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Attenuation of long-range temporal correlations in the amplitude dynamics of alpha and beta neuronal oscillations in patients with schizophrenia

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ABSTRACT

Although schizophrenia was previously associated with affected spatial neuronal synchronization, surprisingly little is known about the temporal dynamics of neuronal oscillations in this disease. However, given that the coordination of neuronal processes in time represents an essential aspect of practically all cognitive operations, it might be strongly affected in patients with schizophrenia. In the present study we aimed at quantifying long-range temporal correlations (LRTC) in patients (18 with schizophrenia; 3 with schizoaffective disorder) and 28 healthy control subjects matched for age and gender. Ongoing neuronal oscillations were recorded with multi-channel EEG at rest condition. LRTC in the range 5–50 s were analyzed with Detrended Fluctuation Analysis. The amplitude of neuronal oscillations in alpha and beta frequency ranges did not differ between patients and control subjects. However, LRTC were strongly attenuated in patients with schizophrenia in both alpha and beta frequency ranges. Moreover, the cross-frequency correlation between LRTC belonging to alpha and beta oscillations was stronger for patients than healthy controls, indicating that similar neurophysiological processes affect neuronal dynamics in both frequency ranges. We believe that the attenuation of LRTC is most likely due to the increased variability in neuronal activity, which was previously hypothesized to underlie an excessive switching between the neuronal states in patients with schizophrenia. Attenuated LRTC might allow for more random associations between neuronal activations, which in turn might relate to the occurrence of thought disorders in schizophrenia.

Introduction

Abnormality in the neuronal connectivity is one of the most dominant theories explaining the pathophysiology of schizophrenia (Andreasen, 2000; Friston, 1998; Stephan et al., 2006). Consequently, since synchronization of neuronal oscillations represents a possible mechanism responsible for the cooperative integrative processing of information in the brain (Fries, 2009; Singer, 1999; Uhlhaas et al., 2009), schizophrenia has been extensively studied with EEG/MEG (Cho et al., 2006; Spencer et al., 2004). EEG studies utilizing nonlinear measures of neuronal interactions have also demonstrated abnormal connectivity in patients with schizophrenia compared to healthy controls (Breakspear et al., 2003; Micheloyannis et al., 2006). Rolls et al. (2008) suggested that the abnormal brain activity in schizophrenia can be viewed on the basis of a dynamical system approach where reduction in excitatory and inhibitory synaptic transmission can lead to rapid changes of neuronal states (attractors) across spatially diverse neuronal populations. Such intermittent activity in turn should lead to excessive neuronal noise and in general to the reduction in signal-to-noise ratio for the processing of information in patients with schizophrenia (Rentrop et al., 2011; Winterer et al., 2004).

A major emphasis in the aforementioned studies is placed on the spatial neuronal interactions. However, another important aspect in schizophrenia—the propagation of neuronal activity in time—has remained largely unaddressed. Assuming that schizophrenia is associated with highly volatile neuronal states (Rolls et al., 2008) and abnormal connectivity (Friston, 1998; Stephan et al., 2006) allowing more erratic switching between neuronal populations, it may be predicted that the temporal pattern of neuronal activities should be more random-like when measured on sufficiently long time scales, e.g., tens of seconds. These time scales are especially relevant for sustained cognitive operations such as logical reasoning, thought continuity and working memory which are known to be affected in schizophrenia (Green, 1996).

In this sense it is important to note that the abnormalities in neuronal processing should not necessarily be manifested only when the cognitive tests and tasks are administered. Due to the fact that in general schizophrenia is associated with drastically affected glutamatergic (Coyle, 2006) and GABAergic activities (Hashimoto et al., 2008),

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the background "resting" state should also reflect abnormalities in neurophysiological functioning and consequently affect perceptual and cognitive neuronal processes which are unfolding on the basis of already compromised neuronal networks.

In the present study we investigated the temporal correlations in neuronal oscillations; these correlations might serve as indicators of how neuronal events are related to each other when separated by long time intervals. Recent studies showed an existence of long-range temporal correlations (LRTC) in the amplitude dynamics of alpha and beta oscillations (Linkenkaer-Hansen et al., 2001, 2004; Nikulin and Brismar, 2004, 2005). The presence of LRTC indicates that the temporal auto-correlations attenuate very slowly in time, according to a power-law. Consequently, such slow attenuation of LRTC is an indication of how neuronal events are developing in time, which in turn is based on the integrity of multiple interconnected populations of neurons. Attenuation of LRTC was previously shown in Alzheimer disease (Montez et al., 2009) and major depressive disorder (Linkenkaer-Hansen et al., 2005).

In the present study we evaluated the serial temporal correlations in patients with schizophrenia and in age and gender-controlled healthy subjects. Given the fact that normal brain functioning relies on structured serial neuronal processing, we hypothesized that LRTC should be attenuated in patients with schizophrenia. In addition, taking into account abnormal connectivity in schizophrenia, we evaluated the relationship of LRTC between different spatial locations and frequency ranges.

