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Limbic hyperactivity associated to verbal memory deficit in schizophrenia

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ABSTRACT

In schizophrenia there seems to be an inefficient activation of prefrontal and hippocampal regions. Patients tend to show worse cognitive performance in functions subserved by those regions as compared to healthy controls in spite of higher regional activation. However, the association between activation abnormalities and cognitive deficits remains without being understood. In the present study, we compared cerebral perfusion using single-photon emission tomography (SPECT) in patients and controls to study the association between activation patterns and cognitive performance in this disease. The SPECT studies were simultaneously obtained with an electrophysiological recording during a P300 paradigm to elicit P3a and P3b components. We included 23 stable patients with paranoid schizophrenia and 29 healthy controls that underwent clinical and cognitive assessments. Patients with schizophrenia showed an increased perfusion in the right hippocampus with respect to healthy controls, they also displayed a statistically significant inverse association between perfusion in the left hippocampus and verbal memory performance. Healthy controls showed an inverse association between perfusion in the left dorsolateral prefrontal (DLPFC) region and working memory performance. P3b but not P3a amplitude was significantly lower in patients. The limbic overactivation in the patients may contribute to their cognitive deficits in verbal memory.

1. Introduction

By functional magnetic resonance imaging (fMRI), an inefficient activation (i.e., higher activation with similar or worse performance) has been described in schizophrenia in prefrontal cortex (Manoach et al., 2000), prefrontal-striatal circuits (Diwadkar et al., 2012) and regions relevant for emotional processing (Habel et al., 2010). This inefficient activation may also be appreciated in siblings of patients with schizophrenia (Liddle et al., 2013), which suggests that this may be a vulnerability marker for that syndrome. Similar findings have been reported with other techniques. Using F18-desoxyglucose positron emission tomography (PET), hippocampal activity was also found to be increased in spite of inferior memory performance in schizophrenia (Heckers et al., 1998). A study using both magnetoencephalographic and fMRI assessments also found a more extended but attenuated fronto-parietal activation during a recognition memory task (Weiss et al., 2009). In general, patients tend to show worse cognitive performance in functions subserved by those regions in spite of higher regional activation, as shown in the review by Manoach and colleagues (2003). This seems coherent with the lessened deactivation of the default mode network (DMN) reported in schizophrenia in comparison to healthy participants (Ongur et al., 2010; Pomarol-Clotet et al., 2008). That inefficient activation may hamper cognition, since the reduced deactivation of the medial prefrontal component of the DMN in patients with schizophrenia has been inversely correlated with working memory performance (Whitfield-Gabrieli et al., 2009).

However, the consequences of regional activation patterns on cognitive performance in this disease are complex and not completely understood to date. A study reported that patients with schizophrenia failed to increase blood flow in comparison to healthy controls during the recall condition of a memory test in spite of higher baseline cerebral blood flow (rCBF) in the hippocampus (Heckers et al., 1998). Moreover, lower prefrontal metabolic

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rates during a simple attentional test predicted slower processing speed outcome in schizophrenia (Molina et al., 2009). Finally, others have reported significant differences in the correlation between blood oxygen-level dependent (BOLD) response to increasing memory load between patients with schizophrenia and controls (Brown et al., 2009). Thus, it is not clear yet if there is a significant association between the amount of activation in key regions and the cognitive deficit extent in schizophrenia.

To further contribute to clarifying the association between activation patterns and cognitive performance in schizophrenia we compared cerebral perfusion during a standard P300 task between patients and controls, as well as the neuropsychological correlates of perfusion patterns in both groups with regard to the most replicated cognitive deficits in that syndrome.

2. Materials and methods

We included 23 patients with paranoid schizophrenia (16 males), diagnosed according to DSM-IV-TR criteria, and 29 healthy controls (18 males). Patients were previously treated with atypical antipsychotics (risperidone 16 cases (2–6 mg/d), olanzapine 6 cases (5–20 mg/d), quetiapine 4 cases (300–600 mg/d), aripiprazol 2 cases (10–15 mg/d) and clozapine 8 cases (100–350 mg/d). Thirteen patients received two different antipsychotics. Doses and drugs were unchanged during the 3 months preceding EEG and SPECT procedure acquirements. Doses were converted to chlorpromazine (CPZ) equivalents in milligrams (Woods, 2003) (Table 1).

