Chapter 14

Effects of LSD on Somatosensory and Visual Evoked Responses and on the EEG in Man

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There have been many attempts to define brain mechanisms related to the dramatic behavioral changes elicited by lysergic acid diethylamide (LSD). As Chapman and Walter [1] have noted, electrophysiologic studies of LSD in experimental animals have yielded inconsistent results, probably due to species differences and variable experimental conditions. Similarly, methodological differences may account for variable findings of studies conducted in man, particularly when techniques of differing sensitivity have been used for analyzing the EEG. Neurophysiologic investigations of LSD in man have also been of limited scope, usually being confined to one kind of observation, e.g., EEG or evoked responses in one sensory modality.

In the present investigation, a relatively broad range of electrophysiologic effects of LSD in man was examined with the aid of recently developed procedures for quantifying electrophysiologic data. Effects of LSD on the EEG and on visual and somatosensory evoked responses were studied in the same subjects. Although some workers have failed to observe significant EEG effects of LSD [2], others have noted frequency increases [3, 4] and reduction of electrical output [5]. Present results indicate that clear EEG changes may be demonstrated by using a form of period analysis [6]. Previous investigations of LSD effects on averaged human cerebral evoked responses have been confined to single-channel recordings. Chapman and Walter [1] found that responses to light flash were reduced in amplitude after 115 μg of LSD and, particularly, that the late rhythmic components were reduced or abolished. Shagass et al. [7] reported that 1 μg/kg had no significant effect on the amplitude of the primary component of the cerebral response to ulnar nerve stimulation, but Shagass and Schwartz [8] did find that LSD, in common with other psychoactive drugs, increased the second negative component of this response. It was hoped that the present study, using two stimulus modalities and recording evoked responses simultaneously from multiple head areas, would help to determine whether changes with LSD are greater in particular brain areas or sensory systems.

Since this investigation was carried out within the context of therapeutic trials of relatively large doses of LSD in patients with conduct problems, the opportunity was also taken to explore possible relationships between electrophysiologic changes and therapeutic effects. The

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possibility that clinical changes could be related to the electrophysiologic data was suggested by previous findings of differences in somatosensory evoked responses between patients with personality disorders and those with psychoneuroses [8, 9] and recent evidence that patients with conduct problems, e.g., sexual deviation, are more likely than psychoneurotics to respond to LSD with an immediate insightful response and subsequent clinical improvement [10, 11].

METHODS

Subjects

There were 17 patients, of whom 16 were male, ranging in age from 19 to 42 years (median, 30 years). All had been recommended for trial of LSD therapy, and they, or their parents if under age, had signed a special experimental-treatment release form. The most frequent disorders in the group involved sexual problems: exhibitionism, four cases; molesting minor girls, two cases; transvestism, one case; homosexuality, one case. Other presenting problems included: alcoholism, four cases; severe passive-aggressive or passive-dependent behavior, two cases; aggressive antisocial behavior, one case; compulsive personality, one case. The lone female patient was a 19-year-old who was in difficulties because of sexual promiscuity, stealing, and lying. With two exceptions patients were known not to have received any medication for several weeks prior to LSD therapy. The exceptions were an alcoholic patient with convulsive disorder who was receiving Dilantin, 100 mg t.i.d., and d-amphetamine, 5 mg t.i.d., and another patient who was given secobarbital, 100 mg, the evening before the test.

Apparatus and Recording Procedure

Recording and stimulus electrodes were chlorided silver disks, affixed with collodion. The somatosensory stimulus was a 0.1-msec electrical pulse, delivered by a direct-current stimulator [12], triggered and timed by a Grass S4 stimulator and isolation unit, to electrodes placed 3 cm apart over the median nerve at the wrist (anode distal); stimulus intensity was 10 mA above the individually determined sensory threshold. A light flash, at intensity 8, from the Grass PS2 photic stimulator provided the visual stimulus. It was delivered to the closed lids with the face of the lamp centered 6 in. from the glabella. Evoked responses were recorded simultaneously from at least six pairs of electrodes in serial bipolar linkage with adjacent leads 6 cm apart; phase reversals so revealed provided information concerning the point of origin of electrical events. Midline derivations, commencing 3 cm below the inion, were used for visual responses. The somatosensory leads were placed 7 cm parasagittally on both sides of the head, with the middle pair 4 cm anterior and 2 cm posterior to the interaural plane. Amplification was by means of Tektronix 122 amplifiers and a subsidiary amplifier permitting a total gain of about 300,000; upper and lower fre-

quency limits were 10 kcps and 0.8 cps. The EEG was stored on tape with a Precision Instrument Model 207 seven-channel recorder for later replay into an Enhancetron ND800 computer, using 512 data points for each average. Responses from some areas were also averaged on line. Analysis times were 500 msec for somatosensory and 1000 msec for visual responses. The stimulus was triggered later than the computer, the delay being 5 or 10% of the total analysis time. The center half of the interval preceding each stimulus was occupied by a microvolt level, square-wave calibration signal entered into the record in series with the input electrodes [13]. Each recording sequence involved 100 stimuli with a repetition interval of 1 sec for somatosensory and 2 sec for photic stimulation. Averaged responses were written out by means of an XY plotter. In addition, averaged responses of 13 subjects were stored on tape with a Norelco 401 recorder by frequency modulating the analog output of the Enhancetron. The responses could be demodulated later and entered into the Enhancetron. This method of tape storage of averages permitted rapid summing of several averaged evoked responses.