Materials and methods

All subjects were informed about the nature and purpose of the study before consenting to participate. The protocol was approved by the institutional human ethics committee of the Karolinska Institute. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The cases consisted of 21 stable outpatients (5 women, 16 men), the age of patients was 37.9 ± 5.1 years (mean $\pm$ standard deviation). All patients were interviewed by an experienced psychiatrist (EGJ) and met DSM-III-R and DSM-IV diagnostic criteria for schizophrenia ($n = 18$) or schizoaffective disorder, bipolar type ($n = 3$). Diagnoses were based on interviews and reviews of medical records as previously described (Ekholm et al., 2005; Vares et al., 2006). Briefly, in a semi-structured interview the patients were subjected to the Structured Clinical Interview for DSM-III-R (Spitzer et al., 1988) and the psychosis modules (chapters 17–19) of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990) which both were used to assess life-time psychiatric symptoms. The Scales for Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scales for Assessments of Positive Symptoms (SAPS) (Andreasen, 1984) were used to evaluate symptoms during the last month. In addition, the patients' life-long psychiatric records were scrutinized. Thereafter a life-time diagnosis according to DSM-III-R/DSM-IV was given taking all available information, i.e. data from the last and previous interviews (for all of the participants a previous similar research interview was performed 5 years before the present investigation) and from the medical records. All of the patients were in remission, i.e. they have not been hospitalized during the last 18 months. None of the patients fulfilled criteria for a present alcohol or drug abuse/dependence diagnosis. Duration of illness ranged from 5.7 to 26.3 years (mean 14.9 ± 6 years). Of the patients three were prescribed first-generation antipsychotics, twelve second-generation antipsychotics, and four both first-generation and second-generation antipsychotics, whereas two patients did not take any drugs. Among the medicated patients the haloperidol equivalent dose (Woods, 2003) ranged from 0.5 to 19.6 units (mean $\pm$ S.D. 6.4 ± 4.3 units) and the defined daily doses (DDDs) varied between 0.1 and 6.0 (1.4 ± 1.2) (World Health Organization, 2007). Two subjects were prescribed mood stabilizers, three antidepressants and four benozodiazepines on a regular basis.

The comparison group consisted of 28 healthy subjects (7 women, 21 men) recruited randomly from the Swedish population registry. The age of the subjects was 35.9 ± 7.1 years. Fisher's exact test showed that the gender ratio was not significantly different between control subjects and patients ($P = 1$). The age also did not differ between the two groups of subjects (t-test, $P < 0.9$). The control subjects were asked about their medical history and individuals with ongoing medication or previous neurological or psychiatric disease or trauma that might affect the brain functioning, were excluded from the participation. Also, none of the control subjects had parents or siblings who were known to have been treated for psychiatric illness.

Task

During the experiment the subjects were in a semi-supine position and were instructed to relax and keep their eyes closed. Every minute a technician asked the subject to open eyes and then to close them after 5 s. These instructions prevented the subjects from becoming drowsy during the eyes-closed periods (Maltez et al., 2004). This procedure was repeated for about 15 min.

Recordings

EEG was acquired with Nervus amplifier (Taugagreining, Reykjavik, Iceland) using 21 electrodes placed according to the International 10–20 system. The impedance of all electrodes was kept below 5 kOhm. EEG was recorded in the 0.05–67 Hz frequency range and sampled at 256 Hz. For the following analysis the data were re-referenced to the arithmetically linked mastoids.

In the clinical environment it is important to reduce the discomfort of patients. Therefore, the preparation time should be short. The 19-channel EEG setup, used in the present study, represents a compromise between on the one hand reduction of the preparation time and on the other still sufficiently large number of electrodes covering the entire scalp (according to the standard 10–20 system). Importantly, such standard EEG setup and sensor space analysis has its advantages as it allows straightforward application and comparison of LRTC methodology/results to already existing data recorded in many clinical and research laboratories around the world.

Analysis

For the analysis we used eyes-closed periods only. The EEG recordings were visually inspected and segments containing artifacts were excluded. Only segments with duration of at least 50 s were selected for further processing. On the average 12 and 13 segments were obtained for control subjects and patients, respectively.

Instantaneous amplitude of neuronal oscillations

In the present study the analysis was based on the instantaneous amplitude (envelope) of the oscillations. As a first step the raw EEG was band-pass filtered with finite impulse response filtering (FIR; 58th order, Hamming window) in the 8–12 and 16–24 Hz range for alpha and beta oscillations, respectively (Nikulin and Brismar, 2004, 2005). The main idea in the present study was to investigate amplitude dynamics of clearly oscillatory processes, and alpha and beta oscillations represent the only neuronal processes which posses pronounced oscillatory patterns in spectra of ongoing EEG/MEG (Linkenkaer-Hansen et al., 2001; Nikulin and Brismar, 2004, 2005). The peaks in other frequency ranges are rare at rest condition and mostly are present during different tasks. Nevertheless, we also performed an analysis in the 30–40 Hz gamma frequency range, where neuronal activity has been previously shown to be affected in patients

with schizophrenia during the task conditions (Cho et al., 2006; Spencer et al., 2004). In addition, we have also analyzed EEG activity in delta (2–4 Hz) and theta (4–7 Hz) frequency ranges. For these last two frequency bands we used FIR filtering with the order 256 for more efficient removal of very low frequency activity (<1 Hz) which might have been contaminated by postural changes and electrode DC-offsets. In case of a higher order of a FIR filter a larger temporal smoothing of the signals is introduced. Yet, the slight positive bias introduced by FIR filtering in delta and theta frequency ranges was small <0.032 as verified with simulations when DFA was applied to white noise data (Nikulin and Brismar, 2004). Importantly, this small bias is identical for processing of data from patients and control subjects.