We scored the clinical status of the patients by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Marital status was stratified into single (single, divorced, separated) or living in couple, employment status as employed (currently studying or working) or unemployed (looking for a job or retired) and educational level as completed academic courses.

Table 1
Demographic, clinical, cognitive and electrophysiological values in the samples and their statistics comparison values (t or χ^2).

	Patients ($n = 23$)	Controls ($n = 29$)	Statistics values (t or χ^2)
Age (years)	38.39 (10.52)	34.03 (13.46)	1.27
Sex distribution (M:F)	16:7	18:11	0.32
Marital status (% single)**	100.00	65.38	8.61
Employment status (% employed)***	11.76	65.38	11.98
School years ***	6.00 (2.13)	13.50 (6.12)	3.89
Illness duration (months)	83.75 (63.77)	N/A	N/A
Treatment dose (CPZ equivalents)	271.51 (98.68)	N/A	N/A
PANSS-positive	19.75 (4.86)	N/A	N/A
PANSS-negative	20.08 (3.66)	N/A	N/A
PANSS-total	74.67 (12.32)	N/A	N/A
Total IQ***	85.55 (15.19)	101.59(11.75)	4.17
Verbal memory***	41.53 (10.15)	53.86 (9.03)	4.41
Working memory*	18.95 (4.76)	22.28 (3.86)	2.66
Motor speed**	53.84 (7.52)	63.97 (13.82)	2.92
Verbal fluency (animals)***	19.63 (4.63)	25.17 (4.90)	3.91
Verbal fluency (letters)*	20.63 (6.44)	25.03 (6.80)	2.24
Processing speed**	46.58 (12.21)	58.38 (13.00)	3.15
Problem solving*	14.05 (5.35)	16.79 (3.93)	2.05
P300 % correct responses (target detection)	81.13 (23.55)	90.76 (20.94)	0.90
P300 reaction time for target detection (ms)	574.45 (80.63)	523.33 (51.74)	1.78
P300 number of correct segments for P3b calculation*	37.56 (24.63)	56.35 (25.89)	2.33
S1 P300 amplitude (μV)	−0.02 (0.65)	0.03 (0.60)	0.29
S2 P300 amplitude (μV; P3a)	0.70 (1.25)	1.14 (1.18)	1.15
S3 P300 amplitude (μV; P3b)**	0.76 (1.18)	1.80 (1.07)	2.95

*$p < 0.05$; **$p < 0.005$; ***$p < 0.001$.
S1: standard condition; S2: distractor condition; S3: target condition.

We recruited healthy controls through newspaper advertisements and remunerated their cooperation. They were previously assessed by a semi-structured psychiatric interview by one investigator (V. Molina) to discard major psychiatric antecedents (personal or familial) and treatments.

The exclusion criteria included total IQ below 70; a history of any neurological illness; cranial trauma with loss of consciousness; past or present substance abuse, except nicotine or caffeine; the presence of any other psychiatric process or drug therapy and treatment with drugs known to act on the central nervous system. We discarded toxic use in patients and healthy controls with the information gathered in the interview and a urinalysis.

We obtained written informed consent from the patients, their families and healthy controls after providing full written information. The research board endorsed the study according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.1. Cognitive assessment

We acquired cognitive assessment by the direct scores from the following subscales of the Spanish version of Brief Assessment in Cognition in Schizophrenia Scale (BACS) (Segarra et al., 2011), administered by trained researchers (V. Suazo, A. Díez): verbal memory (list learning), working memory (digit span), motor speed (token motor task), verbal fluency (categories), attention and processing speed (symbol coding) and executive function/problem-solving (tower of London). We used the Spanish version of the WAIS-III to assess IQ. Cognitive assessment took place within 48 h following the SPECT study.

2.2. Imaging methods

2.2.1. SPECT methods

The single-photon emission computed tomography (SPECT) procedure was performed simultaneously to the EEG recording in all the participants while performing an odd-ball paradigm. The EEG signal was being recorded between 10 min before and 10 min after an intravenous injection of 740 MBq of 99mTc-HMPAO. That paradigm was chosen because P300 amplitudes are consistently found to be reduced in schizophrenia, patients with schizophrenia can be easily engaged in the task, and this task involves regions known to be relevant for schizophrenia and the cognitive functions usually found altered in that syndrome, such as the insula (Linden et al., 1999), frontal (Linden et al., 1999) and parietal lobes (Bledowski et al., 2004) and the hippocampus (Ludowig et al., 2010).

