

Stable quantitative EEG difference in post-LSD visual disorder by split-half analysis: evidence for disinhibition

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Abstract

Hallucinogen persisting perceptual disorder (HPPD) may follow the ingestion of LSD or other hallucinogens in a subset of users. It is characterized by chronic, intermittent or constant visual hallucinations of many sorts persisting beyond the period of acute drug effects. We studied 44 LSD-induced HPPD subjects and 88 matched controls to search for spectral and evoked potential differences using quantitative EEG (qEEG). HPPD subjects demonstrated faster alpha frequency and shorter VER (visual evoked response) latency, consistent with prior animal and human data on response to acute LSD administration which suggest LSD-induced cortical disinhibition. AER (auditory evoked response) latency was prolonged consistent with a differential LSD effect upon visual and auditory systems. The exploratory *T*-statistic significance probability mapping (T-SPM) technique demonstrated HPPD-control differences mostly involving temporal and left parietal scalp regions, confirmed by a split-half analysis. Significant variables were all derived from the long latency flash VER and click AER. None were derived from spectral analyzed EEG data. Canonical correlation between SPM-derived measures and variables reflecting disease severity was highly significant. A between-group stepwise discriminant analysis based upon a full set of qEEG measures demonstrated 87% prospective classification success by jackknifing and 88% success in a separate split-half analysis.

Keywords: Evoked potentials; Electroencephalographic brain mapping; Hallucinogen persisting perceptual disorder

1. Introduction

While drug abuse appears to have been declining over the past half decade, the use of LSD has

steadily risen (Johnston et al., 1993). In 1994 the lifetime prevalence rate of LSD use among high school seniors was 10.5%. Evidence suggests some subjects may suffer long-term consequences from LSD use. Prolonged visual disturbances in certain individuals following LSD have been described for nearly 40 years (Cooper, 1955; Hollister, 1962; Rosenthal, 1964; Robbins et al., 1967; Horowitz, 1969; Holsten, 1976). In a phenomenological study

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of 123 LSD users, LSD 'flashbacks' were described as being predominantly visual, characterized by altered perceptions lasting from fractions of a second to 5 years in duration (Abraham, 1983). Representative symptoms included geometric pseudohallucinations, false fleeting perceptions in the peripheral fields, flashes of color, and afterimagery. These symptoms were stable in half of the sample over a 5-year period, and comprised more enduring phenomena than momentary 'flashbacks' of previous LSD trips. Commonly these phenomena were precipitated by entrance into a dark environment or other conditions of autonomic arousal such as startle. Subsequent psychophysical studies of visual function in LSD users and non-using controls found abnormalities in color identification, dark adaptation and flicker fusion perimetry consistent with chronic visual disinhibition following LSD use (Abraham, 1982; Abraham and Wolf, 1988).

Animal studies provide further evidence for electrophysiological change induced by LSD. In 1952, Delay et al. first described faster alpha frequencies in rabbits following the acute administration of LSD. Alpha acceleration was subsequently verified in cats, humans, and other species (Rinkel et al., 1952; Bradley and Elkes, 1953; Gastaut et al., 1953; Itil and Fink, 1968; Brawley and Duffield, 1972). In 1959, Koella and Wells reported that the latencies of visually evoked potentials (EPs) in rabbits were shortened by LSD.

Faster EEG alpha and short EP latency following acute LSD administration suggests 'enhanced' neural processing. Several lines of evidence suggest that the serotonin-2 (5-HT₂) receptor may be involved in this process, since affinity for the 5-HT₂ receptor correlates with the potency of hallucinogenic drugs (Glennon et al., 1984), and has been found on inhibitory interneurons in the rat pyriform cortex (Aghajanian et al., 1968). Recently Garratt et al. (1993) found that in the rat facial motor nucleus, a region rich in 5-HT₂ cells, LSD resulted in generating a current greater than that generated by 5-HT, and with a prolonged duration (McCall, 1986). Therefore, we hypothesized that LSD disrupts the inhibitory function of 5-HT₂ in HPPD (hallucinogen persisting perceptual disorder), and that such disinhibition

is measurable with quantitative EEG by faster alpha rhythms and shortened EP latencies in HPPD. We also asked whether latency shortening would be limited to the visual system (the source of most hallucinations in HPPD) or might also be seen in the auditory system. On a broader scale we also used the *T*-statistic significance probability mapping (T-SPM) technique (Duffy et al., 1981) to search for electrophysiological differences that might further characterize patients with HPPD, hypothesizing that posterior cerebral regions involved in visual information processing would be more involved than anterior ones. Given the potentially opportunistic nature of the T-SPM approach, we adopted a split-half replication design. Furthermore, we sought to assure ourselves that qEEG variables as a group correlated with clinical symptomatology including the severity of visual disturbances, latency of onset of the disorder from first exposure to LSD, total number of LSD exposures, and the duration of symptoms.

