Gamma Power and Cognition in Patients with Schizophrenia and Their First-Degree Relatives

Álvaro Díez\textsuperscript{a} Vanessa Suazo\textsuperscript{b} Pilar Casado\textsuperscript{c} Manuel Martín-Loeches\textsuperscript{c} Vicente Molina\textsuperscript{a, c, d}

\textsuperscript{a}Basic Psychology, Psychobiology and Methodology Department, School of Psychology, University of Salamanca, and \textsuperscript{b}Neuroscience Institute of Castile and León, University of Salamanca, Salamanca, \textsuperscript{c}UCM-ISCIII Center for Human Evolution and Behavior, Madrid, and \textsuperscript{d}Psychiatry Service, University Hospital of Valladolid, University of Valladolid, Valladolid, Spain

\textbf{Key Words}
Gamma band · Schizophrenia · Cognition · Hyperactivity · Relatives, first-degree

Abstract
Background: Gamma oscillations are essential for functional neural assembly formation underlying higher cerebral functions. Previous studies concerning gamma band power in schizophrenia have yielded diverse results. Methods: In this study, we assessed gamma band power in minimally treated patients with schizophrenia, their first-degree relatives and healthy controls during an oddball paradigm performance, as well as the relation between gamma power and cognitive performance. Results: We found a higher gamma power in the patient group than in the healthy controls at the P3, P4, Fz, Pz and T5 sites. Compared with their relatives, gamma power in the patients was only marginally higher over P3 and P4. We found a nearly significant inverse association between gamma power at F4 and Tower of London performance in the patients, as well as a significant inverse association between gamma power at T5 and verbal memory and working memory scores in the relatives. Conclusion: These results support higher total gamma power in association with schizophrenia and its inverse association with cognitive performance in patients and their first-degree relatives.

Introduction
A role for gamma oscillations in cognitive functions has previously been proposed at least regarding multisensory integration \cite{1}, selective attention \cite{2} and working memory \cite{3}, relating to the gamma band’s capacity to subside transient functional assembly formation \cite{4–7}. On this basis it seems relevant to study gamma power with respect to cognitive dysfunction in schizophrenia \cite{8}. In schizophrenia, reduced spectral power and synchronicity of gamma band response to tasks has been reported in comparison with controls \cite{8}, albeit with some discrepancies \cite{9, 10}. Gamma oscillations arising in response to a task can be divided into evoked (early responses phase-locked to stimulus onset, related to sensory processing) and induced power (later responses related to cognitive processing, not phase-locked to stimulus onset) \cite{11}. In schizophrenia, fewer
induced [12] and evoked [11, 13] responses have been reported.

In this context, previous data suggest that total gamma power (i.e. the sum of baseline power and evoked/induced power responses in this band) may be elevated at least in some patients with schizophrenia in comparison with controls during a cognitive task. Higher gamma noise power (corresponding to power unrelated to task performance) has been reported during a P300 task in schizophrenia [14]. Moreover, higher mean power in the faster bands has been reported in this illness [15], as well as a positive correlation between positive symptoms and gamma power responses [16]. It has been suggested that this association may reflect a cortical hyperexcitability that possibly disturbs the conscious experience [11]. Consistently, administration of typical and atypical antipsychotics reduced gamma power in patients with schizophrenia [17].

Moreover, the possible elevation in total gamma signal in schizophrenia is indirectly supported by functional neuroimaging data. The association between gamma band oscillations and modulation of the BOLD (blood oxygen level-dependent) signal seems particularly strong [18, 19]. Functional magnetic resonance (fMRI) in schizophrenia reveals an excess of brain activity during cognitive tasks along with a hampered outcome [20]. Therefore, the expected task-related fMRI activation pattern might also be evidenced as a total power excess in the gamma band. This could speculatively relate to a hyperactive basal state and be coherent with a diminished capacity for increasing gamma power in response to a task performance. Therefore, it is of interest to investigate whether total (baseline plus evoked) power is elevated in schizophrenia, which could be coherent with other data supporting a hyperactive basal state together with diminished regional activation in this illness.