SPECT studies were acquired 20–30 min after the bolus intravenous injection with a dual-head rotating gamma camera (Axis, Picker) fitted with a fan-beam collimator. SPECT data was obtained over 25 min in step-and-shoot mode (120 steps, 3° steps, 25 s per step) using a symmetric window of 20% centered around 140 keV and a 128 × 128 matrix. Images were reconstructed with an iterative method using a low-frequency pre-filter (order 5; cut-off 0.40 cm^{-1}) and were corrected for attenuation (Chang 0.09/cm). Sixty-four transaxial slices were obtained.

2.3. EEG recording

EEG was recorded by BrainVision-Brain Products (2006), equipment from 17 tin electrodes mounted in an electrode cap (Electro Cap International) of the revised 10/20 International System. Electrode impedance was always kept under 5 kilo-Ohms. The online register was referenced over Cz electrode, the sampling rate was 250 Hz, and the signal was recorded continuously.

2.4. Data analysis

2.4.1. Event-related potentials (P300)

We divided the continuous recording into 650 ms epochs starting 50 ms before stimulus onset. We used an off-line 0.5–70 Hz filter. Artifacts were automatically rejected by eliminating epochs that exceeded a range of ±70 μV in any of the channels. Based on a visual inspection we eliminated any epochs that still presented artifacts. Individual data were included in the analyses if 35 or more useful epochs were available. Overall, the mean rate of rejected segments was of 52.8%.

To elicit P3a and P3b components we employed an odd-ball 3-stimulus paradigm with a 500 Hz-tone target, an infrequent 1000 Hz-tone distracter and a 2000 Hz-tone standard stimulus. Accordingly, participants heard binaural tone bursts (duration 50 ms, rise and fall time 5 ms and intensity 90 dB) presented with random stimulus onset asynchrony of 1000 and 1500 ms. Random series of 600 tones consisted of target, distracter and standard tones with probabilities of 0.20, 0.20 and 0.60, respectively. We asked participants to press a button whenever they detected the target tones, to close their eyes and avoid eye movements and muscle artifacts.

Data were off-line re-referenced to electrodes average activity (Bledowski et al., 2004). We defined baseline as the available 50 ms prestimulus recording. P3a and P3b components were respectively calculated from distracter and target stimulus and defined as the average amplitude in the 300–400 ms interval. Generation of ERP Grand Averages across montage and subsequent topographic EEG magnitude analyses were automatically performed using Brain Vision Software (2006). Spline-interpolated topographical maps of scalp voltage and current source density (CSD) were automatically calculated at the defined P300 interval for distracter and target stimuli.

2.5. Statistics

First, we compared demographic, cognitive and electrophysiological (P3a and P3b amplitude) data between patients and controls using χ^2 or t test for separate samples when indicated. We also assessed the significance of the relations between P3a and P3b amplitude and cognition using partial correlation coefficients (partialling out the effect of age). We assessed the possible significance of the relationships between cognition and P3 amplitude with treatment doses by calculating Pearson's r coefficients between BACS coefficients, P3a and P3b amplitudes and treatment doses expressed in CPZ equivalents.

Second, by Statistical Parametric Mapping 8 (Ashburner et al., 2012) we carried out perfusion comparisons between patients and controls, and also correlative studies between perfusion and cognitive scores. Hence, studies were transformed into a Talairach stereotactic space warping and each individual scan was transformed into a reference template that already conformed to the standard space. Images were reformatted to a final voxel size of $2 \times 2 \times 2$ mm and smoothed using an isotropic Gaussian kernel of $12 \times 12 \times 12$ mm FWHM. The gray-level threshold was set to 0.8; i.e., we only included in the statistical analysis voxels with an intensity level above 0.8 from the mean level of that specific scan. We carried out intensity normalization using proportional scaling, therefore assuming that global brain metabolism was the same for each scan.

Then, we determined perfusion comparisons between groups using t test and calculated correlations between performance in BACS scores and perfusion separately in patients and controls on a voxel-by-voxel basis using the multiple regression design incorporated in the SPM. We included age and gender as covariates in these models. In all cases, we considered as significant the results at uncorrected $p < 0.001$ level if present in more than 100 contiguous voxels.