2. Methods

2.1. Recruitment, inclusion, and exclusion criteria

Forty-four HPPD subjects were recruited over a 6-year period from 1988 to 1993. Sources of referral were from clinicians and self-referrals of subjects seeking consultation. Inclusion criteria were (1) prior use of LSD on at least one occasion; (2) personal experiences of acute affective, perceptual and cognitive changes while using LSD consistent with established symptoms of such experiences; (3) description of the physical form of LSD used consistent with published descriptions (blotter, sugar cube); (4) the absence of hallucinations prior to the first use of the LSD; and (5) the development of chronic daily or continuous (more than once a day) pseudohallucinations evocative of past acute LSD experiences lasting for more than a month, and only occurring after the use of LSD was initiated. Exclusion criteria were (1) presence of current psychosis; (2) medical history consistent with a physical explanation for visual hallucinations; (3) pre-existing diagnosis of seizure disorder; and (4) use of any psychoactive drug within 10 days of evaluation. All subjects were

screened using (1) DSM-III-R criteria for post-hallucinogen perceptual disorder (currently HPPD in DSM-IV); and (2) a visual disturbances inventory for current and lifetime visual hallucinations and pseudohallucinations (Abraham, 1983). Subjects underwent structured diagnostic interviews with a board-certified psychiatrist. Five measures of post-LSD symptomatology were obtained including: (1) the presence or absence of a life history of panic disorder by DSM-III-R criteria, since earlier work by our group reported that uncomplicated panic disorder subjects have a clustering of sensory EP abnormalities localized to the non-dominant temporal region (Abraham and Duffy, 1991); (2) the severity of the visual symptomatology, which was derived from the sum of all disturbances described by each individual from the visual disturbances inventory; (3) the total number of LSD uses in a lifetime; (4) the latency between first dose and onset of chronic symptomatology in months; and (5) the duration of symptomatology in months.

2.2. Population characteristics

2.2.1. HPPD subjects

Subjects ranged in age from 16.6 to 47.4 years. They were matched to 88 control subjects from 15.5 to 47.4 years. Group mean ages did not differ by *T*-test (LSD = 30.1 years, controls = 30.1 years). There were no significant differences in group proportions for handedness and gender by chi-square test (HPPD: males/females = 38/6, right/left = 39/5; controls: males/females = 75/13, right/left = 77/11). The HPPD group described a mean of 8.1 ± 2.9 different forms of lifetime visual disturbances following LSD, with a mean duration of symptoms of 8.97 ± 7.52 years and a median lifetime LSD dose of 16 exposures verified by direct interview recounting each exposure and summing them (range, 1–871). All subjects were free of all psychoactive substances for at least 10 days prior to undergoing a qEEG at the Clinical Neurophysiology Laboratory of the Boston Children's Hospital (CH). Eighty-eight individuals were selected from a pool of over 500 carefully screened and previously studied healthy normal subjects aged 15–70. As closely as possible, subjects were selected, on a two to one basis,

to match the LSD population by age, gender, and handedness. Control subject selection was done by a technologist blind to the data and the objectives of the study. All 88 subjects had been carefully screened to exclude systemic, neurologic and psychiatric illness by a physician. As previously described, all potential subjects with a history of alcoholism, drug abuse of any sort, learning disability, severe head trauma, epilepsy, hypertension, chronic lung disease, kidney disease, diabetes, coronary artery disease, cancer or psychiatric illness were excluded (Duffy et al., 1993a). All controls were screened for overt neurological or medical disease by a physician, and for cognitive abnormality by a psychologist. All were medication free at the time of evaluation and were followed for 2 years after data collection to be sure none subsequently developed neurological disease or disease with impact upon the central nervous system (CNS). All controls had been gathered at CH in the very same laboratory and under the same protocol and equipment as used for study of the LSD subjects.

2.3. Neurophysiologic data acquisition

As described previously (Duffy et al., 1980; Morihisa et al., 1983; Abraham and Duffy, 1991; Duffy et al., 1993a), EEG data were gathered while awake during resting state with eyes open (EOP) and resting with eyes closed (ECL). Long latency EPs were derived to strobe flash (visual evoked response, VER) and to tone-pip (auditory evoked response, AER). Considerable care was taken to minimize artifact due to eye movement, eyeblink, muscle tension, mouth and tongue movement, and gross body or head movement. In the eyes-open states, subjects were given fixation targets and were instructed to suppress blinking but were allowed frequent time outs or 'blink holidays'. In the eyes-closed states thin, fully transparent soft film was laid gently over the eyes to provide the subject with feedback of residual involuntary eye-blinking. The EEG was continuously monitored to detect and avoid state change (e.g. drowsiness).

Data were obtained from 20 scalp electrodes (standard 10–20 placement plus O_z) and four other bipolar electrodes strategically placed to

monitor artifact in the form of vertical and horizontal eye movements and muscle tension resulting from the face, jaw or scalp. A vertical eye movement bipolar channel was placed above and below the right eye. As right and left eye channels typically correlate above 0.8 (unpublished data) and as ophthalmic pathology was not expected in these populations, a left eye vertical movement monitor was not used. A second bipolar pair was placed between the two outer canthi to measure lateral eye movement. A third bipolar channel was recorded between two electrodes placed just below the mid-zygoma bilaterally. This placement is sensitive to temporal and other anterior muscle artifact. A fourth bipolar channel was placed over the posterior neck muscle approximately 3 cm below electrodes O_1 and O_2 . This placement is very sensitive to posterior muscle artifact and EKG. Following amplification by a Grass model 24-D EEG polygraph set to bandpass from 1–300 Hz (Hertz), data were stored for subsequent analyses on a Honeywell 5600E 2-channel FM analogue 1 tape recorder (0–625 Hz bandpass) along with appropriate trial and event markers. A through-system sine wave calibration signal of 100 μ V peak to peak at 10 Hz was recorded for all channels. Data were analyzed off-line after low pass filtering below 90 Hz and digitization at 256 Hz per channel. In this manner, contamination of the EEG spectral frequencies due to undersampling of higher frequency noise (aliasing) was avoided. EEG data utilized for spectral analysis were gathered in 2-s segments which were visually inspected off-line, and those containing artifact were eliminated from subsequent analyses. A minimum of 1 min (30 2-s segments), but often over 2 min, of artifact-free EEG activity was used to form the final mean spectrum for each subject. All spectral data were log-corrected before analysis (Gasser et al., 1982; Zar, 1984; Pollock et al., 1990). As has been our experience (Duffy, 1988), EP data did not significantly deviate from Gaussianity by the *W*-statistic (BMDP program 2D) and needed no correction. EP segments containing eye blink or motion artifact were eliminated on the basis of individually adjustable over-voltage criteria. A minimum of 200 segments, to a maximum of 500 segments, formed the final averaged

EP. EP data were visualized for 512 ms before as well as after time of stimulus onset.