Studying a patient’s first-degree relatives may be relevant to better understand the role of gamma power in schizophrenia. Since heritability is high in this illness [21], similar alterations secondary to genetically mediated systems may be expected in the relatives. In view of (a) the role that candidate genes for schizophrenia such as NRG [22] or DISC [23] have on inhibitory interneuron development, (b) these interneurons’ function in gamma response [24] and (c) the likely inhibitory alteration to transmission in at least part of the patients with schizophrenia [25], it seems logical to investigate gamma power alterations and their association with cognitive performance in both patients and relatives.

To that end, we recorded gamma (35–45 Hz) total power activity (i.e. independent of phase locking) during a P300 oddball paradigm. We examined the correlation of gamma power with cognitive performance in the dimensions more frequently reported to be altered in schizophrenia. Given our interest in total power measurements, we reanalyzed EEG data from a previously reported sample [26] in order to test the hypothesis that total gamma power is elevated and inversely related to cognitive performance in patients and their first-degree relatives.

**Subjects and Methods**

We recruited 30 patients with schizophrenia, 24 of their first-degree relatives and 27 healthy controls. Of the patients, 17 had not previously received any treatment and 13 had dropped their medication before inclusion for a period longer than 1 month. Owing to the acute psychotic state of these patients prior to inclusion, we administered a small amount of haloperidol (2–4 mg) the day before the EEG study, with a wash-out period of approximately 24 h before EEG. The objective was to minimize the likely bias of only including patients able to cooperate with the EEG recording during an acute psychotic episode and without any previous treatment. In order to rule out the acute effects of haloperidol on gamma power, 5 healthy controls consented to be studied by EEG before and 24 h after a 2-mg dose of haloperidol, therefore approximately reproducing the treatment conditions of the patients.

Healthy first-degree relatives included parents or siblings with at least 1 family member diagnosed with schizophrenia. At the time of inclusion, the first-degree relatives had not received any psychiatric axis I diagnosis or psychiatric treatment.

We scored the clinical status of the patients using the Positive and Negative Syndrome Scale [27]. Employment status was stratified 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 intelligence quotient (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 by 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).

---

Gamma Power in Schizophrenia

DOI: 10.1159/000356970
Cognitive Assessment
We acquired cognitive assessment by direct scores from the following subscales of the Spanish version of the Brief Assessment of Cognition in Schizophrenia (BACS) scale [28], administered by trained researchers (A.D. and V.S.): 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, 3rd edition [29] to assess IQ.

EEG Methods
EEG recordings were performed while the participants underwent an oddball task. To elicit P3a and P3b components, a 3-stimulus oddball paradigm was employed with a 500-Hz target tone, a 1,000-Hz distracter tone and a 2,000-Hz standard stimulus tone. Accordingly, participants heard binaural tone bursts (duration: 50 ms; rise and fall time: 5 ms; intensity: 90 dB) presented with random stimulus onset asynchrony of 1,000 and 1,500 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.

Electroencephalographic Recording
The EEG was recorded by BrainVision® equipment (Brain Products GmbH, Munich, Germany) from 17 tin electrodes mounted on an electrode cap (Electro-Cap International Inc., Eaton, Ohio, 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 International 10/20 System. Electrode impedance was always kept under 5 kΩ. The online register was referenced over the Cz electrode, the sampling rate was 250 Hz and the signal was recorded continuously.

Data Analysis
Power Measurements
We divided the continuous recording into 650-ms epochs, starting 50 ms before stimulus onset. We used an offline 0.5- to 70-Hz filter over the unfiltered raw data. Artifacts were automatically rejected by eliminating epochs that exceeded a range of ±70 μV in any of the channels. Based on visual inspection, we eliminated any epochs that still presented artifacts. Visual inspection was performed concurrently by 2 trained researchers and by a double-blind method to avoid any bias during the cleaning process. Individual data were included in the analyses if 45 or more useful epochs were available for each stimulus condition. Overall, the mean rate of rejected segments was of 48.8% (32.04% from manual inspection).

