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# Clozapine Increases EEG Photic Driving in Clinical Responders

*by Yi Jin, Steven G. Potkin, and Curt Sandman*

## Abstract

**Photically driven electroencephalography was tested in 17 chronic schizophrenia patients who were treated with clozapine for 5 weeks. Eight of the 17 patients showed clinical improvement on the Brief Psychiatric Rating Scale (Δ BPRS > 30%) while the other 9 patients remained unchanged (Δ BPRS < 15%). In comparison with the nonresponders, clozapine responders had a significantly greater increase in photic driving in the electroencephalogram (EEG), primarily in the low-frequency range of alpha band (7.2 hertz [Hz], 8.3 Hz, 9.0 Hz, and 9.6 Hz, but not 12.0 Hz). The difference in the resting EEG between the responders and nonresponders did not reach statistical significance. These findings suggested that EEG photic driving might be more sensitive than the resting EEG in detecting the central nervous system drug effect. Further analysis revealed that the increase of EEG photic driving was positively correlated with patients' clinical improvement. Combined with our previous observation in the drug-free schizophrenia patients who had lower EEG photic driving, present results supported the hypothesis that the amount of EEG alpha activity, particularly its synchronization to the external stimuli, could reflect the thalamic function in sensory information processing in schizophrenia.**

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The principal effects of typical neuroleptics on (electroencephalograms) EEGs are an increase in the power of slow activities and an enhancement of EEG synchronization. Because the EEG data have been obtained under varied experimental conditions, in different species, and with various neurophysiological approaches, it is difficult to derive unequivocal conclusions on the pharmaco-EEG profile for each neuroleptic.

In comparison with typical neuroleptics, clozapine (an atypical antipsychotic agent with unique efficacy and side effect properties) displays an atypical EEG profile. In animal studies (Longo 1978), clozapine has a marked synchronization effect by inducing slow waves and spindles in intravenous doses as low as 0.6 mg/kg. Volavka et al. (1981) reported that clozapine differed from the other neuroleptics by producing more EEG slowing and epileptiform activity. Using quantitative power spectral analysis and interactive interval analysis, Roubicek and Prosolt (1975) argued that, in contrast to the observations cited above, clozapine increases the energy in the high-frequency band. Other studies reported decreased power in the alpha frequency band with clozapine (Fink et al. 1979; Saletu and Grunberger 1988). Small et al. (1987), however, observed that schizophrenia patients who responded to clozapine treatment had significantly higher amplitudes in the alpha spectrum than nonresponders in the resting condition.

The present study was designed to (1) find the short-term clozapine

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effects on schizophrenia patients' resting and photic driving EEGs; (2) to identify the EEG changes following clozapine treatment in the various frequency bands and (3) in specific cortical regions; and (4) to determine whether these EEG changes can distinguish treatment responders from nonresponders (table 1).

## Methods

Seventeen *DSM–III–R*-diagnosed chronic schizophrenia patients (American Psychiatric Association 1987) consented to the study. The patients had a chronic course and had been relatively unresponsive to standard neuroleptic drugs. Each patient had a 3-week psychotropic drug washout period before entering the study. EEGs were performed at the end of the washout period and again at the end of a 5-week clozapine treatment. The dose of clozapine in the fifth week ranged from 300 to 500 mg per day. Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) ratings were made by a psychiatrist blind to the treatment condition of the dose at the end of the 3-week washout and again after 5 weeks of clozapine treatment.

**Photic Stimulation.** The test consisted of four experimental conditions, a 10-second resting period, and three 10-second periods of photic stimuli with fundamental frequencies of 2.4 hertz (Hz), 4.5 Hz, and 8.3 Hz. The sequence of the conditions was randomized by the interfaced digital computer and presented through a pair of goggles.