3. Results

3.1. Demographic and neurocognitive data

There were no significant differences in age ($t = 1.27$, $p = 0.21$) or sex distribution ($\chi^2 = 0.32$, $p = 0.57$) between groups (Table 1). Patients had a significantly lower total IQ ($t = 4.17$, $p < 0.001$), and a higher number of single ($\chi^2 = 8.61$, $p < 0.005$) and unemployed ($\chi^2 = 11.98$, $p < 0.001$) individuals. There was a generalized significant neurocognitive deficit in patients (Table 1).

There was a significant negative association between working memory performance and treatment dose in patients ($r = -0.475$, $p = 0.014$), but no other significant associations were observed between treatment dose and cognitive or electrophysiological measurements.

3.2. Perfusion differences and correlates

Patients showed an increased perfusion with respect to controls in the anterior part of the right hippocampus/uncus (Fig. 1 and Table 2). We did not find regions of lower perfusion in our patients as compared to controls.

There was a statistically significant inverse association between performance in verbal memory and perfusion in left hippocampus in patients (i.e., the more perfusion at this level during P300 testing, the worse verbal memory performance during cognitive testing; Fig. 2 and Table 2). Healthy controls did not show any relation between hippocampal perfusion and cognitive performance.

Healthy controls showed an inverse association between working memory performance and perfusion in the left DLPFC region, mostly encompassing Brodmann's area 46 (Table 2, Fig. 3). This relation was not shown by the patients.

There were no other significant relationships between perfusion and neurocognitive performance in patients or controls.

Perfusion was not significantly related to P300 parameters in patients or controls, or to PANSS scores in the patients ($p > 0.05$ in all cases).

3.3. P300 parameters

P3b but not P3a amplitude was significantly lower in patients (Fig. 4 and Table 1). After controlling for the effect of age using partial correlations, there were significant associations between P3a amplitude and verbal fluency ($r = 0.583$; $p = 0.014$), also between P3b amplitude and working memory ($r = -0.479$; $p = 0.05$) and verbal fluency ($r = 0.475$; $p = 0.05$) in the patients.

4. Discussion

In our study, patients with schizophrenia displayed an increased hippocampal perfusion and lower P3b amplitude in comparison to healthy controls during the performance of an odd-ball test. Out of scanner verbal memory scores were inversely related to perfusion in patients left hippocampus.

The hippocampus normally becomes activated during the encoding and retrieval phases of verbal memory tests (Kircher et al., 2008). It seems interesting that the found correlation was precisely between hippocampal perfusion and verbal memory, given the known role of the hippocampus in verbal memory and the replicated memory deficit in schizophrenia (Blanchard and Neale, 1994; Hoff et al., 1992; Manschreck et al., 2000). No

