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Research report

Aberrant brain dynamics in schizophrenia: delayed buildup and prolonged decay of the visual steady-state response

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Abstract

In schizophrenia, aberrant brain activity has been reported both during stimulus processing and at rest. Evoked response amplitude is a function of both the number and synchronization of neurons firing in relation to a stimulus. It is at present unclear whether schizophrenia patients have normal synchronization of neural activity in relation to stimulus processing, and whether the amount and time course of synchronization is related to their evoked response amplitudes. EEG brain dynamics in response to visual steady-state stimulation were assessed in 12 schizophrenia and 12 healthy subjects at three stimulation durations (2, 4, and 6 s). Group differences in the visual evoked potential, the visual steady-state response, and the local coherence of the visual steady-state response were evaluated over time. Schizophrenia patients had smaller and delayed event-related potentials. Moreover, they had a slower buildup of steady-state amplitude following stimulation onset and a prolonged decrease after stimulation offset. Groups did not differ during mid-segments of steady-state stimulation. Increase in coherence to stimulation onset did not differ between-groups, but coherence decay of the visual steady-state response following stimulus offset was delayed in schizophrenia patients. The initial response to visual stimulation among schizophrenia subjects, therefore, may be reduced in amplitude due to weak signal strength, not poor coordination between distant cortical regions. The prolonged recovery function of schizophrenia patients' visual system may indicate abnormal nonlinearity in neural response. These findings have implications understanding the nature of evoked response differences between schizophrenia and normal groups especially in repetitive stimulus paradigms.

Theme J: Disorders of the nervous system
Topic: Neuropsychiatric disorders

Keywords: Schizophrenia; Visual; Steady-state; Event-related potentials; Coherence

1. Introduction

Studies of information processing in schizophrenia frequently rely on measures of event-related brain responses to transient stimuli. The predominant findings in these literatures are that schizophrenia patients have later and smaller event-related responses than do normal subjects [9,22,27,39]. The amplitude effect is especially prominent for lower frequency responses (in the theta and alpha ranges) after long (i.e. >3 s) inter-stimulus intervals [4,31,32].

The latency and magnitude of averaged event-related brain responses to transient stimuli are functions of both stimulus-evoked changes in phasic neural firing and stimulus-induced changes in background EEG activity [21,26]. First, presumably the more neurons are activated in response to a stimulus and/or the increased precision of their phase relationship the greater should be the evoked response power [11,33]. It is unknown how efficiently schizophrenia patients' neural ensembles respond in relation to transient stimuli. It seems reasonable to suppose, however, that either excitatory drive on [10] and/or coordination between [2] neurons firing in relation to a transient stimulus is (are) suboptimal in schizophrenia. Second, there is an inverse relationship between the amount of pre-stimulus theta activity and magnitude of the slow wave components of transient event-related responses [1]. Schizophrenia patients have more low frequency EEG activity than normal both at rest [8] and during the course of stimulus presentation [38]. The possibility that differences in background brain activity,

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rather than differences in stimulus-evoked neural firing, partially account for schizophrenia-normal event-related response amplitude differences cannot be refuted given the extant data.

There are, therefore, two questions to answer regarding the cause(s) of differences between schizophrenia and normal persons on evoked brain responses to transient stimuli. First, do schizophrenia patients have normal synchronization of brain activity in relation to stimulation, and is this synchronization related to magnitude of evoked responses? Second, are background brain activity differences associated with schizophrenia-normal differences in evoked brain response magnitudes? This report will address primarily the first question while providing information for subsequent research addressing the second question.

It is difficult to study the synchronous activity of neural responses using transient stimulation alone. Use of steady-state stimuli [28], however, allows for evaluation of both transient responses and the synchronous oscillation of neural ensembles [12,23,30]. Of additional benefit, steady-state responses as measured with EEG are associated with neural activity in the vicinity of any individual sensor [25], and transient and steady-state responses are similarly sensitive to cognitive manipulations [23,40], suggesting overlap in their neural generators.

Steady-state stimulation has been used in schizophrenia research to assess visual [6,15,17,36], auditory [18], and cognitive processes [20,34]. Researchers have not used steady-state responses to determine (1) whether schizophrenia and normal subjects have similar synchronization of neural activity, and, if so, (2) how long it takes to achieve similar synchronization, (3) whether synchronization among both schizophrenia and normal subjects is associated with magnitude of evoked responses, and (4) whether the decay functions for return of brain states to baseline differs between-groups. Addressing these four questions will be important for evaluating theories of schizophrenia's neuropathological and cognitive correlates and for devising future investigations addressing the causes of schizophrenia-normal differences on evoked response magnitudes.