Visual stimuli (consisting of high intensity stroboscopic flashes) were delivered from a sound-dampened Grass photostimulator Model PS-2, set at intensity 8, placed 25 cm from the subject's closed eyes. At such high intensities pupillary dilatation is not necessary and was not used (Skalka and Holman, 1986). A white-noise generator masked residual clicks. Stimuli were delivered on a pseudorandom basis. The mean interstimulus interval was 2.3 s (range, 1.79–2.82 s). High intensity auditory stimuli were delivered through binaural earphones at 92 dB sound pressure level. The clicks consisted of 50-ms tone pips at 960 Hz with 10-ms rise and fall times. The delivery schedule was the same for the visual stimulation. EEG was carefully monitored for artifact and drowsiness during EP presentation. Off-line data processing was performed on a Masscomp 5000 digital computer. A Nicolet software package was employed for off-line digitization of tape-recorded signals, artifact removal, spectral analysis, signal averaging, topographic mapping, and generation of numerical measures (Duffy et al., 1979, 1981). The end products for each EEG state were 24 spectra and for each EP state 24 EPs, one spectra or EP from each channel (20 scalp and four artifact). Details of this procedure have been previously described (Duffy and McAnulty, 1988).

Two measurements of alpha were generated from ECL data, one reflecting mean alpha frequency and one overall alpha amplitude. First, the mean frequency at each occipital electrode (O_1 , O_z , O_2) was calculated over the 7–13 Hz extended alpha band (Matejcek et al., 1986) using a 'center of gravity' calculation (Duffy et al., 1993b; Savage et al., 1994). This technique for defining dominant alpha frequency was preferred to visually locating the peak in the alpha spectral range since the latter may be indistinct, ambiguous, or of unusual morphology making measurement difficult. Second, alpha amplitude at peak was measured for all three occipital electrodes.

The latency to peak of two major EP components was determined for the AER and VER in the topographic region of their corresponding

overall maximum amplitudes, central C_3 , C_z , and C_4 electrodes for the AER and occipital O_1 , O_z , and O_2 electrodes for the VER. For each electrode, two broad latency ranges were defined, one to permit detection of the first large negative component peak (N_1) and the second to facilitate detection of the second large positive component peak (P_2). For the AER, N_1 was defined between 48 and 160 ms and P_2 between 100 and 260 ms. For the VER, N_1 was defined between 32 and 120 ms and P_2 between 80 and 280 s. The center of gravity technique was used to estimate each component's peak latency in ms, a process much less sensitive to waveform irregularities at or near the component's peak amplitude, and somewhat more sensitive to the overall wave shape of the component (Duffy et al., 1993a; Savage et al., 1994). For example, if a component were asymmetrical about its peak, the centroid would fall more towards the side with larger area beneath the curve. The sets of 24 spectra or 24 EPs, corresponding to the 24 recorded channels, were topographically transformed into a corresponding series of topographic maps of brain electrical activity (Duffy et al., 1979). Data reduction was achieved by banding the EEG spectra in the 4-Hz wide spectral range from 0.5–32 Hz. Early latency of EP data was initially reduced by banding in ten 20-ms wide segments from 50 to 250 ms, chosen because EP factors, derived by principal components analysis, seldom involve time periods less than 50–75 ms and often involve longer periods (Rebert, 1978; Duffy et al., 1990). If a given 20-ms EP band subsequently demonstrated significant between-group difference, the band was moved forward or backward in time in steps of 4 ms to maximize group difference, but adjacent bands were not allowed to overlap in time. From 250–450 ms, banding involved five 40-ms epochs as later components are longer than earlier components. Thus, maps represented the EEG spectral energy in a given 4-Hz band or the EP amplitude in a 20- or 40-ms wide latency range for the 20 scalp electrodes. Regions of interest (ROI) that represented differences among the age groups were identified, using the T -statistic SPM technique (Duffy et al., 1981). These were formed by mapping the between-group T -test at each electrode.

ROIs were identified where the interpolated values exceeded a selected criterion level. In many instances, a value of $T = 2.00$ was chosen which approximated the $P \leq 0.05$ two-tailed level. When T levels were high and/or when $T = 2.00$ delineated an excessively wide scalp region, a higher level, $T = 4.00$, was chosen. To avoid artifact contamination, only ROIs without statistically significant T -values in the four concurrent artifact channels (and for EEG in the beta 5 guard band) were selected. Thus the ROIs were free of significant artifact from vertical and horizontal eye movements and from temporal or occipital muscle activity. Numerical measures were created for each subject corresponding to each ROI (Fig. 1) by using each ROI as a spatial-spectral (FFT data) or spatial-temporal (EP data) template (Duffy et al., 1981, 1984, 1993a). For each subject and ROI, the average value over all data values was determined for all electrodes within the spatial spectral or spatial-temporal limits of the ROI. When two or more EP ROIs followed one another in time and demonstrated very similar spatial patterns by simple visual inspection, they were combined for the creation of numerical measures.