Although central ~10-Hz oscillations are also known as mu oscillations (Pfurtscheller et al., 2006; Ritter et al., 2009), we will solely use the term alpha oscillations specifying when necessary their spatial location. Despite their different spatial distribution, ~10-Hz oscillations in the occipito-parietal and central areas have similar functional significance related to attention and inhibitory processes (Haegens et al., 2012; Palva and Palva, 2007). Beta oscillations on the other hand relate primarily to the maintenance of the current sensorimotor or cognitive state (Engel and Fries, 2010). In our study we concentrated on these two main oscillatory EEG processes with distinct functional significance.

For the extraction of instantaneous amplitude we used the Hilbert transform. Fig. 1A shows an example of the instantaneous amplitude corresponding to the alpha oscillations. Note that the instantaneous amplitude reflects only the amplitude of the oscillations, without the phase information. The signal representing the dynamics of the instantaneous amplitude was used for all the following calculations. The overall mean amplitude of alpha and beta oscillations was calculated by averaging the amplitude values across all available data segments for each channel and subject separately.

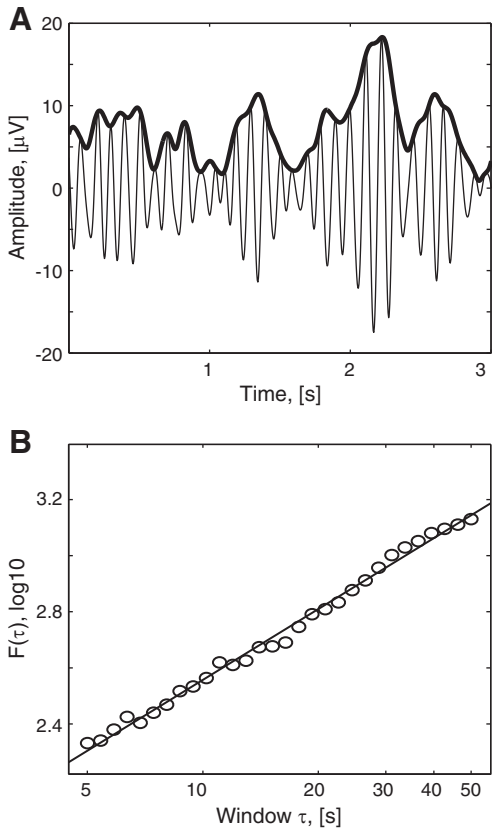

Fig. 1. Amplitude envelope of oscillations and detrended fluctuation analysis. A. An example of band-pass filtered alpha oscillations (thin line) and a corresponding amplitude envelope (thick black line). B. An example of a linear relationship in a double logarithmic plot between the magnitude of fluctuation $F(\tau)$ and τ (one subject, C3 electrode). The slope of the least-squares line is a scaling exponent, which in this case was 0.84.

Detrended fluctuation analysis (DFA)

The DFA method (Kantelhardt et al., 2001; Peng et al., 1995) allows quantifying long-range correlations in the structure of the signals. In case of EEG recordings it translates to the detection of long-range temporal correlations (auto-correlations) in the amplitude dynamics of neuronal oscillations. Note that LRTC refer to the correlation between different time points in EEG activity, not across different spatial locations.

Let $A(t)$ be an instantaneous amplitude of oscillations extracted with the Hilbert transform at time t. Next we calculate a cumulative sum of the signal:

$$Y(t) = \sum_{t'=1}^{t} A(t')$$

The integrated signal $Y(t)$ was then divided into non-overlapping windows of size τ with a length varying from 5 to 50 s distributed equidistantly on a logarithmic scale and altogether there were 30 window sizes in this time range. For each window size τ, the least-squares fitted line was computed and the ordinate of this line is denoted $Y_\tau(t)$. The integrated signal $Y(t)$ was then detrended in each window by subtracting $Y_\tau(t)$ and the variance was calculated as:

$$F^2(\tau) = \frac{1}{N}\sum_{t=1}^{N}\left[Y(t) - Y_\tau(t)\right]^2$$

where N is the number of samples in the window size τ. $F^2(\tau)$ were then calculated for all eye-closed signals. All $F^2(\tau)$ values for a given τ were then averaged and the square root was obtained leading to $F(\tau)$ value. The procedure of calculating $F(\tau)$ was repeated for all window sizes of different τ. Usually the relationship between $F(\tau)$ and τ has a linear form in a double logarithmic coordinate system across many sizes of τ. The slope of the least-squares line in this graph is called the scaling exponent and it quantifies LRTC. Scaling exponents in the 0.5–1 range indicate a presence of persistent temporal correlations. Uncorrelated signals (e.g. for white noise) have a scaling exponent 0.5. Scaling exponents were calculated separately for alpha and beta oscillations, in each channel and subject (Fig. 1B).