Period analysis of primary EEG frequencies was performed by passing the tape-recorded EEG through a circuit detecting zero-crosses in one direction and entering the output into a Mnemotron CAT 400B in the interval histogram mode of operation. This yielded fre-

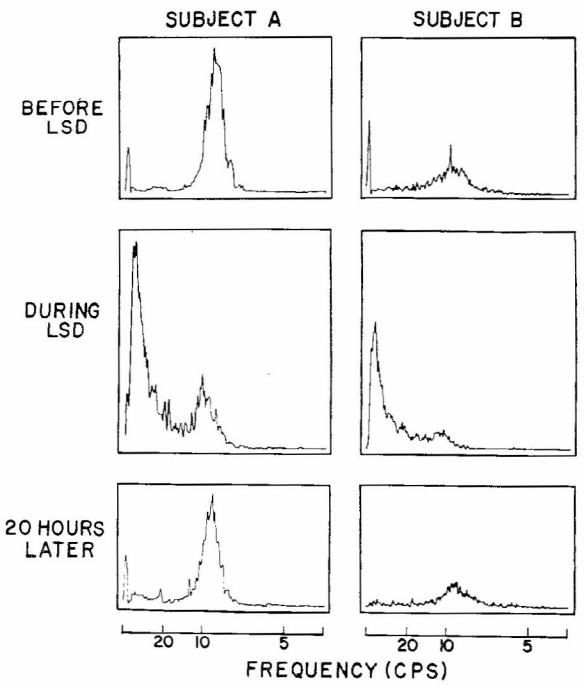

Fig. 1. Distributions of EEG-wave durations for two subjects during somatosensory stimulation; posterior left leads. Note shift to faster frequencies with LSD.

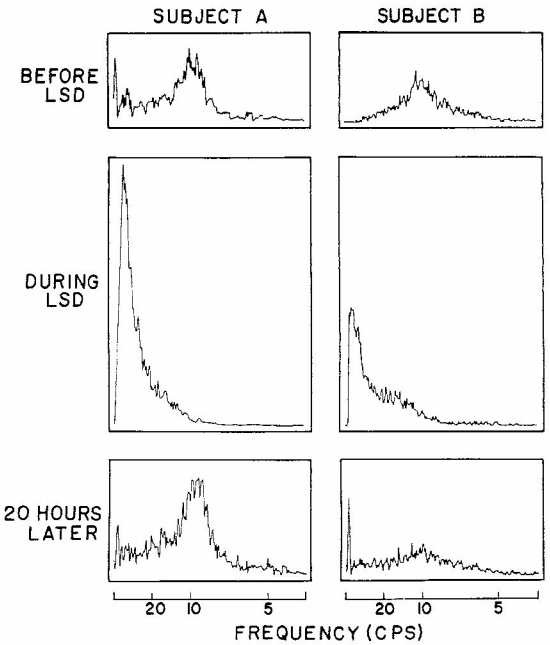

Fig. 2. Distribution of EEG-wave durations for same subjects as Fig. 1 during visual stimulation; leads above and below inion.

quency distributions of the durations of EEG waves crossing the baseline (see Figs. 1 and 2). A gating device restricted the portion of the EEG subjected to period analysis to the analysis time of the relevant evoked responses.

During the course of the study it became possible to attempt quantification of evoked response data with the IBM 7044 computer. This was done for averaged responses which had been stored on tape (visual responses for 13 and somatosensory responses for 11 subjects). All responses for predrug and LSD conditions were summed, and the digital output of the Enhancetron was placed on punched paper tape; it was transferred to digital magnetic tape for programmed quantification by the IBM 7044.

Experimental Procedure

The therapeutic procedure with LSD usually involved three or four intravenous injections, with an interval of at least one week between treatments. In 12 cases the first treatment was administered in the laboratory; recordings were done in conjunction with the second LSD injection for the remaining five. Dosage in all but two cases was the lesser of 2.5 μg/kg or a total dose of 200 μg; in two cases it was 100 μg. Injections were usually given about noon, after five somatosensory and five visual recordings (each the averaged response to 100 stimuli) had

been made. A similar set of 10 averaged recordings was made, commencing about 30 min after LSD injection. Because the subjects' ability to cooperate varied, the LSD recording period ranged in duration from 61 to 136 min, the median being 70 min. In all cases the recordings were made when definite behavioral and physiological changes were evident. After the last recording, the electrodes were removed and the patient was returned to the ward together with his resident physician, who had administered the LSD and remained with him during the recording. The physician usually stayed with the patient almost continuously for 6 to 8 hr after each dose of LSD. Ten patients were brought to the laboratory the morning after LSD administration for repeat recordings; these were made about 20 hr after LSD injection. One of the ten was a patient from whom recording immediately after LSD was not possible because of extreme agitation.

Treatment of Data

In addition to visual inspection of the EEG and individual evoked-response records, the data were quantified in several ways. Evoked-response measurements were carried out on the summed records for each experimental condition, i.e., averaged responses to 500 stimuli. Somatosensory responses were measured by identifying and numbering ten consecutive peaks (Fig. 4) according to a scheme previously developed [14]; the latencies of these peaks were then determined and their amplitudes measured in terms of microvolt deviation from an estimated isoelectric line. Although similar measurements for the visual responses had been planned, it turned out that the electrode placements, which were closer together than those employed in previous studies [15], led to considerable intersubject variability in polarity of response peaks, and measurements based on visual identification of peaks could not be performed satisfactorily.