Data were re-referenced to the electrodes’ average activity [30]. We defined the baseline as the available 50-ms prestimulus recording. P3a and P3b components, respectively, were calculated from distracter and target stimuli and defined as the mean amplitude in the 300- to 400-ms interval. For quantitative event-related EEG analysis, the recorded signals for those segments (~50 to 600 ms after stimulus) corresponding to the 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, independent of phase locking) in each frequency band was computed, expressed in microvolts squared. The frequency band partition was: delta (0.5–4.0 Hz), theta (4.5–8.0 Hz), alpha (8.5–12.5 Hz), beta-1 (13.0–18.0 Hz), beta-2 (18.5–30.0 Hz) and gamma (35.0–45.0 Hz). According to our a priori hypothesis, in the following analyses we focused on gamma oscillations; nevertheless, further analyses were also conducted in the remaining frequency bands for exploratory purposes.

In order to reduce the number of comparisons and because of gamma band sensitivity to muscular and ocular artifacts, we restricted the comparisons to the following electrodes: F3, F4, P3, P4, T5, T6, Fz and Pz. Data on the other electrode sites are available upon request.

Statistics
We compared age, sex distribution, school years and number of valid segments as well as the percentage of manual rejections between patients, relatives and controls, using ANOVA or χ² tests when indicated. By Student’s t test we tested whether P3a or P3b amplitudes were reduced in patients as compared with healthy controls.

By multivariate general linear model analysis – with age and sex as covariates and a Bonferroni adjustment for multiple comparisons – we tested the significance of the differences in cognitive scores (including total IQ).

The main study hypothesis was tested using a repeated measures general linear model with a between-subject factor (group) and a within-subject factor (electrode), including age and sex as covariates, to assess the significance of overall differences in total power. By post hoc tests, we looked to identify local differences if significant interactions were detected between groups and electrodes. For exploratory purposes, we also contrasted total power and relative power magnitudes in all frequency bands, using separate contrasts. Relative power was assessed as the ratio between total power in each band and total power not restricted to any frequency band.

We examined the association between cognitive performance and gamma power by stepwise multivariate linear regression (each cognitive variable as dependent variable, gamma power values as independent variables), testing normal distribution and homoscedasticity of the residuals. We did this separately for the patients, relatives and controls groups.

To rule out the effects of acute treatment on gamma power and P3b amplitude, we used the data from the specific control group before and after receiving haloperidol with a Wilcoxon test for related samples.

Results
As expected, relatives were significantly older than patients (p < 0.001) and controls (p < 0.001). No age difference was found between patients and controls. Sex distribution was not significantly different. Relatives had more years of schooling than the other groups (p < 0.001). The number of valid segments for the analysis was smaller in the patients group (table 1).
P300 (P3b) amplitudes were marginally smaller in the patients (table 1; t = –1.67, d.f. = 56, p = 0.07). P3a did not differ between patients and controls (table 1; t = –0.21, d.f. = 56, p = 0.83). IQ was significantly lower in patients than in relatives (p = 0.001) and controls (p < 0.001; table 1).

Patients showed worse performance than controls in verbal memory, working memory, motor speed, verbal fluency, processing speed and problem-solving domains (table 1). Patients only displayed significantly worse performance in verbal fluency (p = 0.014) when compared with their relatives. Relatives only showed significant slowness in processing speed when compared with controls (p = 0.049).

**Gamma Power Comparisons**

The repeated measures general linear model revealed a significant interaction between group and electrode (Huynh-Feldt’s type III sum of squares = 0.007; F = 2.053; p = 0.05). The between-subjects test revealed a significant effect for group in gamma power at P3 (type III sum of squares = 0.002; F = 5.089; p = 0.008), P4 (type III sum of squares = 0.001; F = 4.737; p = 0.012), T5 (type III sum of squares = 0.009; F = 4.722; p = 0.012) and Fz (type III sum of squares <0.001; F = 3.547; p = 0.034) sites, as well as at Pz at a trend level (type III sum of squares <0.001; F = 2.939; p = 0.059; table 2).

Pairwise comparisons revealed significantly higher gamma power values in patients when compared with controls at P3 (between-means difference = 0.011; 95% CI: 0.001–0.020; p = 0.019), P4 (between-means difference = 0.006; 95% CI: 0.001–0.012; p = 0.022), T5 (between-means difference = 0.024; 95% CI: 0.004–0.044; p = 0.011), Fz (between-means difference = 0.004; 95% CI: 0.000–0.008; p = 0.032) and, at a trend level, Pz sites (between-means difference = 0.005; 95% CI: 0.000–0.010; p = 0.070).

