

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

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Key Words

Gamma band · Schizophrenia · Cognition · Hyperactivity · Relatives, first-degree

association with schizophrenia and its inverse association with cognitive performance in patients and their first-degree relatives.

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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

Introduction

A role for gamma oscillations in cognitive functions has previously been proposed at least regarding multi-sensory integration [1], selective attention [2] and working memory [3], relating to the gamma band's capacity to subtend transient functional assembly formation [4–7]. On this basis it seems relevant to study gamma power with respect to cognitive dysfunction in schizophrenia [8]. In schizophrenia, reduced spectral power and synchronicity of gamma band response to tasks has been reported in comparison with controls [8], albeit with some discrepancies [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) [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).

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 k Ω . 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 μ V 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 χ^2 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).

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

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

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; ^a $p < 0.05$, ^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.

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 2. Gamma power values in the study groups

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

Raw values are shown as μV^2 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; ^a $p < 0.10$ in comparison with relatives (Bonferroni correction).

Table 3. Total power values in the study groups for the remaining frequency bands: δ (0.5–4 Hz), θ (4.5–8 Hz), α (8.5–12.5 Hz), β_1 (13–18 Hz) and β_2 (18.5–30 Hz), using covariates age and sex

	Patients					Relatives					Controls				
	δ	θ	α	β_1	β_2	δ	θ	α	β_1	β_2	δ	θ	α	β_1	β_2
F3	0.524 (0.208)	0.143 (0.088)	0.195 (0.134)	0.059 (0.034)	0.041 (0.025)	0.576 (0.243)	0.143 (0.095)	0.168 (0.162)	0.050 (0.027)	0.030 (0.017)	0.573 (0.242)	0.139 (0.064)	0.144 (0.123)	0.044 (0.026)	0.032 (0.032)
F4	0.571 (0.230)	0.148 (0.081)	0.193 (0.133)	0.062 (0.033)*	0.041 (0.026)	0.623 (0.253)	0.137 (0.076)*	0.168 (0.156)	0.053 (0.025)	0.036 (0.021)	0.563 (0.272)	0.128 (0.060)	0.155 (0.160)	0.041 (0.022)	0.030 (0.027)
P3	0.659 (0.284)	0.133 (0.065)	0.400 (0.347)	0.108 (0.087)**	0.041 (0.021)**, a	0.574 (0.243)	0.121 (0.074)	0.287 (0.349)	0.076 (0.044)	0.029 (0.015)	0.597 (0.243)	0.113 (0.064)	0.251 (0.328)	0.052 (0.028)	0.025 (0.013)
P4	0.629 (0.292)	0.138 (0.069)	0.446 (0.319)	0.118 (0.140)*	0.038 (0.016)*	0.487 (0.186)	0.110 (0.070)	0.277 (0.293)	0.077 (0.060)	0.030 (0.017)	0.537 (0.238)	0.109 (0.054)	0.271 (0.242)	0.055 (0.029)	0.027 (0.014)
T5	0.924 (0.539)	0.240 (0.157)	0.406 (0.350)	0.132 (0.066)*	0.077 (0.039)***	0.901 (0.435)	0.276 (0.245)	0.447 (0.654)	0.119 (0.051)	0.056 (0.024)	0.825 (0.385)	0.213 (0.152)	0.399 (0.815)	0.094 (0.053)	0.046 (0.024)
T6	0.911 (0.584)	0.261 (0.189)	0.597 (0.559)	0.136 (0.094)	0.058 (0.022)	0.857 (0.590)	0.239 (0.190)	0.412 (0.421)	0.116 (0.061)	0.055 (0.029)	0.874 (0.443)	0.236 (0.141)	0.482 (0.558)	0.122 (0.094)	0.071 (0.085)
Fz	0.614 (0.233)	0.182 (0.101)	0.217 (0.151)	0.058 (0.038)*	0.035 (0.018)**	0.647 (0.323)*	0.176 (0.122)	0.171 (0.165)	0.046 (0.024)	0.025 (0.014)	0.571 (0.279)	0.173 (0.089)	0.162 (0.157)	0.038 (0.022)	0.022 (0.013)
Pz	0.658 (0.330)	0.121 (0.055)	0.408 (0.361)	0.087 (0.067)**	0.030 (0.016)	0.640 (0.328)	0.108 (0.064)	0.259 (0.337)	0.061 (0.043)	0.022 (0.011)	0.656 (0.333)	0.118 (0.083)	0.264 (0.364)	0.046 (0.026)	0.022 (0.023)

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; ^a $p < 0.05$ 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.