Two types of programs were attempted on the data prepared for analysis with the IBM 7044 computer. In one type, the evoked responses were divided into a series of successive segments, the timing of which was arbitrarily decided from previous experience with the location of peaks. For somatosensory responses there were: six 10-msec intervals beginning 15 msec after the stimulus, one interval from 75 to 100 msec, two 50-msec intervals from 100 to 200 msec, and two 100-msec intervals from 200 to 400 msec. For visual responses there were: seven 25-msec intervals from 25 to 200 msec after the flash, four 50-msec intervals between 200 and 400 msec, and four 100 msec intervals from 400 to 800 msec. For each time segment the computer program yielded estimates of the minimum and maximum amplitudes, as microvolt deviations from a computer-estimated isoelectric line, and the time of occurrence, in milliseconds, of these minima and maxima. In addition, the area above and below the isoelectric line was computed for each time segment.

Fourier series were computed by the second type of program. These are based on the assumption that a complex wave may be analyzed into sine-wave constituents [6]. Coefficients, reflecting the contribution of 20 sine-wave frequencies at equal intervals, were computed for two time spans of each evoked response. Times after stimulus covered were: somatosensory, 10–110 and 10–410 msec; photic, 20–200 and 20–820 msec. It should be emphasized that representation of a particular frequency in the Fourier series does not mean that it was present in reality; the data show only what combination of sine waves could represent the response.

The output of the first program was punched on cards and analysis of variance in the treatment by subjects design [16] to test for LSD effects was performed by computer.

RESULTS

EEG Changes

Visual inspection of the EEG tracings yielded the general impression that there was some decrease in amplitude of rhythms, increased muscle artifact, and a tendency for increased alpha frequency. There were, however, exceptions; occasionally, alpha amplitude appeared to be increased. The interval histograms, depicting frequency distributions of wave durations, revealed more uniform changes across subjects than the impressions gathered from inspecting the EEG. Figure 1 shows the histograms of two typical subjects obtained from the most posterior somatosensory leads (derivation 1-2, Fig. 3) during median nerve stimulation. Figure 2 shows similar distributions obtained from the leads about the inion during photic stimulation. The changes associated with LSD consisted of a reduction of activity at frequencies below 10 cps and an increase of activity at faster frequencies. The histograms obtained for the EEG taken 20 hr after LSD closely resembled those obtained before drug administration.

The interval histograms were quantified by dividing them into three frequency bands: 4–7.9, 8–12.5, and 12.6–25 cps. The frequency corresponding to the peak count for each band was determined, and also the height of this peak. In addition, an estimate of the area of each band was obtained by summing the heights of five equally spaced wave durations within it. Table I gives the mean values for these measurements and the significance of differences by "t" tests (two-tailed). The mean peak frequency of the 8–12.5 cps (alpha) band increased by 1.4 cps in both areas after LSD ($p < 0.001$), and there were also significant frequency increases in the 12.6–25 cps band. With LSD, the mean height of the peak frequency was significantly reduced in the 4–7.9 cps band for both areas and increased in the fast frequency band, but significantly so only for the somatosensory area. The mean area estimates reflected the shifts toward more fast and less slow activity with LSD and were significant for two of the three frequency bands for each derivation. Only one

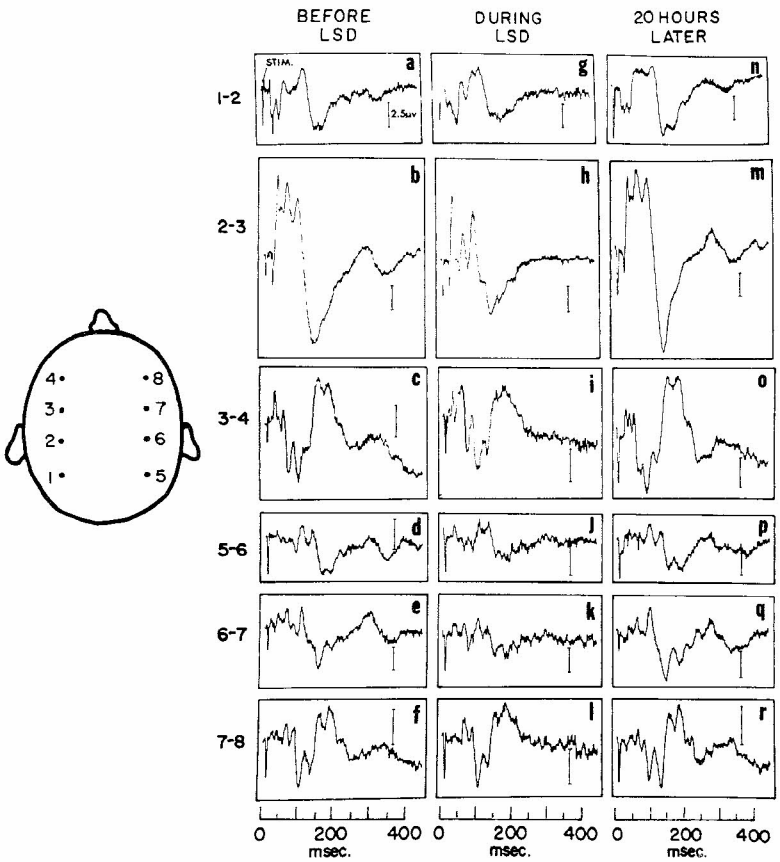

Fig. 3. Averaged somatosensory responses to 500 stimuli before, during, and 20 hr after LSD. All calibrations 2.5 μV. In this and subsequent figures, upward deflection indicates relative positivity of posterior lead of pair. Note that LSD changes are most marked in record h.

of 14 subjects showed a reversal of trend in the area, height, and 8–12.5 cps peak frequency differences indicated as statistically significant in Table I.