The BMDP statistical software package was employed (Dixon, 1988). To minimize the effects of a wide age range upon the ROI-generated measures, data were first Z transformed by comparison to age-appropriate groupings of our normative data base (John et al., 1988). Effects of age were removed from alpha and EP peak measures by regression (BMDP program 6R). Group difference was estimated by discriminant function analysis (program 4M). The relationship between all clinical measures of LSD symptomatology and electrophysiological measures was assessed by canonical correlation (program 6D). Estimates of Gaussianity employed program 2D.

3. Results

3.1. Alpha measures

Alpha centroid measures demonstrated significant between-group differences for all three occipital electrodes, with higher frequencies for the

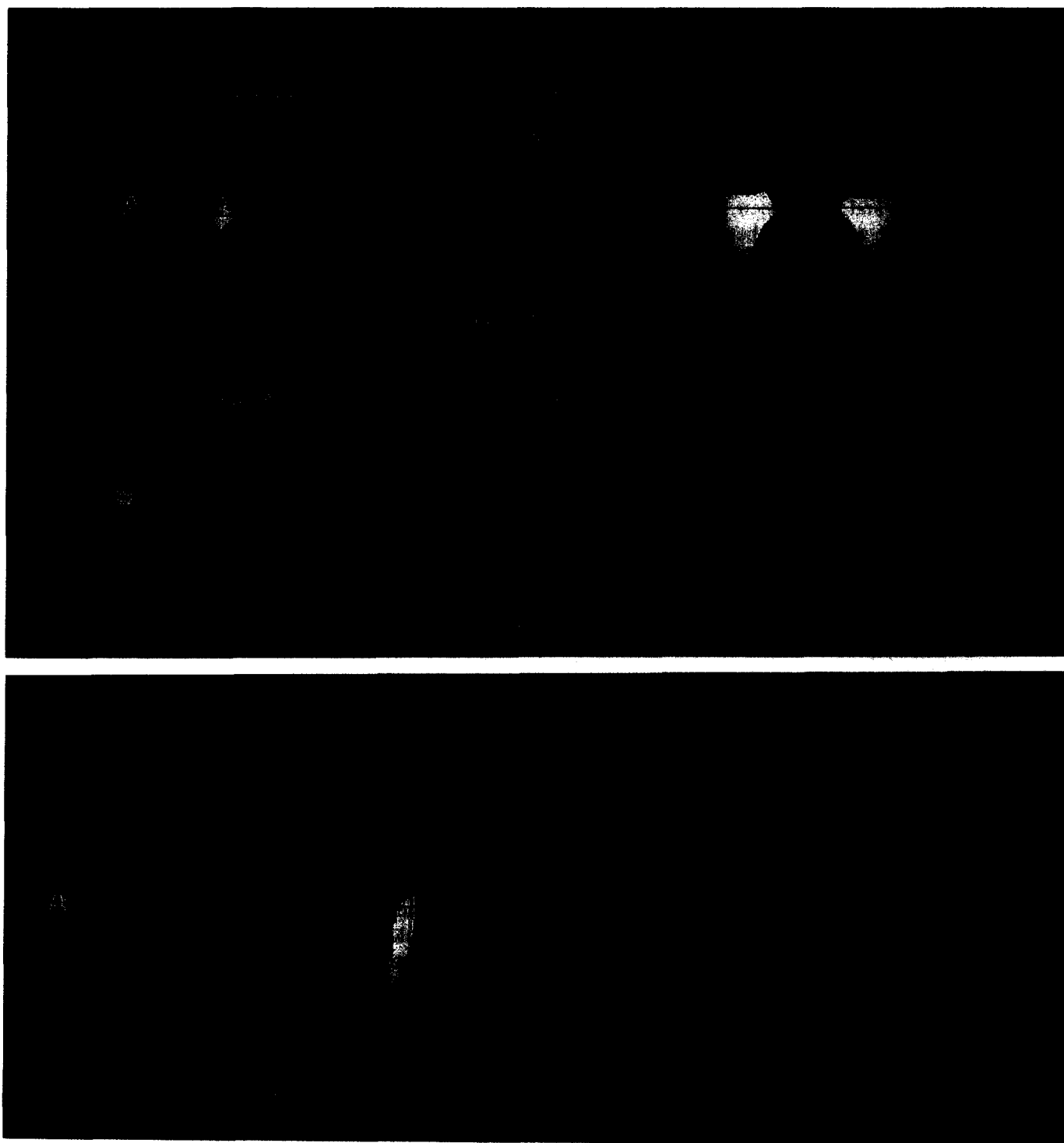


Fig. 1. (*Top*) Illustrative cases of qEEG abnormalities in HPPD. **Case 1A:** A 26-year-old computer programmer used LSD at the age of 18 on 15 occasions; 31 months later the patient experienced the abrupt onset of an intense LSD-like set of visual and

Table 1
Alpha centroid variables

State	Peak	Electrode	LSD mean	Control mean	T-value	P-value
ECL	Alpha	O ₁	9.84	9.68	2.044	0.05
ECL	Alpha	O ₂	9.84	9.70	2.707	0.01
ECL	Alpha	O ₂	9.83	9.68	2.646	0.01

LSD group in each case (Table 1). No significant differences in alpha amplitude were found.