In the present study, checkerboard stimuli flashing at 6.4 Hz were used to evoke transient and steady-state responses among schizophrenia and normal subjects. Stimulation (6 Hz) was selected because schizophrenia patients show a variety of deviations from normal on brain activity in the theta frequency range [4,8]. It is hypothesized that: (1) event-related potentials (P1–N1–P2 complex) to the onset of visual stimulation will be smaller among schizophrenia patients; (2) schizophrenia patients will take longer to reach asymptotic steady-state coherence and magnitudes than will normal subjects; (3) schizophrenia and normal subjects will not differ on steady-state coherence and amplitudes after prolonged stimulation; and (4) schizophrenia patients' brain states will take longer to return to baseline than normal. The latter hypothesis assumes that high background theta activity among schizophrenia patients is a function of higher than normal gain control in this frequency range. Such a neural system is more likely to reach saturation, resulting in, as with any other saturated amplifier system, significant nonlinearity, and increased settling time with prolonged echo effects, a state-of-affairs that could also generate hallucinatory phenomena [35].

2. Materials and methods

2.1. Participants

Twelve schizophrenia (DSM IV) in-patients (7 male, 5 female) were recruited from a local psychiatric facility. Their mean age was 30.4 (range: 18–54 years). The mean duration of Illness was 3.6 years. All patients were clinically stable on antipsychotic medication for >4 weeks (8 on atypical and 4 on typical antipsychotics). Of importance, the extant data are inconsistent with the thesis that these antipsychotic medications worsen steady-state visual evoked potentials [16]. Twelve healthy controls were matched for age (mean age 30.6, range 19–50 years), handedness (Edinburgh inventory), and gender status (i.e. 7 male, 5 female). All participants were paid for participation.

2.2. Stimuli and procedure

Stimuli were pairs of red checkerboards presented bilaterally to the left and right visual hemifields and synchronously flashing at a fixed rate of 6.4 Hz. They were presented on a 19-in computer monitor with a refresh rate of 70 Hz, and the red checks had a brightness of 6.3 Cd/m^2. Brightness was modulated as a square-wave function, synchronized to the refresh rate of the monitor, with five retraces of checkerboard presentation (71.4 ms) followed by six retraces of a black screen (85.7 ms), resulting in 6.4-Hz stimulation. Stimuli subtended a visual angle of 11° horizontally and 8° vertically, the eccentricity of the inner border of the stimuli to the left and right being 2.8°. Each checkerboard contained 8 × 8 checks and subtended 2.7° of visual angle, each check subtending 0.33°. The distance between the screen and the subjects' eyes was 1.7 m. The flashing stimuli were presented for 2000, 4000 or 6000 ms with an inter-trial interval that was randomly varying between 8000 and 12 000 ms. A fixation point was marked in the center of the screen and was present throughout the experiment. The order of presentation durations was randomized. Occasional pairs of checkerboards (8% of trials) differing in brightness of red (i.e. having a luminance of 12.3 Cd/m^2) served as target stimuli, and participants were asked to respond to these stimuli with a key press. Trials with target stimuli were not included in EEG analyses to avoid contamination with motor processes and brightness differences. Two blocks of 32 trials in each duration condition were presented, resulting in a total of 64 trials per duration. Subjects were first presented with examples of

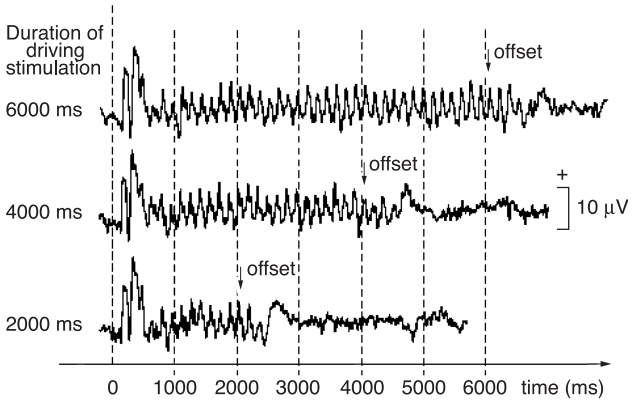

Fig. 1. Individual VEP traces for an individual subject at recording site Poz of the International 10–20 System. Time series are shown for the three duration conditions (2000, 4000, and 6000 ms) of steady-state stimulation.

the stimuli, and were asked to perform the task until it was clear that they understood the instructions and were able to properly perform the task.