For the statistical analysis we used t-test and Pearson's coefficient of correlation on logarithmically transformed amplitude and scaling exponent values. The logarithmic transformation ensured normal distribution according to the Lilliefors test. Apart from a greater statistical power of parametric over non-parametric tests, the use of t-test was further justified by the fact that non-parametric testing can suffer even more than t-test when parametric assumptions are not justified (Zimmerman, 1998).

Cross-frequency correlations between scaling exponents belonging to alpha and beta oscillations

We also analyzed whether scaling exponents belonging to alpha and beta oscillations were correlated with each other. In this way the cross-frequency correlation of scaling exponents was addressed and it was done for all channels. Let A_i and B_j be the vectors containing logarithmically transformed scaling exponents of control subjects for alpha and beta oscillations at channels i and j, respectively. A cross-frequency correlation $r_{i,j}$ for these two vectors is then calculated according to:

$$r_{i,j} = \frac{\mathrm{cov}\left(A_i, B_j\right)}{\sigma_{A_i}\sigma_{B_j}}$$

where cov is covariance and σ is a standard deviation.

Elements $r_{i,j}$ form then the matrix $\boldsymbol{R}$ representing all possible (channel-wise) cross-frequency correlations between scaling exponents belonging to alpha and beta oscillations. The rows and columns in this matrix are indicated by indices i and j, respectively. $\boldsymbol{R}$ was obtained in patients ($\boldsymbol{R_P}$) and in healthy controls ($\boldsymbol{R_H}$). In order to take into account a different number of control subjects ($n=28$) and patients ($n=21$) we used unbiased estimation of correlation coefficient, which takes into account degrees of freedom (Olkin and Pratt, 1958; Zimmerman et al., 2003).

Cross-frequency phase synchronization (CFS) is another measure and it quantifies interactions between the two processes (Palva et al., 2005; Nikulin and Brismar, 2006). Mathematically, the correlations shown in the present study ($r_{i,j}$) are not bound to be defined by CFS. This is because phase measure is not dependent on the amplitude or the overall amplitude dynamics reflected in scaling exponents.

Results

Amplitude of neuronal oscillations

The spatial distribution of the instantaneous amplitude is presented in Fig. 2. The alpha oscillations had the maximum amplitude for the control subjects over the parieto-occipital areas and for patients over parieto-central areas (Figs. 2A and B). A comparison of across-channels averaged amplitudes (Fig. 2E) showed no significant difference between control subjects and patients. We also tested for the difference in alpha amplitude separately for each electrode and found no significant differences.

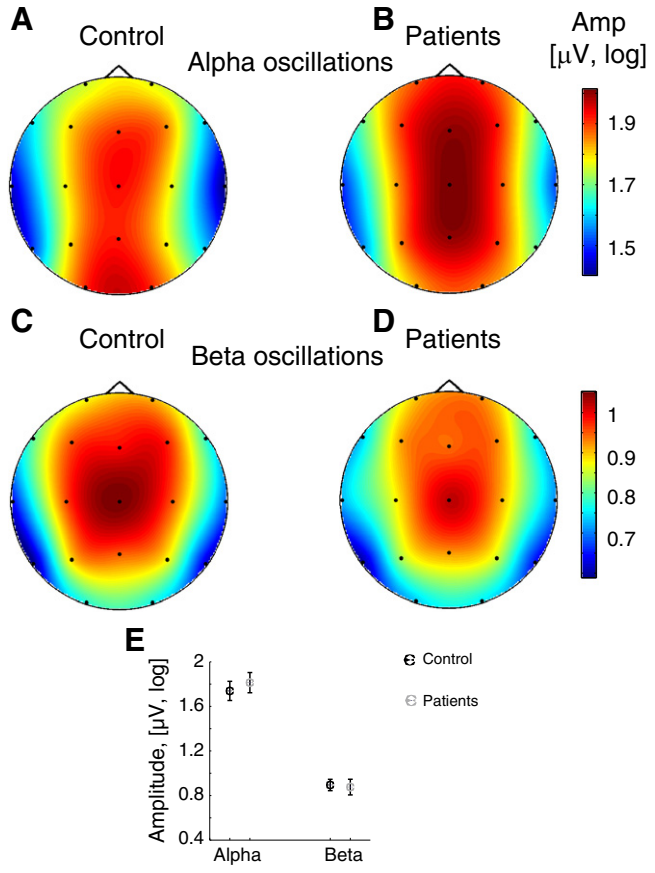

Fig. 2. Effect of schizophrenia on amplitude of neuronal oscillations. Topographic plots of the amplitude of alpha oscillations in control subjects (A) and patients (B) and of beta oscillations in control subjects (C) and patients (D). Grand average of alpha and beta amplitudes across subjects and channels (E) did not differ between control subjects and patients. In all plots the amplitudes were transformed using a natural logarithm. Error bars—standard error of the mean for across-channel averaged amplitudes. n.s.—Not significant.