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 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), β_1 (13–18 Hz), β_2 (18.5–30 Hz) and γ (35–45 Hz), using covariates age and sex

	Patients						Controls					
	δ	θ	α	β_1	β_2	γ	δ	θ	α	β_1	β_2	γ
F3	0.544 (0.083)*	0.144 (0.063)	0.184 (0.078)	0.062 (0.033)	0.045 (0.024) ^a	0.021 (0.013)	0.608 (0.109)	0.141 (0.040)	0.148 (0.096)	0.052 (0.023)	0.035 (0.010)	0.016 (0.007)
F4	0.558 (0.078)	0.145 (0.059)	0.173 (0.067)	0.063 (0.030)*	0.042 (0.026)	0.018 (0.008)	0.614 (0.125)	0.133 (0.051)	0.145 (0.095)	0.053 (0.022)	0.038 (0.013)	0.017 (0.007)
P3	0.510 (0.089)**	0.104 (0.036)	0.256 (0.108)	0.077 (0.035)*	0.034 (0.019)	0.019 (0.013)* ^a	0.572 (0.162)	0.110 (0.032)	0.201 (0.155)	0.073 (0.034)	0.032 (0.021)	0.013 (0.007)
P4	0.478 (0.088)	0.106 (0.036)	0.288 (0.111)	0.079 (0.049)	0.033 (0.020)	0.017 (0.007) ^a	0.543 (0.164)	0.108 (0.030)	0.224 (0.155)	0.077 (0.043)	0.035 (0.022)	0.012 (0.004)
T5	0.511 (0.082)	0.130 (0.038) ^a	0.201 (0.079)	0.078 (0.029)	0.048 (0.024) ^a	0.032 (0.021)* ^b	0.531 (0.123)	0.144 (0.041)	0.196 (0.119)	0.073 (0.028)	0.036 (0.018)	0.021 (0.011)
T6	0.479 (0.104)	0.130 (0.043)	0.259 (0.112)	0.073 (0.037)	0.037 (0.022)	0.023 (0.014)	0.525 (0.129)	0.132 (0.039)	0.208 (0.124)	0.076 (0.039)	0.039 (0.023)	0.020 (0.012)
Fz	0.558 (0.098)	0.161 (0.063)	0.180 (0.080)	0.054 (0.030)	0.033 (0.018) ^a	0.014 (0.005)	0.621 (0.114)	0.159 (0.054)	0.139 (0.089)	0.044 (0.019)	0.027 (0.017)	0.011 (0.007)
Pz	0.533 (0.100)*	0.102 (0.033)	0.261 (0.114)	0.066 (0.026)**	0.026 (0.015)	0.012 (0.002)** ^b	0.624 (0.152)	0.103 (0.028)	0.181 (0.139)	0.058 (0.028)	0.025 (0.017)	0.009 (0.004)

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; ^a $p < 0.05$, ^b $p < 0.001$ in comparison with relatives (Bonferroni correction).

Table 5. Power (μV^2) and P3b amplitude (μV) values in healthy controls ($n = 5$) before and 24 h after receiving 2 mg of haloperidol, following the procedure undergone by the patients (Wilcoxon test)

	Mean \pm SD	Z
Gamma power F3 – basal	0.015 \pm 0.014	-0.405
Gamma power F3 – haloperidol	0.012 \pm 0.008	(0.686)
Gamma power F4 – basal	0.014 \pm 0.013	-0.135
Gamma power F4 – haloperidol	0.013 \pm 0.019	(0.893)
Gamma power P3 – basal	0.014 \pm 0.015	-1.219
Gamma power P3 – haloperidol	0.009 \pm 0.005	(0.223)
Gamma power P4 – basal	0.023 \pm 0.033	-0.674
Gamma power P4 – haloperidol	0.015 \pm 0.015	(0.500)
Gamma power T5 – basal	0.028 \pm 0.022	-2.023
Gamma power T5 – haloperidol	0.020 \pm 0.014	(0.043)
Gamma power T6 – basal	0.044 \pm 0.061	-0.674
Gamma power T6 – haloperidol	0.037 \pm 0.046	(0.500)
Gamma power Fz – basal	0.015 \pm 0.016	-0.135
Gamma power Fz – haloperidol	0.012 \pm 0.009	(0.893)
Gamma power Pz – basal	0.019 \pm 0.028	-1.095
Gamma power Pz – haloperidol	0.016 \pm 0.020	(0.273)
p3b amplitude Pz – basal	2.895 \pm 1.995	-0.674
p3b amplitude Pz – haloperidol	3.009 \pm 1.565	(0.500)

Values in parentheses are p values.