Evoked-Response Changes—Qualitative Observations

Inspection of the serial averaged evoked-response recordings indicated that, for most subjects, the five averaged responses for each sensory modality taken before LSD differed from the five taken after it was given. Although there was variability between the records for each experimental condition, the pre-LSD responses resembled one another and those taken 20 hr later more than they resembled the LSD tracings. The relative consistency of responses under each condition provided

Table I. Mean Interval Histogram Measurements

Frequency range (cps)	Somatosensory			Visual		
	Pre-LSD	LSD	20 hr	Pre-LSD	LSD	20 hr
			Peak frequency (cps)			
4–7.9	7.8	7.7	7.8	7.6	7.2	7.5
8–12.5	9.7	11.1‡	9.6	10.8	12.2‡	10.8
12.6–25	16.0	21.4†	15.4	15.6	19.2*	15.4
			Height of peak			
4–7.9	20.3	8.7†	20.4	27.0	10.1†	20.4
8–12.5	74.7	62.5	73.9	85.4	62.9	67.8
12.6–25	24.8	67.3†	30.6	66.0	88.9	61.8
			Area			
4–7.9	10.7	6.6	8.9	29.6	17.6‡	27.4
8–12.5	210.8	147.7*	203.4	282.2	110.6*	203.9
12.6–25	57.0	170.3‡	73.0	206.3	269.0	201.5

N = 14 for pre-LSD and N = 10 for 20-hr means.
*$0.01 < P < 0.05$ for difference from pre-LSD mean.
†$0.001 < P < 0.01$.
‡$P < 0.001$.

additional justification for the practical measure of summing five averaged responses for purposes of quantitative analysis. However, the nature of LSD changes in any one subject was not the same for all head areas, and subjects varied in the response features which showed change. Thus, although LSD produced changes in all subjects, consistent between-subject alterations in specific aspects of the responses required statistical demonstration.

The summed somatosensory responses of one subject are shown in Fig. 3. The greatest changes with LSD occurred in records from the primary sensory area contralateral to the stimulated wrist (leads 2-3, records b, h, and m). The changes consisted of amplitude reduction of all peaks and abolition of slow-voltage fluctuations later than about 200 msec after the stimulus. These changes were no longer evident in the 20-hr record, which resembled that taken before LSD. Figure 4 provides a more detailed view of the first 200 msec of the response from leads 2-3 in Fig. 3. In addition to amplitude reduction, the successive peaks were clearly separated in the LSD response, and they returned to the baseline, whereas they were confluent and remained above the baseline in the other records. Figure 4 also illustrates the system of numbering consecutive peaks; points 2 and 3 are omitted because, as is usually the case in subjects over age 30 [14], they were not visible in this subject's responses.

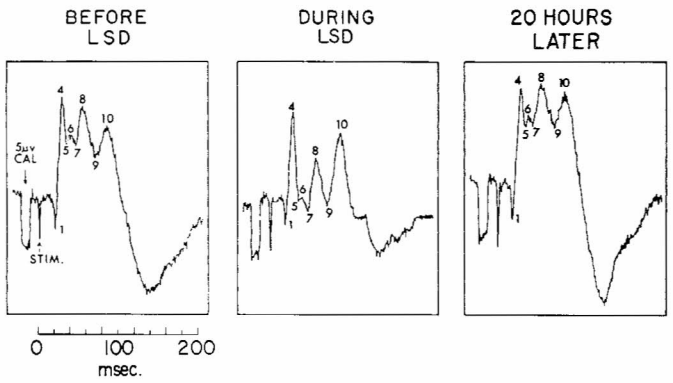

Fig. 4. Somatosensory (primary locus) records b, h, and m of Fig. 3 displayed over shorter time to show more detail. Note system of numbering consecutive peaks. Peaks 2 and 3 not visible in this subject.

Figure 5 shows the summed visual responses of the subject of Figs. 3 and 4. The records taken on the day following LSD injection suggest an incomplete reversal of the changes with LSD. Note that, with LSD, there were minimal changes in the record from leads 2-3, which would be regarded as most likely to pick up from the primary visual area, whereas adjacent derivations showed more marked alterations. With LSD the after-rhythm was of greater amplitude and faster frequency (e.g., compare record g with records a and m). The after-rhythms obtained from leads 1-2 and 3-4 were almost perfectly out of phase with one another; this indicates that they were probably originating near the midpoint between leads 2 and 3, so that the low voltage of 2-3 may be interpreted as an isopotential effect. It may therefore be concluded that, in this subject, LSD produced increased-amplitude after-rhythm of posterior origin, the frequency of which was faster than that recorded before drug administration. The most anterior derivation (leads 6-7) contains a mixture of events related to the electroretinogram and eye movement following flash stimulation. The changes seen in Fig. 5 involved mainly amplitude reduction of the relatively slow phenomena connected with eye movement. Although this occurred in several subjects, opposite effects were seen in others.

