Regular Article

Structural correlates of cognitive deficit and elevated gamma noise power in schizophrenia

Vanessa Suazo, MSc, Álvaro Díez, PhD, Carlos Montes, MSc and Vicente Molina, MD, PhD

1Neuroscience Institute of Castilla y León, 2Basic Psychology, Psychobiology and Methodology Department, School of Psychology, University of Salamanca, 3Biomedical Research Institute of Salamanca, 4Radiophysics Service, University Hospital of Salamanca, Salamanca, 5Psychiatry Service, University Hospital of Valladolid, University of Valladolid, Valladolid, Spain, and 6Mental Health Sciences Unit, Faculty of Brain Sciences, University College London, London, UK

Aims: The aim of this study was to assess the relation between cognition, gray matter (GM) volumes and gamma noise power (amount of background oscillatory activity in the gamma band) in schizophrenia.

Methods: We explored the relation between cognitive performance and regional GM volumes using voxel-based morphometry (VBM), in order to discover if the association between gamma noise power (an electroencephalography measurement of background activity in the gamma band) and cognition is observed through structural deficits related to the disease. Noise power, magnetic resonance imaging and cognitive assessments were obtained in 17 drug-free paranoid patients with schizophrenia and 13 healthy controls.

Results: In comparison with controls, patients showed GM deficits at posterior cingulate (bilateral), left inferior parietal (supramarginal gyrus) and left inferior dorsolateral prefrontal regions. Patients exhibited a direct association between performance in working memory and right temporal (superior and inferior gyri) GM densities. They also displayed a negative association between right anterior cerebellum volume and gamma noise power at the frontal midline (Fz) site.

Conclusion: A structural deficit in the cerebellum may be involved in gamma activity disorganization in schizophrenia. Temporal structural deficits may relate to cognitive dysfunction in this illness.

Key words: cerebellum, gamma oscillations, noise power, schizophrenia, working memory.

The extent to which cognitive and cerebral anatomical abnormalities in schizophrenia are related to each other is unclear. Further understanding of the possible relation between structural and cognitive deviation in schizophrenia could be achieved by assessing the relation between GM volumes and neurophysiological measures known to be associated to cognition in this disease. Gamma oscillations can be of interest in this respect, since they may contribute to coherent percepts construction by the brain and to the strengthening and weakening of synaptic links. Gamma band alterations have been reported in schizophrenia, possibly through GABA hypofunction, which may also contribute to structural alterations in schizophrenia.

Noise power is among the gamma-related measurements previously used in schizophrenia literature and it is defined as the amount of background oscillatory activity assessed while the participant is engaged in a task. More specifically, this term refers to the amount of scalp-recorded power not temporally locked to stimuli, quantified as the power difference in each band (gamma in this case) between the magnitude of single trials (i.e., total signal) and
the magnitude in the averaged signal.11 Our group and others have found significant associations between gamma noise power and cognition in schizophrenia.6–10

Noise power measurements may convey relevant information for the investigation of altered cortical information processing in schizophrenia. An over-abundance of noise power may reflect an excessive extension of cortical activation at the expense of adequate selection of neural populations and cognitive performance. As functional neuroimaging reveals a disorganized and/or excessive brain activity during cognitive tasks, along with a hampered activation of regions usually involved in those tasks,12 we may hypothesize that an excess of gamma noise power plays a relevant role in schizophrenia.

Given the possible association between structural brain deficits and cognition in schizophrenia, we decided to explore the relationship between cognitive performance and regional anatomy in our sample. Moreover, it may be of interest to evaluate whether the association between noise power and cognition is observed through structural deficits. We selected lateral and medial frontal electrodes with this purpose because: (i) medial and lateral structural abnormalities are consistently reported in schizophrenia;15–17 and may potentially hamper an adequate organization of gamma oscillations;18 and (iii) our previous results showed an increase in gamma noise power at Fz in schizophrenia patients9 as well as a significant inverse association between gamma noise power at F3 and F4 and cognitive performance.8 We hypothesized that patients with schizophrenia would exhibit deficits in frontal regions that would be associated with deficits in cognitive domains and higher gamma noise power.

