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Frontal gamma noise power and cognitive domains in schizophrenia

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ABSTRACT

The cognitive deficit profile is different among individuals with schizophrenia. We quantified the amount of electroencephalographic activity unlocked to stimuli onset (noise power) over frontal regions regarding deficit in cognitive domains. Forty-six patients with schizophrenia and 27 healthy controls underwent clinical, cognitive and electrophysiological assessments. Noise power studies may be considered complementary but not equivalent to induced power studies. We compared gamma and theta noise power magnitude during a P300 paradigm between subsets of patients divided according to cognitive deficit in key domains and controls. Patients displayed higher gamma noise power activity at Fz site and significantly lower performance in all cognitive domains when compared to controls. The subset of patients with cognitive deficit for working memory and problem solving/executive functions domains displayed significantly higher frontal–lateral noise power values in comparison to the subset of patients without cognitive deficit and controls. Patients with significant cognitive deficits in domains with greater frontal contribution are also characterized by an abnormally higher gamma band noise power over the frontal region. Our data may endorse various biological subsets within schizophrenia, characterized by the presence or absence of a significant cognitive deficit in frontal domains.

1. Introduction

The schizophrenia phenotype varies in terms of biological underpinnings (Honea et al., 2005) and cognitive profile (Dickinson et al., 2007), which lead researchers to propose distinct pathological pathways within the disorder (Tandon et al., 2009).

One replicated biological finding in schizophrenia is a hyperactive pattern in regions not involved in the task being performed while areas expected to be functional appear hypoactive (Manoach, 2003; Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009). Such a pattern can be a possible substrate for the cognitive deficit that many patients exhibit and seems coherent with the extant data that suggests a lower synaptic inhibitory activity in schizophrenia (Lewis et al., 2005; Uhlhaas et al., 2010). Interestingly, recent data support the existence of a subset of patients with schizophrenia with clear frontal GABA neuron-related deficits (Volk et al., 2012).

Since GABA neurotransmission seems relevant in the generation (Whittington et al., 1995; Bartos et al., 2007) and modulation (Brown et al., 2007; Teale et al., 2008) of high-frequency oscillations in the brain, a deficit in normal inhibition could lead to an impaired selection of neural assembly related to task that may hamper performance.

The relevance of GABAergic system for these oscillations cannot be isolated from its interaction with other neurotransmission systems. First, parvalbumin-positive interneurons possess NR2A and NR2B type NMDA receptors (Kinney et al., 2006), making them susceptible to changes in glutamatergic conduction that may in turn contribute to an inhibitory cortical dysfunction, in particular in a hypo-NMDA state (Cull-Candy et al., 2001; Loftis and Janowsky, 2003). The administration of NMDA antagonists to animal models has been demonstrated to lead to gamma activity decrease (Cunningham et al., 2006; Zhang et al., 2008), albeit with some contradictory data (Pinault, 2008; Roopun et al., 2008) probably reflecting the complexity of the neurotransmission processes involved. Moreover, cholinergic (Rodriguez et al.,

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2004; Wespatat et al., 2004) and dopaminergic (Ito and Schuman, 2007; Andersson et al., 2012) activities are also involved in the modulation of gamma oscillations and response synchronization.

An approach to assess in vivo that pattern of cortical activity plausibly associated to inhibition deficits is therefore to quantify the amount of electroencephalographic (EEG) activity unrelated to a given task's performance. In this respect, the study of theta and gamma oscillations seems accurate considering these bands are involved in local neural circuits coordination underlying higher cerebral functions, probably in relation to their capacity to subtend transient functional assembly formation (Singer, 1993). These frequency bands may contribute to coherent percepts construction by the brain and to the strengthening and weakening of synaptic links (Buzsáki, 2006b) and, in the case of gamma oscillations, to neural activity integration within and between regions in a range of cognitive functions (Singer, 1999). Higher baseline auditory steady-state response in the 40 Hz (i.e., gamma) band has been reported in schizophrenia (Spencer, 2011).

Among the possibilities to assess collective neural activity organization stands quantifying the amount of bioelectrical activity not related to the task being performed by employing a "noise power" measurement (Möcks et al., 1988). Noise power is quantified as the averaged electrical power in each band of the EEG resulting from the difference between the power of the averaged signal, which is related to the task being performed, from the corresponding power of the averaged total signal (which is comprised of the background EEG activity, unrelated to task processing, and the task-related signal).

Higher noise power in patients with schizophrenia in relation to healthy controls may be expected as a correlate of an excessive extension of cortical activation at the expense of adequate selection of neural populations and cognitive performance. In fact, an increase in broadband noise power has been reported in schizophrenia (Winterer et al., 2004). During a preparatory control task, gamma power was lessened in frontal electrodes in the high-control vs. low-control conditions in patients with schizophrenia while it was higher in healthy controls (Minzenberg et al., 2010), suggesting a hyperactive basal state at this level in the former. Recently, we reported a gamma noise power elevation in minimally treated patients with schizophrenia over frontal, central and parietal regions (Suazo et al., 2012). We also found similar results in a population of both chronic and minimally treated patients with schizophrenia when studying electrode clusters through principal component analysis, resulting in an elevated gamma noise power over a factor coherent with the default mode network (DMN) topography, and a significant inverse association between the same measure over a fronto-lateral factor and the working memory and problem solving outcome (Diez et al., 2013).

It would be of interest to investigate if such associations between frontal noise power and cognition are specific to a certain domain or whether this neurophysiological measure relates to a more widespread cognitive deficit. In the first case, the association between a plausible biological deviation and a clinically relevant deficit, also plausibly arising from the same region, might be a contributing step towards identifying a specific subtype within the schizophrenia syndrome. This hypothetical subtype might be contributed by significant inhibitory transmission alterations, since GABA function is essential for the brain's oscillatory activity (Buzsáki, 2006a) and may be altered in a proportion of schizophrenia cases (Volk et al., 2012).