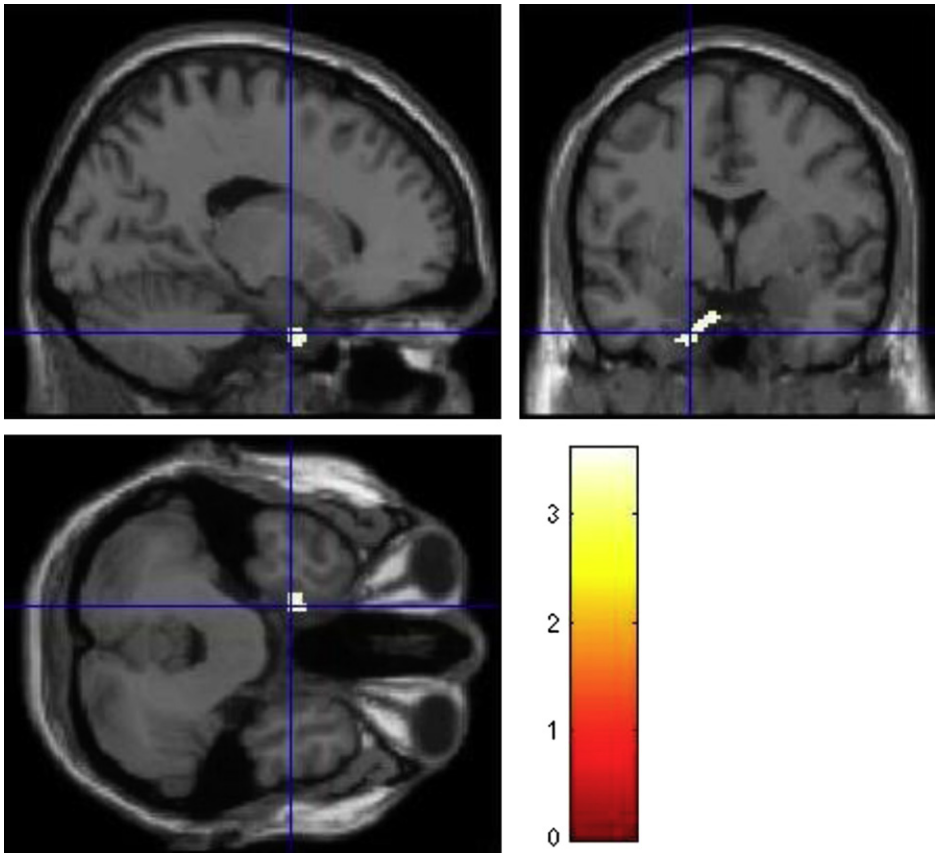

Fig. 1. Increased perfusion in hippocampus in patients as compared to healthy controls.

associations were detected between perfusion elsewhere and other cognitive domains in the patients.

Although the anterior hippocampal hyperactivity in patients may seem counterintuitive in the light of the consistently reported structural atrophy at this level, that hyperactivity is congruent with previous data obtained with F18-PET in a completely different sample (Molina et al., 2005b). Others have shown, using fMRI, that patients with schizophrenia overactivated the parahippocampal and mesial temporal regions during the encoding phase of a verbal memory task with respect to healthy controls (Ragland et al., 2004), being performance slightly although significantly worse in the former. Taken together, with the referred data showing excessive hippocampal activation at rest that did not increase perfusion with memory load (Heckers et al., 1998), our present data suggests that an abnormally increased limbic activation at baseline interferes with the regional capacity to support verbal memory in schizophrenia. Speculatively, the interneurons alteration reported for hippocampus in schizophrenia (Konradi et al., 2011) might contribute to the observed hyperactive pattern.

Table 2
Talairach coordinates of the maxima, voxel extension and *t* values of significant results.

	Coordinates	Voxel extension	t value
Higher perfusion in patients	−10, −1, −27 (right hippocampus)	109	3.61
Inverse correlation perfusion vs verbal memory (patients)	32, −20, −17 (left hippocampus)	252	3.89
Inverse correlation perfusion vs working memory (controls)	37, 28, 17 (left DLPFC)	119	4.93

Our patients were performing an odd-ball task during the SPECT acquisition; thus, the results indicate that patients with higher perfusion values in the hippocampus (i.e., this structure is likely involved in this sort of task (Ludowig et al., 2010)) also had the worst verbal memory performance. The situation might be analogous to that found for the prefrontal cortex, where patients were found to hyperactivate this region in order to obtain similar or worse behavioral data than controls (Callicott et al., 2000; Manoach et al., 2000, 1999).

Furthermore, our data support the presence of limbic hyperactivity in schizophrenia during the performance of an odd-ball task. The odd-ball paradigm has important attention load; we previously reported in a completely different sample that first-episode patients with evolution to schizophrenia showed a significantly higher hippocampal metabolism than healthy controls during the performance of a different attentional test (the Continuous Performance Test) (Molina et al., 2005b). This suggests that the limbic region becomes overactivated in patients with schizophrenia during tasks that require its involvement.

Interestingly, a significant direct correlation between hippocampal volume and verbal memory performance as well as an inverse correlation between NAA to Cho ratio and verbal memory performance has been recently reported in first-episode patients with schizophrenia (Hasan et al., 2011). In elderly healthy participants, an association between hippocampal volume (direct) and NAA to Cr ratio (inverse) to verbal memory scores (Zimmerman et al., 2008) has been found. Moreover, a negative association between hippocampal volumes and NAA concentration was described in younger patients with schizophrenia but not in healthy controls (Klar et al., 2010). Taken together, other groups results (Heckers et al., 1998) and our own, suggest that an overactivation of