**EEG Recording.** Subjects were seated in a comfortable chair and were asked to close their eyes and relax throughout the testing period. EEG electrodes were placed at Fz, Pz, and Oz locations and referenced to linked mastoids. Electro-oculograms were also monitored simultaneously by the electrodes at both outer canthuses. These signals were amplified with a Nihon Hohden EEG–4321B polygraph with a band pass filter (0.1–35 Hz, –3 decibels). A threshold filter was established on each channel to diminish the contaminating effect of eye movements and other artifacts. EEG segments with any potential change greater than ± 75 μV were rejected. From the amplifiers, the EEG was directly sampled by a 10-bit AC–DC converter at the rate of 100 Hz.

**Data Analysis.** Eight EEG epochs for each condition were estimated by a fast Fourier transform routine with a 10-second rectangular window, through which four EEG power spectra were yielded in steps of 0.1 Hz. Energies of EEG responses to the stimuli at the fundamental frequencies or the frequencies of higher harmonics (integral multiplications of the fundamental frequencies) were measured. In the present study, four consecutive resting frequency bands, named delta (< 4 Hz), theta (4.1–7.0 Hz), alpha (7.1–12.0 Hz), and beta (> 12.1 Hz), and five frequencies (7.2 Hz, 8.3 Hz, 9.0 Hz, 9.6 Hz, and 12.0 Hz) of photic driving in alpha band were calculated (Jin et al. 1990).

## Results

After a 5-week treatment with clozapine, 8 of the 17 schizophrenia patients (6 males, 2 females, ages 29.3 ± 5.8 years) had a greater than 30-percent decrease in their BPRS score (mean = 40.9%) and were grouped as clozapine responders. The other 9 patients (8 males, 1 female, age = 31.6 ± 6.4 years) who had less than 30 percent BPRS change (mean = 8.0%) were grouped as nonresponders.

**Table 1. Percentage change[1] of resting electroencephalogram in clozapine responders ($n$ = 8) and nonresponders ($n$ = 9)**

| | Frontal | | | | Parietal | | | | Occipital | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Delta | Theta | Alpha | Beta | Delta | Theta | Alpha | Beta | Delta | Theta | Alpha | Beta |
| Responder | −10.1 | 105.2 | 67.1 | 43.4 | 7.9 | 54.4 | 65.8 | −48.2 | 20.5 | 90.4 | 117.1 | 23.9 |
| Nonresponder | 4.7 | 57.0 | 31.9 | 18.7 | 27.2 | 30.0 | 31.5 | −3.1 | 55.7 | 38.8 | 13.2 | 12.3 |

*Note.*—Repeated measures analyses of variance across three lobes, four bands, and two groups: $F$ = 0.26; $df$ = 1,13; $p$ = 0.62.

[1]Percentage change = 100 × (pre-post)/pre.

There were no significant differences in age or gender between the two groups (age: $p > 0.4$; sex: Fisher's exact test, $p = 0.58$).

Before the treatment, there were no significant differences of resting EEG ($F_{1,15} = 0.14$, $p > 0.5$) or photically driven EEG ($F_{1,15} = 0.05$, $p > 0.5$) between clozapine responders and nonresponders. Multivariate analysis of covariance (MANCOVA) was applied to address any influence of the baseline measures on the posttreatment results. MANCOVA of the percentage change after clozapine treatment in resting EEG across the four frequency bands (delta, theta, alpha, and beta) and three electrodes (Fz, Pz, and Oz) showed no difference between clozapine responders and nonresponders (table 1, $F_{1,15} = 0.06$, $p > 0.5$). Differences in resting alpha band over the three leads did not reach statistical significance either ($F_{1,15} = 1.83$, $p > 0.5$).

MANCOVA for group difference of the percentage change in EEG photic driving was statistically significant ($F_{1,15} = 12.60$, $p < 0.03$), indicating that overall increase of photic driving in the alpha frequency range is greater in treatment responders than in nonresponders (table 2 and figures 1–4). Main effects interactions of placement by group ($F_{2,29} = 1.32$, $p > 0.05$) and harmonic by group ($F_{4,59} = 2.53$, $p < 0.05$) were statistically significant. In responders, clozapine increased the power of photic driving in the alpha range across the three electrode placements except at 12.0 Hz. In nonresponders, however, only the responses at lower frequencies (7.2 Hz and 8.3 Hz) increased and did so to a smaller degree (figures 2–4).