In the present study, considering that the relevance frontal function alterations may have in schizophrenia we continue our earlier work, which associated frontal-like noise power elevation with worst cognitive outcome (Suazo et al., 2012; Diez et al., 2013). Using factor analysis we identified a distinct frontal factor, whose noise power values were associated to cognitive performance in patients (Diez et al., 2013). Therefore we presently address the specific hypothesis that patients with a clinically significant performance deficit during tasks with greater frontal involvement would be identified by a less efficient cortical function over frontal regions (i.e., abnormally high noise power values as compared to both non-deficit cases and healthy controls). This could be relevant as a step towards disentangling the phenotypic and biological variation within the schizophrenia syndrome. However, the mere demonstration of a noise power increase in patients with as compared to patients without deficit, in the absence of a significant elevation as compared to healthy controls, would not support the possibility of a distinct biological substrate for that kind of deficit.

2. Materials and methods

2.1. Participants

We included 46 patients with schizophrenia (DSM-IV-TR) and 27 controls; including 22 stable patients, treated in the long-term, and 24 untreated cases who received a minimal treatment prior to the EEG examination (minimally treated patients), of the latter 14 first episodes.

During the preceding year the stable patients had been treated with atypical antipsychotics (risperidone 11 participants (2–6 mg/d)), olanzapine six participants (5–20 mg/d), quetiapine two participants (300–600 mg/d) and clozapine five participants (100–350 mg/d). Two cases received two different antipsychotics in their treatment. Doses and drugs were unchanged during the 3 months preceding EEG recordings.

Prior to their inclusion minimally treated patients had not received any previous treatment (first episode patients) or they had dropped their medications for longer than 1 month. Owing to an acute psychotic state of these patients we administered a small amount of haloperidol (2–4 mg during 24 h or less, which amounted to three doses) 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, although cases suffering from agitation or severe behavioral problems were not included. Participants' level of cooperation was assessed by the number of correct responses during the P300 evocation task. We discarded significant haloperidol effects on gamma and theta noise power in five controls (Table SM1).

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

We recruited controls through newspaper advertisements and remunerated their cooperation. They were previously assessed by a semi-structured psychiatric interview to discard major psychiatric antecedents 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; any other psychiatric process or treatment and treatment with drugs known to act on the central nervous system. We discarded toxic use in all participants with the information gathered in the interview and a urinalysis.

We obtained written informed consent from all participants after providing full written information. The research board endorsed the study according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Cognitive assessment

We acquired cognitive assessment by the direct scores from the following subscales of the Spanish version of Brief Assessment in Cognition in Schizophrenia Scale (BACS) (Segarra et al., 2011): verbal memory (list learning), working memory (digit span), motor speed (token motor task), verbal fluency (categories), attention and processing speed (symbol coding) and executive function/problem solving (tower of London). We used the Spanish version of the WAIS-III (Wechsler, 1997) to assess IQ.

To test our hypothesis we divided the patients into those less than or equal to −2 s.d. from the mean value of the controls for each neuropsychological test (cognitive deficit criterion) and those who did not fulfill this requirement. By doing so, we intended to segregate groups whose cognitive handicap was more likely to hamper real life performance.

2.3. EEG methods

The EEG methods have been reported in detail elsewhere (Suazo et al., 2012; Diez et al., 2013) and are described in detail in the Supplementary materials. Essentially, EEG recordings were performed during an auditory odd-ball task in which P3a and P3b were elicited. The EEG was recorded by Brain Vision® (Brain Products GmbH; Munich, Germany) equipment from 17 tin electrodes mounted in an electrode cap (Electro-Cap International, Inc.; Eaton, OH, USA), impedance kept under 5 kΩ. The online register was referenced over Cz electrode and off-line re-referenced to electrodes average activity (Bledowski et al., 2004). The sampling rate was 250 Hz and the signal was recorded continuously. We selected noise power values at F3, F4 and Fz electrodes (revised 10/20 International System) for the analysis according to our *a priori* hypothesis. See Supplementary material for detailed information on EEG recording.

For quantitative event-related EEG analysis, the recorded signals (−50 ms to 600 ms post-stimulus, target condition) were submitted to specific band filtering and spectrum analysis by a fast Fourier transform yielding spectral values separately for theta (4.5–8 Hz) and gamma (35–45 Hz) frequency bands. The absolute magnitude (averaged total power) in each frequency band was computed expressed in μV^2.

As described in previous articles (Suazo et al., 2012; Diez et al., 2013), we calculated noise power magnitude, which is subsequently denoted as "noise power", following the recommendations of Möcks et al. (1988) and Winterer et al. (2004). This calculation was based on 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® software (Brain Products GmbH, Munich, Germany, 2006) for the time window from −50 to 600 ms for the target stimuli and after the specific band filtering (see Supplementary materials).

For every individual participant, band and electrode, we calculated the averaged noise power from the already extracted averaged total power (the sum of the signal and noise power) and SNR (the average signal power quotient divided by the average noise power) by the following formula:

$$\text{Avg noise power} = \frac{\text{avg total power}}{\text{SNR}+1}$$

This way, a quantification of the noise part of the power activity related to the event is approximated and "noise power" is equivalent with activity that is not time-locked to the stimuli (see Supplementary material for details).

2.4. Statistics

We tested for differences in gender distribution, marital and employment status between patients and controls by Chi square or *t* tests, when indicated. We compared age, educational level, cognitive performance, P3a and P3b amplitude, between patients and controls by *t* tests for independent samples. A repeated-measures ANOVA (band [two levels] and electrode [three levels] as within-subjects factors and group [minimally treated patients, chronic patients and controls] as between-subjects factor) was performed looking for global group effects on noise power. This was followed by an ANOVA with a Tamhane post-hoc correction to assess the possible differences in theta and gamma noise power between both patients' subgroups (stable and minimally treated) as well as between each of them and the healthy controls. Noise power values and P3 amplitudes were compared in healthy controls before and after a dose of haloperidol using Wilcoxon tests for related samples.

Our main hypothesis was that higher frontal noise power values would be found in patients with larger deficit in cognitive functions of greater frontal contribution. This was tested by comparing the gamma and theta noise power between patient subsets respectively fulfilling or unfulfilling the deficit criterion in each cognitive domain (score ≤ -2 s.d. compared to control's mean). We used Mann–Whitney *U* test in these comparisons because some of the patient's resulting subsets were not normally distributed. We set significance level at $p=0.0083$ applying the Bonferroni correction method (0.05/6 electrodes *x* band combinations; $p=0.02$ was considered a statistical trend accordingly) and these criteria were also applied for the rest of comparisons in the study in order to facilitate comprehension of the results.