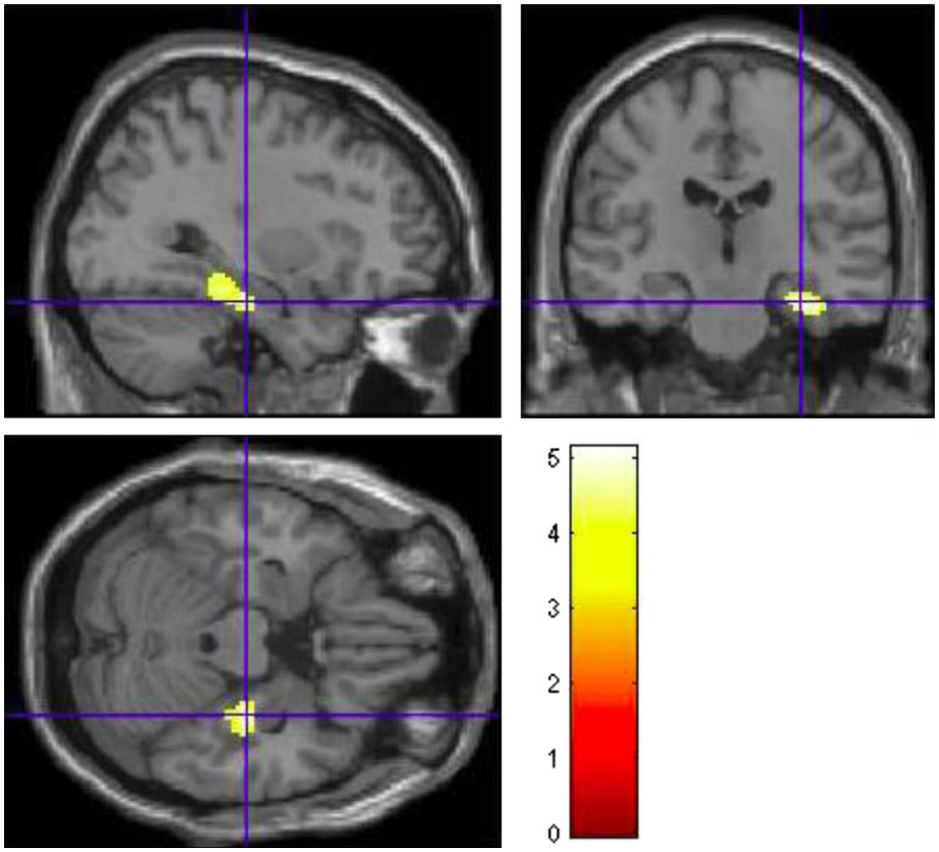

Fig. 2. Significant inverse association between verbal memory and perfusion in the patients.

