Chapter 4

Actions of Lysergic Acid Diethylamide on Averaged Human Cortical Evoked Responses to Light Flash

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INTRODUCTION

The capacity of minute amounts of lysergic acid diethylamide (LSD) and similar agents to induce profound subjective and behavioral abnormalities makes these substances of continuing interest from the point of view of their possible role in defining neurophysiological alterations associated with psychotic behavior, regardless of whether the behavioral states induced by these agents are specifically related to spontaneously occurring schizophrenic psychoses, or whether they are simply examples of a more generalized toxic delirium induced by highly potent agents that act with an unusual time course.

However, the hope that observations of the effects of these agents on electrophysiological indicators of brain activity will aid in defining relevant aspects of neurophysiological changes in psychoses is yet to be fulfilled. Indeed, electrophysiological methods for assessing brain activity are themselves still in an active and apparently early stage of development. Few if any clearly established findings about the nature of electrophysiological changes associated either with naturally occurring or with drug-induced psychoses are presently available. It is well known that simple visual inspection of EEG patterns recorded from the scalp has been largely unrewarding in defining relevant changes in schizophrenic patients [1] or in normal subjects who have received LSD [2]. On the other hand, more detailed quantitative methods for analyzing the EEG [3] and studies of evoked cortical responses [4] have recently shown promise of helping to expose electrophysiological abnormalities in records from psychotic patients.

Despite a number of studies of the actions of LSD on the spontaneous cortical activity of laboratory animals [5-12], no simply stated conclusion can summarize them. Species differences and the variety of anesthetic procedures employed obviously are relevant to this lack of agreement. In the rabbit, Rinaldi and Himwich [10] observed EEG arousal patterns following administration of 1 to 15 μg/kg of LSD and slow patterns characteristic of drowsiness following 20μg/kg. In cats anesthetized with barbiturate, Langfitt and Finney [13] found that LSD, 100-150 μg/kg, eliminated the characteristic barbiturate spindles, but in unanesthetized animals amounts as large as 300 μg/kg were without apparent effect. In contrast, Delay et. al. [6] found

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that LSD induces flattening of the cortical EEG in the cat that can be prevented by pretreatment with barbiturates. With unanesthetized animals, a low-voltage fast pattern was consistently replaced by a slower pattern after LSD (500 μg/kg). With animals anesthetized with pentobarbital, the slow pre-LSD pattern was not changed in frequency unless there was progression to electrical silence.

The recent development of precisely placed implanted electrode methods suitable for long-term observations and the application of computer methods for analysis of electrophysiological data [14, 15] also appear to offer more potent methods for uncovering meaningful relationships between psychosis and brain activity. Reports of paroxysmal spiking and slow-wave activity in deep brain sites of schizophrenic patients [16, 17] are provocative but as yet difficult to interpret as regards their significance for electrophysiological aspects of psychoses per se.

In laboratory animals, LSD in relatively large amounts induces long-lasting paroxysmal activity in rhinencephalic sites [18, 19].

A number of investigators have studied the effects of LSD on evoked responses in laboratory animals. The responses evoked by auditory, visual, or tactile stimuli have been recorded from the retina [20] lateral geniculate body [21], and cortex [7, 22, 23]. With small (20-50 μg/kg) amounts of LSD, Purpura [22] observed increased auditory, somatic, and visual evoked responses; larger amounts (70-100 μg/kg) resulted in decreased potentials. Rovetta [23], however, observed no significant effects on sensory evoked cortical responses following administration of 40 μg/kg, and Langfitt and Finney [13] also failed to observe significant changes in sensory evoked responses recorded from the cortex following administration of LSD in amounts up to 200 μg/kg or more. Evarts [21] found no consistent changes in the cortical response to stimulation in the lateral geniculate radiation pathways even after amounts as large as 1000 μg/kg.