3.2. EP component latencies

For the VER, there were no significant N₁ latency differences; however, strong P₂ differences were evident at all three occipital electrodes with the LSD group demonstrating a shorter peak latency in each instance (for O₁, $P < 0.01$; for O₂, $P < 0.001$; and for O₂, $P < 0.001$). For the AER, the N₁ latency demonstrated significant between group differences by

T-test at C₃ and C₄ but not C_z, with the LSD group exhibiting longer latencies. No P₂ AER difference was noted (Table 2). There was no significant difference in any EP component latency between HPPD subjects with or without evidence of panic disorder by T-test.

3.3. Group differences by SPM

No between-group difference was delineated by the T-SPM procedure using relative or absolute spectral data in the EOP and ECL states. However, 11 of 40 possible combined VER and AER

affective disturbances lasting a night. At 25, he suffered the spontaneous onset of hourly flashing white lights centrally and black dots in his peripheral fields which have continued for the past 10 years. Topographic brain maps are shown during the 380- to 420-ms epoch of the visually evoked potential. The upper left map represents the subject's data and the upper middle map the age-appropriate control data for the same post-stimulus latency epoch. The right upper image is a significance probability map (SPM) showing Z-scores resulting from a comparison of the data underlying the upper two maps. Values above $Z = 2.00$ are shown as orange tinged white. Note the region of statistically deviant Z-scores in both mid posterior temporal regions. Maximum Z-value was 2.61 SD at electrode T₄. Indicated scale relates to the Z-SPM. This SPM matches findings found in analyses of all HPPD subjects compared with Controls using a T-statistic in Fig. 3, V372 Region of Interest. **Case 2:** A 23-year-old musician used LSD on 16 occasions over a 4-month period at the age of 20. Within 2 months, he began to notice a progressive, continuous visual disorder characterized by flashes of color, persisting afterimages, haloes around objects, a grainy texture to the sky, and the lingering trails of objects as they passed through his visual field. The graininess in the visual field interfered with night vision. He suffered a panic attack on at least one occasion, but visual symptoms were not correlated. Topographic brain mapping is illustrated during the 260- to 300-ms epoch of an auditorily evoked potential study in the same format as Fig. 1A. Values greater than $Z = -4.00$ are shown in blue-tinged white. Note the region of statistically deviant Z-scores in the left posterior temporal region. Maximum Z-score was -5.14 in the left posterior temporal (T₃) electrode. This SPM finding is comparable to that found in analyses of all HPPD subjects compared to Controls using a T-statistic in Fig. 3, A252 Region of Interest.

Fig. 2. (Bottom) T-Statistical probability maps for two sensory evoked potential variables in HPPD compared with controls. Each represents the T-test of the 44 member LSD population compared with the 88 member control population. Red-orange colors mean a positive deviation and blue colors a negative deviation of the LSD population mean values from control mean values. Both images are scaled from zero to maximum T-value achieved, shown as either red-white or blue-white. In Fig. 2A, the SPM corresponding to the flash VER for 20 ms starting at 96 ms is shown. Maximum T-value was $+3.30$ at electrode T₄. ROI V96 was derived from this SPM as all regions with T-values above $+2.00$ (Fig. 2). Electrodes T₄, T₆, C₄, and P₄ within the ROI were used to for the numerical feature corresponding to ROI V96. In Fig. 3B, the SPM corresponding to the click AER for 40 ms beginning at 332 ms is shown. Maximum T-value was -4.96 at electrode P₃. ROI A332 was derived from this SPM incorporating all regions with T-values below (more negative than) -4.00 . In combination with A252 and A292, A332 was used to form the numerical feature called A252 involving electrodes P₃, T₅, and O₁. P₄ was not included as it did not pass criterion T level for the full 120 ms of A252.

Table 2
Evoked potential peak centroid variables

State	Peak	Electrode	LSD mean	Control mean	T-value	P-value
AER	N ₁	C ₃	101.60	96.81	2.044	0.05
AER	N ₁	C _z	100.85	96.51	1.833	NS
AER	N ₁	C ₄	102.15	97.07	2.223	0.05
AER	P ₂	C ₃	183.75	189.25	1.743	NS
AER	P ₂	C _z	180.08	186.17	1.867	NS
AER	P ₂	C ₄	183.99	189.87	1.893	NS
VER	N ₁	O ₁	72.90	72.08	0.317	NS
VER	N ₁	O _z	70.75	69.65	0.454	NS
VER	N ₁	O ₂	69.37	70.66	0.533	NS
VER	P ₂	O ₁	168.36	180.86	3.324	0.01
VER	P ₂	O _z	160.61	163.15	3.958	0.001
VER	P ₂	O ₂	164.21	179.56	4.186	0.001

T-SPM values demonstrated ROIs exceeding the $P \leq 0.05$ level. Five were derived from AER and six from VER data. Four ROIs (Figs. 2 and 3) prominently involved the right mid- to posterior temporal region (V96, V144, A124, A144). Four broadly involved the left posterior quadrant (V240, A252, A292, A332). Three regions were broadly bihemispheric, one bifrontal (A60) and two bi-temporal but also involving adjacent central regions (V332, V372). For the production of numerical measures, three combinations were made on the basis of spatial similarity: (V332 + V372), (A124 + A144), and (A252 + A292 + A332). Measures resulting from such combinations are subsequently referred to by the designation of the first ROI of the series. As expected, all seven numerical measures demonstrated significant between-group differences by *T*-test (Table 3) even after regression for age. To estimate the stability of the ROI-generated measures, we divided our entire population in two on the basis of position within the data file (odds and evens). Next we compared the HPPD and control populations within each half, measure by measure. Note that all but A124 demonstrated similar responses on both values of the population. In addition, there was no significant difference in the entire HPPD population on any ROI-derived measure between those with a history of panic attacks and those without by *T*-test.

