Abnormal EEG Responses to Photic Stimulation in Schizophrenic Patients

by Yi Jin, Steven G. Potkin, Dan Rice, John Sramek, Jerome Costa, Robert Isenhart, Chris Heh, and Curt A. Sandman

Abstract

Numerous studies have differentiated schizophrenic patients and normal controls in electroencephalography (EEG) spectral patterns recorded at rest. We replicated the resting EEG spectral differences between these groups and observed significant differences in periodic photic stimuli on the EEG spectra. Drug-free schizophrenic male patients (n = 8, mean age = 23.9) and normal male controls (n = 11, mean age = 24.3) were studied. Eighty seconds of EEG were collected from each subject for each of four experimental conditions: one resting and three photic-driving conditions (2.38, 4.54, and 8.33 Hz). Eye movement and other movement artifacts were minimized by use of an automatic amplitude threshold filter. Although large eye movements could be excluded as confounding factors, the filter could not for certain exclude small eye movements. Subjects were instructed to keep their eyes closed throughout. A significant difference was found between the groups both at rest and following photic stimulation in EEG activity. This result was characterized by increased delta activity and decreased alpha activity in schizophrenic patients at rest. The EEG activity following the photic driving also differentiated the groups. Schizophrenic patients had decreased sensitivity to the photic stimulation in the alpha range for spectra derived from both fundamental and harmonic analysis.

Electroencephalography (EEG) is one of the noninvasive techniques in the study of cerebral functioning. Before the ready availability of computerized data analysis, EEG frequencies had been distinguished by visual inspection into delta (0.5–3 Hz), theta (3–7 Hz), alpha (7–13 Hz), and beta (13 Hz and above) bands, with each successive frequency band considered to represent greater central nervous system arousal. The development of the fast Fourier statistical transformation stimulated the application of a variety of spectral analysis techniques that combine frequency and amplitude to reveal the relative power for each frequency or in various frequency bands (Johnson 1980).

Schizophrenic patients have more delta activity during rest than do normal controls and other psychopathological groups (Buchsbaum et al. 1982; Guenther et al. 1986). Some researchers have argued that this increased slow frequency activity is due to an excess of eye movement (Karson et al. 1987). Although the significance of these observations is uncertain, EEG abnormalities do correlate with cerebral structural and functional pathology of the brain. Low alpha frequency in schizophrenic patients is postively correlated with the enlargement of cerebral ventricles (Karson et al. 1988) and hypothesized to reflect abnormalities of alpha-generating structures bordering the cerebral ventricles. During the recording of resting EEG, the mental state of the subject is uncontrolled. Mental state can be controlled by employing a standard activation task while the EEG activity is being measured. However, it is difficult to assess alpha activity in the activated brain because most forms of stimulation block alpha activity (Lindsley 1961).

Reprint requests should be sent to Dr. S.G. Potkin, Dept. of Psychiatry and Human Behavior, University of California, Irvine Medical Center, 101 City Drive South, #88, Orange, CA 92668.

Vogel et al. (1974, 1985) developed a dynamic method of measuring the EEG "driving" response to photic stimulation that permits assessment of alpha during activation. EEG driving refers to synchronization of the EEG rhythm with the frequency of stimulation (e.g., flashing lights). Response to driving may reflect neurotransmitter functioning (Klaiber et al. 1972; Steriade and Llinas 1988). Amphetamine reduces alpha EEG response to driving, and phenothiazine enhances alpha driving (Vogel et al. 1974). The similarity of amphetamine psychosis to schizophrenia and the effectiveness of dopamine blockers in treatment of both conditions have provided much of the support for the dopamine hypothesis of schizophrenia. To the best of our knowledge, however, no power spectral studies of photic-stimulated EEG in schizophrenia have been reported. The purpose of the present study is to test the utility of photic-driving EEG spectra in schizophrenia.

Methods

Subjects. Eight male inpatients (mean age = 23.9) who met *DSM-III* (American Psychiatric Association 1980) criteria for schizophrenia participated in the study. All were drug free for 2 weeks before the EEG testing session. In addition, 11 healthy male volunteers (mean age = 24.3) with no personal or family history of psychiatric illness were age matched to the patient group.