In addition to studying potentials evoked by sensory stimulation, several investigators have also studied the influence of LSD on the response resulting from electrical stimuli applied directly to the cortex adjoining the recording electrode (direct cortical response) and on the response to stimuli applied to a point symmetrically opposite to the recording electrode in the contralateral hemisphere (transcallosal evoked response). Marrazzi and Hart observed decreased transcallosal responses in 1955 [24]. Also, Purpura [25] observed that evoked recruiting responses following stimulation of midline thalamic structures were inhibited by small amounts of LSD. He postulated [25, 26] that LSD inhibits axodendritic synaptic transmission but facilitates transmission in the axosomatic synapses of direct sensory projection pathways to the cortex. The importance of seemingly minor details of experimental procedure in observations with LSD is emphasized by the failure of Langfitt and Finney [27] to observe consistent alterations in direct or transcallosal evoked responses after LSD administration.

Observations on evoked cortical responses in man became possible with the development of averaging techniques that permit separation of the relatively small amplitude evoked response from the relatively large amplitude background of spontaneous electrical changes in human cortex. Shagass and Schwartz [28] observed alterations in certain aspects of the cortical re-

sponse to ulnar nerve stimulation in psychiatric patients. From other studies [29] they concluded that LSD in amounts that resulted in major changes in affect, personality, and thinking (1 μg/kg) did not alter the amplitude of the major component of the evoked response. In the present observations, the actions of LSD on the cortical response to light flash were studied with normal human volunteers. The amounts of the agent administered were in the range of those commonly used to induce major behavioral and subjective changes.

METHOD

Eleven volunteer subjects were studied. All were in good physical health and none had a history of significant psychiatric disorder. Two subjects became too uncooperative for EEG recording after receiving the agent and were excluded (sodium amytal was rapidly effective in diminishing the degree of psychotic reaction with conspicuous excitement and apprehension that they exhibited). Of the remaining nine, all but one exhibited major changes in mood, personality, and thinking but continued to be cooperative. Seven of these characterized the experience as pleasant or very pleasant; one found it an extremely unpleasant, anxiety-provoking, although worthwhile experience. The remaining subject reported no change in feeling state. Subjective effects of the drug became apparent 30-60 min after ingestion of the agent. All subjects received 115 μg of the agent (dosage range from 1.4 to 2.3 μg/kg) by mouth with 100 cc water.

The electroencephalogram (EEG) was recorded with conventional apparatus (Grass Instrument Company). Light flash was provided by a Grass photic stimulator directed to the closed eyes at maximal intensity. A stimulus was delivered every 2 sec for a total of 150 stimuli. During stimulation the subjects lay supine in a darkened room. The sound of the photic stimulator at the moment of flash was masked by white noise. A recording electrode was attached to a point in the occipital region 2 cm above and 2 cm lateral to the inion and referred to an indifferent electrode attached to the neck. Responses were averaged by means of a special purpose digital computer (Computer of Average Transients, Mnemetron Corporation). The period from the time of flash to 1 sec after flash was averaged on line for a total of 150 stimuli. This determination was repeated at least once before and at intervals 1, 2, 3, and 4 hr after ingestion.

The averaged evoked responses were plotted with an x-y recorder to a scale on which 1 sec of real time equaled 25 cm. These averaged responses were then digitized at a sampling rate of 250 per sec by means of the Oscar digitizer (Benson Lehner Corporation). The data presented in this paper are limited to the control response recorded shortly before ingestion of LSD and a repeat response recorded 2.5 hr after ingestion. Of these two, the recording that demonstrated the widest range of deflection was used to define the range for digitizing. The highest upward deflection was assigned the value 999 and the lowest 000 for each pair of individual records. A spectral analysis of each averaged response was computed with the aid of the computer at the Health Sciences Computing Facilities, University of California, Los Angeles (Program Biomed 02T).