3.4. Discriminant analysis

All 132 subjects (44 HPPD and 88 control) were studied by stepwise discriminant analysis. The seven ROI-derived EP variables, all three ECL alpha centroid variables, and the three EP centroid latency variables reaching significance at the 0.01 level or better (VER P2) were allowed to enter stepwise discriminant analysis. A back-stepping approach was used. Based upon just four remaining variables (V240, A124, A252, and O₁ alpha ECL, denoted as O_{1C}), a 33:1 subject to variable ratio, the discriminant function was significant (Wilk's lambda = 0.538 $F = 27.25$, $df = 4, 127$, $P \leq 0.0001$). Eighty-seven percent of all subjects were correctly classified directly and by jackknifing (Table 4A).

Next we proceeded with a split-half design test of a discriminant function of EPs, using BMDP 7 M's ability to randomly assign subjects into training and test sets. Here the choice of variables and the discriminant function were based upon the training set. The training set's discriminant function was then applied to the test set. Once again all 13 variables were entered and then the back-stepping process allowed to proceed. 7 M randomly assigned 63 subjects (42 control, 21 HPPD) to the training set and 69 subjects (46 control, 23 HPPD) to the test set. The inequality of the sets was determined by the random seed algorithm of 7 M. Four variables were again chosen (V144,

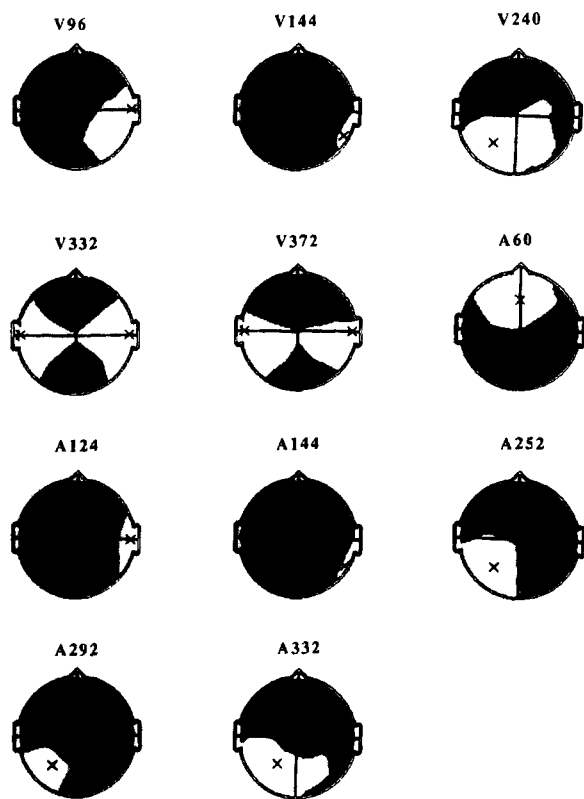


Fig. 3. Statistically derived regions of interest in HPPD compared with controls. Eleven regions of interest are shown in white upon a black background within schematic maps of the head. Above each ROI is the corresponding numerical feature's designation with V standing for VER and A for AER. The numerical portion of the name refers to the start of a 20- or 40-ms post-stimulus epoch. These ROIs were derived from *T*-statistic SPM as described in the text. Two standard deviations were used to define all ROI except for V240, A252, A292, and A332 where four standard deviations were used. All ROIs are shown for 20-ms epochs except for V332, V372, A252, A292, and A332 where 40-ms epochs were used. The X indicates the location of the electrode where they occurred and are as follows: V96 = +3.30@T4, V144 = -2.21@T6, V240 = -2.72@P3, V332 = -3.56@T4 and T3, V372 = -3.62@T3 and T4, A60 = +3.76@FZ, A124 = -3.96@T4, A144 = -2.42@T6, A252 = -5.15@P3, A292 = -4.84@P3, A332 = -4.94@P3. The 11 ROIs were used to form seven numerical features. ROIs V332 and V372 were combined to form feature V332. A124 and A144 formed feature A124. A252, A292, and A332 were used to form feature A252.

A124, A252, O_{1C}) on the basis of the training set data, a 16:1 ratio of subjects to variables. The resulting function was significant (Wilks' lambda

= 0.477, $F = 15.9$, $df = 4,58$, $P \leq 0.0001$) (Table 4B). The retrospective training set classification was 85.7% correct. Next this classification function was applied to the test set where overall classification success was 88.4%.

Classification of HPPD subjects dropped from 90.5% to 82.6%, an 8.7% reduction. This is well within the expected 10–15% reduction often seen in qEEG data. Surprisingly, the controls demonstrated a 9.6% improvement in classification success (from 83.3% to 91.3%). In our experience this is also within expectations on the basis of random variation. The slightly different choice of variables between the whole population discriminant analysis and the split-half replication study (V240 in the first and V144 in the second) simply reflects the relative uniqueness of the smaller training set compared with the entire data set. It is likely that many variables could have served as well. The stepping algorithm always picks just the very best, discarding those correlating with chosen variables. Note the similarity in overall classification success between the whole population jackknifing (87.1%) and the split-half study (88.4%), both of which can be taken as prospective measures of the robustness of our qEEG variables in discriminating between control subjects and HPPD patients. Thus the split-half replication can be considered successful.