Procedures. All subjects were seated in a comfortable chair (with neck and arm rest) in an acoustically and electrically shielded dark chamber adjacent to the room containing the experimental equipment. The subjects were instructed to relax and keep their eyes closed throughout the testing period. The testing period consisted of four different experimental conditions: one 10-second resting condition and three 10-second photic stimuli conditions. The stimuli had fundamental frequencies of 2.38 Hz, 4.54 Hz, and 8.33 Hz. (The power spectra corresponding to each of these three stimuli conditions are depicted in figures 1 and 2.) The order of presentation of the three stimuli was randomized. The photic stimuli were presented to the subject through goggles (Grass Instruments) and interfaced to a Grass Model 79 photic stimulator. The photic stimulator was controlled by a parallel distributed processing 11/34 computer. EEG activity was collected for the entire duration of each condition, so that 80 seconds (8 trials × 10 sec/trial) of EEG activity were collected for each condition from each subject (figures 1 and 2). Trials in which the threshold filter criterion was exceeded were not recorded by the computer and not subsequently analyzed.

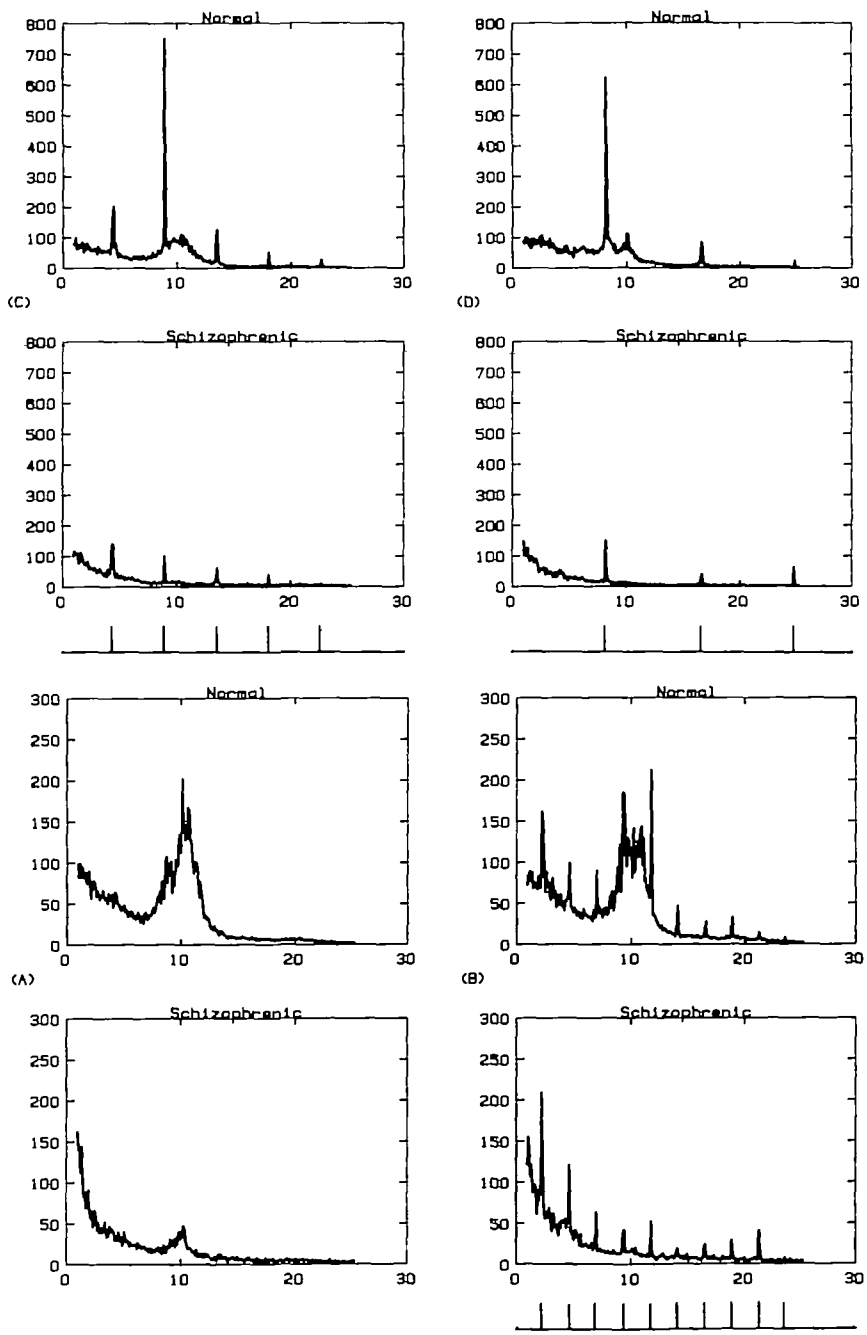
Recording. EEG activity was recorded with gold-cup electrodes placed with adhesive paste at the locations Fz and Pz of the international 10–20 system and referred to linked mastoids. These signals were amplified with Grass Model 7B amplifiers with the filters having corners at 0.1 and 35 Hz. From the amplifiers, the EEG activity was sampled by a 10-bit A/D convertor at the rate of 100 Hz. To eliminate eye movement and other artifacts, a threshold filter was used to automatically reject the trials with waveform amplitudes greater than 150 microvolts (peak-to-peak). Preliminary studies of intentional eye movements (blinking and horizontal movements) in the eyes-closed condition indicated that the threshold was effective in detecting large artifacts. One hundred percent of the EEG trials with these intentional blinks and horizontal eye movements were rejected. Neither blinks nor intentional large horizontal eye movements affected the recorded EEG activity during the driving conditions. The possibility of contamination due to small (1° to 3°) eye movements could not be excluded by our procedure.