METHODS

Demographic characteristics, clinical, cognitive, noise power and magnetic resonance imaging (MRI) assessments were obtained in 17 drug-free paranoid patients with schizophrenia, of them 10 first episode (FE), and 13 healthy controls. These participants had been included in a previous study where gamma noise power values were compared between patients with schizophrenia and controls.7

The patients had not received any previous treatment (FE patients) or they had dropped their medications before inclusion for a period longer than 1 month. The mean illness duration for the latter was of 63.3 months (SD 109.7).

Owing to an acute psychotic state of drug-free patients prior to inclusion, we administered a small amount of haloperidol (2–4 mg) the day before the electroencephalography (EEG) study to all patients (i.e., as their only treatment), with a washout period of approximately 24 h before EEG. We discarded significant effects of haloperidol on noise power in five healthy controls approximately reproducing the treatment conditions of drug-free patients. This was done by recording the EEG in the same conditions as those of the study in the five healthy controls. After informed consent, the EEG was recorded in both groups before and 24 h after receiving 2 mgs of haloperidol. Results and detailed methods are reported elsewhere;9 essentially, we did not detect any differences in P300 or in noise power between the pre- and post-haloperidol conditions in the healthy controls.

We scored the clinical status of the patients by the Positive and Negative Syndrome Scale (PANSS).19 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.

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.M.) 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 controls with the information gathered in the interview and a urinalysis.

We obtained written informed consent from the patients and 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).

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),20 administered by trained researchers (V.S., A.D.): 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 Wechsler Adult Intelligence Scale (WAIS)-III to assess IQ.

EEG methods
EEG recordings were performed while the participants underwent an oddball task. To elicit P3a and P3b components, an oddball 3-stimulus paradigm was employed with a 500-Hz-tone target, a 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 the participants to press a button whenever they detected the target tones, to close their eyes and avoid eye movements and muscle artifacts.

EEG recording
The EEG was recorded by BrainVision (Brain Products GmbH; Munich, Germany) equipment from 17 tin electrodes mounted in an electrode cap (ElectroCap International Eaton, OH, USA). The electrode sites were Fp1, Fp2, F3, Fz, F4, F7, F8, C3, Cz, C4, P3, Pz, P4, T5, T6, O1 and O2 of the revised 10/20 International System. Electrode impedance was always kept under 5 kΩ. The online register was referenced over Cz electrode, the sampling rate was 250 Hz and the signal was recorded continuously.

Data analysis
Event-related potentials
We divided the continuous recording into 650 ms epochs starting 50 ms before stimulus onset. We used an off-line 0.5 to 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 analysis if 40 or more useful epochs were available for each stimulus condition. Overall, the mean rate of rejected segments was of 21.1%. The average number of segments used was of 45.9 (SD 20.5) for the target tone, 174.2 (SD 79.0) for the standard tone, and 46.2 (SD 21.2) for the distracter tone.

Data were re-referenced to electrodes average activity.21 We defined baseline as the available 50-ms prestimulus recording. P3a and P3b components were respectively calculated from distracter and target stimuli and defined as the mean amplitude in the 300–400-ms interval. For quantitative event-related EEG analysis, the recorded signals (−50–600-ms post-stimulus, target condition) were submitted to specific band filtering and spectrum analysis by a fast Fourier transform yielding spectral values. The absolute magnitude (averaged total power) in each frequency band was computed expressed in μV.2 Frequency band partition for gamma was 35–45 Hz.