2.3. Electrophysiological recordings

EEG recordings were made using a Neuroscan 64-channel system digitized at a rate of 400 Hz, referenced to Cz, and converted to the average reference off-line. EEG was segmented stimulus-locked to obtain epochs containing 1000 ms prior to and 8000 ms after onset of the stimulus train (see Fig. 1). Blinks were corrected using the algorithm proposed by [3]. Other artifacts were removed using BESA 2000 Software [3,13]. Subsequently, interpolation of bad channels (maximum = 3 bad channels) and removal of trials that contained remaining artifacts or excessive alpha was performed, based on visual inspection of each channel and epoch. Individuals with schizophrenia exhibited a slightly higher rate of trials discarded on that basis (mean = 7.2 bad trials, S.D. = 4.4) than control (mean = 4.9, S.D. = 2.1) trials, but this difference failed to reach significance.

2.4. VEP measures

Measures for VEP amplitude and latency at the initiation of visual stimulation were obtained by averaging across duration conditions. Based on grand average and visual inspection of individual VEPs, three time segments were identified, containing P1 (120–190 ms), N1 (190–290 ms) and P2 (290–390 ms) components of the VEP (see Fig. 2). These were measured at the posterior electrodes also used for SSVEP amplitude and coherence analyses, namely at sites Po7 and Po8 of the International 10–20 System, and their immediate neighbors (see Fig. 3). A similar approach for concurrently assessing VEP and SSVEP was proposed by Müller and Hillyard [23]. We defined the peak amplitude as the maximum deflection in the respective time segment. The latency of the maximum within each segment was determined following the same procedure. Differences in VEP amplitudes and latencies were evaluated using ANOVAs having the within-subjects factor LATENCY (P1, N1, P2) and the between factor GROUP (controls, patients). Post hoc comparisons were evaluated using Tukey's HSD test.

2.5. Spectral measures

Two parameters were used to assess oscillatory activity in EEG prior to, during, and after oscillatory stimulation, namely local spectral coherency and time-varying amplitude in the 6.4-Hz range. All spectral measures were determined for evoked activity as reflected in the VEP following time-domain averaging for epochs ranging from 1000 ms prior to 8000 ms after train onset. The 6.4-Hz

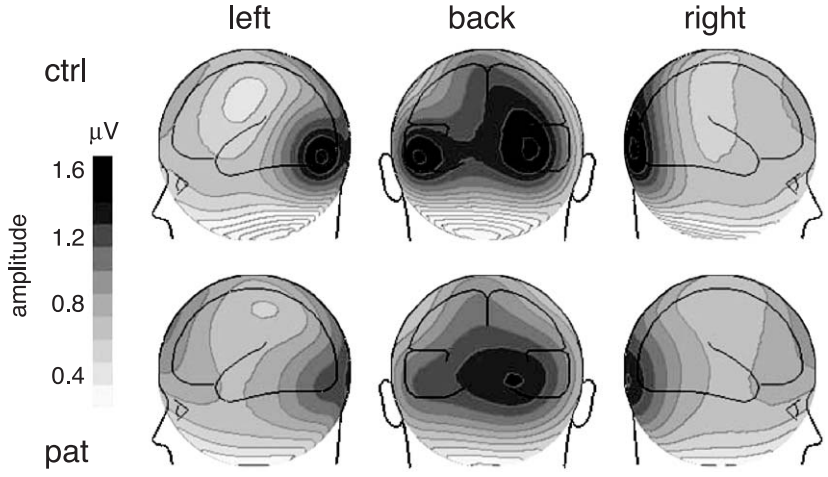

Fig. 2. Contour plots of grand averaged steady-state evoked response amplitudes averaged over all duration conditions and time for schizophrenia and normal subjects.