Results

Resting EEG data and EEG data during driving conditions were analyzed separately across electrode placement, the three fundamental driving frequencies (2.38, 4.54, and 8.33 Hz), and the harmonics generated for each of the driving frequencies. Power for each frequency band was normalized before further analysis by dividing power at a given frequency response by total power. Two analyses were computed: (1) a mixed model analysis of variance with repeated measures for electrode placement and driven spectral harmonics, and (2) a stepwise discriminant function analysis to generate equations that best separated normal controls from schizophrenic patients.

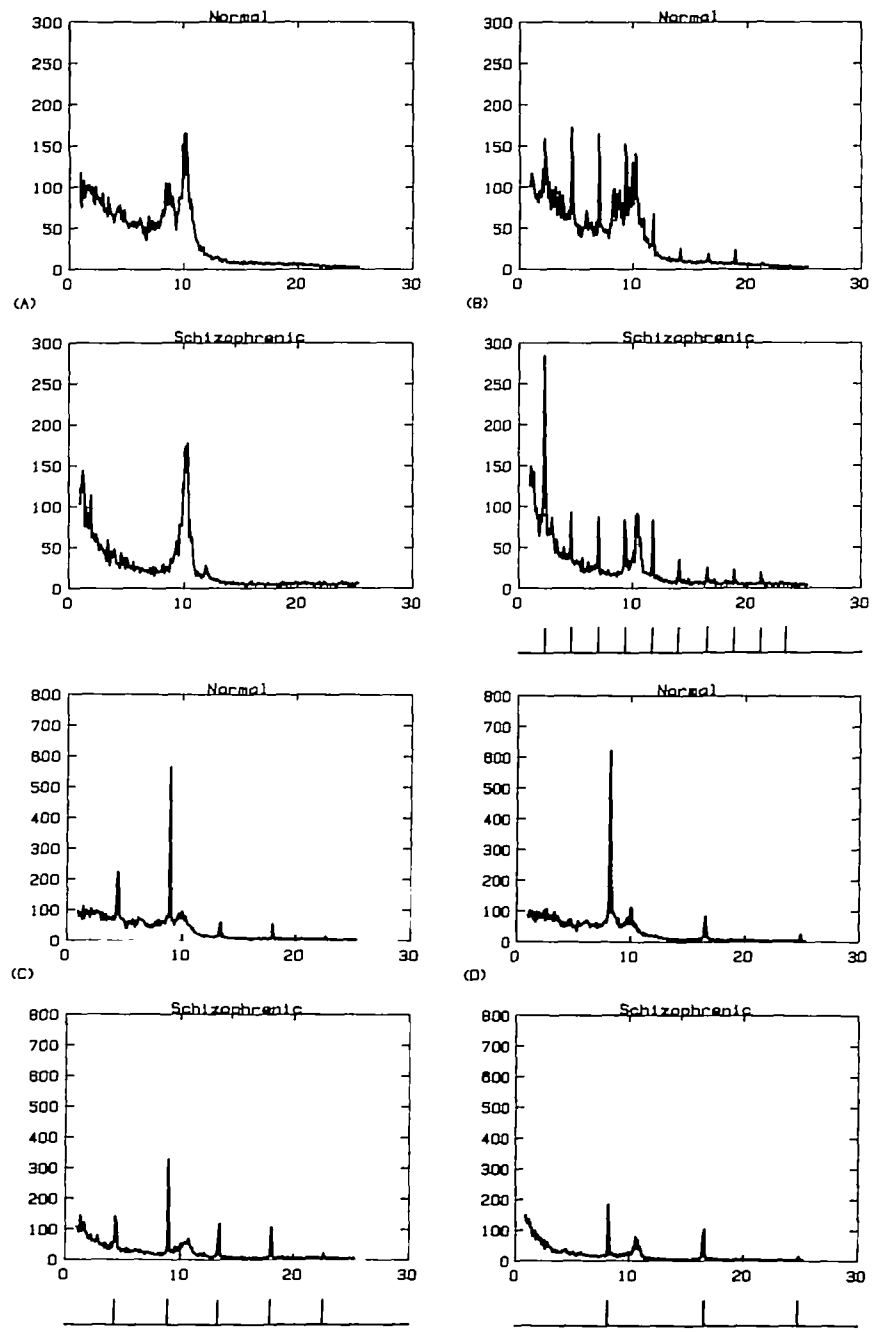
Resting Condition. Differences between schizophrenic patients and normal controls in resting EEG were obtained from the result of a multivariate analysis of variance by comparing spectral profiles first for total power and then separately for delta, theta, alpha, and beta frequency bands. Total power was not significantly different at Fz ($F = 0.02$, $df = 1,17$, $p < 0.89$) or at Pz ($F = 2.13$, $df = 1,17$, $p < 0.16$) placements. Schizophrenic patients had more relative power than did