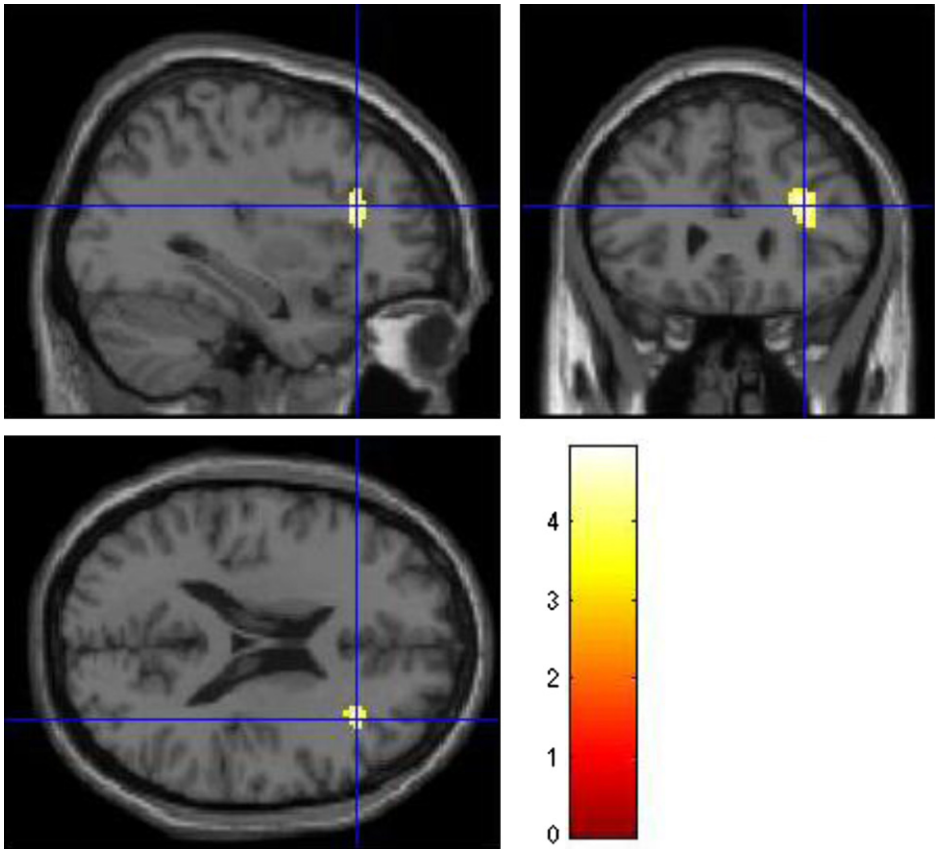

Fig. 3. Significant inverse association between working memory and DLPFC (area 46) perfusion in the healthy controls.