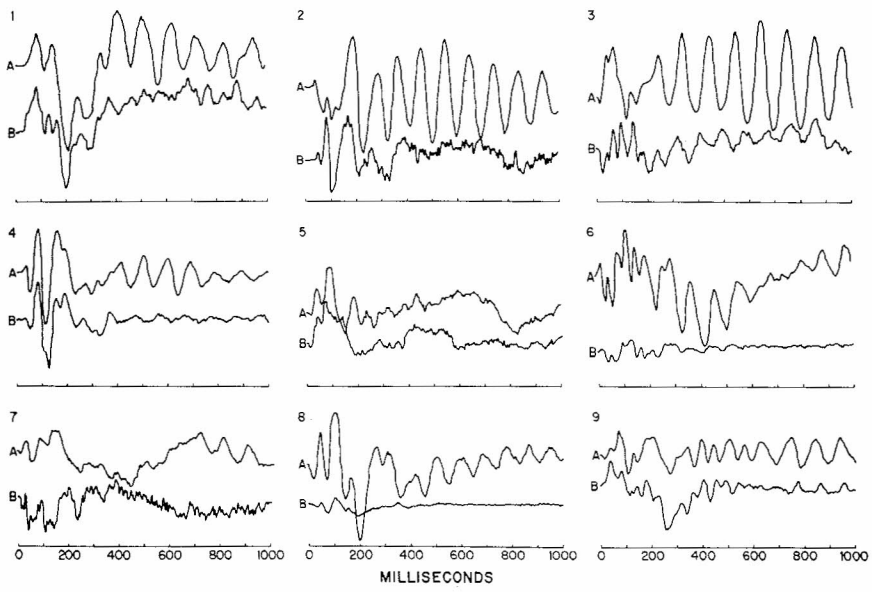

Fig. 1. Averaged evoked responses to brief light flash before and after LSD in 9 normal subjects. Responses labeled "A" were recorded immediately before LSD ingestion; responses labeled "B" were recorded 2.5 hr after ingestion of 115 μg of LSD. An upward deflection indicates a negative potential at the occipital electrode.

RESULTS

The averaged evoked response to light flash for nine subjects immediately before and 2.5 hr after ingestion of LSD is presented in Fig. 1. The response to light before LSD was, in large part, in keeping with the observations of other investigators [30-34]. Cobb and Dawson [32] describe the earliest deflection recorded from the occiput as a 1—1.5 μv deflection, positive in polarity with respect to other parts of the scalp, with a latency of 20-25 msec. This is followed by a negative potential with a peak at 40-50 msec, a larger positive potential at 55-65 msec and a large (5-10 μv) negative potential peaking at 90-100 msec, followed by a series of waves with a period of about 100 msec. Monnier and Berger [33] distinguished 3 major components, labeled b-, c-, and d-waves. The b-wave is a positive wave with a peak latency of 65-75 msec; the c-wave is a negative component with a peak latency of 100-140 msec; and the d-wave is a positive component at

TABLE I

Mean Peak Latencies (msec)
(Peaks Labeled According to Cigánek)

	I	II	III	IV	V	Va	VI	VII
Mean Pre-LSD	49.5	68.7	93.3	111.5	131.3	208.0	234.4	262.0
Mean Post-LSD	51.8	75.5	93.8	120.9	136.2	227.7	252.0	292.4
Change	+2.3	+6.8	+0.5	+9.4	+4.9	+14.7	+17.6	+30.4

180-220 msec. In accordance with the labeling system presented by Cigánek [34], recording from midline occipital-parietal electrode pairs and with polarity defined in terms of the occipital electrode, three major components can be discerned. The first, termed the primary evoked response, consists of: a) a negative potential at average peak latency of 39 msec, b) a positive potential at 53 msec, and c) a negative potential at 73 msec. This component is followed by a secondary response consisting of: d) a positive potential at 94 msec, e) a negative at 114 msec, and f) a positive at variable times but greater than 134 msec; and thereafter a "ringing response" consisting of a rhythmic after-discharge close to the frequency of the alpha rhythm. There has been disagreement between several investigators as to the definition of the polarity of these components [32].