When compared with relatives, patients only showed marginally higher gamma values at P3 (between-means difference = 0.011; 95% CI: 0.000–0.023; p = 0.054) and P4 (between-means difference: 0.007; 95% CI: –0.001 to 0.014; p = 0.080). There were no statistically significant differences in gamma power between relatives and healthy controls.

### Table 1. Demographic, clinical and cognitive values and P300 parameters of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Relatives</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>33.53 (9.91)b</td>
<td>53.24 (14.96)***</td>
<td>33.65 (13.21)</td>
</tr>
<tr>
<td>Sex distribution (M:F), n</td>
<td>18:12</td>
<td>10:14</td>
<td>17:10</td>
</tr>
<tr>
<td>School years</td>
<td>12.47 (2.59)b</td>
<td>19.30 (3.33)***</td>
<td>13.00 (5.74)</td>
</tr>
<tr>
<td>Employment status, % employed</td>
<td>37.50*</td>
<td>66.34</td>
<td>66.67</td>
</tr>
<tr>
<td>Positive symptoms, n</td>
<td>20.83 (4.01)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Negative symptoms, n</td>
<td>16.79 (4.77)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Total PANSS score</td>
<td>75.96 (11.78)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Total IQ</td>
<td>82.19 (16.76)***, b</td>
<td>102.60 (14.65)</td>
<td>101.94 (12.43)</td>
</tr>
<tr>
<td>Verbal memory score</td>
<td>36.10 (12.14)***</td>
<td>40.50 (13.38)</td>
<td>53.90 (8.75)</td>
</tr>
<tr>
<td>Working memory score</td>
<td>17.10 (6.50)*</td>
<td>18.17 (3.33)</td>
<td>22.32 (3.75)</td>
</tr>
<tr>
<td>Motor speed score</td>
<td>53.00 (16.03)*</td>
<td>55.50 (13.54)</td>
<td>64.29 (13.61)</td>
</tr>
<tr>
<td>Verbal fluency score</td>
<td>16.30 (5.07)*.a</td>
<td>21.91 (6.11)</td>
<td>25.323 (5.147)</td>
</tr>
<tr>
<td>Processing speed score</td>
<td>39.79 (13.81)***</td>
<td>38.91 (13.58)*</td>
<td>58.64 (12.95)</td>
</tr>
<tr>
<td>Problem-solving score</td>
<td>13.35 (5.36)**</td>
<td>14.36 (5.045)</td>
<td>16.77 (3.80)</td>
</tr>
<tr>
<td>P3a amplitude</td>
<td>0.89 (1.12)</td>
<td>0.90 (1.25)</td>
<td>1.18 (1.17)</td>
</tr>
<tr>
<td>P3b amplitude</td>
<td>1.17 (1.55)</td>
<td>1.07 (2.26)</td>
<td>1.81 (1.05)</td>
</tr>
<tr>
<td>Number of valid target segments</td>
<td>45.06 ba</td>
<td>71.92</td>
<td>56.96</td>
</tr>
<tr>
<td>Manual artifact target rejections, %</td>
<td>34.63a</td>
<td>16.92</td>
<td>24.04</td>
</tr>
<tr>
<td>Correct responses, %</td>
<td>72.57 (32.07)</td>
<td>94.92 (6.50)</td>
<td>90.08 (21.95)</td>
</tr>
<tr>
<td>Reaction time, ms</td>
<td>616.06 (86.87)</td>
<td>527.95 (111.18)</td>
<td>524.42 (53.73)</td>
</tr>
</tbody>
</table>

Values in parentheses denote SD. Significant differences with respect to healthy controls or relatives are shown in the corresponding column. PANSS = Positive and Negative Syndrome Scale.

* p < 0.05, ** p < 0.01, *** p < 0.001, in comparison with controls; + p < 0.05, b p < 0.001, in comparison with relatives (Bonferroni correction). No other significant cognitive differences were found between patients and relatives. N/A = Not applicable.
Changes with Haloperidol in Healthy Controls

Gamma power lessened significantly with haloperidol over T5 ($z = -2.02; p = 0.043$). We did not find any other significant changes with haloperidol in gamma power for the remaining electrodes studied (table 5). In all cases, the power values after haloperidol were lower than the corresponding basal values. There was no significant effect of haloperidol on P3b amplitude.