We tested that possible noise power differences were not due to differences in gender distribution, age, academic level, symptoms or level of cooperation during the task by comparing male/female ratio, age, number of completed academic courses, PANSS scores and percentage of correct responses between the corresponding patient subsets.

When significant noise power differences were found in the comparisons between patients fulfilling and not fulfilling deficit criterion in any cognitive domain, we tested whether the same differences could be found in minimally treated patients alone (i.e., comparing minimally treated patients with and without equivalent cognitive deficit) also using Mann–Whitney *U* test. This comparison intended on verifying that noise power differences were not due to an effect of medication or chronicity.

In a second step, we planned to investigate whether larger cognitive deficits were associated to abnormally high noise power values. To do so, we compared separately the noise power of patients fulfilling the cognitive deficit criterion in those domains that resulted significantly different in the previous step with the corresponding values of controls.

We also explored whether similar power differences were present over other locations (i.e., other electrodes) by comparing noise power over each of the remaining 14 electrodes between the resulting subgroups of patients.

Finally, we followed two steps to discard a possible artifactual contribution to the gamma noise power differences between our groups. EEG power in the gamma band has been associated to ocular microsaccades (concentrated in the 100–300 ms post-stimuli period, Yuval-Greenberg and Deouell, 2011) or to a nearby (neck, forehead) muscular activity (see, Pope et al., 2009) showing that influence of electromyogram on the recorded gamma activity is maximum on the circumferential electrodes. Therefore, to discard a major ocular contribution to gamma noise power, we first assessed noise power in this band for two separate time windows (early: 100–300, and late: 350–550 ms post-stimuli onset), and then we compared patients deficit/non-deficit subsamples between each other and versus controls separately for the early and late periods using Mann–Whitney *U* tests. Second, to rule out muscular artifacts from other origins we studied noise power values at those electrode sites where these artifacts can be expected to be more intense (Fp1, Fp2, T5, T6, O1 and O2).

3. Results

There were no significant differences in gender, age or educational level distribution between patients and controls. Marital and employment status were significantly different between these groups ($\chi^2=18.24$, df=1, $p<0.001$; $\chi^2=15.24$, df=1, $p<0.001$; Table 1). The repeated measures MANOVA revealed significant effects for band (Wilk's $\lambda=0.459$, $F=81.220$, $p<0.001$), electrode (Wilk's $\lambda=0.865$, $F=5.327$, $p=0.007$), electrode × group (Wilk's $\lambda=0.870$, $F=2.442$, $p=0.05$), band × electrode (Wilk's $\lambda=0.852$, $F=5.908$, $p=0.004$) and for band × electrode × group (Wilk's $\lambda=0.840$, $F=3.100$, $p=0.018$). On the other hand, the ANOVA revealed significant between-groups differences in noise power for gamma band at F3 ($F=3.277$, df=2, $p=0.044$), F4 ($F=3.798$, df=2, $p=0.027$) and Fz ($F=22.865$, df=2, $p<0.001$) (Table 1). Post-hoc analysis revealed higher gamma noise power values for stable patients in comparison to minimally treated patients at F4 (between means difference=0.008, 95% CI 0.001–0.015, $p=0.029$). For Fz, gamma noise power was significantly higher for stable patients in comparison to minimally treated patients (between means difference=0.006, 95% CI 0.002–0.011, $p=0.006$) and controls (between means difference=0.009, 95% CI 0.004–0.013, $p<0.001$), and for minimally treated in comparison to healthy controls (between means difference=0.002, 95% CI 0.000–0.004, $p=0.016$). There were no significant differences between groups for the theta band.

Taken together, patient's cognitive performance was significantly lower in all areas (Table 1). Out of the 46 patients, cognitive deficit criteria were met in the following subsets: verbal memory (23 participants), working memory (22 participants), motor speed (8 participants), verbal fluency (20 participants), attention and processing speed (17 participants) and problem solving/executive function (15 participants).

Compared to controls, P3b amplitude (but not P3a) was significantly lower in patients ($t=2.44$, df=71, $p=0.017$; Table 1 and Fig. SM1). The percentage of correct responses in the odd-ball task was not significantly different. Reaction time for correct responses was significantly higher for patients ($t=3.746$, df=35, $p=0.001$; Table 1).

3.1. Comparisons between groups of patients with and without cognitive deficits

Patients fulfilling working memory deficit criterion displayed significantly higher noise power values in the gamma band at F3 ($U=118.0$, $z=3.07$, $p=0.002$; Fig. 1) than patients without this deficit (Table 2). This still held for the comparison between

Table 1
Demographic, clinical, neurocognitive and electrophysiological values in patients and healthy controls (including pre- and post-haloperidol). Minimally treated patients are shown separately for comparison. Differences with respect to healthy controls are shown in the columns corresponding to each subgroup. There were no significant differences in electrophysiological measures in healthy controls before and after a dose of haloperidol (Wilcoxon test).