3.5. Canonical correlation

The canonical correlation between the neurophysiological measures (First Set) and the clinical measures of symptom severity, latency of onset of HPPD, total lifetime number of LSD exposures, and duration of symptoms (Second Set) was highly significant for one canonical variate by Bartlett's test. The first canonical correlation was 0.728, $P < 0.0001$. The First Set canonical variate correlated most highly with variables A252, A144, and V240. The Second Set canonical variate correlated highly with all clinical variables (Table 5).

4. Discussion

Data confirm our initial hypothesis that subjects with a history of chronic post-LSD visual

perceptual disorder demonstrate alpha acceleration and shortened flash VER latency. These findings do not depend upon the inclusion of patients co-morbid for panic disorder. Our alpha and visual EP findings appear to be consensually validated by similar observations in acute LSD electrophysiological experiments in a number of species including humans. Thus there appears to be a similarity between acute and chronic LSD-induced neurophysiologic change in humans much as there is between acute and chronic positive hallucinatory symptoms. While it is not established if the mechanisms behind acute and chronic LSD effects are identical, it appears that the subjective reports of LSD effects acutely, and after the fact (which share common features) have similar electrophysiological findings. Of interest, the click AER also demonstrates latency change but in the opposite direction with slightly prolonged latencies. The differential effect between the auditory and visual modalities ap-

pears to parallel the relative scarcity of auditory compared with visual symptoms in such individuals. It could reflect differences between neurochemical function in these two sensory systems.

Long-term disinhibition has been suggested as a cause for symptoms and electrophysiological findings in LSD-induced HPPD (Abraham and Gogia, *in press*). Partial evidence supporting cortical involvement in LSD-induced hallucinogenesis comes from the studies of Krill et al. (1963) who administered LSD to 24 peripherally blind subjects, 13 of whom developed visual (but not auditory) hallucinations. Cortical disinhibition is supported by the observation that when certain HPPD subjects rub one eye, imagery is generated in the contralateral, non-stimulated eye (Abraham, 1983). How LSD may chronically disinhibit the cortex is unknown. LSD is believed to act as a partial agonist at serotonin-2 (5-HT₂) receptors (Glennon et al., 1984). The receptor is widely distributed in the cerebral cortex (Pazos et al.,

Table 3
Split-half *T*-test analysis of SPM-derived variables

Variable	Group	HPPD mean	Control mean	<i>T</i> -value	<i>P</i> -value
V92	All	12.181	-1.099	3.626	0.001
	A	10.494	-4.863	2.909	0.01
	B	13.867	2.666	2.200	0.05
V144	All	44.851	343.91	7.217	0.001
	A	69.844	363.07	5.464	0.001
	B	19.858	340.549	4.806	0.001
V240	All	10.038	40.074	5.794	0.001
	A	13.622	37.996	3.083	0.01
	B	6.453	42.151	5.280	0.001
V332	All	-21.586	-3.357	-3.280	0.001
	A	-20.444	1.458	3.266	0.01
	B	-22.728	-8.171	2.131	0.05
A60	All	-3.459	-16.802	4.231	0.001
	A	-0.542	-15.069	3.046	0.01
	B	-6.375	-18.536	2.963	0.01
A124	All	-3.918	0.582	2.191	0.05
	A	-3.848	0.285	1.960	0.05
	B	-3.988	0.878	1.450	NS
A252	All	-5.260	4.777	6.315	0.001
	A	-3.733	4.800	4.380	0.001
	B	-6.788	4.753	4.600	0.001

All data shown after correction for age by regression; All, entire population: 44 HPPD vs. All 88 controls, *df* = 130; A, 1st pseudorandomly chosen half (evens in data file): 22 HPPD vs. 44 controls, *df* = 64; B, 2nd pseudorandomly chosen half (odds in data file): 22 HPPD vs. 44 controls, *df* = 64.

1985; Garratt et al., 1993), is found on the inhibitory interneurons in the rat pyriform cortex (Sheldon and Aghajanian, 1990), and may be situated on GABAergic interneurons elsewhere in the brain (Morilak, 1993 #2). On the other hand, 5-HT₂ interneurons may serve an excitatory function in the neocortex (personal communication, G. Aghajanian, 1995). One possible explanation for the apparently permanent nature of HPPD in certain individuals is that LSD may be neurotoxic to inhibitory neurons, which then leads to chronic visual disinhibition. Why LSD induces HPPD in some subjects but not others is unknown but may speak for some neural risk factor not yet established. One possibility is a preliminary report that the 5-HT₂ receptor in platelets of HPPD subjects appears to have a greater affinity for LSD than that of non-affected LSD user controls (Abraham et al., unpublished data). Other possibilities for this disorder include behavioral sensi-

tization, kindling of visual epilepsy, and drug-induced mutagenesis.

Exploratory analyses of electrophysiological difference, using the T-SPM process (Duffy et al., 1981), demonstrate multiple regions of electrophysiological difference (Fig. 1). None of the findings involve spectral analyzed EEG data; all involve either the long latency flash VER or click AER. It is unlikely, therefore, that contamination of EP data by residual background EEG contributes to our findings. Ten of the 11 regions of interest (ROI) shown involve the temporal and/or left parietal regions. Only one region primarily involved the frontal scalp. It is of interest that temporal lobe disorders often present with sensory disturbances, including hallucinations. For example, McCarley et al. (1993) report left temporal neurophysiologic and anatomical changes in schizophrenia. Partial complex seizures of temporal lobe origin may involve sensory hallucina-

Table 4a

Discriminant function analysis: significance of discriminant using entire population^a

Classification functions		Group	
Variable number	Variable name	Control	HPPD
15	V240	0.12754	0.9101
18	A124	−0.17093	−0.30272
19	A252	−0.57917	−0.75738
20	O1C	92.27673	94.32107
	Constant	−448.43356	−467.73264

Classification matrix

Group	Percent correct	Number of cases classified into group	
		Control	HPPD
Control	87.5	77	11
HPPD	86.4	6	38
Total correct	87.1%		

Jackknifed classification matrix

Group	Percent correct	Number of cases classified into group	
		Control	HPPD
Control	87.5	77	11
HPPD	86.4	6	38
Total correct	87.1%		

^a U-Statistic (Wilks' lambda) 0.538; F-statistic = 27.25, df = 4,127, P ≤ 0.001.