Figure 6 shows visual-response tracings from another subject. In this instance, changes in the early part of the response were most marked in the 3-4 derivation; with LSD the amplitude of the first large positive and negative peaks was reduced. As in Fig. 5, the 2-3 derivation showed little change in amplitude of after-rhythm, whereas adjacent leads showed a definite increase. With LSD the frequency of the after-rhythm increased from 10.4 to 12.8 cps. Although Figs. 5 and 6 suggest that responses recorded from lead pair 2-3 may not reflect alterations which can be observed clearly in recordings from other electrode placements, this was not always the case. Figure 7 shows lead 2-3 responses of three subjects in which definite changes of various types

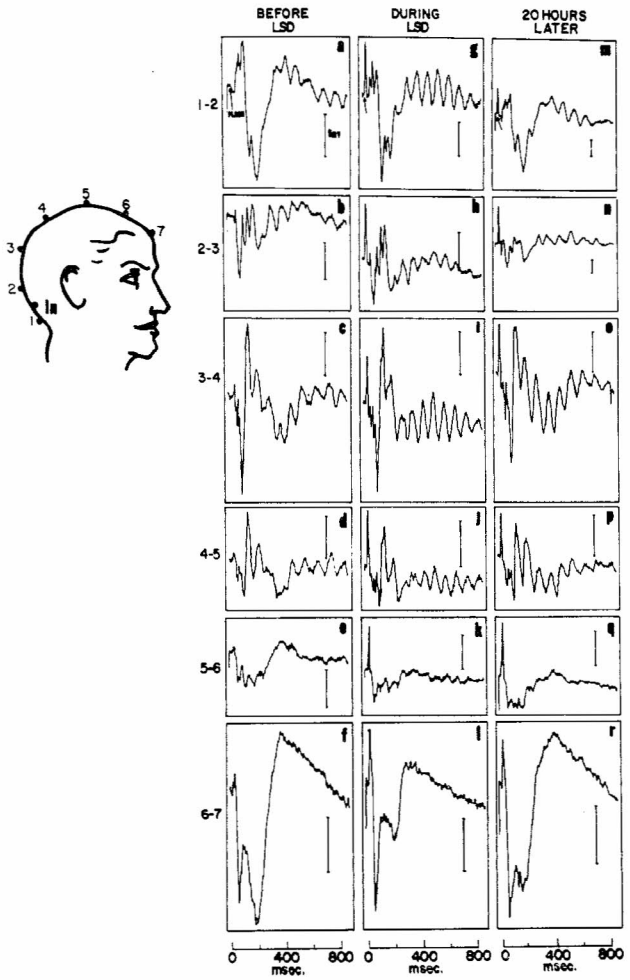

Fig. 5. Averaged visual responses to 500 stimuli, same subject as Figs. 3 and 4. All calibrations, 5 μV. Note increased and more rapid after-rhythms in g and i and reduction of slow component in l.

occurred. All three subjects showed reduced amplitude of the negative peak at 70 to 80 msec latency, but only in subject c was the positive deflection following this negative peak reduced. Increased after-rhythm frequency and little amplitude change occurred with LSD in subjects a and b, while subject c showed complete abolition of after-rhythm. Similar abolition of after-rhythm was observed in four of 16 subjects, while the frequency of after-rhythm was increased in nine of the remaining 12 and decreased in three. If abolition of after-rhythm be considered the extreme of frequency increase, these results would support the conclusion that LSD generally increases after-rhythm frequency.

Somatosensory Response Measurements

Measurements of amplitude and latency for the eight peaks of the summed somatosensory responses from the contralateral primary area (leads 2-3) were available for 15 subjects. The mean amplitude and latency values together with the results of "t" tests comparing values obtained before and during LSD are shown in Table II. The results indicate a general tendency for reduction in the amplitude of positive deflections; significant decreases occurred in peaks 4, 5, 6, and 10. In addition, there was one significant latency decrease; the initial negative deflection was earlier with LSD.