Stepwise discriminant function analysis based on the change of EEG photic driving variables revealed a clear separation between the clozapine responders and nonresponders. Conservative jackknifed estimation showed an overall 94.1 percent correct classification. Only one case was misclassified.

Figure 5 shows the significant correlation ($r = 0.53$, $p < 0.05$) between the change in clinical improvement (BPRS) and the change in average EEG photic driving.

**Table 2. Percentage change of electroencephalogram photic driving in clozapine responders (CR) and nonresponders (NR)**

| | Frontal | | Parietal | | Occipital | |
|---|---|---|---|---|---|---|
| Frequency (Hz) | CR | NR | CR | NR | CR | NR |
| 7.2 | 223.9 | 47.8 | 158.2 | 85.9 | 260.8 | 87.0 |
| 8.3 | 41.1 | 22.0 | 38.8 | 11.6 | 88.9 | 14.9 |
| 9.0 | 72.1 | −25.9 | 81.1 | −26.9 | 148.2 | −40.3 |
| 9.6 | 41.6 | −36.1 | 78.3 | −34.6 | 80.1 | −34.3 |
| 12.0 | −18.4 | 0.5 | −5.6 | −4.7 | 31.1 | −30.7 |

*Note.*—Repeated measures analyses of variance across three lobes, five harmonics, and two groups: $F = 5.93$; $df = 1,13$; $p = 0.03$. Hz = hertz.

## Discussion

These results of EEG photic driving suggest that clozapine treatment responders have significantly greater increase of EEG response in the alpha range following photic stimulation than nonresponders. This effect is located not only at the frontal area but also at parietal and occipital locations. The augmentation of photic driving is more pronounced at the lower frequency range of alpha band (figures 1–4, 7.2 Hz and 8.3 Hz). Rice et al. (1989) reported that photic driving in alpha range is highly correlated with resting total alpha power, suggesting that the photic driving might share a common neural mechanism with the resting spontaneous alpha activity. If this is the case, the present finding supports the argument of Fink et al. (1979) and Saletu et al. (1986) that clozapine increases the abundance of slow frequencies. However, our study is not consistent with their finding that clozapine also has a specific influence on activity in the lower part of the beta band by increasing its power.

In the present study, clozapine treatment increased resting alpha EEG energy more in responders than in nonresponders, although statistical significance was not reached. To explain the difference between the photic driving EEG and resting EEG, we suggest that the driving is superior to the resting in terms of signal-to-noise ratio. Regan (1989) explained that the power of photic driving is concentrated into a few discrete frequency bands that are very narrow and must occupy a very small fraction of the total EEG bandwidth, whereas biological noise is distributed throughout the EEG frequency band. Consequently, the signal-to-noise ratio of such an evoked potential would be much greater within these narrow bands than at neighboring frequencies.

**Figure 1. Differences of percentage changes in electroencephalogram (EEG) photic driving between clozapine responders and nonresponders. Values of "Frontal," "Parietal," and "Occipital" are the total energy of all five EEG resonant responses in the alpha frequency range**

