Journal of Psychiatric Research 47 (2013) 843–850

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Limbic hyperactivity associated to verbal memory deficit in schizophrenia

Vanessa Suazo [a,b], Álvaro Díez [a,c], Pilar Tamayo [a,d], Carlos Montes [a,e], Vicente Molina [a,b,f,g,*]

[a] Institute of Biomedical Research (IBSAL), Salamanca, Spain
[b] Neuroscience Institute of Castilla and Leon, University of Salamanca, Spain
[c] Basic Psychology, Psychobiology and Methodology Department, School of Psychology, University of Salamanca, Spain
[d] Nuclear Medicine, University Hospital of Salamanca, Spain
[e] Radiophysics, University Hospital of Salamanca, Spain
[f] Psychiatry Service, University Hospital of Valladolid, Spain
[g] Psychiatry Department, School of Medicine, University of Valladolid, Spain

ARTICLE INFO

Article history:
Received 3 May 2012
Received in revised form
21 January 2013
Accepted 7 February 2013

Keywords:
Schizophrenia
Perfusion
P300
Hippocampus
DLPFC region

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

* Corresponding author. Department of Psychiatry School of Medicine, University of Valladolid Avenida de Ramón y Cajal, 7, 48005 Valladolid, Spain.
E-mail address: vmolina@med.uva.es (V. Molina).

0022-3956/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jpsychires.2013.02.007

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.