The spatial amplitude distribution of the beta oscillations showed the maximum over the central areas for both normal subjects and patients (Figs. 2C and D). Expectedly, the beta oscillations had a considerably smaller amplitude than the alpha oscillations, but across-channels averaged amplitude of beta oscillations was not significantly different in patients compared to control subjects (Figs. 2E and F) and tests performed separately for each channel showed no difference between the two groups.

Scaling exponents of neuronal oscillations

Fig. 1B shows an example of scaling behavior in the amplitude dynamics of neuronal oscillations for one of the control subjects. The plot shows data for 5 to 50 s and one can observe a good linear relationship between the logarithm of the time scale and the logarithm of the amplitude fluctuations $F(\tau)$. For the control subjects the median value and inter-quartile range (in brackets) for the exponents of alpha oscillations were 0.72 (0.64–0.79) and for patients 0.64 (0.6–0.7).

The spatial distribution of the scaling exponents (natural logarithm values) for alpha oscillations is presented in Figs. 3A and B. For both groups of subjects the maximum was over the parieto-occipital areas with an additional spatial maximum over the frontal areas in the patients. However, the scaling exponents in patients were significantly attenuated ($P<0.05$) as demonstrated by a comparison of across-channels averaged alpha scaling exponents (Figs. 3E and F). Comparison of the scaling exponents for each channel separately showed 10 electrode locations (Fig. 3B, dots in magenta color) where a significant ($P<0.05$, t-test) attenuation of the scaling exponents occurred in patients. This significant drop in the alpha scaling exponents was observed for the continuous cluster of electrodes above parieto-temporal areas. According to the binomial testing (Montez et al., 2009), the probability of obtaining an equal or larger number of electrodes than 10 (a total number of electrodes showing significant differences with $P<0.05$) was negligibly small, $P<1e-09$.

Figs. 3C and D show the spatial distribution of the scaling exponents for beta oscillations. Both groups of subjects had spatial maximum over the occipital and centro-temporal areas. In the control subjects the median value and inter-quartile range (in brackets) for the exponents were 0.66 (0.61–0.73), and in patients 0.6 (0.55–0.67).

Comparison of across-channels averaged exponents (Figs. 3E and F) revealed significantly lower beta scaling exponents in patients compared to the control subjects ($P<0.01$), indicating that the patients had a similar decline in the beta scaling exponents as in the case of alpha scaling exponents.

Comparison at each electrode location showed 12 positions (magenta colored) where significant attenuation of the scaling exponents occurred in patients (Fig. 3D). For beta scaling exponents the significant attenuation occurred in a continuous cluster over frontal, central and occipito-parietal areas. According to the binomial testing (Montez et al., 2009), the probability of obtaining an equal or larger number of electrodes than 12 (a total number of electrodes showing significant differences with $P<0.05$) was negligibly small, $P<1e-12$.

Neither the amplitude nor the scaling exponents of delta/theta/gamma neuronal activity showed any significant differences between patients and control subjects when tested with across-channel averaged values or with the binomial testing (not illustrated).

Effect of medication

The possible drug effect on the scaling exponents was studied in the patients. Neither alpha nor beta scaling exponents calculated from any of the electrode positions were significantly correlated with the haloperidol equivalent dose ($P>0.25$).