Figure 1. Difference of frontal electroencephalographic power spectra between normal controls and schizophrenic patients



Note.—(A) resting condition; (B) low frequency (2.38 Hz) stimulus condition; (C) median frequency (4.54 Hz) stimulus condition; (D) high frequency (8.33 Hz) stimulus condition.

Figure 2. Difference of parietal electroencephalographic power spectra between normal controls and schizophrenic patients



Note.—(A) resting condition; (B) low frequency (2.38 Hz) stimulus condition; (C) median frequency (4.54 Hz) stimulus condition; (D) high frequency (8.33 Hz) stimulus condition.

controls in the delta frequency at Fz ($F = 7.57$, $df = 1,17$, $p < 0.01$) but not at Pz ($F = 1.45$, $df = 1,17$, $p < 0.24$) placement. Although the threshold filter was applied, the probability of small eye movement contamination on the frontal channel had not been ruled out. Schizophrenic patients had less theta power at Pz ($F = 9.52$, $df = 1,17$, $p < 0.01$) but not at Fz ($F = 0.07$, $df = 1,17$, $p < 0.80$) placement. They also had less alpha power at Fz ($F = 7.57$, $df = 1,17$, $p < 0.01$) and a trend toward less at Pz ($F = 4.02$, $df = 1,17$, $p < 0.06$) placements than normal controls. In summary, schizophrenic patients had less frontal alpha and more frontal delta power in their resting spectral EEG.

Driving Conditions. Before analyzing the effects of driving on EEG activity, the spectra were normalized by dividing power at each frequency response by the total power of each condition. Main effects for diagnosis ($F = 9.91$, $df = 1,17$, $p < 0.01$), photic-driving frequency ($F = 37.92$, $df = 2,34$, $p < 0.01$), and harmonic ($F = 122.36$, $df = 4,68$, $p < 0.01$) were statistically significant. As expected, the driving frequency × harmonic interaction was significant ($F = 9.44$, $df = 8,136$, $p < 0.01$), indicating that harmonic power was related to driving frequency. The electrode placement × driving frequency interaction ($F = 3.20$, $df = 2,34$, $p < 0.05$) reflected a different response at the Fz and Pz placements. Significant three-way (diagnosis × harmonic × driving frequency) ($F = 2.51$, $df = 16,192$, $p < 0.01$) and four-way (electrode placement × diagnosis × harmonic × driving frequency) ($F = 2.08$, $df = 16,192$, $p < 0.01$) interactions were further analyzed with simple effects tests.