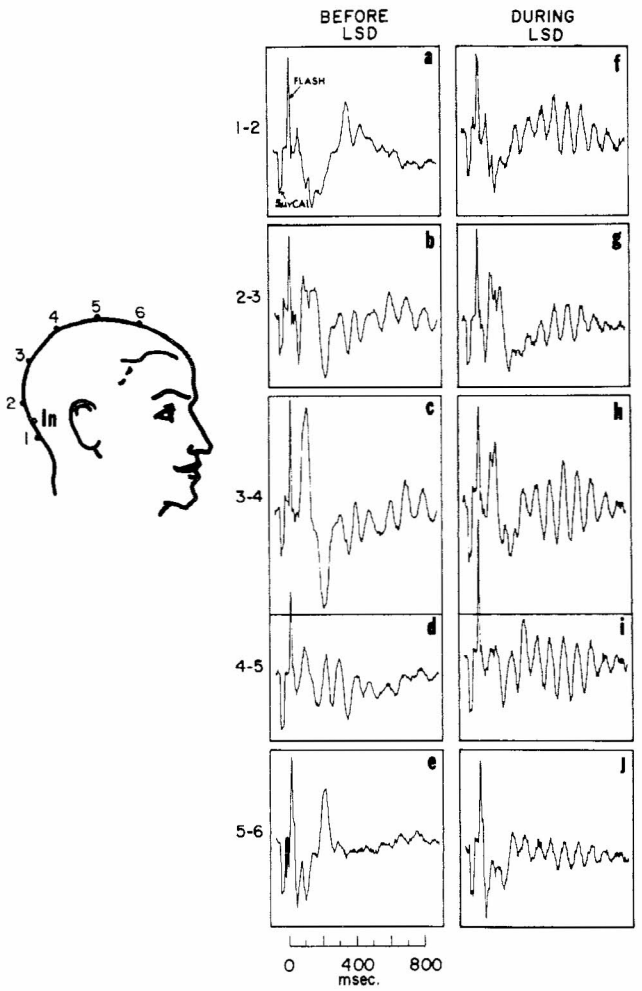

Fig. 6. Visual responses, average of 500, one subject. Note increased after-rhythm frequency and reduction of early components in h and j.

The significant findings obtained by hand measurement of the somatosensory responses were not duplicated by computer analysis of the findings in 11 subjects for whom they were available. Analysis of variance with respect to LSD effects on amplitudes and latencies of maxima and minima in successive time segments yielded no significant findings for the response from leads 2-3. Of 264 analyses of variance carried out on maxima and minima, 15 were significant at the 0.05 level, three at the 0.01 level, and one at the 0.001 level. Though this number exceeds the yield of significant P values expected by chance (13.2 at the 0.05 level), the only trend suggested by the findings was amplitude reduction (eight of 10 amplitude differences). However, this occurred at

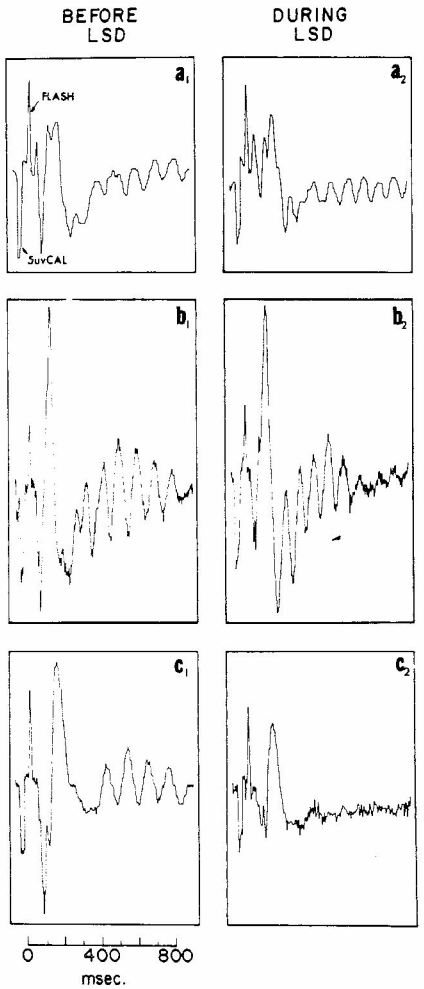

Fig. 7. Visual responses from leads 2-3 of Figs. 5 and 6; 500 responses each; three subjects. Note increased after-rhythm frequency in a_2 and b_2, blocking and amplitude reduction in c_2.

Table II. Mean Somatosensory Response Values (Hand Measurement, N = 15)

	Amplitude (μV)		Latency (msec)	
Peak	Before	LSD	Before	LSD
1	−1.60	−1.60	21.9	21.2*
4	3.82	3.06*	30.1	29.8
5	2.56	1.30*	33.9	33.4
6	3.99	2.37†	38.9	38.5
7	1.05	−0.11	49.8	47.0
8	2.30	1.69	61.2	57.9
9	−0.78	−1.53	81.2	82.6
10	2.37	1.24*	110.0	106.2

*$0.01 < P < 0.05$.
†$P < 0.01$.

different times and in several electrode derivations. Analysis of computer measurements of positive and negative areas provided only three significant LSD effects at the 0.05 level in 176 analyses—this would be expected by chance. The total area above and below the isoelectric line before and after the 75-msec latency point also did not change significantly with LSD.

In order to determine whether LSD exerted a directional trend upon the coefficients of the Fourier series, changes for each frequency were evaluated by sign test. No significant differences were found for any of the somatosensory channels.

Visual Response Measurements

Quantitative analysis was restricted to the data for 13 subjects obtained from computer measurements. Over 15 time segments, from six lead placements, 180 F ratios were computed for maximum and minimum amplitudes, and equal numbers for their respective latencies and for areas above and below the baseline. Table III shows the number of F ratios indicating significant LSD effects for each electrode derivation. It is apparent that the number of significant shifts with LSD well exceeded chance expectation and that the changes occurred mainly in activity recorded from the posterior half of the head, i.e., between leads 1 and 4.