Inspection of Fig. 1 indicates the difficulties met in assigning labels to the components of individual records in the complex train of alterations that make up the evoked response to flash in man. While the first 3 or 4 peaks can often be labeled for a given individual with fair confidence before and after LSD, there is even greater uncertainty about the later peaks. It appears hazardous to assume, particularly with the later peaks, that a given peak can be identified as the same electrophysiological component in a record from another individual. Table I, which presents an attempt to label the peaks according to the method offered by Cigánek [34] is presented with this caution in mind. A t-test analysis of the individual peaks in this way failed to indicate a significant alteration in the interval between the flash and each peak considered individually during the first 400 msec after the flash. However, the small differences in average latency for each peak before LSD as compared with after LSD are all in the direction of increased latency, arguing for a small increase in latency, particularly in the later

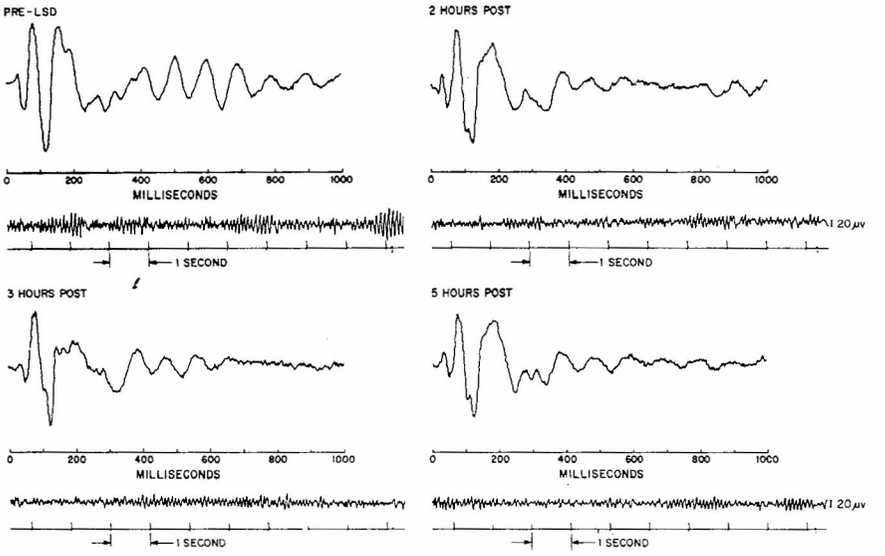

Fig. 2. Evoked response to light flash in a single subject before and 2, 3 and 5 hr after LSD. The late periodic oscillations, much reduced 2 hr after ingestion, have begun to return at 5 hr after ingestion.