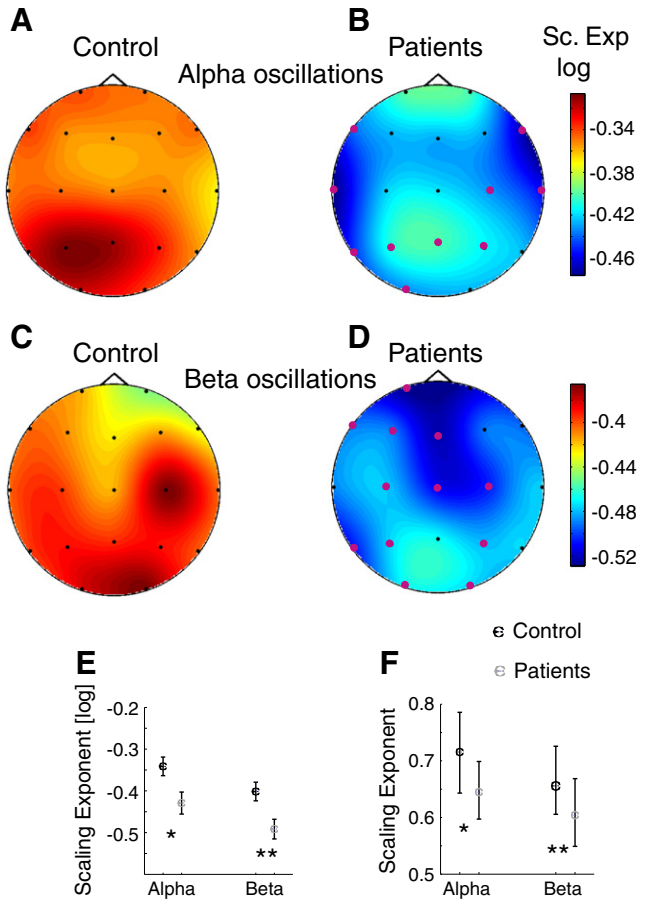

Fig. 3. Effect of schizophrenia on scaling exponents of neuronal oscillations. Topographic plots of the scaling exponents of alpha oscillations in control subjects (A) and patients (B), and of beta oscillations in control subjects (C) and patients (D). Electrode locations are marked in magenta color in (B) and (D) where the scaling exponents were significantly ($P<0.05$) attenuated in patients compared to control subjects. Sc. Exp. is scaling exponent. Grand average of scaling exponents (E) across subjects and channels. Error bars—standard error of the mean for across-channels averaged scaling exponents. Note that in all plots the scaling exponents were transformed using a natural logarithm. Error bars indicate standard error of the mean, $^{*}P<0.05$; $^{**}P<0.01$. (F) Median values of all scaling exponents (across subjects and channels). Error bars—inter-quartile range (between 25 and 75 percentiles of pulled together scaling exponents). Statistical testing for original values of the scaling exponents was performed with non-parametric Wilcoxon rank sum test. $^{*}P<0.05$; $^{**}P<0.01$.

Correlation between scaling exponents belonging to alpha and beta oscillations

The correlation between alpha and beta exponents (cross-frequency correlation) was analyzed in patients and control subjects. This cross-frequency correlation was calculated at each electrode position, and between different electrode positions. The spatial distribution of the cross-frequency correlation is illustrated in Fig. 4 where each electrode position contains a miniature topographic map. Fig. 4A illustrates the cross-frequency correlation between the alpha scaling exponent at each position and beta scaling exponent at all other electrodes in control subjects, and Fig. 4B shows the corresponding data for patients. In Figs. 4C and D the same data is illustrated in the reverse mode, i.e. how the beta scaling exponent at each electrode position correlates with the scaling exponents of alpha oscillations at all other electrode positions. In both patients and control subjects the cross-frequency correlations had generally high values around each electrode site. The most notable difference was the larger strength of the cross-correlations in the patients, especially in the posterior regions as indicated by red areas in Figs. 4B and D. Fig. 4F shows also a distribution of correlation coefficients $r_{i,j}$ for control subjects and patients. Note that patients had very large correlations (>0.6) and that in general the correlations had positive values.

The difference in cross-frequency correlation was tested statistically. For the comparison of correlation coefficients (shown in Fig. 4) between control subjects and patients, we pulled together all $r_{i,j}$ coefficients for patients into one variable and for control subjects into another variable and compared these two variables with Wilcoxon paired (for channels) signed rank test. In this way we estimated overall strength of correlation in one comparison, without the need to perform multiple comparisons. The test performed between patients and control subjects on all cross-correlation coefficients $r_{i,j}$ showed a significantly ($P<0.05$) larger correlation for patients. In order to take into account just a very few insignificant negative $r_{i,j}$ coefficients we performed Wilcoxon paired test for the rectified $r_{i,j}$ coefficients as well. This test also showed significantly larger correlation for patients ($P<0.05$).

Discussion

The main finding of the present study is that the long-range temporal correlations for up to 50 s in the amplitude dynamics of alpha and beta oscillations were attenuated in patients with schizophrenia as compared to healthy control subjects. Moreover, we observed that in patients there was a spatially distributed association between altered behavior of alpha and beta oscillations primarily in parieto-occipital regions. In the present study we analyzed neuronal dynamics in the resting state, which allows studying the background state of the neuronal network, on the basis of which task related activities are unfolding. Furthermore, it has become increasingly recognized that the rest condition is not a blank state but rather is associated with "thought wandering" (Montez et al., 2009; Smallwood and Schooler, 2006), involving memory retrieval, planning, etc. In this sense neuronal dynamics at rest are also relevant for the understanding of thought disorders in schizophrenia.

LRTC in schizophrenia

The values of the scaling exponents were in agreement with the values from the previous studies showing an existence of long-range temporal correlations in neuronal oscillations recorded with EEG/MEG (Linkenkaer-Hansen et al., 2001, 2004; Nikulin and Brismar, 2004, 2005). The fact, that the amplitude of the oscillations did not differ between patients and control subjects, indicates that the neural circuitry responsible for generation of rhythmic activity per se was not affected. Moreover, although the scaling exponents were attenuated in patients with schizophrenia, their median values for alpha and beta oscillations were >0.6, thus indicating that LRTC were still preserved and only attenuated. An attenuation of the scaling exponents without any decline in the amplitude of the oscillations has similarly been observed in early-stage Alzheimer disease (Montez et al., 2009). A likely explanation for the attenuation of LRTC in the present study is that the formation of spatio-temporal neuronal clusters was affected as we will show below.

We are aware of only one previous EEG study on long-range temporal correlation in schizophrenia (Slezin et al., 2007), where the authors found a decrease in the fractal exponents for the amplitude of alpha oscillations (as in the present study) and an increase in the exponents of the theta oscillations. Beta oscillations and the association between the oscillation behavior of different frequency bands and brain regions were not studied. The limitation of the study by Slezin et al. (2007) is that it is based on spectral analysis, which is affected by non-stationarities in EEG, which is avoided by the use of DFA in the present study. Moreover, the largest time scale was 10 s, contrary to 50 s used in the present study.