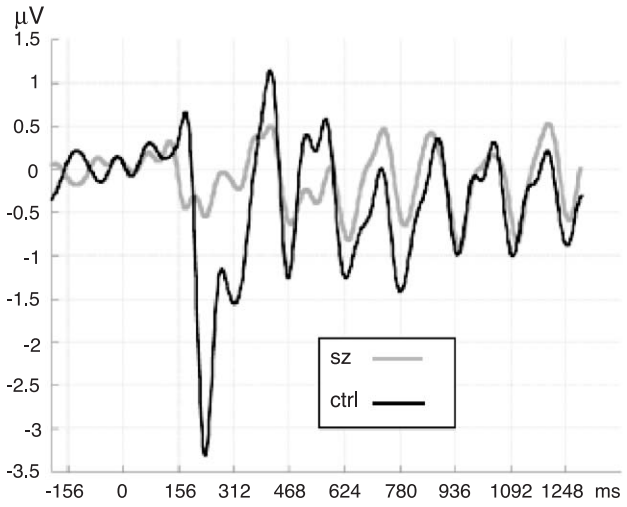

Fig. 3. Grand mean VEP signal for a regional electrode mean containing Po7, Po8 and their immediate neighbors. Time series are shown for schizophrenia patients ($n = 12$, gray line) and controls ($n = 12$; black line). Gridlines show the period of the 6.4-Hz steady-state stimulation. Note: positive is up.

components of the Fourier spectrum for these averaged VEPs were estimated in analysis windows of 125 sample points (312.5 ms), comprising overlapping, Welch-tapered Discrete Fourier Transform windows of 62 sample points (155 ms). This produced a frequency resolution of 6.4 Hz for the parameters in question. To obtain time-varying estimates of coherence and amplitude, the analysis window was shifted in steps of 50 ms (20 sample points) from 987.5 ms before to 7962.5 ms after stimulus onset, resulting in 180 estimates.

For each stimulus duration, magnitude-squared coherence was computed as an estimate of correspondence between signals recorded at different electrode sites in the frequency domain. To this end, we employed an approach similar to the one suggested by Shrinavasan et al. [33]. For time series x and y, recorded at pairs of channels within the cluster selected, spectra were determined for time-domain-averaged data as described above, using Welch's periodogram method [37]. Subsequently, the cross-spectral density (CSD) between channels was obtained as the product of complex DFT of x, multiplied by the complex conjugate of DFT of y, resulting in a complex vector reflecting cross-spectra at different frequencies. Coherence estimates were then determined as the squared absolute value (magnitude) of the CSD, divided by the product of power spectra for x and y. Magnitude-squared coherence can be regarded as an equivalent to linear correlation in the frequency domain. Compared to measures of phase-locking [19], coherence as used here is not independent of signal amplitude. Because we were interested in coherence changes as a function of time and condition, this measures seems appropriate for our purpose.

Mean *local spectral coherence* was estimated at the driving frequency of 6.4 Hz at two posterior electrode clusters located around sites Po7 and Po8 of the International 10–20 System, where the SSVEP signal was most pronounced (see Fig. 2). Mean coherence was obtained by estimating coherence between all pairs in these electrode clusters and computing an average after Fisher Z-transformation of each coherence index. Values were re-transformed to their original metric after averaging. Each cluster comprised Site Po7/Po8, respectively, and its five nearest neighbors. To control for effects of volume conduction, and to test the local specificity of findings, coherence for identical numbers of electrodes and time windows was computed at sites around Cz, where the SSVEP signal was small. As a second measure of SSVEP, we computed

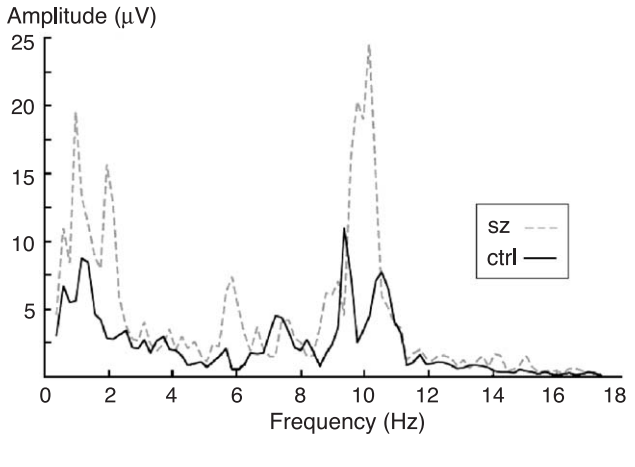

Fig. 4. Pre-experimental EEG power in the 12 s prior to the initiation of steady-state stimulation for schizophrenia and normal subjects.