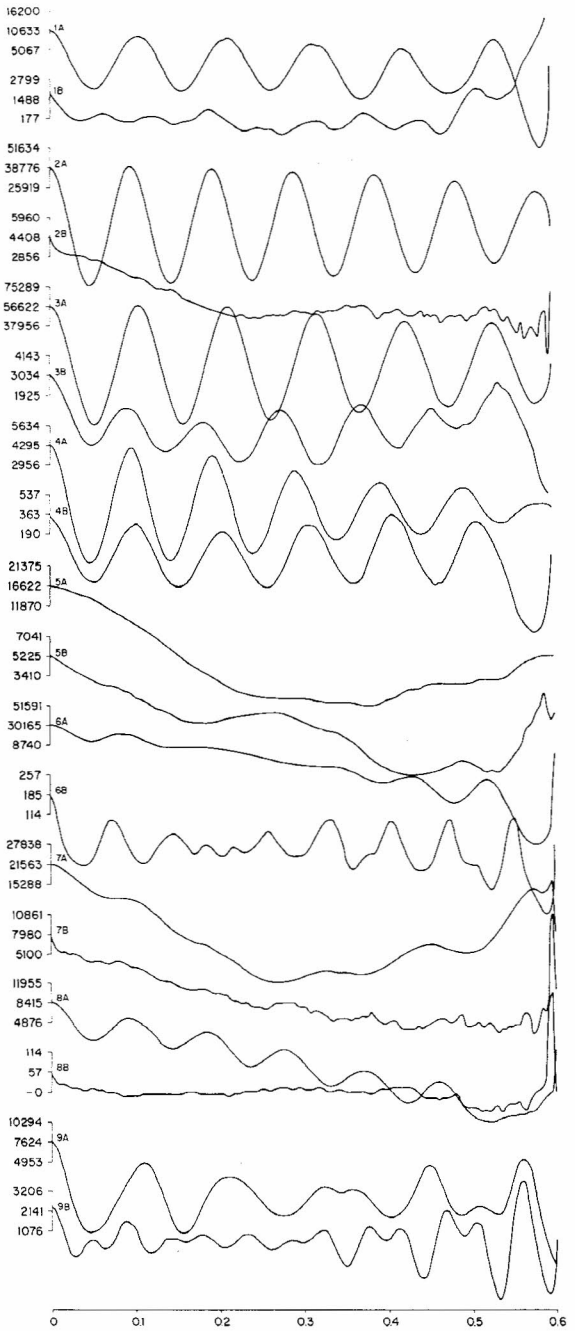

Fig. 3. Graphs of the autocovariance functions (up to a lag 0.6 sec) of the interval from 400-1000 msec after flash for the averaged evoked responses displayed in Fig. 1.