Dimension or scale	Patients ($n=46$)	Minimally treated patients ($n=24$)	Controls ($n=27$)
Age (years)	35.39 (10.21)	32.67 (10.4)	33.04 (13.16)
Gender distribution (M:F)	30:16	14:10	17:10
Education (completed courses)	9.93 (4.10)	12.44 (2.71)	11.20 (2.68)
Marital status (% single)	91.30***	87.50**	55.55
Employment status (% employed)	21.74***	29.17**	66.67
Total IQ	81.91 (13.54)***	80.48 (14.52)***	102.78 (12.44)
PANSS positive	20.17 (4.46)	20.68 (4.09)	n/a
PANSS negative	19.23 (5.56)	17.045 (4.91)	n/a
PANSS total	76.11 (14.49)	75.77 (12.06)	n/a
BACS verbal memory	36.71 (11.38)***	34.83 (11.57)***	53.52 (8.96)
BACS working memory	16.69 (5.54)***	16.57 (5.29)***	22.26 (3.75)
BACS motor speed	51.39 (14.19)***	53.17 (17.15)*	63.85 (14.05)
BACS verbal fluency	16.74 (4.59)***	15.92 (4.47)***	25.11 (4.57)
BACS processing speed	38.44 (12.96)***	37.78 (11.54)***	57.85 (11.56)
BACS problem solving	12.93 (5.56)***	12.91 (5.55)***	17.26 (3.01)
P3b % of targets detected	72.23 (30.04)	63.42 (35.77)*	90.09 (21.95)
P3b reaction time (ms)	622.08 (99.36)***	630.46 (100.75)*	524.43 (53.73)
P3b number of valid trials	46.00 (23.62)	44.88 (21.15)	56.96 (25.59)
P300 amplitude Pz S1 (μV)	0.210 (0.735)	0.274 (0.701)	0.074 (0.635)
P300 amplitude Pz S2 (μV)	0.890 (1.092)	0.921 (1.087)	1.182 (1.179)
P300 amplitude Pz S3 (μV)	1.028 (1.834)*	1.164 (1.632)	1.818 (1.058)
Theta noise power F3 (μV^2)	0.091 (0.046)	0.088 (0.049)	0.091 (0.050)
Theta noise power F4 (μV^2)	0.093 (0.039)	0.095 (0.045)	0.079 (0.037)
Theta noise power Fz (μV^2)	0.111 (0.053)	0.120 (0.062)	0.109 (0.058)
Gamma noise power F3 (μV^2)	0.013 (0.011)	0.009 (0.007)	0.009 (0.014)
Gamma noise power F4 (μV^2)	0.013 (0.012)	0.010 (0.012)	0.009 (0.009)
Gamma noise power Fz (μV^2)	0.011 (0.006)#	0.007 (0.002)#	0.005 (0.003)

S1, frequent tone; S2, distracter tone; S3, target tone.

* $p<0.10$.
** $p<0.01$.
*** $p<0.001$; (χ^2 or t-test).
# $p<0.008$ for the noise power differences (t-test, significant after Bonferroni correction).

minimally treated patients considered alone fulfilling ($n=12$; 0.012 μV^2 (0.010)) or not ($n=11$; 0.006 μV^2 (0.002); $U=18.0$, $z=2.96$ $p=0.002$) this criterion.

Patients fulfilling problem solving/executive function deficit criterion did not display significant differences in gamma noise power at F3 ($U=143.5$, $z=1.83$, $p=0.070$; Fig. 1), F4 ($U=146.5$, $z=1.76$, $p=0.080$) or Fz ($U=189.5$, $z=0.69$, $p=0.488$) in comparison to patients without this deficit (Table 3). However, significant differences at F4 were found in the comparison between minimally treated patients fulfilling ($n=7$; 0.018 μV^2 (0.020)) or not ($n=15$; 0.007 μV^2 (0.004); $U=13.0$, $z=2.78$, $p=0.004$) this criterion. Similar trend level differences over F3 were found as well in the comparison between minimally treated patients fulfilling ($n=7$; 0.015 μV^2 (0.012)) or not ($n=15$; 0.007 μV^2 (0.002); $U=20.0$, $z=2.29$, $p=0.020$) this criterion.

Supplementary material (Figs SM2 and SM3) depict spectral power distribution in patients with and without deficit in working memory and problem solving/executive functions domains, including for each cognitive dimension the comparison between groups with and without deficit, and the comparison between deficit condition and control group.

There were no significant noise power differences for gamma or theta bands between patients fulfilling and not fulfilling cognitive deficit criterion in verbal memory, motor speed, verbal fluency, and attention and processing speed (Tables SM2–SM5).

Patients with working memory deficit were slightly but significantly older than those without this deficit and there was a significantly higher proportion of females among the former (Table 2). Age and gender were not significantly different in patients with problem solving/executive deficit as compared to those without this deficit. In order to discard the possible influence of those gender differences we employed a post-hoc analysis to compare noise power values for female vs. male for control group using t test. Then we assessed the influence of age on noise power in the controls by linear regression. No significant effects of age or gender were found on noise power at any location ($p>0.10$ in all cases).

Clinical scores were not different for patients with and without cognitive deficit in working memory and problem solving/executive function domains. There were no significant differences between patient's subgroups in the percentage of correct responses.

3.2. Comparisons with controls according to deficit severity

The subgroup of patients with working memory deficit showed significantly lower scores with respect to controls in the same cognitive domain, while the subgroups of patients without this deficit did not exhibit significant differences with respect to controls in this domain. The same relation was also obtained for problem solving/executive function domain.

Patients with working memory deficit showed significantly higher gamma noise power values at F3 ($U=113.5$, $z=3.69$, $p<0.001$; Fig. 1), F4 ($U=156.0$, $z=2.84$, $p=0.005$) and Fz ($U=85.5$, $z=4.25$, $p<0.001$), see Table 2. Patients without this deficit only showed higher noise power values for gamma at Fz ($U=163.5$, $z=2.86$, $p=0.004$; Table 2). Noise power differences were not found for the theta band. Minimally treated patients with working memory deficit ($n=12$) also showed significantly higher gamma noise power at Fz ($U=61.0$, $z=3.07$, $p=0.002$) and at a trend level over F3 ($U=83.0$, $z=2.41$, $p=0.015$). Minimally treated patients without this deficit ($n=11$) did not display significant differences in noise power.