Gamma Power and P300 Parameters

In controls, gamma power at P3 was directly related to P3b amplitude ($R^2 = 0.2796$; β coefficient = 0.528; $t = 3.11$; $p = 0.005$). In this group, gamma power at F3 was inversely related to reaction time ($R^2 = 0.240$; β coefficient = -0.490; $t = -2.31$; $p = 0.033$).

In the patients there was a similar direct relation between gamma power at Pz and P3b amplitude ($R^2 = 0.150$; β coefficient = 0.388; $t = 2.18$; $p = 0.038$), but we did not detect any association between gamma power and reaction time. In the relatives, we did not find any relation between gamma power and P300 parameters.

Gamma Power and Cognition

In the patients, gamma power at F4 was inversely related to performance in the Tower of London test, at a marginally significant level ($R^2 = 0.136$; β coefficient = -0.369; $t = -1.947$; $p = 0.063$; fig. 1).

In relatives, verbal memory performance was inversely related to gamma power for T5 ($R^2 = 0.227$; β coefficient = -0.477; $t = -2.23$; $p = 0.039$; fig. 1). Gamma power at T5 also was related inversely to working memory ($R^2 =$

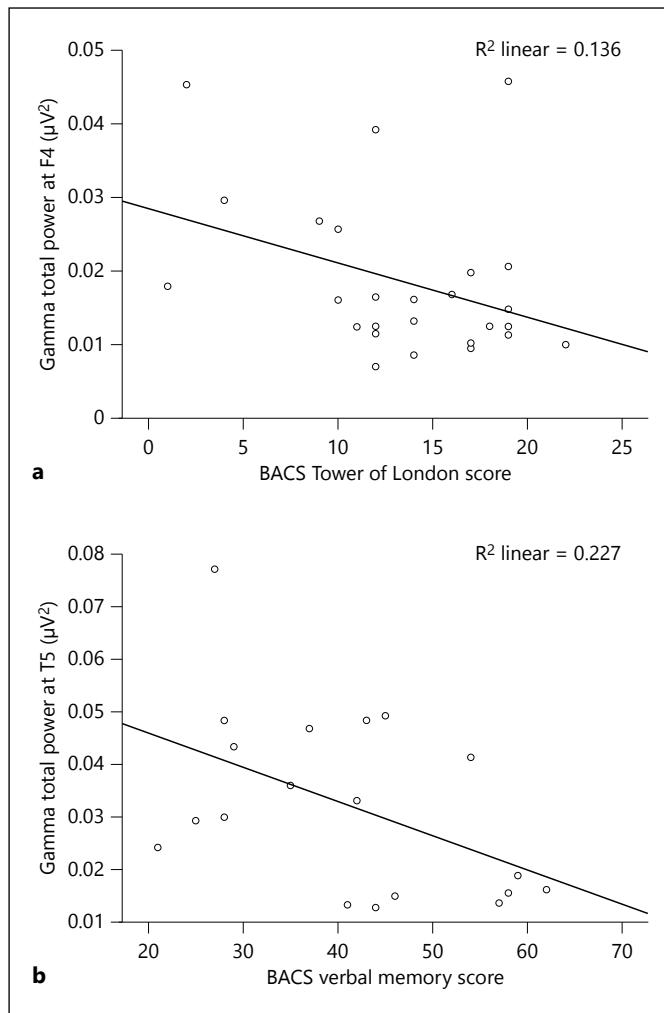


Fig. 1. a Association between patients' gamma power at F4 site and problem-solving performance (Tower of London test). **b** Association between relatives' verbal memory score and gamma power at the T5 site.

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 ($R^2 = 0.237$; 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 subtend some psychotic 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.

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Disclosure Statement

The authors have no conflicts of interest to declare.

References

- 1 Lakatos P, Chen CM, O'Connell MN, Mills A, Schroeder CE: Neuronal oscillations and multisensory interaction in primary auditory cortex. *Neuron* 2007;53:279–292.
- 2 Doesburg SM, Roggeveen AB, Kitajo K, Ward LM: Large-scale gamma-band phase synchronization and selective attention. *Cereb Cortex* 2008;18:386–396.
- 3 Jensen O, Kaiser J, Lachaux JP: Human gamma-frequency oscillations associated with attention and memory. *Trends Neurosci* 2007; 30:317–324.
- 4 Tallon-Baudry C, Bertrand O, Peronnet F, Pernier J: Induced γ -band activity during the delay of a visual short-term memory task in humans. *J Neurosci* 1998;18:4244–4254.
- 5 Singer W: Synchronization of cortical activity and its putative role in information processing and learning. *Annu Rev Physiol* 1993;55: 349–374.