Table 3 shows total power magnitudes and significant between-group comparisons in the remaining frequency bands (delta, theta, alpha and beta-1 and -2), revealing higher beta-1 and beta-2 power in the patients at P3, P4, T5 and Fz, and also at Pz for beta-1. The relative power comparisons (table 4) showed higher values for the gamma band (P3, T5 and Pz) and smaller values for the delta band (F3, P3 and Pz) in the patients in comparison with the controls.

Table 2. Gamma power values in the study groups

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th></th>
<th>Relatives</th>
<th></th>
<th>Controls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>raw values</td>
<td>estimates</td>
<td>raw values</td>
<td>estimates</td>
<td>raw values</td>
<td>estimates</td>
</tr>
<tr>
<td>F3</td>
<td>0.021 (0.021)</td>
<td>0.020 (0.004)</td>
<td>0.014 (0.007)</td>
<td>0.015 (0.005)</td>
<td>0.018 (0.026)</td>
<td>0.018 (0.004)</td>
</tr>
<tr>
<td>F4</td>
<td>0.018 (0.010)</td>
<td>0.019 (0.003)</td>
<td>0.017 (0.012)</td>
<td>0.016 (0.003)</td>
<td>0.017 (0.018)</td>
<td>0.017 (0.003)</td>
</tr>
<tr>
<td>P3</td>
<td>0.024 (0.021)</td>
<td>0.024 (0.003)*</td>
<td>0.012 (0.005)</td>
<td>0.013 (0.003)</td>
<td>0.013 (0.009)</td>
<td>0.013 (0.003)</td>
</tr>
<tr>
<td>P4</td>
<td>0.021 (0.010)</td>
<td>0.020 (0.002)*</td>
<td>0.012 (0.006)</td>
<td>0.013 (0.002)</td>
<td>0.014 (0.009)</td>
<td>0.013 (0.002)</td>
</tr>
<tr>
<td>T5</td>
<td>0.053 (0.043)</td>
<td>0.053 (0.006)*</td>
<td>0.031 (0.016)</td>
<td>0.034 (0.008)</td>
<td>0.029 (0.021)</td>
<td>0.029 (0.006)</td>
</tr>
<tr>
<td>T6</td>
<td>0.039 (0.026)</td>
<td>0.038 (0.006)</td>
<td>0.029 (0.015)</td>
<td>0.032 (0.008)</td>
<td>0.042 (0.045)</td>
<td>0.041 (0.006)</td>
</tr>
<tr>
<td>Fz</td>
<td>0.015 (0.006)</td>
<td>0.014 (0.001)*</td>
<td>0.011 (0.008)</td>
<td>0.013 (0.001)</td>
<td>0.011 (0.006)</td>
<td>0.010 (0.001)</td>
</tr>
<tr>
<td>Pz</td>
<td>0.015 (0.009)</td>
<td>0.015 (0.001)</td>
<td>0.009 (0.005)</td>
<td>0.011 (0.002)</td>
<td>0.011 (0.008)</td>
<td>0.010 (0.002)</td>
</tr>
</tbody>
</table>

Raw values are shown as $\mu$V² and the corresponding estimates result from the correction using covariates age and sex. Values in parentheses denote SD. *p < 0.05 in comparison with controls; *p < 0.10 in comparison with relatives (Bonferroni correction).

Table 3. Total power values in the study groups for the remaining frequency bands: $\delta$ (0.5–4 Hz), $\theta$ (4.5–8 Hz), $\alpha$ (8.5–12.5 Hz), $\beta_1$ (13–18 Hz) and $\beta_2$ (18.5–30 Hz), using covariates age and sex