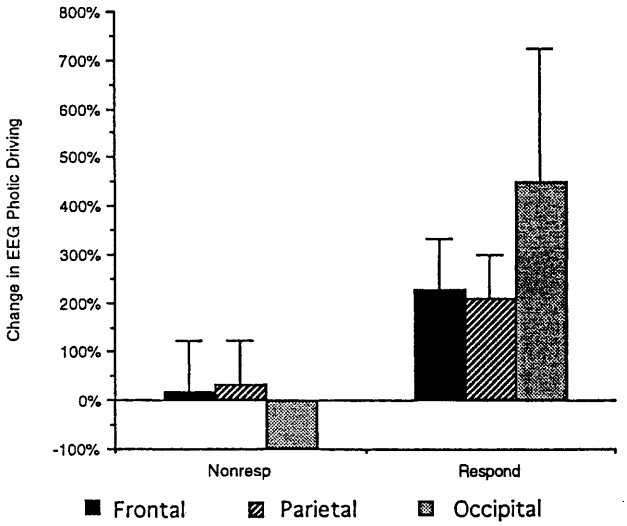



**Figure 2. Comparison of percentage changes in electroencephalogram (EEG) photic driving between clozapine responders and nonresponders at frontal area**

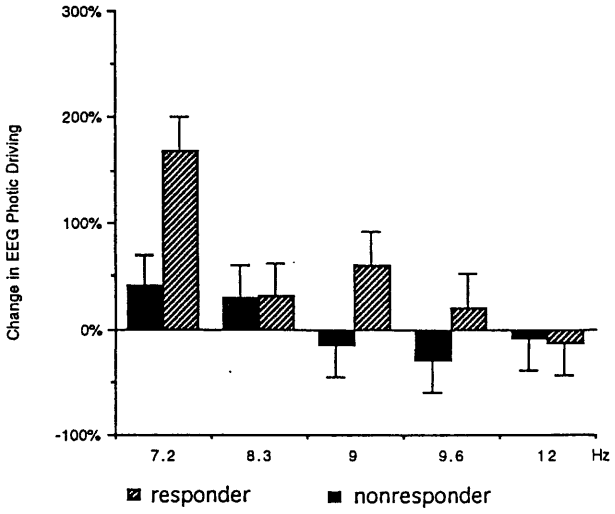



**Figure 3. Comparison of percentage changes in electroencephalogram (EEG) photic driving between clozapine responders and nonresponders at parietal area**

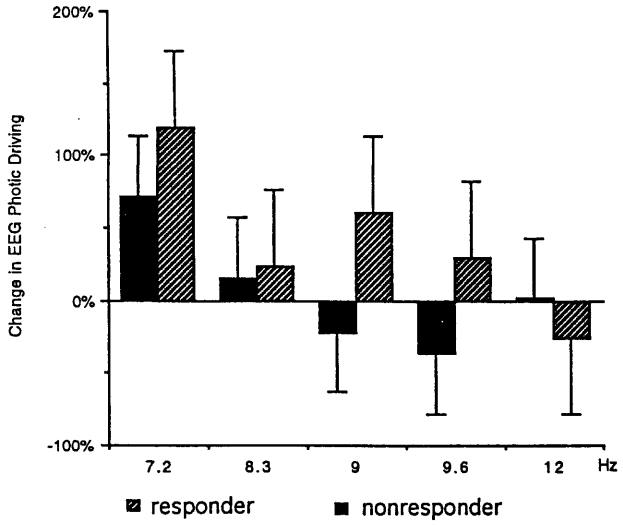



**Figure 4. Comparison of percentage changes in electroencephalogram (EEG) photic driving between clozapine responders and nonresponders at occipital area**