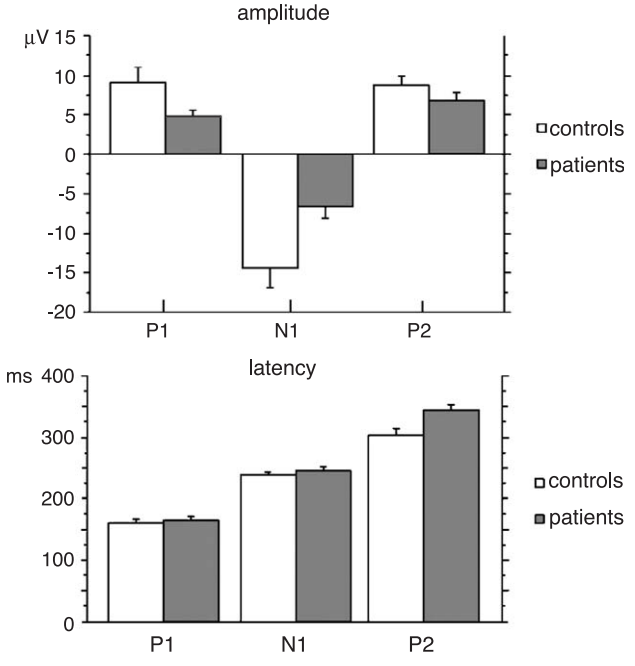

Fig. 5. Grand mean amplitude (top panel) and latency (bottom panel) for VEP deflections P1, N1, and P2, for controls (left) and schizophrenia patients (right). Bars indicate standard errors.

the time-varying amplitude of the SSVEP [24] for each stimulus duration and sensor by evaluating the complex modulus of the 6.4-Hz Fourier component. For statistical analysis, time averages of amplitude and coherence were formed in five 950-ms time windows. These comprised mean amplitude and coherence during (1) baseline (the 950 ms prior to stimulus onset), (2) first and (3) last second of steady-state stimulation (first and last 950 ms, respectively), and (4) first and (5) second second following offset of the steady-state stimulation. Mean coherence and amplitude means for the five time windows were submitted to ANOVAs with the between-subjects factor GROUP (2; patients, controls) and the within-factor TIME (5; baseline, ssr1, ssr2, offset1, offset2), for each of the duration conditions. Post hoc comparisons were evaluated using Tukey's HSD tests. Coherence and amplitude decay were evaluated by following up significant effects of TIME with linear trends (contrast analysis) for values in TIME segments 3 to 5 for each group separately. This analysis will reflect the amplitude and coherence trend after offset of stimulation with the expectation that the last second of SSVEP>first second after offset>second second after offset.

2.6. EEG during pre-experimental baseline

Spectra were computed to quantify the amount of EEG power as a function of frequency during the 12 s prior to initiation of the experiment with subjects fixating the central cross. The power spectra were derived using the same procedure as described above, but without the time-domain averaging given that there was only one 12-s epoch per subject.