Noise power
We calculated noise magnitude, which is subsequently denoted as ‘noise power’, following the recommendations of Möcks et al.11 and Winterer et al.10 This calculation was based on the signal-to-noise ratio (SNR), a measure of the quality of the EEG signal applied to each band; it is calculated by the Brain Vision Software22 for the time window from −50 to +600 ms for the target stimuli. The SNR was then calculated from the quotient of the average signal power divided by average noise power:

\[
\text{SNR} = \frac{\text{Avg Signal Power}}{\text{Avg Noise Power}}.
\]

As neither the signal nor the noise in the EEG recording is known exactly, average noise power must be estimated with statistical methods. In this process, it is assumed that noise will be eliminated by averaging. Thus, average noise power for each channel is calculated from the total of the squares of the differences between the EEG value and the average value, divided by the number of points minus 1:

\[
\text{Avg Noise Power} = \frac{\sum_{n=1}^{N} \sum_{k=1}^{K} (A_{kn} - \bar{A})^2}{K \times N - 1}.
\]

Where N is the number of segments, K is the data point number in the segment, \(A_{kn}\) is the amplitude of
each point, and $\bar{A}$ is the average total amplitude (separately for each channel):

$$\bar{A} = \frac{\sum_{n=1}^{N} \sum_{k=1}^{K} A_{nk}}{K \times N}.$$  

The average total power of a channel is a result of the mean of the squares for all data points of the channel before averaging:

$$\text{Avg Total Power} = \frac{\sum_{n=1}^{N} \sum_{k=1}^{K} A_{nk}^2}{K \times N}.$$  

It can be assumed that the signal and the noise are uncorrelated. Consequently, the average power of the signal is equal to the difference between the average total power and the average noise power:

$$\text{Avg Signal Power} = \text{Avg Total Power} - \text{Avg Noise Power}.$$  

### MRI methods

#### MRI acquisition

MRI was performed with a GENERAL ELECTRICS 1.5T scanner. For each participant, a 3D T1 acquisition was obtained with the following parameters:

- **TR** = 12 ms, **TE** = 4.3 ms, Flip angle: 20°, 1.02 × 1.02, **FOV** = 260 mm × 260 mm, **matrix size** = 256 × 256, 120 slices (thickness 1.5 mm).

All scans in the patient and control groups were acquired in the same system with the same protocol. The VBM procedure transforms the resolution to the standard Montreal Neurological Institute brain in Talairach coordinates system.

### Image processing

The T1-weighted MRI scans were recorded using a diffeomorphic image registration algorithm, DARTEL-based VBM, implemented using SPM8 software in the MATLAB 7.6/R2008a environment. DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) is an SPM8 toolbox. This algorithm records inter-subject images using diffeomorphisms that preserve the objects’ properties through deformations, twisting and stretching the images. To record the images, a template is generated using images from control participants, and each patient’s image is deformed to this template using diffeomorphisms.

Using DARTEL, GM differences between patients and controls were assessed at voxel level. Total intracranial volume was included in the model as nuisance variables. The level of significance was set at a voxel level of $P \leq 0.001$ (uncorrected) and a cluster level of $kE \geq 100$ voxels for whole-brain analysis.

### Statistical analysis

We assessed the significance of the association between GM and cognitive scores and, on the other hand, GM and gamma noise power values at Fz, F3 and F4 separately in patients and controls. These correlations were calculated on a voxel-by-voxel basis, using the multiple regression design incorporated in the SPM8, and included the same nuisance variable as the comparison between the patients and controls. In accordance with that comparison, the level of significance was set at $P < 0.001$ uncorrected ($kE \geq 100$ voxels).

The output for each comparison was a statistical parametric map that revealed the location of GM abnormalities in the brain. These areas were superimposed over a T1-weighted template.

### RESULTS

There were no significant differences in age or sex distribution between patients and controls. There were some significantly different cognitive and electrophysiological values between the groups. See Table 1.

#### GM volumes

In comparison with controls, patients showed GM deficits at posterior cingulate (bilateral), left inferior parietal (supramarginal gyrus) and left inferior dorsolateral prefrontal regions (Table 2; Fig. 1). There was also a region of increased GM density in brainstem in the patients (Table 2).

#### Correlations with cognitive scores

In the healthy controls, there was a direct association between BACS scores in problem solving (Tower of London) performance and right superior dorsolateral prefrontal GM, and between verbal memory performance and right temporal pole GM densities (Table 2).

In the patients, there was a direct association between working memory performance and right temporal (superior and inferior gyri) GM densities. In this group, problem-solving performance was positively related to right insular and medial occipital
volumes. Finally, performance speed was positively associated to superior parietal, superior and middle temporal, pulvinar thalamic and insular volumes (all right-sided) in the patients. These results are shown in Table 2 along with the corresponding statistics and coordinates illustrated in Figure 2.