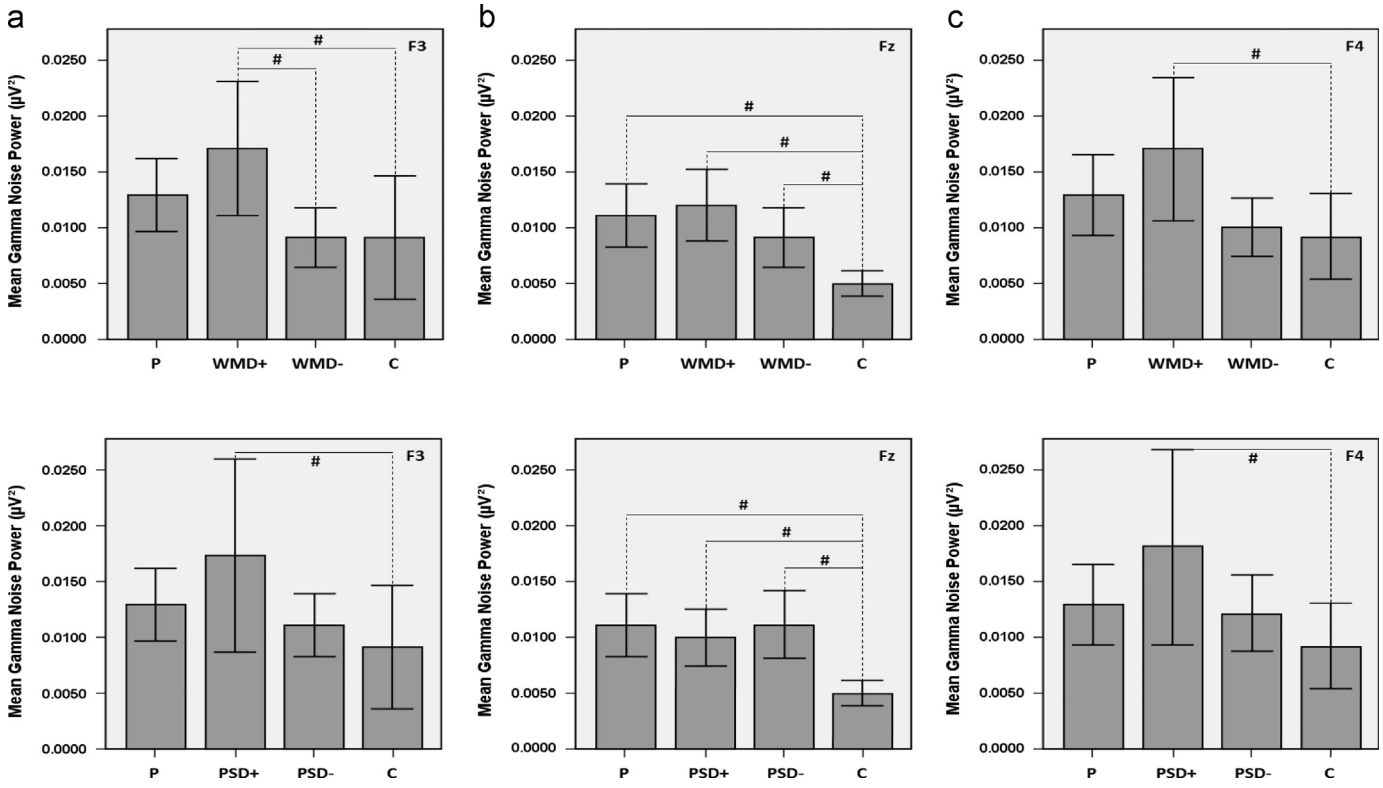

Fig. 1. Gamma band noise power at F3 (a), Fz (b) and F4 (c); comparisons between groups of patients and healthy controls including with and without working memory (above) and problem solving/executive function deficit (below) subgroups. # $p < 0.008$ for the noise power differences (t test or Mann–Whitney U test, significant after Bonferroni correction); error bars: 95% CI; P, patients; C, controls; WMD+ patients with working memory deficit; WMD-patients without working memory deficit; PSD+ patients with problem solving deficit; PSD-patients without problem solving deficit.

Table 2
Patient's comparisons, with and without significant deficit in the working memory domain. Differences between patient's subgroups are shown in the first column. Differences with respect to healthy controls are shown in the columns corresponding to each subgroup. Data from the healthy controls are shown for comparison.

Dimension or scale	Deficit ($n=22$)	Non-deficit ($n=23$)	Controls ($n=27$)
Age (years)*	38.91 (11.67)	32.57 (7.46)	33.04 (13.16)
Gender distribution (M:F)*	11:11	18:5	17:10
Total IQ**	77.57 (12.30)***	87.50 (11.46)***	102.78 (12.44)
PANSS positive	20.22 (4.22)	19.81 (4.81)	n/a
PANSS negative	20.33 (5.52)	18.25 (5.65)	n/a
PANSS total	76.72 (14.58)	75.69 (15.27)	n/a
BACS verbal memory***	31.57 (8.67)***	42.52 (10.01)***	53.52 (8.96)
BACS working memory***	12.00 (3.22)***	21.17 (2.92)	22.26 (3.75)
BACS motor speed	49.64 (15.83)**	53.26 (12.85)*	63.85 (14.05)
BACS verbal fluency	15.50 (4.99)***	18.17 (3.76)***	25.11 (4.57)
BACS processing speed**	33.10 (11.67)***	44.35 (11.12)***	57.85 (11.56)
BACS problem solving*	10.75 (6.03)***	14.96 (4.46)	17.26 (3.01)
P3b % of targets detected	60.58 (35.94)***	83.88 (17.89)	90.09 (21.95)
P3b reaction time (ms)	665.66 (114.10)***	578.50 (60.72)*	524.43 (53.73)
P3b number of valid trials	40.50 (18.40)*	51.74 (27.34)	56.96 (25.59)
P300 amplitude Pz S1 (μV)	0.161 (0.808)	0.230 (0.679)	0.074 (0.635)
P300 amplitude Pz S2 (μV)	0.842 (1.162)	0.895 (1.054)	1.182 (1.179)
P300 amplitude Pz S3 (μV)	0.779 (1.525)**	1.312 (1.424)	1.818 (1.058)
Theta noise power F3 (μV^2)	0.094 (0.040)	0.086 (0.052)	0.091 (0.050)
Theta noise power F4 (μV^2)	0.099 (0.037)	0.086 (0.040)	0.079 (0.037)
Theta noise power Fz (μV^2)	0.107 (0.042)	0.112 (0.063)	0.109 (0.058)
Gamma noise power F3 (μV^2)#	0.017 (0.014)#	0.009 (0.006)	0.009 (0.014)
Gamma noise power F4 (μV^2)	0.017 (0.015)#	0.010 (0.007)	0.009 (0.009)
Gamma noise power Fz (μV^2)	0.012 (0.007)#	0.009 (0.006)#	0.005 (0.003)

S1, frequent tone; S2, distracter tone; S3, target tone. Deficit: ≤ -2 s.d. from the mean value of the healthy controls. Non-deficit: > -2 s.d. from the mean value of the healthy controls.