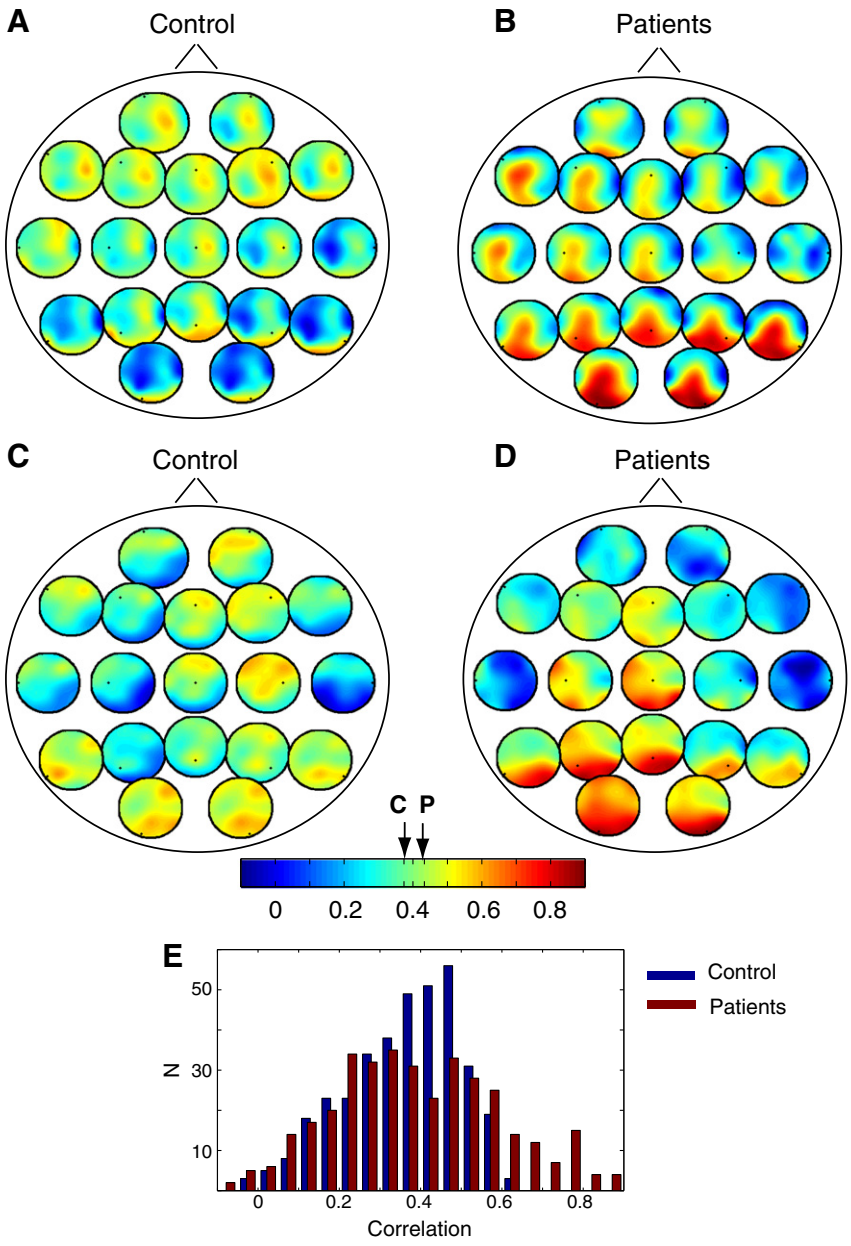

Fig. 4. Effect of schizophrenia on the cross-frequency correlation of scaling exponents. Cross-frequency correlations for control subjects (A, C) and patients (B, D). Each of four subplots contains miniature maps showing the topography of the cross-frequency correlations $r_{i,j}$ (see Materials and methods) between the given channel and all other channels. In (A) and (B) the cross-frequency correlations between scaling exponents of alpha oscillations at the given electrode location (marked by smaller black dot) and scaling exponents of beta oscillations at all other electrode locations. In (C) and (D) the same data represented in the reverse manner showing the cross-frequency correlations between scaling exponents of beta oscillations at the given electrode location and scaling exponents of alpha oscillations at all other electrode locations. Color bar shows the strength of the cross-frequency correlations. The C- and P-arrows show the significance threshold for correlation coefficient for control subject and patients, respectively. For calculation of correlation in some subjects channels were deleted due to the excessive amount of artifacts, however since less than 1% of channels was deleted due to noise in control subject and patients, there was no need to introduce different degrees of freedom for calculation of significance threshold shown for the color bar. (E) The histograms of all cross-frequency correlation values for patients and control subjects.

Rolls et al. (2008) have suggested that in schizophrenia there might be a higher probability for cortical neuronal networks to wander from one neuronal state to another leading to highly intermittent neuronal dynamics and a decrease in the neuronal signal-to-noise ratio as observed with EEG (Rentrop et al., 2011; Winterer et al., 2004). This could be due to the combined effects of abnormal regulation of NMDA receptor functioning (Coyle, 2006) and decrease of GABAergic activity (Hashimoto et al., 2008) in schizophrenia affecting the stability of specific neuronal states (attractors, Rolls et al., 2008).