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th></th>
<th>Relatives</th>
<th></th>
<th>Controls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta$</td>
<td>0.524 (0.208)</td>
<td>0.134 (0.034)</td>
<td>0.168 (0.025)</td>
<td>0.168 (0.041)</td>
<td>0.176 (0.242)</td>
<td>0.186 (0.041)</td>
</tr>
<tr>
<td>$\theta$</td>
<td>0.571 (0.888)</td>
<td>0.133 (0.034)</td>
<td>0.168 (0.041)</td>
<td>0.168 (0.041)</td>
<td>0.176 (0.242)</td>
<td>0.186 (0.041)</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.697 (0.230)</td>
<td>0.133 (0.034)</td>
<td>0.168 (0.041)</td>
<td>0.168 (0.041)</td>
<td>0.176 (0.242)</td>
<td>0.186 (0.041)</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.689 (0.230)</td>
<td>0.133 (0.034)</td>
<td>0.168 (0.041)</td>
<td>0.168 (0.041)</td>
<td>0.176 (0.242)</td>
<td>0.186 (0.041)</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>0.689 (0.230)</td>
<td>0.133 (0.034)</td>
<td>0.168 (0.041)</td>
<td>0.168 (0.041)</td>
<td>0.176 (0.242)</td>
<td>0.186 (0.041)</td>
</tr>
</tbody>
</table>

Significant differences with respect to controls or relatives are shown in the corresponding column. Values in parentheses denote SD. *p < 0.05. **p < 0.01. ***p < 0.001 in comparison with controls; *p < 0.05 in comparison with relatives (Bonferroni correction).

Table 3 shows total power magnitudes and significant between-group comparisons in the remaining frequency bands (delta, theta, alpha and beta-1 and -2), revealing higher beta-1 and beta-2 power in the patients at P3, P4, T5 and Fz, and also at Pz for beta-1. The relative power comparisons (table 4) showed higher values for the gamma band (P3, T5 and Pz) and smaller values for the delta band (F3, P3 and Pz) in the patients in comparison with the controls.
Table 4. Relative power values in the study groups for all frequency bands; δ (0.5–4 Hz), θ (4.5–8 Hz), α (8.5–12.5 Hz), β₁ (13–18 Hz), β₂ (18.5–30 Hz) and γ (35–45 Hz), using covariates age and sex.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>δ</td>
<td>0.544</td>
<td>0.144</td>
<td>0.184</td>
<td>0.062</td>
<td>0.045</td>
<td>0.021</td>
<td>0.133</td>
<td>0.140</td>
<td>0.018</td>
<td>0.017</td>
<td>0.033</td>
<td>0.176</td>
<td>0.009</td>
<td>0.109</td>
<td>0.110</td>
<td>0.020</td>
</tr>
<tr>
<td>θ</td>
<td>0.807</td>
<td>0.085</td>
<td>0.078</td>
<td>0.033</td>
<td>0.024</td>
<td>0.013</td>
<td>0.100</td>
<td>0.096</td>
<td>0.022</td>
<td>0.010</td>
<td>0.082</td>
<td>0.012</td>
<td>0.009</td>
<td>0.086</td>
<td>0.082</td>
<td>0.020</td>
</tr>
<tr>
<td>α</td>
<td>0.104</td>
<td>0.256</td>
<td>0.077</td>
<td>0.034</td>
<td>0.019</td>
<td>0.572</td>
<td>0.010</td>
<td>0.020</td>
<td>0.073</td>
<td>0.032</td>
<td>0.013</td>
<td>0.658</td>
<td>0.004</td>
<td>0.109</td>
<td>0.124</td>
<td>0.020</td>
</tr>
<tr>
<td>β₁</td>
<td>0.478</td>
<td>0.106</td>
<td>0.288</td>
<td>0.033</td>
<td>0.017</td>
<td>0.543</td>
<td>0.108</td>
<td>0.027</td>
<td>0.035</td>
<td>0.012</td>
<td>0.039</td>
<td>0.004</td>
<td>0.116</td>
<td>0.025</td>
<td>0.124</td>
<td>0.004</td>
</tr>
<tr>
<td>β₂</td>
<td>0.511</td>
<td>0.108</td>
<td>0.078</td>
<td>0.048</td>
<td>0.032</td>
<td>0.531</td>
<td>0.144</td>
<td>0.196</td>
<td>0.073</td>
<td>0.021</td>
<td>0.036</td>
<td>0.021</td>
<td>0.135</td>
<td>0.070</td>
<td>0.040</td>
<td>0.023</td>
</tr>
<tr>
<td>γ</td>
<td>0.479</td>
<td>0.130</td>
<td>0.259</td>
<td>0.073</td>
<td>0.023</td>
<td>0.525</td>
<td>0.132</td>
<td>0.076</td>
<td>0.039</td>
<td>0.020</td>
<td>0.115</td>
<td>0.019</td>
<td>0.119</td>
<td>0.039</td>
<td>0.023</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>0.014</td>
<td>0.112</td>
<td>0.037</td>
<td>0.022</td>
<td>0.014</td>
<td>0.129</td>
<td>0.039</td>
<td>0.022</td>
<td>0.023</td>
<td>0.012</td>
<td>0.115</td>
<td>0.019</td>
<td>0.119</td>
<td>0.039</td>
<td>0.023</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>0.098</td>
<td>0.080</td>
<td>0.030</td>
<td>0.018</td>
<td>0.009</td>
<td>0.114</td>
<td>0.054</td>
<td>0.089</td>
<td>0.019</td>
<td>0.017</td>
<td>0.098</td>
<td>0.019</td>
<td>0.060</td>
<td>0.020</td>
<td>0.015</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>0.033</td>
<td>0.114</td>
<td>0.026</td>
<td>0.022</td>
<td>0.012</td>
<td>0.624</td>
<td>0.103</td>
<td>0.181</td>
<td>0.058</td>
<td>0.025</td>
<td>0.009</td>
<td>0.624</td>
<td>0.105</td>
<td>0.193</td>
<td>0.045</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Significant differences with respect to controls or relatives are shown in the corresponding column. Values in parentheses denote SD. *p < 0.05, **p < 0.01 in comparison with controls; *p < 0.05, **p < 0.001 in comparison with relatives (Bonferroni correction).
0.292; β coefficient = –0.541; t = –2.69; p = 0.017). In this group, gamma power at F3 was directly related to performance in the Tower of London test (R² = 0.237; β coefficient = 0.487; t = –2.22; p = 0.04).