* $p < 0.10$.
** $p < 0.01$.
*** $p < 0.001$; ($\chi 2$ or Mann–Whitney U tests).
\# $p < 0.008$ for the noise power differences (Mann–Whitney U test, significant after Bonferroni correction).

Table 3
Patient's comparisons, with and without significant deficit in the problem solving/executive function domain. Differences between patient's subgroups are shown in the first column. Differences with respect to healthy controls are shown in the columns corresponding to each subgroup. Data from the healthy controls are shown for comparison.

Dimension or scale	Deficit ($n=15$)	Non-deficit ($n=29$)	Controls ($n=27$)
Age (years)	39.33 (13.48)	32.52 (6.87)	33.04 (13.16)
Gender distribution (M:F)	7:8	21:8	17:10
Total IQ*	73.93 (14.55)***	86.61 (10.92)***	102.78 (12.44)
PANSS positive	20.08 (4.41)	19.95 (4.63)	n/a
PANSS negative	20.69 (4.31)	18.25 (6.41)	n/a
PANSS total	76.08 (17.72)	75.60 (13.19)	n/a
BACS verbal memory	33.00 (11.54)***	39.10 (10.82)***	53.52 (8.96)
BACS working memory***	13.29 (4.91)***	18.90 (4.63)**	22.26 (3.75)
BACS motor speed	47.40 (12.64)***	52.66 (14.97)**	63.85 (14.05)
BACS verbal fluency*	14.73 (4.08)***	17.93 (4.60)***	25.11 (4.57)
BACS processing speed**	30.67 (11.39)***	43.21 (11.26)***	57.85 (11.56)
BACS problem solving***	6.60 (3.85)***	16.21 (2.72)	17.26 (3.01)
P3b % of targets detected	57.42 (38.09)*	84.07 (15.01)	90.09 (21.95)
P3b reaction time (ms)	628.84 (139.86)*	616.67 (57.99)***	524.43 (53.73)
P3b number of valid trials	41.80 (18.07)*	48.28 (26.55)	56.96 (25.59)
P300 amplitude Pz S1 (μV)	0.167 (0.786)	0.243 (0.729)	0.074 (0.635)
P300 amplitude Pz S2 (μV)	0.827 (0.993)	0.974 (1.151)	1.182 (1.179)
P300 amplitude Pz S3 (μV)*	0.544 (1.405)**	1.369 (1.369)	1.818 (1.058)
Theta noise power F3 (μV^2)	0.097 (0.051)	0.089 (0.045)	0.091 (0.050)
Theta noise power F4 (μV^2)	0.101 (0.041)	0.092 (0.037)	0.079 (0.037)
Theta noise power Fz (μV^2)	0.115 (0.054)	0.111 (0.055)	0.109 (0.058)
Gamma noise power F3 (μV^2)	0.017 (0.016)#	0.011 (0.007)	0.009 (0.014)
Gamma noise power F4 (μV^2)	0.018 (0.017)#	0.012 (0.008)	0.009 (0.009)
Gamma noise power Fz (μV^2)	0.010 (0.005)#	0.011 (0.007)#	0.005 (0.003)

S1, frequent tone; S2, distracter tone; S3, target tone. Deficit: ≤ -2 s.d. from the mean value of the healthy controls. Non-deficit: > -2 s.d. from the mean value of the healthy controls.

* $p < 0.10$.
** $p < 0.01$.
*** $p < 0.001$ (χ^2 or Mann–Whitney U tests).
\# $p < 0.008$ for the noise power differences (Mann–Whitney U test, significant after Bonferroni correction).

Patients with problem solving/executive function deficit showed higher gamma noise power at F3 ($U=81.5$, $z=3.18$, $p=0.001$; Fig. 1), F4 ($U=90.0$, $z=2.95$, $p=0.003$) and Fz ($U=59.5$, $z=3.76$, $p<0.001$), see Table 3. Patients without this deficit only showed more gamma noise power than at Fz ($U=175.5$, $z=3.54$, $p<0.001$; Table 3). Minimally treated patients with problem solving/executive function deficit ($n=7$) showed higher gamma noise power at Fz (0.009 μV^2 (0.002) vs. 0.005 μV^2 (0.003); $U=28.0$, $z=2.83$, $p=0.003$), and at a trend-level over F3 (0.015 μV^2 (0.012) vs. 0.009 μV^2 (0.014); $U=42.0$, $z=2.24$, $p=0.024$) and F4 (0.018 μV^2 (0.020) vs. 0.009 μV^2 (0.009); $U=42.0$, $z=2.24$, $p=0.024$). Minimally treated patients without this deficit ($n=15$) did not display significant gamma noise power differences.

3.3. Differences over early and late time windows

There were significant differences between patients with and without cognitive deficit, separately for working memory and problem solving domains, in both early and late gamma noise power values at F3, F4 and Fz (Table SM6). Patients classified according to their performance in other domains did not differ in early or late noise power windows.

3.4. Differences over other electrode sites

Patients with working memory deficit showed more gamma noise power at C3 ($U=135.5$, $z=2.67$, $p=0.008$), C4 ($U=113.5$, $z=3.17$, $p=0.002$), F7 ($U=97.5$, $z=3.53$, $p<0.001$) and T6 ($U=129.000$, $z=2.82$, $p=0.005$) than patients without this deficit. No differences were found for gamma noise power at other electrode sites or theta noise power at any electrode site (Table SM7). Also, no differences were found for theta noise power at any electrode site for patients with vs. without problem solving/executive function deficit (Table SM8). In particular, no noise power differences were found at circumferential electrodes (Fp1, Fp2, T5, T6, O1 or O2).

4. Discussion

Our data show that patients primarily characterized by significant cognitive deficits in domains with greater frontal contribution are also characterized by higher gamma noise power over the frontal region, also present in minimally treated patients with similar deficit and not extending to theta band or gamma parietal and occipital locations. Noise power differences over frontal–lateral electrodes in the gamma band were found only between patients with and without working memory deficit, and between minimally treated patients with and without problem solving/executive functions deficits, but not between patient's subsets with and without deficits in other domains.