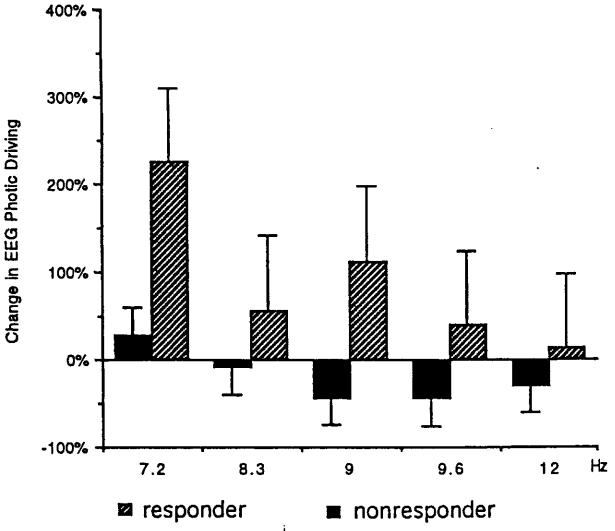
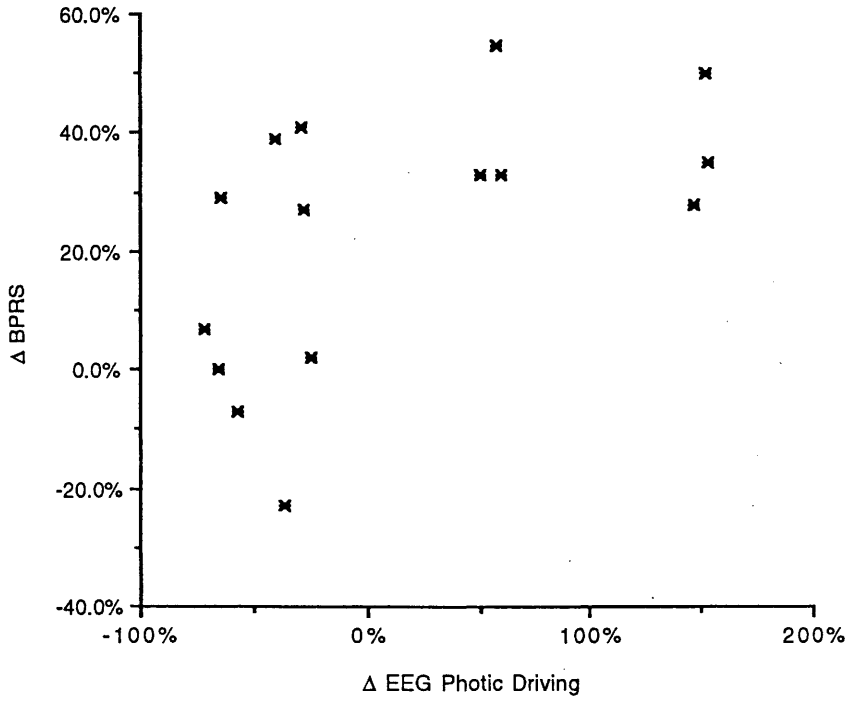


**Figure 5. Relationship between improvement of clinical symptoms (Δ BPRS) and percentage increase in electroencephalogram (EEG) photic driving in the alpha frequency range (Δ EEG) following a 5-week clozapine treatment ($n$ = 15, $r$ = 0.53, $p < 0.05$)**




BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962).

Discriminant function analysis on alpha-frequency photic driving demonstrated that the EEG paradigm used in the present study is sensitive and specific in differentiating the schizophrenia patients who are clinically responders to the clozapine treatment from those who are the nonresponders to the treatment.

Several studies have proved that the thalamus plays a critical role in generating synchronized EEG activities (Adrian 1941; Morisson and Bassett 1945; Anderssen and Anderson 1968; Villablanca 1974; Steriade and Llinas 1988; Lopes da Silva 1991). According to Carlsson's striato-thalamo-cortical model for schizophrenia (1988), the clozapine effects on EEGs may also be due to the direct blockage of dopamine receptors in the striatal neuronal pathway, which consequently releases the inhibition of the striatum on the thalamus. It is generally believed that the thalamus is working not only as a relay for afferent sensory information to the cortex but also as a unifying entity that operates as the ultimate gatemaster (Geyer and Braff 1987; Oke and Adams 1987; Bunney 1988; Carlsson 1988; Rice et al. 1989; Jin et al. 1990). Accordingly, the amount of synchronized EEG, particularly those to the external stimuli, may reflect the thalamic functioning in sensory information processing. In the present study, the differences of EEG photic driving between treatment responders and nonresponders may imply a biological difference in thalamic functioning between clozapine responders and nonresponders.

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