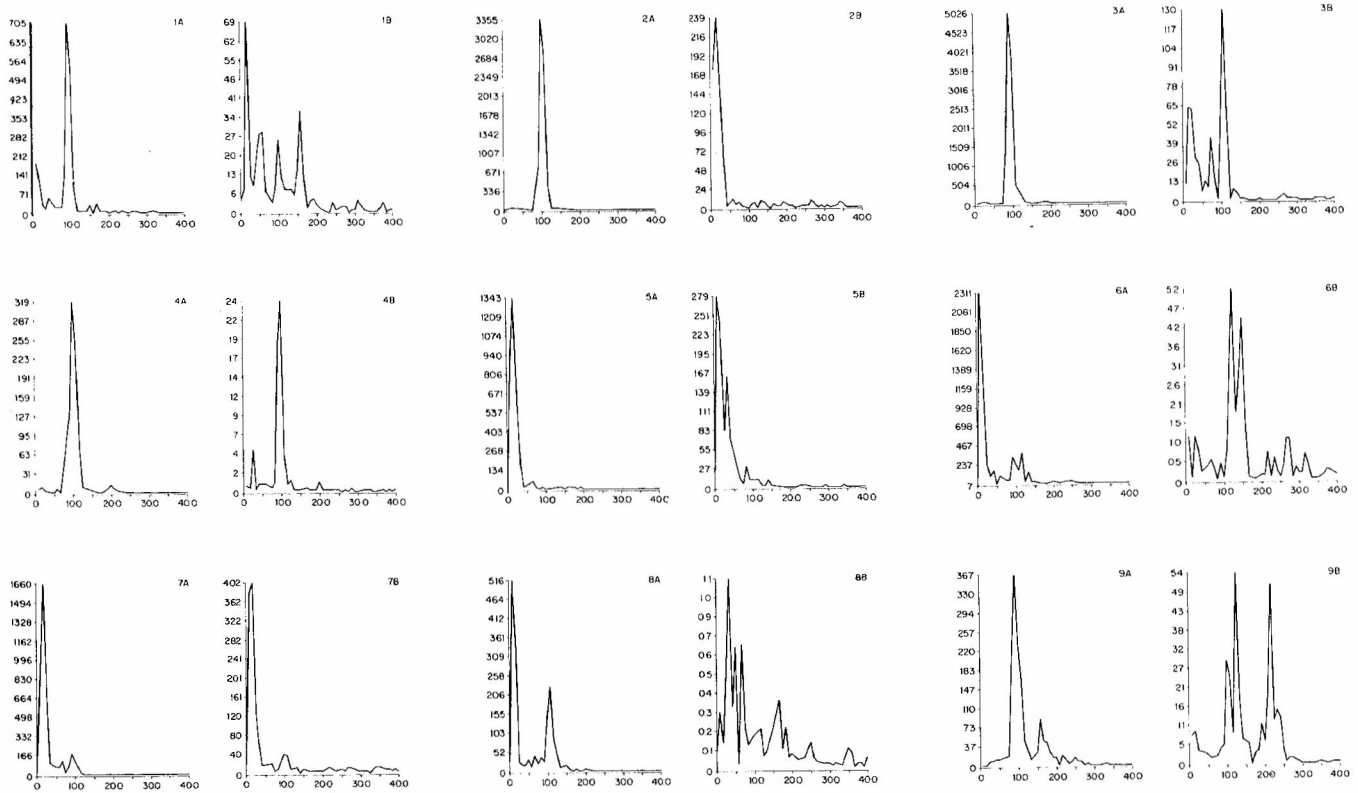

Fig. 4. Graphs of the power spectral estimates of the interval from 400–1000 msec after flash for the averaged evoked responses displayed in Fig. 1. Ordinate, power spectral estimate; abscissa, frequency from 0 to 40 cycles/sec.

TABLE II

Frequencies (cycles per second) of Peak Power Spectral Estimates During the Interval 0-400 Milliseconds After Flash, Before and After LSD

Subject	Pre-LSD		Post-LSD		Change in Frequency	Change in Power	Power Post LSD/Pre-LSD
	Frequency	Power	Frequency	Power			
1	2.50	1604	3.75	674	+1.25	-930	0.42
	12.50	248	10.00	139	-2.50	-109	0.56
2	5.00	457	3.75	231	-1.25	-226	0.50
	11.25	1107	10.00	518	-1.25	-589	0.47
3	3.75	191	5.00	171	+1.25	-20	0.89
	11.25	600	11.25	101	0	-499	0.16
4	3.75	206	5.00	192	+1.25	-14	0.93
	10.00	363	10.00	338	0	-30	0.93
5	2.50	496	2.50	1099	0	+603	2.21
	8.75	346	10.00	22	+1.25	-324	0.63
6	2.50	596	6.25	51	+3.75	-545	0.86
	11.25	387	11.25	13	0	-364	0.33
7	2.50	848	2.50	653	0	-195	0.77
	6.25	185	10.00	418	+3.75	-233	2.26
8	5.00	1564	3.75	23	-1.25	-1541	0.01
	13.75	404	8.75	9	-5.00	-395	0.02
9	2.50	77	2.50	1308	0	+1231	16.99
	7.50	417	6.25	320	-1.25	-97	0.77

components. The amplitude of the maximal positive to negative components during the initial 400 msec is altered more consistently. It is reduced in 8 of the 9 subjects after LSD. Also apparent from inspection of Fig. 1 is a consistent dramatic reduction, and sometimes elimination, of the late "ringing" response 400-1000 msec after the flash. Figure 2 presents the time course of these changes in one subject and indicates that a major reduction in the amplitude of the "ringing" response can occur without disappearance of the alpha rhythm in the EEG.

Since the cortical response to light flash can be viewed as a train of recurrent waves as well as a series of single responses arriving at different times, it was thought appropriate to analyze these averaged evoked responses also by means of time series analysis. In addition to power spectral analysis, cross spectral analysis was used to contrast records taken before LSD with those taken after LSD. The wave forms in the early part of the response (from the instant of flash to 300-400 msec after flash) appeared by inspection to be qualitatively different from the period of late "ringing." Therefore, spectral analysis based on the entire epoch of 1000 msec was contrasted with analysis of the first 500 msec and the second 500 msec, treated separately. Inspection of the autocovariance plots from this analysis indicated that separate treatment resulted in a more sinusoidal

TABLE III

Frequencies (cycles per second) of Peak Power Spectral Estimates During the Interval 400-1000 Milliseconds After Flash, Before and After LSD