Healthy controls did not show any significant association between gamma power and cognitive performance in any of the BACS domains.

**Discussion**

In our patients, we found higher gamma power in bilateral parietal, frontocentral and left temporal electrodes: inversely related (p = 0.06) to performance in the Tower of London test at the F4 site in the patients, and significantly and inversely related to verbal and working memory scores at T5 in the relatives. In the latter group, gamma power at F3 was directly related to performance in the Tower of London test.

Our patients only showed marginally lower P300 amplitudes. This may be related to the average reference used here, which can possibly lower the average amplitude of the P300 potential and, consequently, the statistical significance of the differences. Moreover, other groups have reported nonreduced P3b amplitudes in first-episode patients with schizophrenia in studies with relatively modest sample sizes such as ours [31, 32]. With a larger sample size, our findings (i.e. marginal amplitude reduction in patients) could become statistically significant, although these results may also suggest that including a subset of cases with normal P300 amplitudes could contribute to reducing the significance of the P3b differences found here.

Gamma power elevation may reflect a hyperactive cortical substrate in patients with schizophrenia and their relatives, since gamma oscillations possibly play a role in neural assembly formation underlying perceptive and cognitive tasks [4–7]. Thus, more gamma power may be secondary to broader neural assembly recruitment during the same task, these assemblies being involved or not in task performance. It may also be coherent with an excess of basal activity that does not decrease with cognitive demands, in line with recent findings on the default mode network, whose activity has been reported not to decrease in schizophrenia as expected in the general population when the subject is engaged in a task [33–35]. Given the mentioned coupling between gamma oscillations and the fMRI signal [18, 19], higher power in the gamma band in our patients may be reflecting the complex cortical dysfunctional basal hyperactivation proposed in schizophrenia; perhaps, in consequence, they also exhibit a lower capacity for adequate task-related activation [36]. In this context, the present results are consistent with fMRI results showing increased activation in schizophrenia during a similar cognitive performance outcome [37]. Our patients showed a direct association between P3b amplitude and gamma power at Pz, possibly indicating that greater activation is required for obtaining similar results in this group. This would also be coherent with the inverse association between frontal gamma power and cognitive performance in the Tower of London test found in the patients, since the basal hyperactivation could hamper task performance.