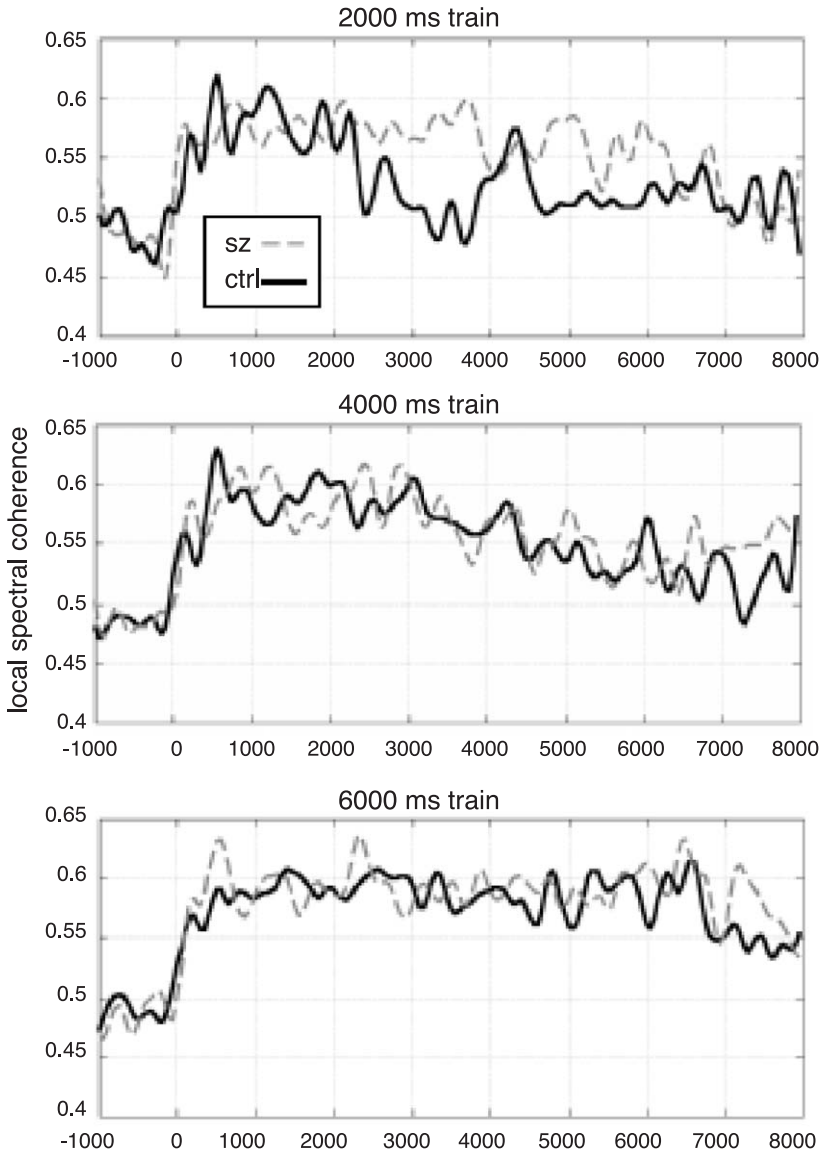

Fig. 6. Grand mean time course of local spectral coherence, computed at posterior sites around Po7 and Po8. Data from 12 schizophrenia patients (dashed gray line) and 12 control participants (solid black lines) are shown for three duration conditions (2000 ms, top; 4000 ms, middle; 6000 ms, bottom).

3. Results

3.1. Pre-testing EEG activity

As has been reported in multiple previous investigations, schizophrenia patients had significantly more power in the delta and theta ranges than did normal subjects (see Fig. 4). This figure also illustrates the significant difference in theta range activity between-groups, and further supports present use of the 6.4-Hz steady-state stimulus.

3.2. Behavioral results

No differences were found in the response accuracy for detection of the targets. Patients operated at a level of 86% correct responses and controls at a level of 89% correct responses. Differences of 41 ms were seen on reaction times, with schizophrenia patients being slower (mean = 516 ms, S.E.M. = 84 ms) than controls (470 ms; 54 ms), but this difference did not reach significance, $F < 1.0$.

3.3. VEP measures

VEP amplitude showed the predicted interaction of LATENCY and GROUP ($F(2,44) = 7.9$, $p < 0.01$), with schizophrenia patients showing decreased amplitudes for all the VEP components (Tukey's HSD p's < 0.05) and the greatest decrease in patients being present for the N1 component (see Fig. 5, top). VEP Latency was generally enhanced in the patients, compared to controls (GROUP: $F(1,22) = 5.9$, $p < 0.05$, see Fig. 5, bottom), which was due to significantly enhanced P2 latency in the patient group (LATENCY × GROUP: $F(2,44) = 4.1$, $p < 0.05$). Accordingly, tests revealed that only P2 latencies were greater in schizophrenia patients than in controls (Tukey's HSD $p < 0.05$).

3.4. Local coherence measures

Main effects of TIME were observed across duration conditions, reflecting variation of local spectral coherence as a function of stimulation (see Fig. 6), with enhanced coherence during stimulus presentation, compared to baseline and offset periods. This was the case for the 2000 ms ($F(4,88) = 14.9$, $p < 0.01$), 4000 ms ($F(4,88) = 22.9$, $p < 0.01$), and 6000 ms durations ($F(4,88) = 38.0$, $p < 0.01$). This effect interacted with GROUP only for the 2000 ms duration ($F(4,88) = 3.7$, $p < 0.05$), showing differential time course of coherence decay in schizophrenia patients versus controls. Tukey's HSD tests revealed that patients showed higher coherence during the second second after stimulation offset compared to controls. This effect was reflected in controls showing continuous linear decrease of local coherence for the last three TIME bins ($F(1,11) = 18.2$, $p < 0.01$), whereas the patients did not ($F(1,11) < 1$, see Fig. 7).