Subject	Pre-LSD		Post-LSD		Change in Frequency	Change in Power	Power Post-LSD/Pre-LSD
	Frequency	Power	Frequency	Power			
1	0.8	186	1.7	69	+0.9	-117	0.37
	9.2	705	5.8	29	-3.4	-676	0.04
2	1.7	49	1.7	239	0	+190	4.88
	10.0	3355	10.8	5	+0.8	-3350	0.00
3	2.5	27	1.7	65	-0.8	+38	2.40
	9.2	5026	10.8	130	+1.6	-4896	0.02
4	1.7	9	2.5	5	+0.8	-4	0.55
	10.0	319	10.0	24	0	-295	0.07
5	1.7	1343	0.8	279	-0.9	-1064	0.20
	6.7	57	8.3	31	+1.6	-26	0.54
6	0.8	2311	0.8	1	0	-2310	0.00
	11.7	369	12.5	5	+0.8	-364	0.01
7	1.7	1660	1.7	402	0	-658	0.24
	9.2	179	10.0	42	+0.8	-137	0.23
8	0.8	516	3.3	1	+2.5	-515	0.00
	10.8	225	10.0	0	-0.8	-225	0.00
9	5.0	12	1.7	9	-3.3	-3	0.75
	9.2	367	12.5	54	+3.3	-313	0.14

appearance of the autocovariance. Also, the spectral analysis of the early epoch showed a different pattern of power distribution than that of the later epoch, suggesting that the early and late responses should be treated separately. Division into an early epoch (0-400 msec) and a late epoch (400-1000 msec) proved most satisfactory.

Figure 3 presents the plots of the autocovariance for the late (400-1000 msec) interval. Figure 4 presents the plots of the spectral estimates for this interval at frequencies up to 40 cycles/sec. A reduction in amplitude at almost all frequencies for all 9 subjects is apparent. Table II lists the frequencies of maximal power spectral estimates for the early epoch, and Table III lists these for the late epoch. Table IV presents the amplitude of the regions of peak spectral density before and after LSD for the early epoch, and Table V for the late epoch. Tables IV and V also list the transfer functions for amplitude for early and late epochs. The transfer function for amplitude can be thought of as a factor required to convert the amplitude of the pre-LSD record to that of the post-LSD record; thus, values of less than unity indicate a reduced amplitude after LSD. In addition to amplitude changes, a transfer function for phase differences is also listed in Tables IV and V. Phase is expressed in fractions of a circle; i.e., 180° out of phase = 0.50.

TABLE IV

Frequencies (cycles per second) of Regions of Peak Amplitude of Cross Spectrum; Interval 0-400 Milliseconds After Flash

Subject	Cross Spectrum		Transfer Function from Before LSD to After LSD	
	Frequency	Amplitude	Amplitude	Phase
1	2.50	1032	0.64	0.94
	12.50	150	0.59	0.94
2	5.00	222	0.48	0.83
	10.00	756	0.69	0.93
3	3.75	199	1.04	0.24
	11.25	253	0.42	0.86
4	5.00	200	1.01	0.10
	10.00	353	0.97	0.99
5	2.50	751	1.51	0.09
	8.75	135	0.39	0.91
6	6.25	146	0.35	0.94
	11.25	76	0.19	0.93
7	2.50	748	0.88	0.47
	6.25	142	0.76	0.21
8	3.75	158	0.15	0.02
	12.50	35	0.16	0.06
9	2.50	336	4.33	0.89
	6.25	312	1.13	0.02

These analyses show a pattern of general reduction in amplitude following LSD for both the early and late epochs. The reduction is most consistent for the faster frequencies (more than 3 cycles/sec). The peak amplitudes in this range for 8 of the 9 subjects both during the early and late epochs were reduced. For slow frequencies (up to 3 cycles/sec) during the first 400 msec amplitude was reduced in 5 subjects, unchanged in 2, and increased in 2. For faster frequencies during the early epoch, 7 were reduced and 1 was increased. For slow frequencies during the late epoch, amplitude was reduced in 7 subjects and increased in 2. The faster frequencies in the late epoch (above 3 cycles/sec) showed the greatest and most consistent reduction in amplitude (average transfer function 0.27); amplitude was reduced in all subjects.