- 6 Rutishauser U, Ross IB, Mamelak AN, Schuman EM: Human memory strength is predicted by theta-frequency phase-locking of single neurons. *Nature* 2010;464:903–907.
- 7 Uhlhaas PJ, Pipa G, Lima B, Melloni L, Neuenschwander S, Nikolic D, Singer W: Neural synchrony in cortical networks: history, concept and current status. *Front Integr Neurosci* 2009;3:17.
- 8 Uhlhaas PJ, Singer W: Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci* 2010;11:100–113.
- 9 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.
- 10 Coyle JT: Glutamate and schizophrenia: beyond the dopamine hypothesis. *Cell Mol Neurobiol* 2006;26:365–384.
- 11 Herrmann CS, Frund I, Lenz D: Human gamma-band activity: a review on cognitive and behavioral correlates and network models. *Neurosci Biobehav Rev* 2010;34:981–992.
- 12 Minzenberg MJ, Firl AJ, Yoon JH, Gomes GC, Reinking C, Carter CS: Gamma oscillatory power is impaired during cognitive control independent of medication status in first-episode schizophrenia. *Neuropsychopharmacology* 2010;35:2590–2599.
- 13 Spencer KM, Nestor PG, Perlmuter R, Niznikiewicz MA, Klump MC, Frumin M, Shenton ME, McCarley RW: Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc Natl Acad Sci USA* 2004;101:17288–17293.
- 14 Winterer G, Coppola R, Goldberg TE, Egan MF, Jones DW, Sanchez CE, Weinberger DR: Prefrontal broadband noise, working memory, and genetic risk for schizophrenia. *Am J Psychiatry* 2004;161:490–500.
- 15 Gattaz WF, Mayer S, Ziegler P, Platz M, Gasser T: Hypofrontality on topographic EEG in schizophrenia: correlations with neuropsychological and psychopathological parameters. *Eur Arch Psychiatry Clin Neurosci* 1992;241:328–332.
- 16 Herrmann CS, Demiralp T: Human EEG gamma oscillations in neuropsychiatric disorders. *Clin Neurophysiol* 2005;116:2719–2733.
- 17 Jones NC, Reddy M, Anderson P, Salzberg MR, O'Brien TJ, Pinault D: Acute administration of typical and atypical antipsychotics reduces EEG gamma power, but only the pre-clinical compound LY379268 reduces the ketamine-induced rise in gamma power. *Int J Neuropsychopharmacol* 2012;15:657–668.
- 18 Scheeringa R, Fries P, Petersson KM, Oostenveld R, Grothe I, Norris DG, Hagoort P, Bastiaansen MC: Neuronal dynamics underlying high- and low-frequency EEG oscillations contribute independently to the human BOLD signal. *Neuron* 2011;69:572–583.
- 19 Niessing J, Ebisch B, Schmidt KE, Niessing M, Singer W, Galuske RA: Hemodynamic signals correlate tightly with synchronized gamma oscillations. *Science* 2005;309:948–951.
- 20 Manoach DS: Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophr Res* 2003;60:285–298.
- 21 Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, Venturi P, Jones LA, Lewis SW, Sham PC, Gottesman II, Farmer AE, McGuffin P, Reveley AM, Murray RM: Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. *Arch Gen Psychiatry* 1999;56:162–168.
- 22 Fisahn A, Neddens J, Yan L, Buonanno A: Neuregulin-1 modulates hippocampal gamma oscillations: implications for schizophrenia. *Cereb Cortex* 2009;19:612–618.
- 23 Steinecke A, Gampe C, Valkova C, Kaether C, Bolz J: Disrupted-in-schizophrenia 1 (DISC1) is necessary for the correct migration of cortical interneurons. *J Neurosci* 2012;32:738–745.
- 24 Gonzalez-Burgos G, Lewis DA: NMDA receptor hypofunction, parvalbumin-positive neurons, and cortical gamma oscillations in schizophrenia. *Schizophr Bull* 2012;38:950–957.
- 25 Lewis DA, Sweet RA: Schizophrenia from a neural circuitry perspective: advancing toward rational pharmacological therapies. *J Clin Invest* 2009;119:706–716.
- 26 Suazo V, Díez A, Martín C, Ballesteros A, Casado P, Martín-Loeches M, Molina V: Elevated noise power in gamma band related to negative symptoms and memory deficit in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2012;38:270–275.