Correlation with noise power
Patients showed a negative association between right anterior cerebellar lobe volume and gamma noise power at Fz (coordinates 20−31−30; t = 5.62, voxel extent 189; Fig. 2).

There was no association between brain volumes and noise power values in the controls group. We did not find any association between P3b amplitude and noise power or performance during the oddball test in the patients.

DISCUSSION
We examined the structural and neurophysiological data of interest in relation to cognitive performance in a sample of drug-free patients with schizophrenia. Our results partially agree with previous reports in which authors described an association between temporal-parietal structural deficits and performance in composite measures of attention, working memory and executive functioning in FE patients with schizophrenia.2 Temporal volumes have also been positively associated with memory performance in female patients with schizophrenia.24 Together, these data and our results suggest a possible temporal GM deficit’s contribution to cognitive alteration in this illness. Although we did not detect significant GM temporal reduction in our cases as a whole, its significant relation with working memory may be coherent with a reduced right temporal GM density in a subset of cases, which may also be characterized by more severe working memory deficits. In turn, this could be compatible with the heterogeneous clinical (and biological) picture of schizophrenia.

We also found a significant insular volume impact on two cognitive measures of our patients’ sample. Decreased insular volumes constitute a replicated finding in schizophrenia literature.25 Our data suggest a cognitive impairment associated to this decrease, in agreement with the cognitive role described for the insula.26

Table 1. Demographic, clinical, cognitive and electrophysiological data in patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.29 (10.48)</td>
<td>30.92 (11.48)</td>
</tr>
<tr>
<td>Sex distribution (M:F)</td>
<td>10:7</td>
<td>10:3</td>
</tr>
<tr>
<td>PANSS Total</td>
<td>74.20 (11.21)</td>
<td>NA</td>
</tr>
<tr>
<td>PANSS Positive</td>
<td>20.93 (4.28)</td>
<td>NA</td>
</tr>
<tr>
<td>PANSS Negative</td>
<td>16.53 (3.94)</td>
<td>NA</td>
</tr>
<tr>
<td>WAIS Total***</td>
<td>83.50 (13.33)</td>
<td>102.85 (14.55)</td>
</tr>
<tr>
<td>BACS-verbal memory***</td>
<td>37.21 (11.72)</td>
<td>54.54 (8.00)</td>
</tr>
<tr>
<td>BACS-working memory**</td>
<td>16.33 (5.69)</td>
<td>22.62 (3.75)</td>
</tr>
<tr>
<td>BACS-motor speed**</td>
<td>49.41 (18.15)</td>
<td>65.92 (13.44)</td>
</tr>
<tr>
<td>BACS-verbal fluency***</td>
<td>17.00 (5.39)</td>
<td>24.54 (5.19)</td>
</tr>
<tr>
<td>BACS-executive speed**</td>
<td>38.64 (13.15)</td>
<td>57 (14.99)</td>
</tr>
<tr>
<td>BACS-problem solving</td>
<td>14.08 (4.94)</td>
<td>16.31 (5.30)</td>
</tr>
<tr>
<td>P3b amplitude at Pz*</td>
<td>0.98 (1.73)</td>
<td>2.28 (0.92)</td>
</tr>
<tr>
<td>P300 (% of correct responses)</td>
<td>82.24 (13.43)</td>
<td>88.66 (26.66)</td>
</tr>
<tr>
<td>Fz noise power</td>
<td>0.007 (0.002)</td>
<td>0.005 (0.003)</td>
</tr>
<tr>
<td>F3 noise power</td>
<td>0.010 (0.011)</td>
<td>0.009 (0.013)</td>
</tr>
<tr>
<td>F4 noise power</td>
<td>0.010 (0.011)</td>
<td>0.008 (0.009)</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01; ***P < 0.001 in comparison to healthy controls; t test for independent samples. Values displayed as mean (SD) if not otherwise established in the table.