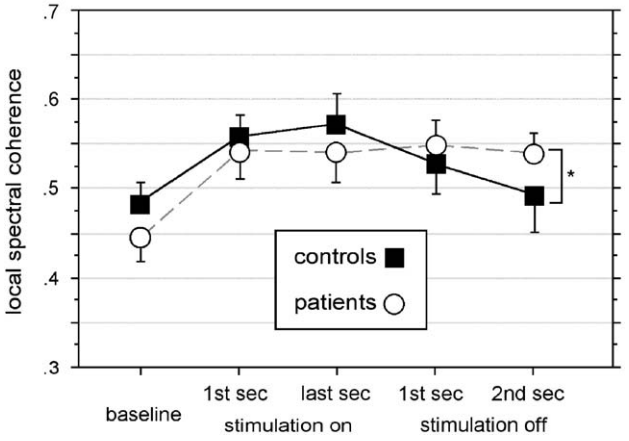

Fig. 7. Interaction plot showing mean local spectral coherence during baseline and subsequent time segments for the short (2000 ms) duration condition. Controls (black squares) had stronger coherence enhancement in response to stimulation than patients (white circles). After stimulation offset, patients' coherence decay was delayed compared to controls.

3.5. Amplitude measures

ANOVAs revealed a marked and fast increase of 6.4-Hz amplitude in controls that was absent in the patients (see Fig. 8). Also, power was enhanced when stimulation was present, demonstrating the presence of SSVEP. Accordingly, an effect of TIME was observed across duration conditions (2000 ms train: $F(4,88) = 29.3$, $p < 0.01$; 4000 ms train: $F(4,88) = 32.3$, $p < 0.01$; 6000 ms train: $F(4,88) = 35.8$, $p < 0.01$). This effect interacted with GROUP for the 2000 ms ($F(4,88) = 3.6$, $p < 0.05$), 4000 ms ($F(4,88) = 2.8$, $p < 0.05$), and 6000 ms durations ($F(4,88) = 3.5$, $p < 0.05$). Tukey's HSD tests indicated that, across categories, these interactions were due to a difference in the first second of steady-state stimulation, where controls showed maximum amplitude while the patients showed similar amplitudes during the first and last second of stimulation (Tukey's p's < 0.05), and lower amplitude among the patients during the last second of stimulation for the 6000 ms duration (Tukey's HSD $p < 05$). Accordingly, controls showed a more pronounced linear amplitude decrease following stimulation offset (linear trend 6000 ms duration: $F(1,11) = 23.7$, $p < 0.01$; 4000 ms duration: $F(1,11) = 19.2$, $p < 0.01$; 2000 ms duration: $F(1,11) = 18.7$, $p < 0.01$) than did the patients (6000 ms duration: $F(1,11) = 6.8$, $p < 0.05$; 4000 ms duration: $F(1,11) = 6.8$, $p < 0.05$; 2000 ms duration: $F(1,11) = 5.1$ $p < 0.05$).

3.6. Cz results

Local spectral coherence and regional amplitudes showed small but significant changes in response to steady-state stimulation. This finding is attributable to the effects of volume conduction and projection of posterior sources to more distant sensors. Importantly, analyses of the Cz data revealed smaller signal, enhanced noise, more inter-

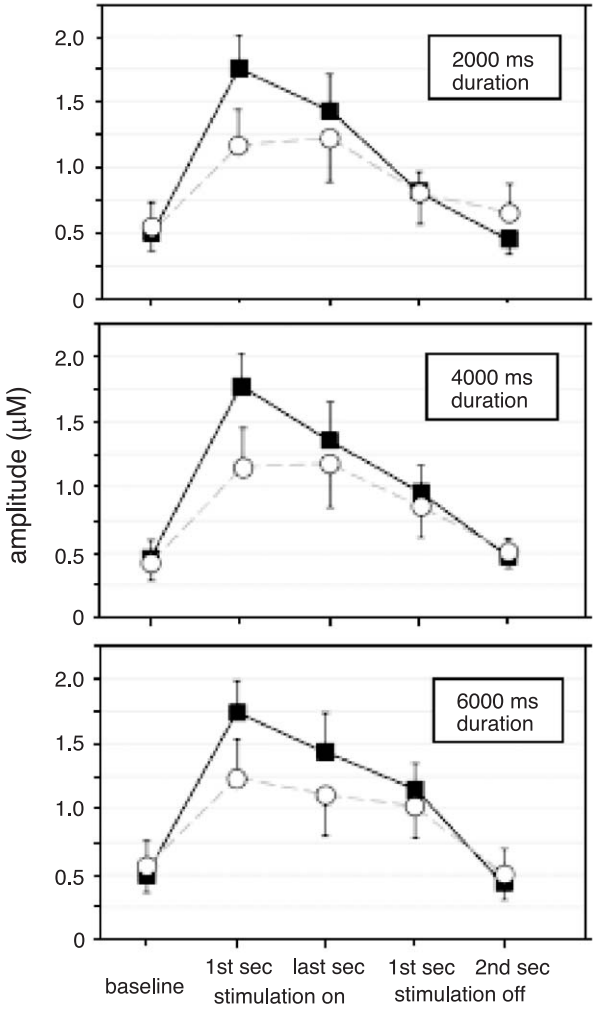

Fig. 8. Interaction plot showing mean 6.4-Hz spectral amplitude during baseline and subsequent time segments for the three duration conditions. Controls (black squares) showed stronger amplitude enhancement in the first second of stimulation than patients (white circles). For the long stimulation condition (bottom), the patients also had smaller amplitude during last second of stimulation.