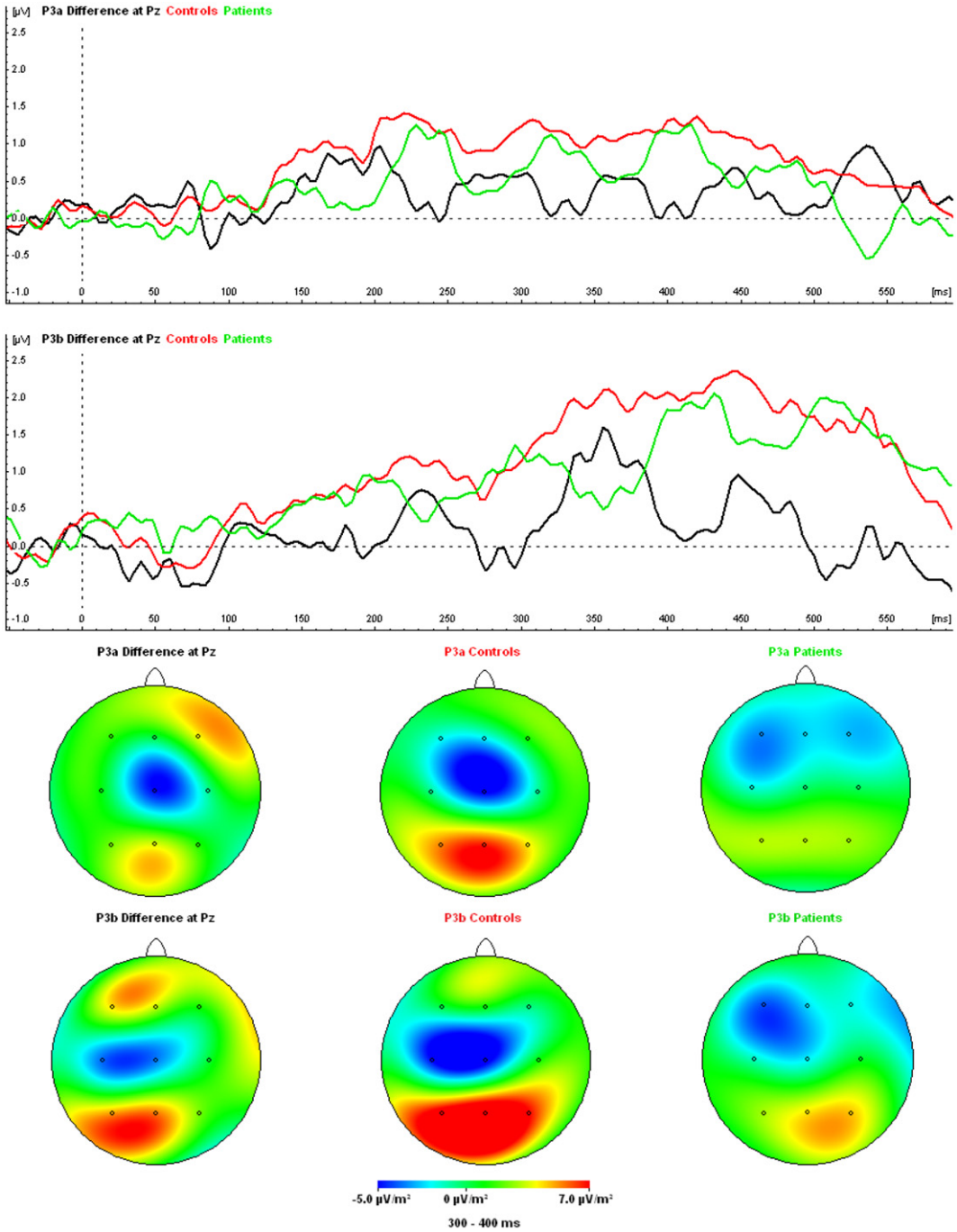

Fig. 4. P3a and P3b amplitude (μV) differences between patients and healthy controls at Pz site.

hippocampus in schizophrenia may contribute to the frequently described anatomical and/or the N-Acetyl-aspartate concentration reduction (Steen et al., 2005) at that level, in addition to a deleterious effect on memory. Moreover, the limbic hyperactive pattern in our patients is coherent with data supporting a reduced deactivation of the DMN in schizophrenia (Ongur et al., 2010; Pomarol-Clotet et al., 2008), which hippocampus is a part of (Buckner et al., 2008).

In the above cited study (Ragland et al., 2004), limbic overactivation was accompanied by a hypoactivation of the prefrontal region, which may help to conciliate other cognitive deficits association with prefrontal hypo- instead of hyperactivation in schizophrenia (Molina et al., 2009).

In our sample the patient's right hippocampus was hyperactive with respect to controls while memory deficits were associated to overactivation in the patient's left side. It could be speculated that during the odd-ball task the dominant side would have increased its perfusion more in the controls; therefore, decreasing the size of the differences in the patients. However, it was the dominant side's amount of overactivation that hampered memory in the patients. This laterality pattern may not apply to other parameters found to be altered in schizophrenia (e.g. the structural or biochemical parameters). In our study, controls showed an inverse association between DLPFC activity and working memory, which may indicate that healthy participants with worse memory performance overactivated that region, the most implicated region in the working

memory task. This may also indicate that the association between inefficient activation and hampered cognitive performance is dimensionally distributed in the healthy and ill populations. In turn, this common pattern association may have to do with the DMN, whose functions have been proposed to be involved in daydreaming (Mason et al., 2007). Since in that study participants with a higher DMN activity were self-described as daydreamers it is possible that a hyperactive hippocampus (in the patients) or DLPFC (in the controls) during a task, as a consequence of a lesser deactivation in that network, would lead to more internal mentation and thus interfere with performance in the corresponding stimulus-driven test. The smaller amount of deactivation deficit in patients with schizophrenia in comparison to healthy controls (Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009) could contribute to the globally worse performance in the former.

Our study has limitations. First, sample size is small and patients were medicated, which probably influences upon perfusion. However, the effect of both typical and atypical antipsychotics upon perfusion is to decrease it (Holcomb et al., 1996; Lahti et al., 2003; Molina et al., 2005a), thus not explaining by itself the hyperactive pattern in our patients. We did not obtain baseline and activation SPECT studies because of the amount of ionizing radiation this would entail on the participants.

Conflict of interest

The authors have no conflicts of interest to declare.

Contribution from each author

Vanessa Suazo contributed to the acquisition, analysis and interpretation of data; drafting and reviewing the manuscript critically; approving the manuscript and certifying other authors' substantial contributions. Alvaro Díez contributed to the acquisition, analysis and interpretation of data; drafting and reviewing the manuscript critically; approving the manuscript and certifying other authors' substantial contributions. Pilar Tamayo contributed to the acquisition and interpretation of data; reviewing the manuscript critically; approving the manuscript and certifying other authors' substantial contributions. Carlos Montes contributed to the analysis and interpretation of data; reviewing the manuscript critically; approving the manuscript and certifying other authors' substantial contributions. Vicente Molina contributed to the conception and design of the manuscript; analysis and interpretation of data; drafting and reviewing the manuscript critically; approving the manuscript and certifying other authors' substantial contributions.

Disclosure

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All authors have approved the final manuscript. The authors have no conflicts of interest to declare.

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