Table 4b
Split-half replication: significance of training set discriminant^a

Training set classification functions		Group	
Variable number	Variable name	Control	HPPD
14	V144	0.00008	– 0.00329
18	A124	– 0.67470	– 0.89506
19	A252	– 0.81707	– 1.04774
20	OIC	90.39869	94.16162
	Constant	– 434.10141	– 470.72269

Classification matrix of training set			
Group	Percent correct	Number of cases classified into group	
		Control	HPPD
Control	83.3	35	7
HPPD	90.5	2	19
Total correct	85.7%		

Classification matrix of test set			
Group	Percent correct	Number of cases classified into group	
		Control	HPPD
2nd control	91.3	42	4
2nd HPPD	82.6	4	19
Total correct	88.4%		

^aU-Statistic (Wilks' lambda) 0.477; F-statistic = 15.9, *df* = 4,58, *P* ≤ 0.001.

Table 5
Canonical correlation

Eigenvalue	Canonical correlation	Number of eigenvalues	Bartlett's test for remaining eigenvalues		
			Chi-square	<i>df</i>	Tail probability
0.529	0.728	1	124.94	52	0.0000
0.135	0.368	2	33.02	36	0.611
0.073	0.271	3	15.31	22	0.849
0.048	0.220		6.03	10	0.813

Canonical variable loadings					
First set canonical variable with first set variables			Second set canonical variable with second set variables		
V96	– 0.466	O1C	– 0.315	Severity	0.979
V144	0.634	OZC	– 0.283	Dose	0.973
V240	0.580	O2C	– 0.284	Latency	0.953
V332	0.429	O1P	0.357	Duration	0.983
A60	– 0.444	OZP	0.399		
A124	0.350	O2P	0.426		
A252	0.713				

tions (Hughes and Olson, 1981; Hughes, 1982). However, interpretation of our findings, and such ROI in general, is not always straightforward. It is important, therefore, to note that the seven ROI-derived measures demonstrated a significant and very strong multivariate correlation with the four measures of clinical severity (Table 5). Thus the ROI measures may relate to the mechanisms responsible for post-LSD symptomatology, subject to the long recognized caveats against equating correlation with causality (Wright, 1921).

Both the SPM process and the stepwise discriminant analysis have the potential of opportunistically 'tuning in noise' or otherwise capitalizing on chance since both procedures usually involved analyses of very many variables (Maus and Endresen, 1979; Abt, 1981, 1983; Duffy, 1988). Fortunately, it has recently been demonstrated that the basic underlying dimensionality of qEEG is much less than one might anticipate on the basis of variables initially collected (Duffy et al., 1992, 1995), which reduces the theoretical potential for false positives. Nonetheless, studies using SPM and discriminant analyses must always be prepared to demonstrate replicability. Opportunistic or chance findings would, by definition, not be expected to replicate. In this study, individual SPM/ROI-derived measures demonstrate strong replication when the original population is divided in half (Table 3). All measures showed less significance in both halves than on the entire population as would be expected given the smaller populations involved. All but measure A124 replicated. It was just at the 0.05 level when analyzed as part of the entire population, and lost significance on one of the halves partly due to the smaller population, and probably because of the distribution of the finding across the two halves. Overall, SPM-derived measures were reasonably consistent in this split half analysis. Thus, despite the fact that SPM/ROI-derived measures may be difficult to explain, they are quite stable in addition to correlating well with clinical variables.

When the seven measures and six centroid variables were considered together in multivariate space, stepwise discriminant analysis on the entire population correctly classified 87.1% of all subjects (Table 4A). Jackknifing (Lachenbruch and

Mickey, 1968), a test of prospective classification power when second populations are not available, also indicated 87.1% correct classification. However in some circumstances jackknifing may not provide a reliable prospective estimate. For this reason we undertook a randomized split-half analysis, choosing variables and forming the discriminant classifier on half the population and testing it on the other half. In this case, the second or training set was 88% properly assigned, very close to the 87% estimate by jackknifing of the entire population. Despite the fact that the stepwise discriminant process may occasionally fail to replicate, that was not the case for these data. It may be that our use of a subject to variable ratio of greater than the 10:1 optimal value suggested by Foley (1972) facilitated the successful split half analysis.

In summary, use of LSD may lead to chronic hallucinatory, largely visual, symptoms that resemble acute symptoms. Acutely in both animals and man, electrophysiological studies demonstrate faster alpha and shortened visual EP latencies. These effects are present in patients with chronic post-LSD hallucinosis as well. These are unusual findings in that most pathology and medications slow alpha and prolong EP latency if they have any effect at all (Savage et al., 1994). We speculate that LSD acts via partial chronic disinhibition of the visual nervous system. Additional electrophysiological abnormalities, delineated by the T-SPM procedure, appear stable and correlate with disease severity. What they tell us about the physiological underpinnings of HPPD remains uncertain and the focus of further study.

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