LRTC describe dynamics of neuronal activations over long stretches of time. The fact that the scaling exponents were attenuated in patients with schizophrenia indicates that the neuronal events in time are more loosely relating to each other than in healthy subjects. We hypothesize that weaker temporal correlations might thus correspond to the general framework suggested by Rolls et al. (2008) where the pathophysiology of schizophrenia is related to the excessive amount of variability and noise in neuronal activations.

The attenuation of the alpha scaling exponents occurred to a large extent in electrodes over the parieto-occipital areas where these oscillations usually are generated (Niedermeyer, 1999). Alpha oscillations were demonstrated to reflect active inhibition of task irrelevant neuronal process/areas (Klimesch, 1996; Worden et al., 2000) and it was suggested that they reflect segregation of neuronal processes involved in cognition (Palva and Palva, 2007). The fact

that GABAergic activity is reduced in schizophrenia patients (Hashimoto et al., 2008) might indicate that inhibitory mechanisms and consequently the segregation of neuronal activity, subserved by alpha oscillations, will not function adequately. The unconstrained rapid switching between the neuronal states would then lead to an attenuation of the scaling exponents of the alpha oscillations.

Many electrodes showing attenuation of beta LRTC were located over the fronto-central areas where beta oscillations are usually generated (Niedermeyer, 1999). It has been hypothesized that beta oscillations may signal unchanging motor or cognitive states (Engel and Fries, 2010). As a consequence, attenuated beta LRTC would indicate a potential for high probability of switching between the mental states, which would be a corollary to the increased neuronal variability in schizophrenia (Rolls et al., 2008; Winterer et al., 2004).

In addition to alpha and beta oscillations, we also analyzed neuronal activity in the delta, theta, and gamma frequency range but found no significant differences between patients and control subjects in the strength of the scaling exponents. On the one hand this finding might indicate that LRTC in schizophrenia are primarily affected in alpha and beta frequency ranges. On the other hand since the phase portrait of oscillations is not very well defined for spontaneous delta, theta, and gamma oscillations, the amplitude envelope represents in addition a strong contribution from background 1/f neuronal activity, which might have affected estimation of oscillatory dynamics and differences between the patients and control subjects.

We did not find significant correlations between the haloperidol equivalent dose and scaling exponents in any of the electrodes or frequency bands. The lack of significant correlations argues against the effects of anti-psychotic drugs accounting for differences in LRTC between patients and control subjects.

Cross-frequency correlations between scaling exponents of alpha and beta oscillations

The strongest cross-frequency correlations between the scaling exponents were observed over the parieto-occipital areas in the patients, where also attenuation of alpha and beta LRTC occurred.

It is important to note that cross-frequency correlation in the present analysis refers to how the changes in the scaling exponents were cross-correlated, and not to the correlation between neuronal oscillations. The data show that the smaller are LRTC in one frequency band the smaller they will be in another. This would correspond to a situation when similar and strongly dominating factors (such as affected synaptic transmission mentioned above) would lead to the attenuation of alpha and beta scaling exponents and consequently the cross-frequency correlations of scaling exponents would be stronger in patients than in healthy subjects. This is because in healthy subjects the neuronal dynamics in both frequency bands are shaped primarily by the normal intrinsic neuronal mechanisms specific to each frequency band (Buzsáki and Draguhn, 2004; Pfurtscheller and Lopes da Silva, 1999), without the presence of an additional strong comodulator—a pathological synaptic transmission in the case of schizophrenia.

Parieto-occipital areas demonstrated strong cross-frequency correlations, and in addition these areas showed a spatial overlap between attenuation of LRTC in alpha and beta frequency ranges. Interestingly, posterior cortical areas are also associated with the generation of a P300 component (Polich, 2007), which is one of the most strongly attenuated event-related potentials in schizophrenia (Bramon et al., 2004; Jeon and Polich, 2001) indicating disrupted information processing. As we discussed above, abnormal neuronal dynamics might be an indication of affected underlying synaptic transmission, which in turn can also give rise to the attenuation of the P300 component.

In general a word of caution should be mentioned when interpreting sensor-space data. Due to the volume conduction cortical sources are not necessarily located right below the maxima of the topographies. However, we would like to mention that the topographies of alpha oscillations, obtained in the present study, are in line with the previously well-established topographies of cortical oscillations in sensor-space, showing large alpha oscillations for occipito-parietal areas (Niedermeyer, 1999; Nunez et al., 2001). The corresponding cortical sources, recovered with inverse methods, are usually located in the vicinity of these distributions (Babiloni et al., 2011; Gómez et al., 2006).

It is concluded that the attenuation of scaling exponents for alpha and beta oscillations in schizophrenia may be the result of the affected synaptic transmission accompanied by an increased variability in neuronal activity. A modulation of the neuronal dynamics by a similar and strongly dominating factor would similarly explain that these attenuations were correlated between frequency bands and brain regions. We hypothesize further that the attenuated temporal correlations on the scale of tens of seconds might relate to more random like neuronal activity, which ultimately can be associated with thought disorders in schizophrenia.

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