BACS, Brief Assessment in Cognition in Schizophrenia Scale; NA, not applicable; PANSS, Positive and Negative Syndrome Scale; WAIS, Wechsler Adult Intelligence Scale.
Given the role of the prefrontal cortex in executive functions, it seems remarkable that, although significantly decreased in our patients, contrary to our expectations, GM volumes in this region were unrelated to cognitive performance. In a previous study, *a priori* focused on prefrontal anatomy and metabolism, we described that patients with a larger GM volume deficit had a worse outcome in working memory tasks than those without this deficit.\(^{27}\) This study was carried out in a predominantly chronic sample, which may contribute to the discrepancy. It is possible that frontal functional alterations may be more related to cognitive deficits in the early stages of schizophrenia; this could be compatible with the association between cognition and noise power previously described in the present sample.\(^{8}\) However, results in larger samples have shown direct correlations between dorsolateral prefrontal volumes and working memory and verbal fluency composite scores in FE patients,\(^{7}\) which suggests we should not dismiss these associations only on the basis of our sample size. Alternatively, since the pattern of anatomical abnormalities is very different across MRI studies in schizophrenia,\(^{13}\) different alterations may contribute to cognitive deficits across samples.

Contrary to our hypothesis, gamma noise power and cognitive deficits were associated with different anatomical substrates. We have reported in another study, whose sample overlaps with the present one, that frontal noise power was inversely related to deficits in working memory and problem-solving.\(^{8}\) In spite of the association between noise power and cognition, frontal volumes were not associated to noise power values or cognitive deficits in these tests in the patients in the present study. Thus, it seems likely that the reported noise power excess does not

| Table 2. (a) Gray matter volume differences between patients and controls \((P<0.001)\). (b,c) Regions significantly correlated with performance in cognitive domains in (a) patients and (b) controls |
|---|---|---|
| **(a) Between-group differences** | **Regions** | **Coordinates** | **Voxel extension** |
| Patients > controls | Brain stem | 5–43 −32 | 1305 |
| Patients < controls | Bilateral posterior cingulate | 12–7 43 | 281 |
| | Left inferior DLPF | −51 21 4 | 250 |
| | Left paracentral | −12–25 48 | 201 |
| | Left supramarginal | −50–48 31 | 184 |
| **(b) Significant associations in patients** | **Regions** | **Coordinates** | **T** | **Voxel size** |
| Working memory | Superior temporal (R) | 57−15 3 | 5.65 | 100 |
| | Inferior temporal (R) | 62−30−23 | 5.62 | 294 |
| Problem-solving | Insula (R) | 47−1−9 | 5.66 | 164 |
| | Medial occipital (R) | 5−52 27 | 7.24 | 379 |
| Processing speed | Superior Parietal (R) | 17−28 82 | 5.93 | 119 |
| | Superior Parietal (R) | −26–60 63 | 11.73 | 236 |
| | Superior temporal (R) | 62 0 3 | 8.34 | 357 |
| | Middle temporal (R) | 72−31−14 | 6.65 | 419 |
| | Middle temporal (R) | 60 2−23 | 6.02 | 561 |
| | Pulvinar thalamus (R) | 20−28 3 | 6.00 | 153 |
| | Insula (R) | 42−4 15 | 7.05 | 616 |
| **(c) Significant associations in controls** | **Regions** | **Coordinates** | **T** | **Voxel size** |
| Problem-solving | DLPF (R) | 23 21 49 | 10.95 | 220 |
| Verbal memory | Temporal pole (R) | 36 18−33 | 11.75 | 100 |

DLPF, dorsolateral prefrontal; R, right.

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relate directly to gray matter volume deficits in schizophrenia, and its contribution to altered cognition can be mediated through other mechanisms. Speculatively, this could contribute to schizophrenia’s phenotypic diversity, since different mechanisms may contribute to different cognitive profiles across patients. Nevertheless, the poor spatial resolution of scalp-recorded EEG must be taken into account, that is, the structural correlates implied in the present findings (worse performance with less insula, parietal and temporal regions values) are not utterly incompatible with the described relation between gamma noise power and cognitive deficit in these areas.