To obtain some indication of the direction of change and the portion of the response involved, the 15 time segments were divided into three groups; the distribution and direction of significant F ratios in relation to this division are shown in Table IV. Greater positivity was taken as amplitude increase. The data suggest that, during the first 150 msec of the response, amplitude tended to decrease and that later changes were more often increases. However, 14 of 18 significant area differences were decreases. Since the decreases were equally distributed

Table III. Number of Significant LSD Effects in Analysis of Measured Visual Responses

Leads	Amplitude	Latency	Area
1-2	8	3	5
2-3	2	4	4
3-4	6	3	6
4-5	3	3	3
5-6	1	2	0
6-7	0	1	0
P			
<0.05	9	11	13
<0.01	10	5	5
<0.001	1	0	0

Table IV. Location of Time of Significant LSD Effects in Visual Responses

Time after stimulus (msec)	Amplitude		Latency		Area	
	Increase	Decrease	Increase	Decrease	Increase	Decrease
25–150	1	8	4	3	2	4
150–300	3	1	1	2	0	5
300–800	4	3	3	3	2	5

Table V. Mean Coefficients from Fourier Series of Visual Area 2-3 Showing Significant Change with LSD

Frequency (cps)	Pre-LSD	During LSD	Frequency (cps)	Pre-LSD	During LSD
15	25.5	10.5*	1.25	86.7	34.1†
20	25.3	9.6†	2.50	46.1	22.8†
25	23.7	9.2†	3.75	47.0	12.7*
30	22.1	8.2†	5.00	26.3	8.4*
35	25.1	8.0†	8.75	9.3	3.7*
45	13.3	6.2*	15.00	4.0	1.4*
65	11.8	3.7†	16.25	4.1	1.3†
70	7.4	2.7*	17.50	3.8	1.0†
75	8.4	2.2*	18.75	3.3	1.3*
80	7.2	2.4*	21.25	3.0	1.2*
85	6.6	2.1†	23.75	2.8	0.8*

*$0.01 < P < 0.05$.
†$P < 0.01$.

for positive and negative areas and over the time course of the response, it appears that the amplitude changes after 150 msec were mainly reductions of negative deflections. The overall trend of LSD effect would then be interpretable as amplitude reduction. There was no consistent direction to the latency changes.

The significance of changes with LSD on individual coefficients of the Fourier series was ascertained by sign test. Although there was a tendency for coefficients to be lower with LSD in the four most posterior derivations, statistically significant changes were found only for the data of leads 2-3 (3 and 9 cm above the inion). For this derivation, 11 of 20 coefficients were significantly reduced in each of the series for the periods 20 to 220 and 20 to 820 msec after the stimulus. The mean values of the significant coefficients are given in Table V. Since the pattern of reduction was quite uniform the data indicate a general decrease of amplitude; they do not reveal the frequency shifts with LSD which were apparent from visual analysis of the recordings.

Relationship Between Clinical Changes and Physiologic Data

The information concerning clinical effects of LSD consisted of the case history, detailed notes on behavior during the LSD sessions, and progress notes. Follow-up information was available for variable periods of time from a few weeks to more than one year. In general, and in agreement with our previous follow-up data [11], the clinical reaction to LSD within 24 hr of treatment was indicative of the later course of events. An insightful response with convincing resolution to alter behavior and a feeling of being "a better person" than before the treatment was associated with subsequent behavior improvement. All available information was used to classify the therapeutic response on a scale ranging from 0 to ++++. Some indication of the criteria may be gained from the five cases summarized in Table VI. The classification

Table VI. Examples of Therapeutic-Response Classification

Case	No. R	Response rating	Symptoms	Clinical effect
R.Y.	2	0	Carrying concealed weapons, lying, on parole	Arrested for stealing 2 days after discharge
W.E.	2	+	Molesting minors, dissociative reaction	Feels better, no new insight or attitudes
G.N.	4	++	Transvestite	Insight into behavior; improved for >3 months
T.W.	3	+++	Exhibitionism	Insight, wife reports greater "maturity," obvious attitudinal change
W.K.	3	++++	Exhibitionism	"Evil self left him," no trouble for >6 months

of response, although open to criticism, could reasonably be accepted as roughly dividing the group into those with more or less favorable response. The distribution of ratings was as follows: 0, six cases; +, two; ++, four; +++, two; and ++++, one. The physiological changes with LSD were examined for differences between patients with ratings of + or less and ++ or more.

Changes in somatosensory evoked responses appeared to be related to the therapeutic-response ratings. The essential finding was that those with "better" clinical responses had shown a greater change with LSD in the response from the primary area 2-3. This result was obtained with the amplitude of peak 4 in the hand-measured data and with computer-determined areas totalled for 15–75 msec after the stimulus. Mean peak-4 amplitudes decreased by 1.34 μV in those with "better" response ratings, compared with 0.08 μV in the "worse" group ($p < 0.01$ by t-test). Mean area change was an increase of 58.9 units in the "better" and a decrease of 33.4 units in the "worse" group ($p < 0.02$). The visual responses from area 2-3 showed a similar tendency, which failed to achieve statistical significance. The EEG-interval histogram findings were unrelated to the change ratings.

It should be noted that the pre-LSD peak-4 amplitude was significantly greater in the "better" responders (means of 5.05 and 2.40 μV, respectively; $P < 0.05$). This would mean that clinical response to LSD could be predicted almost as well from evoked-response amplitude prior to LSD administration as from change with the drug.