Our patients showed significant power elevations in beta-1 and -2 waves, with a similar topographical distri-
bution for gamma waves, and similar results for relative power analysis. This is coherent with previous results displaying elevated power in the faster bands in schizophrenia [15]. Fast oscillations may contribute to forming local neuronal assemblies [38], which, according to our results, may suggest a relative deficit in the integration of activities from distant regions in schizophrenia. Relative power reductions in the slower bands were also noted, in accordance with previous data [39].

The relatives showed power values midway between those of the patients and healthy controls. These values were not significantly different when compared with the patients, although we cannot discard that higher power values in the relatives were an effect of older age [40]. In the relatives, an association was found between higher gamma power at the T5 site and worse performance in the verbal and working memory domains, much like in the group of patients. This may indicate that the cortical hyperactivity pattern which hampers cognitive performance can also be found, to a moderate degree, in first-degree relatives of patients with schizophrenia. However, the direction of the association between frontal gamma power and problem-solving performance was direct in the relatives, perhaps indicating that the required regional effort to achieve performance was higher in the relatives when compared with controls. In the patients, the amount of overactivation may be even higher, hindering them from achieving better performance.

Global gamma band power elevation is coherent with some phenomenological views of schizophrenia. Normal participants with higher ‘transliminality’ (the threshold at which unconscious processes enter into consciousness) exhibited higher gamma power on the midline when compared with participants with lower transliminality [41]. It has been proposed that a central disturbance in schizophrenia is that of ‘ipseity’ [42], i.e. functions that should go unnoticed appear in the conscious field and consequently disturb the sense of self. This seems coherent with the view that a hyperexcitable cortex, as reflected in an elevated gamma power, may subvert some psychiatric basic experiences.

There are other limitations to our study, apart from its sample size. First, the age of the relatives was higher than that of the other groups due to inclusion of siblings and parents. Second, our patients had received an acute treatment with haloperidol by the time of their inclusion, even if this is not a likely explanation for the findings here reported, since we did not detect higher gamma power in controls after haloperidol administration and a wash-out period similar to that in acute patients. If any, the effect of haloperidol was to lessen the magnitude of gamma power for a short period, and thus is unlikely to justify its elevation in the patients.

Another limitation is that since we used a measure of total power, we cannot decide whether the gamma power elevation observed in our patients is due to evoked (in-phase) or induced (out-of-phase) oscillations or rather associated with a basal hyperactive state. Therefore, our results are difficult to compare with those obtained in studies assessing evoked, induced and phase synchronicity of gamma responses in schizophrenia [43–45]. In any case, our data seem coherent with a globally elevated cortical gamma activity inversely related to cognitive performance in patients with schizophrenia and their relatives that could be associated with a reduced evoked response as described in other studies [8], which could be investigated using adequate methods.

Acknowledgments

The present study was supported by grants from the Fondo de Investigaciones Sanitarias (Instituto de Salud Carlos III; FIS PI080017; FIS PI1102303) and Gerencia Regional de Salud de Castilla y León (GRS 249/A/08, GRS 613/A/11) to V.M.; a predoctoral research grant from the Consejería de Educación – Junta de Castilla y León and the European Social Fund to A.D.; and a predoctoral scholarship from the University of Salamanca and Santander Bank to V.S.

Disclosure Statement

The authors have no conflicts of interest to declare.

References


Barr MS, Farzan F, Tran LC, Chen R, Fitzgerald PB, Daskalakis ZJ: Evidence for excessive frontal evoked gamma oscillatory activity in schizophrenia during working memory. Schizophr Res 2010;121:146–152.


Gonzalez-Burgos G, Lewis DA: NMDA receptor hypofunction, parvalbumin-positive neurones, and cortical gamma oscillations in schizophrenia. Schizophr Bull 2012;38:950–957.


Diez/Suazo/Casado/Martin-Loeches/Molina

DOI: 10.1159/000356970

128

Neuropsychobiology 2014;69:120–128

116


Gonzalez-Burgos G, Lewis DA: NMDA receptor hypofunction, parvalbumin-positive neurones, and cortical gamma oscillations in schizophrenia. Schizophr Bull 2012;38:950–957.


