrontal (r: 0.53, p=0.065) and negatively with right temporal (r: -0.66, p=0.014).

In patients PE correlated positively with left occipital area (r: 0.44, p=0.066).

Table 4. Correlation between relCBF and CP/PE during WCST performance

During WCST performance	HEALTHY SUBJECTS (N=13)				SCHIZOPHRENIA PATIENTS (N=18)			
	Total correct responses (CP)		Total number of perseverative errors (PE)		Total correct responses (CP)		Total number of 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 Fronto-basal	0.49	0.086	0.03	0.932	0.24	0.346	-0.38	0.116
Left Fronto-basal	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	-0.11	0.717	0.28	0.355	-0.43	0.072	0.65	0.004**
Left Occipital	0.08	0.797	0.23	0.450	-0.09	0.721	0.28	0.257
Total Right Frontal (RFB+RPF)	0.35	0.239	0.23	0.439	0.30	0.218	-0.33	0.186
Total Left Frontal (LFB+LPF)	0.64	0.017*	0.10	0.739	0.28	0.26	-0.43	0.075

DISCUSSION

As expected, PE was significantly higher in patients than in controls. Total correct responses were higher in controls although there were no significant differences between groups.

CP in normality, during WCST execution, correlated positively with the relCBF of left frontobasal (orbitofrontal) region and with left global frontal cortex activity and negatively with right and left parietal. These findings suggest that the better or correct performance the higher frontal and lower parietal relCBF. In other words frontal activation and parietal deactivation may represent the cortical pattern of CP during WCST performance. PE correlated negatively with left temporal region. This means that activation of temporal region may also participate in WCST performance. According with the study of Tien (Tien et al. 1998), perseveration is associated with hypoactivity which may explain planning failures.

CP in schizophrenia does not show that same frontal correlation pattern as it does in healthy subjects. Right occipital relCBF correlated negatively CP and positively with PE. Also PE correlated positively with right parietal region. Therefore, the higher PE the higher right parietal and occipital activation.

During WCST performance controls preferentially activate brain's left side, even during PE, whereas patients mainly increase their right cortex activity. Further analysis will be necessary in order to point out the atypical laterality of network implicated in schizophrenia.

Frontal and parietal regions and CP in healthy subjects and between PE and occipital and PE in schizophrenia patients, correlate also at rest. These finding suggest that patterns of CP and PE performance may be influenced by resting relCBF of frontal and temporal regions.

Methodological limitations.

This study has some methodological limitations.

SPECT has a limited spatial and temporal resolution. For this reason, we decided to choose those regions that clearly show functional significance and that may be easily defined by SPECT.

Atypical neuroleptics may alter the cortical CBF and may also influence the WCST-performance. However, our goal was to test the neural correlate of correct and perseverative performance. Although this question need further investigation, it seems clear that new neuroleptics have little effect in negative symptoms and

cognitive symptoms (Green 2002). On the other hand, none of the three atypical neuroleptics in our study exerts a worsening effect on WCST perseveration parameters (little improvement has been reported after short and long-term treatment, Meltzer et al. 1999). In future studies the question should be addressed as to whether atypical neuroleptics could modify the relCBF redistribution patterns. Regarding statistical analysis, some reviewers demand a more stringent criteria for "statistical significance" than the conventional $p<0.05$, which could be done by using Bonferroni adjustment. However, this method may be unnecessary and deleterious to sound statistical inference. Adjusting statistical significance for the number of tests that have been performed on study data (the Bonferroni method) creates more problems than it solves. Simply describing what test of significance has been performed and why, is generally the best way of dealing with multiple comparisons (Perneger 1998).

CONCLUSIONS

Differences in relCBF patterns between schizophrenia patients and healthy subjects during WCST performance are found in two parameters, CP and PE. According to our results successful WCST performance is directly related with higher left frontal activity in healthy subjects. However, the severity of PE during WCST in schizophrenia seems to be related to lower left frontal and higher right parieto-occipital activity. This may represent a cortical activity redistribution pattern related to perseveration in schizophrenia.

Further studies using tools with better spatial and temporal resolution, such as functional magnetic resonance imaging, should be conducted in order to re-examine our findings, and also to test if cortical PE patterns are related with performance rather than with schizophrenia specifically.

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