DISCUSSION

Perhaps the clearest and most consistent effects of LSD demonstrable in this study were the EEG-frequency changes. The results are in agreement with those of other workers, such as Gastaut et al. [3] and Anderson and Rawnsley [4]. Elkes et al. [2] did not report frequency increases, but found that alpha became "more responsive." Evarts [17], reviewing studies of LSD effects on the human EEG, was inclined to emphasize the variability of results and the discrepancy between "minimal alteration of EEG" and "extremely marked subjective effects." From the standpoint of visual inspection of EEG tracings, one can hardly disagree with Evart's use of the term, "minimal." On the other hand, inspection of our wave-duration histograms (Figs. 1 and 2) might lead one to conclude that the changes with LSD were quite marked. The impression of effect obviously depends on the method used for EEG analysis. Another factor which may have contributed to the relative consistency of our findings is that the EEG was recorded during sequences of sensory stimulation. However, evoked-response effects of LSD were more variable than EEG-frequency changes.

The EEG-period-analysis method used here was selected mainly because it is easy to perform in a laboratory with averaging equipment. Although we obtained satisfactory results, which suggest that the method may find wide application, one may question whether or not one of several

other models for quantifying the EEG [6] might have given superior results. The recent findings of Fink et al. [18] suggest that this is unlikely. They used a digital computer to compare several methods for studying drug effects and found that "period analysis provides the most efficient analysis model."

Increase of EEG frequencies with LSD was paralleled by increased frequency of visually evoked after-rhythms. However, although the group effects were similar, there was no significant correlation between changes in EEG and after-rhythm frequency, i.e., individuals might show a large change in one and a small change in the other. This supports the view that the mechanisms governing after-rhythms are not identical with those governing alpha rhythm [19]. Both could be affected by a third mechanism, e.g., one related to central "arousal," which could exert a general influence, although the responses in several affected systems would not be uniform.

The significant evoked-response changes with LSD demonstrated here consisted of reduced amplitudes of both somatosensory and visual responses and earlier onset of the former. These results support Chapman and Walter's [1] conclusion that LSD reduces amplitude and suggest that the effects are not specific to one sensory system. We did not, however, observe the consistent reduction or abolition of after-rhythms which they found; this may have been due to differences in lead placement and the fact that multiple leads gave us greater scope to observe different effects. Our observation that the frequency of visually evoked after-rhythms may increase without reduction, or even increase, of amplitude suggests that the effects are more complex than indicated by the interpretation, based on amplitude reduction, that LSD exerts an inhibitory influence on cortical evoked responses [1]. Purpura [20] demonstrated that LSD in relatively low doses augments specific primary responses and inhibits recruiting responses. He postulated that this differential effect was dependent on the anatomical arrangement of synapses, proposing that LSD inhibits axodendritic and facilitates axosomatic synapses. To the extent that it is possible to predict events in averaged human evoked responses from this synaptic classification one would expect the earliest evoked-response components to be enhanced and the later ones to be reduced by LSD. Present results do not agree with this expectation, since there was amplitude reduction of early components.

Two observations made here suggest the possibility that LSD may speed central events; these are the reduction of somatosensory response latency and increased frequency of after-rhythms. Also supporting this idea is the increase of EEG frequency. Although the association of reduced amplitude with shorter latency may seem paradoxical, such an association has been repeatedly observed at the opposite end of the scale, e.g., increased amplitude and prolonged latency occur together in sleep [21]. The fact that the electrophysiological concomitants of LSD action appear to be opposite to those associated with sleep suggests that we may be dealing with a state of heightened "arousal" or activation. Many behavioral effects of LSD support this idea, e.g., increased per-

ceptual sensitivity and anxiety. Furthermore, during the course of a treatment session, most subjects report that their thoughts go on so rapidly that they cannot take time out to talk about them.

The results suggesting that evoked-response characteristics may be prognostic of therapeutic response to LSD are intriguing. However, the small size of the sample and the exploratory nature of this part of our study, which did not include rigorous predetermined clinical criteria applied on a blind basis, suggest that the findings be viewed with caution until confirmed. Since electrophysiologic changes did not persist for 24 hr, it is not likely that they were directly related to the therapeutic effects, in the sense of persistently altered central nervous system functioning.

The yield of results from the computer analyses conducted in this study was somewhat disappointing. This seems attributable mainly to the fact that we used arbitrarily fixed time intervals in an attempt to replicate the kind of data obtained previously by hand measurements. The attempt was only partially successful because of the variable timing of evoked-response events and because much information that the eye has learned to disregard was computed. More suitable programs for evoked-response quantification should be developed as experience is gained.

SUMMARY

The effects of a single large intravenous dose of LSD on EEG frequency content and on somatosensory and visual averaged evoked responses recorded from six head areas were studied in 17 patients undergoing trials of LSD therapy. In ten subjects recordings were also made on the following day. The evoked-response data were measured and analyzed by computer as well as by the usual methods. The results indicated that LSD increases EEG frequency, generally reduces amplitude of evoked responses, and increases the frequency of visually evoked after-rhythms. Coefficients of the Fourier series, when significantly changed did not shift in pattern, suggesting only amplitude decrease and not frequency shift. The degree of change in some aspects of somatosensory responses was related to a rough classification of therapeutic response to LSD, as was one predrug amplitude measure. An attempt was made to integrate the findings in relation to the hypothesis that LSD induces a central state of "hyperactivation."

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