- 27 Kay SR, Fiszbein A, Opler LA: The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261–276.
- 28 Segarra N, Bernardo M, Gutiérrez F, Justicia A, Fernández-Egea E, Allas M, Salfont G, Contreras F, Gascón J, Soler-Insa PA, Menchon JM, Junque C, Keefe RS: Spanish validation of the Brief Assessment in Cognition in Schizophrenia (BACS) in patients with schizophrenia and healthy controls. *Eur Psychiatry* 2011;26:69–79.
- 29 Wechsler D: Wechsler Adult Intelligence Scale, ed 3. San Antonio, Psychological Corporation, 1997.
- 30 Bledowski C, Prvulovic D, Hoehstetter K, Scherg M, Wibrall M, Goebel R, Linden DE: Localizing P300 generators in visual target and distractor processing: a combined event-related potential and functional magnetic resonance imaging study. *J Neurosci* 2004;24:9353–9360.
- 31 Almeida PR, Vieira JB, Silveira C, Ferreira-Santos F, Chaves PL, Barbosa F, Marques-Teixeira J: Exploring the dynamics of P300 amplitude in patients with schizophrenia. *Int J Psychophysiol* 2011;81:159–168.
- 32 McCarley RW, Salisbury DF, Hirayasu Y, Yurgelun-Todd DA, Tohen M, Zarate C, Kikinis R, Jolesz FA, Shenton ME: Association between smaller left posterior superior temporal gyrus volume on magnetic resonance imaging and smaller left temporal P300 amplitude in first-episode schizophrenia. *Arch Gen Psychiatry* 2002;59:321–331.
- 33 Ongür D, Lundy M, Greenhouse I, Shinn AK, Menon V, Cohen BM, Renshaw PF: Default mode network abnormalities in bipolar disorder and schizophrenia. *Psychiatry Res* 2010;183:59–68.
- 34 Pomarol-Clotet E, Salvador R, Sarró S, Gomar J, Vila F, Martínez A, Guerrero A, Ortiz-Gil J, Sans-Sansa B, Capdevila A, Cebamano JM, McKenna PJ: Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? *Psychol Med* 2008;38:1185–1193.
- 35 Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW, Shenton ME, Green AI, Nieto-Castanon A, LaViolette P, Wojcik J, Gabrieli JD, Seidman LJ: Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc Natl Acad Sci USA* 2009;106:1279–1284.
- 36 Manoach DS: Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophr Res* 2003;60:285–298.
- 37 Manoach DS, Gollub RL, Benson ES, Searl MM, Goff DC, Halpern E, Saper CB, Rauch SL: Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. *Biol Psychiatry* 2000;48:99–109.
- 38 Womelsdorf T, Fries P: Neuronal coherence during selective attentional processing and sensory-motor integration. *J Physiol Paris* 2006;100:182–193.
- 39 Doege K, Bates AT, White TP, Das D, Boks MP, Liddle PF: Reduced event-related low frequency EEG activity in schizophrenia during an auditory oddball task. *Psychophysiology* 2009;46:566–577.
- 40 Fernández A, Zuluaga P, Abásolo D, Gómez C, Serra A, Méndez MA, Hornero R: Brain oscillatory complexity across the life span. *Clin Neurophysiol* 2012;123:2154–2162.
- 41 Fleck JL, Green DL, Stevenson JL, Payne L, Bowden EM, Jung-Beeman M, Kounios J: The transliminal brain at rest: baseline EEG, unusual experiences, and access to unconscious mental activity. *Cortex* 2008;44:1353–1363.
- 42 Saas LA, Parnas J: Explaining schizophrenia: the relevance of phenomenology; in Chung M, Fulford B, Graham G (eds): *Reconceiving Schizophrenia*. New York, Oxford UP, 2007, pp 63–92.
- 43 Basar-Eroglu C, Brand A, Hildebrandt H, Karolina Kedzior K, Mathes B, Schmiedt C: Working memory related gamma oscillations in schizophrenia patients. *Int J Psychophysiol* 2007;64:39–45.
- 44 Lee KH, Williams LM, Haig A, Gordon E: 'Gamma (40 Hz) phase synchronicity' and symptom dimensions in schizophrenia. *Cogn Neuropsychiatry* 2003;8:57–71.
- 45 Symond MP, Harris AW, Gordon E, Williams LM: 'Gamma synchrony' in first-episode schizophrenia: a disorder of temporal connectivity? *Am J Psychiatry* 2005;162:459–465.