According to our data, patients showed an inverse relation between cerebellar volume and noise power.

**Figure 1.** Regions significantly decreased in patients in relation to healthy controls. (a) Gray matter density observed in right posterior cingulate, (b) left inferior dorsolateral prefrontal region, (c) left paracentral region and (d) left supramarginal region.
at Fz. To serve as a reminder, we a priori selected Fz, F3 and F4 as predictors, given the literature review, our previous findings and the aims of the study. The described association is not likely causal, but rather may represent the presence of an underlying factor contributing to both alterations. Given the anatomical distance between cerebellum and medial frontal sites, that association might reflect an underlying mechanism common to both alterations, which may have to do with an inhibitory dysfunction, described as follows. GABA transmission plays a fundamental role in the generation and modulation of gamma rhythms in the brain, and this kind of transmission is prevalent in the cerebellum. Gamma responses can be recorded at different levels of the brain and cerebellum. Post-mortem findings

Figure 2. Direct association (a) between gray matter volumes and working memory, problem-solving and processing speed scores in the patients; and (b) between gray matter volumes and problem-solving scores and gray matter volumes in healthy controls. (c) Inverse association between gamma noise power at Fz and gray matter volumes in the patients.

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support a deficit in GABA transmission at cerebellum in schizophrenia.\textsuperscript{32,33} Given the excitotoxic effects proposed for an inhibitory deficit,\textsuperscript{7} GABA alterations may contribute to both gamma noise power excess at Fz site and volumetric deficits in cerebellum, in addition to their association. An association has been described between cognitive deficit and both cerebellar structural deficit\textsuperscript{34} and gamma noise power excess.\textsuperscript{8–10} Some researchers,\textsuperscript{35} but not others,\textsuperscript{34} found significant deficits in the cerebellar lobes in schizophrenia, where our data reveal an association with noise power. Speculatively, this may sustain the presence of patients with and without cerebellar reductive and, if our results are confirmed, increase noise power in the gamma band.

The fact that we did not find cerebellar anatomical abnormalities may relate to sample size, as some patients may have both altered noise power and cerebellar anatomical deficits, while others may have preserved cerebellar structure and less increased noise power values. In this case, it seems possible that the significant correlation would still hold without cerebellar deficits in the patients, which could however be detected in a larger sample.

EEG-recorded gamma activity may be secondary to ocular artifacts (microsaccades).\textsuperscript{36} However, this would not justify the association between gamma noise power and MR measurements found in our sample. These spontaneous movements subserve ocular fixation and are observed in tests performed with eyes open, up to 250 ms after stimulus onset.\textsuperscript{37} Thus, they can be expected to be more intense with eyelids open, when fixation can take place, while our participants were recorded with their eyelids closed. There is still the possibility that muscular artifacts from other origins (e.g. neck or forehead) may influence the differences between cases and controls. However, electromyogram’s influence on gamma activity is maximum on the circumferential electrodes, and less likely to affect the activity recorded at F3, F4 and Fz.

Our study has the clear limitation of sample size (of both patients and controls), which led us to use uncorrected $P$-values, although a minimum extent of 100 contiguous voxels may offer a reasonable protection against type I errors. Moreover, simultaneously using EEG values may supply relevant information, and the patterns of findings seem biologically plausible. In any case, replication is needed to confirm the cerebellum’s involvement in gamma activity disorganization in schizophrenia.

ACKNOWLEDGMENTS

The present work was supported by the Fondo de Investigaciones Sanitarias (Instituto de Salud Carlos III) (FIS PI1102203) and the Gerencia Regional de Salud de Castilla y León (GRS 613/A/11) grants to V. Molina, a predoctoral scholarship from the University of Salamanca and Santander Bank to V. Suazo, a predoctoral research grant from the Consejería de Educación – Junta de Castilla y León and the European Social Fund (EDU/1486/2008) and a Marie Curie Intra European Fellowship within the 7th European Community Framework Programme (330156-CODIP) to A. Diez. All authors have approved the final manuscript. The authors have no conflicts of interest to declare.

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