group variability, and no significant difference between patients and controls on any measure.

4. Discussion

Our findings suggest (1) patients and controls differ regarding local coherence in visual cortical areas during post-processing periods, whereas during visual task performance, differences in coherence might not be present; (2) the decay of local coherence in time suggests that for shorter duration stimulation (2000 ms), a higher level of synchronization is maintained in the absence of stimulation in schizophrenia patients; (3) regardless of steady-state stimulus duration, controls have the same linear recovery function while schizophrenia patients have less pronounced recovery either because of prolonged decay of (for 2000 ms duration) or inability to maintain the steady-state response (for 6000 ms duration). The implications of these findings for understanding macroscopic brain responses recorded from schizophrenia patients will be discussed below.

Consistent with other research [4,9,27], schizophrenia patients had smaller VEP amplitudes, especially for the N1, than controls to the initiation of visual stimulation. This was true despite the fact that coherence during the first second of steady-state stimulation did not differ between-groups, suggesting that (1) there is not a simple relationship between local spectral coherence and VEP amplitude in patients and (2) lower evoked response amplitudes in schizophrenia are more likely a function of weak signal strength rather than poor coordination between distant cortical regions. There are two possibilities for why the largest schizophrenia-control difference occurs at the time of the N1: (1) because the amplitude of the transient evoked response at this latency is associated with cognitive processes, perhaps specifically related to attention [5], that are disrupted in schizophrenia; and/or (2) stimulus induced activity in the VEP frequency range, which happens to peak at the time of the N1, [29] is lower than normal during the initiation of the SSVEP among schizophrenia patients. The reduced amplitude effect was reflected in lower SSVEP amplitude during the first second of stimulation, which suggests that the VEP and SSVEP modulations cannot be differentiated if the driving frequency or its subharmonics are in the frequency range of the evoked response to transient stimuli. It will be important, therefore, to evaluate the generality of the present findings across different driving frequencies.

The present results provide clues about how effects associated with the evoked response to transient stimuli and/or stimulus-induced changes in background brain activity can be separated. For instance, it may be possible to evaluate whether schizophrenia patients differ on stimulus-evoked responses independent of background brain activity by providing transient stimuli during periods when background brain activity is equal between-groups. Measuring VEPs in response to transient stimuli during steady-state stimulation (when "background brain activity" has been "equalized" between-groups by a task-irrelevant steady-state stimulus) may provide an opportunity to disentangle effects associated with stimulus-evoked and stimulus-induced changes in neural activity [23,30]. Evaluating this possibility will be the purpose of subsequent investigations.

Differences in ongoing brain activity alone do not account for why schizophrenia and normal subjects differ only on evoked response amplitudes after long but not short inter-stimulus intervals [4,32]. One possibility for this effect, however, is related to the organizing influence of a stimulus. When stimuli are far apart in time, schizophrenia and normal subjects may differ more on evoked response amplitudes because of differences in background state. When stimuli are more closely spaced in time, the preceding stimulus may serve to similarly organize the neuronal firing of both schizophrenia and normal subjects. This possibility

suggests that it may be especially difficult to properly interpret between-groups differences on evoked response amplitudes in studies with widely different inter-stimulus intervals within a single trial (e.g. as in paired stimuli and mismatch negativity paradigms) [7,14]. For instance, in paired-stimuli studies, the first stimulus occurs after a long inter-stimulus interval (e.g. 8 s) and the second stimulus occurs after a short inter-stimulus interval (e.g. 500 ms). An interaction between subject group and ongoing brain dynamics as a function of inter-stimulus interval alone could account for between-groups similarities and differences on event-related response amplitudes. By using steady-state stimulation for optimal time periods, however, it may be possible to determine whether differences in evoked responses to transient stimulus events or induced changes in background brain dynamics account for schizophrenia-normal differences during repetitive stimulation studies.

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