The power for all harmonics in the alpha range was significantly greater and topographically distinct in normals as compared with schizophrenic patients (see table 1). Specifically, over the lead of Fz (figure 1), the harmonics of the 2.38 Hz stimulus were significant at the frequencies of 7.14 Hz ($p < 0.01$), 9.52 Hz ($p < 0.01$), and 11.90 Hz ($p < 0.01$). Only the second harmonic (9.08 Hz) of 4.54 Hz stimulus ($p < 0.05$) and the fundamental frequency of the 8.33 Hz stimulus ($p < 0.01$) reached statistical significance. The pattern in Pz was slightly different (figure 2). The second (4.76 Hz) ($p < 0.05$) and third (7.14 Hz) ($p < 0.01$) harmonics of low frequency stimulus and the fundamental frequency at 8.33 Hz were significant (table 1).

Discriminant Function Analysis

Three variables all in the alpha frequency (Fz: 9.52 Hz, $F = 15.07$, $df = 1,17$; Pz: 9.08 Hz, $F = 6.59$, $df = 1,16$; Pz: 9.08 Hz, $F = 10.52$, $df = 1,14$) were selected in the stepwise discriminant function analysis on the basis of their multivariant F value. Ninety-five percent accuracy of group classification was achieved in the conservative Jackknifed classification procedure using these three alpha variables.

Discussion

Consistent with previous investigations (Morihisa et al. 1983; Guenther et al. 1986), the present study indicates that at rest, schizophrenic patients have more power than normal subjects in the delta range over the frontal regions. Karson et al. (1987) argued that increased slow delta activity over frontal region was due to an excess of undetected eye movement. Since schizophrenic patients do exhibit more eye movement and blinking than normal subjects, this is an important methodological consideration (Stevens 1978; Matsue et al. 1986). However, in the present study, most eye movements and other artifacts would trigger our automatic filter and would not be recorded. Our analyzed data represent eight 10-second epochs in which the threshold filter was not triggered.

The general problem of artifact filtering is complex, as discussed by Karson et al. (1987). The threshold filtering may confuse paroxymal brain activity with artifact and may not detect small artifacts, which may have a cumulative effect. Therefore, it is important to be aware of the possible contaminating effect of eye movements on EEG data, particularly that for frontal slow activities. However, these artifacts still could not account for all the differences in the photic-driving experiments.

In an ongoing replication study of 8 additional schizophrenic patients and 11 normal subjects, we used simultaneous electrooculogram (EOG) channel recording. A difference between schizophrenic patients and normal controls in alpha range spectra following photic driving was observed when spectral power (< 2 Hz) in the EOG channel was covaried ($F = 8.04$, $df = 1,46$, $p < 0.01$). Also, no spectral differences between normal controls and schizophrenic patients were seen in the EOG channel in the trials accepted for analysis by the threshold filter.

Normal subjects display two predominant types of harmonic EEG responses to the photic stimuli: the first is at the fundamental frequency of the stimuli and the second is at

Table 1. Relative power of electroencephalographic response to photic stimuli in normal controls (N) and schizophrenic patients (S)

Response	(Hz)	Stimulation (SD)											
		Frontal placement						Parietal placement					
		(L) 2.38 Hz		(M) 4.54 Hz		(H) 8.33 Hz		(L) 2.38 Hz		(M) 4.54 Hz		(H) 8.33 Hz	
		S	N	S	N	S	N	S	N	S	N	S	N
Delta	2.38	0.034 (0.011)	0.029 (0.005)					0.035 (0.012)	0.030 (0.005)				
Theta	4.54			0.025 (0.008)	0.029 (0.013)					0.026 (0.009)	0.031 (0.010)		
	4.76	0.016 (0.006)	0.016 (0.003)					0.015[1] (0.004)	0.018 (0.003)				
Alpha	7.14	0.015[1] (0.003)	0.019 (0.003)					0.016[2] (0.004)	0.023 (0.006)				
	8.33					0.022[2] (0.007)	0.045 (0.015)					0.024[1] (0.005)	0.040 (0.021)
	9.08			0.017[1] (0.004)	0.045 (0.020)					0.024 (0.011)	0.033 (0.019)		
	9.52	0.015[2] (0.004)	0.032 (0.009)					0.019 (0.008)	0.028 (0.009)				
	11.90	0.011[2] (0.004)	0.022 (0.009)					0.015 (0.002)	0.014 (0.004)				
Beta	13.62			0.013 (0.006)	0.018 (0.010)					0.017 (0.008)	0.014 (0.004)		
	16.66					0.012 (0.008)	0.020 (0.012)					0.015 (0.014)	0.016 (0.005)
	18.16			0.009 (0.004)	0.010 (0.004)					0.010 (0.006)	0.010 (0.004)		
	22.70			0.006 (0.002)	0.008 (0.003)					0.007 (0.003)	0.006 (0.002)		
	25.00					0.008 (0.009)	0.008 (0.005)					0.006 (0.004)	0.006 (0.002)

Note.—L = low frequency; M = medium frequency; H = high frequency.