Patients with cognitive deficits displayed significantly higher noise power values than controls at frontal–lateral (F3 and F4) electrode sites, while patients without cognitive deficit displayed similar noise power values (i.e., not significantly different) to those obtained by the healthy controls in these locations. This does not only allude to a correlational nature of our results (i.e., as we obtained in our previous work, Suazo et al., 2012; Diez et al., 2013), but to a clearer discrimination between deficit and non-deficit patients. We did not find any significant differences in the percentage of correct responses during the P300 evocation task

between patients and controls or between the different patients' subgroups. This balance confirms that the quality of our data ensures that patients maintained an acceptable level of cooperation and excludes this factor as a possible explanation for our results.

Recent evidence support a role of synchronization of evoked gamma oscillatory responses in general cognitive functions (Uhlhaas et al., 2009), including multisensory integration (Lakatos et al., 2007), selective attention (Doesburg et al., 2008) and working memory (Jensen et al., 2007). A strong linear correlation between the power of evoked gamma oscillations and working memory load in the prefrontal cortex has been already established in humans (Williams and Boksa, 2010). Our results suggest that gamma bands' capacity to subtend those functions is inefficiently used in patients with schizophrenia with clinically significant deficits in the working memory and problem solving/executive function domains.

Results consistent with such a possibility have been reported with the use of time–frequency analysis to assess the power changes in the different EEG bands during encoding, maintenance and/or retrieval of a working memory task. Higher gamma activity values in frontal regions with a lack of modulation in response to difficulty in the N-back task have been reported in schizophrenia (Basar-Eroglu et al., 2007; Barr et al., 2010), while healthy controls have evidenced frontal gamma activity increase with higher working memory demands (Howard et al., 2003; Basar-Eroglu et al., 2007; Haenschel et al., 2009). Using repeated transcranial magnetic stimulation (rTMS) and following a long-interval cortical inhibition paradigm, patients with schizophrenia displayed fewer decreases in gamma band power of the dorsolateral prefrontal cortex than healthy controls and bipolar patients (Farzan et al., 2010), whilst gamma oscillations were increased in the same cortical regions during the N-back conditions with the greater cognitive demand in controls (Barr et al., 2009). In this context, our results suggest a higher gamma power at rest and/or under low cognitive demands that cannot increase as expected under relatively greater demands in schizophrenia.

Consistent with the above stated and our results, due to higher background activation (i.e., higher noise power), the association between gamma activity and cognitive performance may fail in a subset of patients with schizophrenia, which may lead to a distinct substrate for their cognitive deficits. Their elevated baseline gamma activity may hamper the required flexibility for higher cognitive demands.

Literature studying noise power in schizophrenia is scarce (e.g., Winterer et al., 2004). The possible relationship between this parameter and more frequently used gamma activity measurements, such as evoked or induced responses in this band, could be investigated. Evoked signals (i.e., phase-locked to the stimulus) do not cancel out after averaging. Thus, averaged signal power is likely to represent the power of the evoked signals and consequently "noise power" would include induced (not phase-locked) and spontaneous EEG signals. Thus, the higher noise power exhibited by our patients with cognitive deficit in frontal domains is coherent with an excess of gamma power unlocked to the stimuli (out of phase) that may interfere with working memory and, to a lesser extent, problem solving/executive function when present over lateral frontal regions. An excess of unlocked activity may interfere with the oscillatory activity evoked by a cognitive task in the same band. Since noise power is a measure of activity unlocked to stimuli onset, it may be considered complementary to evoked power and both stimulus related (i.e., both depends on a stimulus onset but the former rise with a variant latency and is thought to depend, at least in the induced part, on the following stimuli-driven cognitive processing, Uhlhaas et al., 2009; Herrmann et al., 2010). In this context, information provided by noise power and induced measurements may be partially overlapping.

Higher Fz gamma noise power was common to our patients with and without cognitive deficits in working memory and problem solving/executive function domains, suggesting that some degree of higher noise power could be common to patients with schizophrenia, while a significant frontal noise power elevation may be restricted to a subset of patients, those phenotypically defined as having a significant deficit in cognitive functions more dependent on the frontal lobe. This is coherent with a dimensional distribution of the underlying biological alteration, which might be similar but more widespread in participants with higher noise power over frontal–lateral electrodes. Fz site is placed over the medial frontal region, a key structure in the so-called default mode network (DMN) (Broyd et al., 2009), a set of regions more active at rest whose activity decreases with engagement in a task. An impaired task-related deactivation of the DMN has been reported in schizophrenia (Pomarol-Clotet et al., 2008), which could have some relation to the higher noise power over Fz site in our patients. Accordingly, in a previous report we showed an elevated gamma activity unrelated to task processing over regions coherent with the DMN topography (including Fz site) in a sample of both stable-chronic and minimally treated patients with schizophrenia. However, in that report DMN and frontal–lateral regions differed in their relation with cognitive performance, since only the latter presented a significant inverse relation with frontal cognitive outcome (working memory and problem solving). Those results, together with the ones obtained in the present study, support the idea of differential underlying inhibitory mechanisms related to illness manifestation.

In schizophrenia, some neurobiological alterations are most likely established during critical developmental stages of late adolescence. First, there is some evidence of an excessive synaptic pruning during these stages, probably through the cellular processes of partial apoptosis (Jarskog et al., 2005; Glantz et al., 2006). Also, the GABAergic system is consolidated during the last stages of adolescence and early adulthood, when schizophrenia onset typically occurs (Hashimoto et al., 2009). Finally, maturation processes have been related to decreases in action potential duration, propagation time, duration of the release period, and decay time constant of inhibitory post-synaptic currents as a probable consequence of parvalbumin-positive basket-cells signaling changes (Doischer et al., 2008). Consequently, the basis for the higher gamma noise power in our patients might mainly have to do with inhibitory synaptic deficit, since gamma band and cortical GABA dysregulations may be associated in schizophrenia (Buzsáki, 2006a; Keren et al., 2010). Inhibitory interneurons are key for neuronal assemblies selection related to task, for preventing an excessive spreading of excitation (Buzsáki, 2006a) and for the genesis of gamma oscillations (McMenamin et al., 2011). In this context, our data may endorse various subsets within schizophrenia characterized by the presence or absence of a significant synaptic inhibitory alteration, with relevant cognitive consequences, consistent with recent post-mortem findings (Volk et al., 2012).