[1] $p < 0.05$.
[2] $p < 0.01$.

the alpha frequency band regardless of the frequency of stimulation (see figures 1 and 2). This pattern does not occur among the schizophrenic patients. Schizophrenic subjects have spectral peaks to the fundamental frequency of the stimulus, but do not have robust harmonic responses in the alpha range.

EEG changes at different conditions have been viewed as an index of central neurotransmitter functioning (Klaiber et al. 1972; Vogel et al. 1974; Steriade and Llinas 1988). Carlsson (1988) reviews evidence for a strong striatal dopaminergic influence on the thalamus via striatopallidothalamic circuit. Interestingly, dopaminergic and adrenergic stimulants such as norepinephrine, monoamine oxidase inhibitors, and amphetamines

tend to reduce the occurrence of EEG driving responses (Jorgensen and Wulff 1958; Wilson and Glotfelty 1958; Vogel et al. 1974) while dopaminergic blocking agents such as the phenothiazines tend to enhance these responses. Similarly, amphetamines mimic or exacerbate schizophrenic symptoms while phenothiazines block amphetamine effects and ameliorate schizophrenic symptoms (Fischman 1987; Freedman 1987).

Other studies suggest that the excitation of the thalamocortical system characterized by desynchronization of EEG activities is mainly controlled by brainstem reticular neurons (Steriade et al. 1977; Kitsikis and Steriade 1981). The probable neurotransmitters involved in this system are acetylcholine (Matsuoka and Domino 1972; Smith et al. 1988) and some peptides (Krnjevic and Schwartz 1967), which excite the sensory relay neurons and depress the inhibitory neurons (Singer 1973).

The potential utility of the EEG spectral profile seen in schizophrenia for purposes of classification was addressed in the stepwise discriminant function analysis. Schizophrenic patients were separated (Jackknifed classification) from normals with a discriminant accuracy of 95 percent with three variables all in the alpha range. Our discriminant function analysis requires replication in view of the small number in our sample. In the aforementioned ongoing replicatory study, 83 percent discrimination was observed with the variables in alpha range.

The attenuated EEG response during photic stimulation in schizophrenic patients is consistent with possible dysfunction in stimulus and information processing. Thalamic filtering is hypothesized to be inhibited by increased dopamine at the level of the striatum that via striatopallidothalamic circuits modulates the thalamus (Swerdlow and Koob 1987; Carlsson 1988). This thalamic effect could be reflected by altered alpha activity at rest and most particularly in response to stimulation. Failure of the thalamus to filter sensory information to the cortex has been hypothesized (Carlsson 1988) to be relevant to the information-processing deficit and to the production of schizophrenic symptoms. Our study demonstrated an alpha rhythm dysfunction in schizophrenic patients both at rest and following photic stimulation. The value of this methodological approach of using photic-stimulated EEG, particularly in the alpha frequency range, is suggested by its relative freedom from eye movement artifact and its power to clearly separate schizophrenic patients from normal subjects.

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The Authors

Yi Jin, M.D., is Staff Research Associate, Department of Psychiatry and Human Behavior, University of California Irvine Medical Center. Steven G. Potkin, M.D., is Professor and Director of Psychiatry Research, Department of Psychiatry and Human Behavior, University of California Irvine Medical Center. Dan Rice, Ph.D., is NIH postdoctoral fellow, Brain Imaging Center, Department of Psychiatry and Human Behavior, University of California, Irvine. John Sramek, Pharm. D., is Psychopharmacology Consultant, Metropolitan State Hospital, Norwalk, CA. Jerome Costa, M.D., is Director of Research, Metropolitan State Hospital, Norwalk, CA. Robert Isenhart is Research Engineer, Department of Psychiatry and Human Behavior, University of California Irvine Medical Center. Chris Heh, M.D., is Assistant Professor in Residence and Attending Chief, Research and Special Treatment Unit, Department of Psychiatry and Human Behavior, University of California Irvine Medical Center. Curt A. Sandman, Ph.D., is Professor in Residence and Vice Chair, Department of Psychiatry and Human Behavior, University of California, Irvine.