We cannot completely discard a muscular and/or ocular gamma band artefact contribution to the noise power of patients with significant deficit in working memory and problem solving (Keren et al., 2010; McMenamin et al., 2011). However, this would not easily justify the specific relation between gamma noise power over frontal electrodes and the performance in tasks with greater frontal load. Moreover, artefacts related to microsaccadic movements of the eye are found in the gamma band of the EEG up to 300 ms after stimulus onset (Martinez-Conde, 2006). Our data showed that noise power elevations were found in the early and later periods (i.e. 100–300 vs. 350–550 ms, Martinez-Conde, 2006) in those cases with significant deficits in tests with greater frontal

contribution. Microsaccades are spontaneous movements subserving ocular fixation (Dien, 1998; Martinez-Conde et al., 2009), hence expectedly less frequent and/or intense with eyelids closed, which was how the EEG of our participants was recorded. Besides, no significant noise power differences at the most peripheric electrodes, where the maximum electromyographic artefacts contribution is expected (Pope et al., 2009), were found between patients defined according to their cognitive profile; with the exception of T6 site in the patients with working memory deficit.

In accordance with our previous work in minimally treated patients (Suazo et al., 2012), we did not find elevated noise power in the theta band. These results can be related to task requirements, since theta power is consistently linked to episodic memory tasks (Klimesch, 2003), while gamma oscillations are associated with top-down attentional processes, being the latter but not the former prominent requirements in the P300 paradigm. Even so, the lack of higher noise power in theta band is discrepant with that reported by Winterer et al. (2004). In part, this may be explained by our partial inclusion of first episode and minimally treated patients, as chronicity and long-term treatment (Galderisi et al., 2009) may have a significant effect on higher theta power in patients with schizophrenia. An association between cognitive impairments and gamma but not theta power has been reported in medicated and unmedicated patients with schizophrenia (Minzenberg et al., 2010). Recently, an abnormal coupling between theta and gamma oscillations has been described in schizophrenia (Kirihara et al., 2012; Koutsoukos et al., 2013), which may represent an interesting approach for understanding alterations in cognitive processing in this disorder.

The present finding of a gamma noise power excess restricted to patients with a specific type of cognitive deficit (i.e., a frontal neurocognitive deficit) supports that under the current criteria for schizophrenia it is unlikely that gamma noise power may be a useful diagnostic tool. However, it may contribute to identify a particular subtype within this syndrome, characterized by a particular frontal region affectation and (speculatively) structures most related to this region (such as thalamic or caudate nuclei). With completely different samples, in previous publications, our group reported structural differences in this region that were related to long-term outcome (Molina et al., 2010) and perfusion differences associated to clozapine response (Molina Rodriguez et al., 1996, 1997). That hypothetical "frontal deficit" subtype may include other traits such as an inhibitory deficit, as shown in some schizophrenia cases (Lewis et al., 2005; Gonzalez-Burgos and Lewis, 2012) and may be coherent with a disorganized gamma activity, given the seemingly close association between gamma activity and inhibitory function (Farzan et al., 2009, 2010). If confirmed, this may represent an interesting opportunity for treatment with drugs (clozapine seems to modulate frontal activity more than other antipsychotics, Lahti et al., 2004; Molina et al., 2005) or other approaches specifically aimed at that frequency band, such as rTMS.

In previous studies we also demonstrate a relation between noise power and negative symptomatology in first-episode and minimally treated patients sample (Suazo et al., 2012). We could not replicate these findings in other precedent work when also including long-time stable medicated patients (Diez et al., 2013), therefore discarding cortical-cognitive functioning anomalies to be the effect of the chronic psychotic state. In the present study, we also failed to find any significant differences in clinical outcome between patients' subgroups, which lead to the same conclusion.

Among our study's limitations, to dichotomize patients into those with and without a large deficit according to the "fulfilling or unfulfilling ≤ -2 s.d. criterion" may be artificial; even though this is a frequent criterion similar to the one used to determine other psychological traits, such as IQ limits, which allow identifying participants with a more likely dysfunction in real life. Although we have followed Winterer et al. (2004) band ranges for the present work, we have not included the high-gamma band (up to 150 Hz), which may yield results of interest. Due to our sample size, we could not assess handedness adequately for the lateralization of our results. Another limitation is the average reference here used together with a low number of electrodes, which has been criticized because it could distort some electrodes' magnitudes (Dien, 1998). However, the 10/20 international system, which is standardly distributed throughout the whole brains surface, guarantees a correct estimation of average activity to reference. Finally, our patients had received at least an acute treatment with haloperidol by the moment of their inclusion. We did not detect significantly higher noise power magnitudes in controls after haloperidol administration and a wash-out period similar to those of acute patients, so this acute treatment is not a likely explanation for the findings here reported. Also, Saletu et al. (1990, 2006) described a significant decrease, but not an increase, in the high-frequency (beta) band activity after single 5 mg doses of haloperidol in patients with schizophrenia with predominantly positive symptomatology. This seems coherent with a noise power reduction with haloperidol, which would argue against a primary role of treatment in the association between cognition and this magnitude in our patients. Moreover, similar associations were found in minimally treated and stable-chronically treated cases, further acknowledging these views. However, to properly rule out possible effects of the brief haloperidol treatment administered to patients on noise power, it would be necessary to replicate these findings in neuroleptic-naïve patients.

As a conclusion, our data point towards various biological subsets within schizophrenia characterized by the presence or absence of a frontal cognitive deficit. These results have some clinical and conceptual implications within the psychosis entity, advancing towards new biological definitions of the syndrome would lead to more reliable diagnostic patterns and specific treatments, and may offer useful dissociated targets for genetic research and new drugs development.

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

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2013.11.001.

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