DISCUSSION

These observations indicate that LSD decreased the amplitude of certain of the components, particularly those components passing a filter at a frequency range of 6-12 cycles/sec, of the complex response to light flash

TABLE V

Frequencies (cycles per second) of Regions of Peak Amplitude of Cross Spectrum; Interval 400-1000 Milliseconds After Flash

Subject	Cross Spectrum		Transfer Function from Before LSD to After LSD	
	Frequency	Amplitude	Amplitude	Phase
1	1.7	97	0.86	0.31
	10.0	115	0.21	0.47
2	1.7	99	2.00	0.08
	10.8	129	0.20	0.10
3	2.5	46	1.67	0.47
	10.0	445	0.11	0.18
4	1.7	4	0.46	0.05
	10.0	89	0.28	0.67
5	1.7	571	0.42	0.87
	6.7	33	0.58	0.98
6	0.8	54	0.02	0.97
	11.7	37	0.10	0.61
7	1.7	823	0.49	0.52
	10.0	71	0.64	0.71
8	0.83	16	0.03	0.98
	6.7	6	0.14	0.94
9	1.7	7	4.10	0.17
	10.0	86	0.36	0.28

recorded from the scalp overlying the occipital cortex. This action is most apparent and consistent in the late rhythmic oscillations termed "ringing" or late after-discharge. There is equivocal evidence of a slight increase in latency of some of the waves in the "secondary response" range.

These observations of a reduced amplitude of certain of the components of the evoked response to flash are in keeping with the formulations of Marrazzi and Hart [24] and Purpura [25] of an inhibitory influence by LSD on cortical evoked responses.

An alternate interpretation of these observations that seems unlikely, but that cannot be ruled out with the present data, would be that each individual flash continues to evoke a response of the usual amplitude, but that the timing of each of the components is now so variable that the averaging technique cancels them; i.e., that the apparent inhibitory influence is an artifact of the averaging process.

The observed action of LSD on the evoked response probably is not specific to the agent. The latency and wave-form of the later components of the evoked response, including the "ringing" phenomenon, are easily influenced by changes in level of arousal and by sedative pharmaceutical

agents [34]. The behavioral state induced by LSD in the amounts used here is an altered state of consciousness qualitatively different from simple drowsiness; yet it apparently has some relationship to the sleep-arousal axis since the flights of imaginative thought and fantasy, as well as other features of the mild or moderate reaction to LSD, are promoted by isolation and quiet and can be interfered with by conversation or other tasks requiring careful focusing of attention. Also, the bursts of paroxysmal activity observed in the rhinencephalon of cats that received large amounts of LSD can be inhibited by strong sensory stimulation or other conditions favoring arousal [19].

The neurophysiological significance of the late ringing response following light flash recorded in man by means of averaging techniques is not well defined. Barlow [35] has noted by computation of autocorrelograms of the EEG during the same epoch from which a late ringing response is recorded that the period of the two is similar but not identical. The late ringing response in averaged evoked response to light flash in human occipital cortex may be identical with the well-known phenomenon of periodic after-discharge observed in many species following sensory stimulation. The primary response of the sensory cortex to an afferent volley is often followed by a train of regularly spaced surface-positive waves with intervals in the range from 50 to 150 msec. This phenomenon has been studied intensively by Chang [36, 37]. He observed that the frequency of these waves is independent of stimulus strength but varies with the state of anesthesia. He noted that repetitive discharges evoked by afferent impulses differ from spontaneous waves in many respects, even though they may happen to have the same frequency. For example, the evoked responses are always surface-positive waves, whereas the spontaneous waves are variable. Also, the spontaneous waves are regulated by the intralaminar nuclei of the thalamus, whereas the evoked waves apparently are not; in contrast, these evoked waves are dependent upon the integrity of the pathways between the cerebral cortex and the relevant specific thalamic nucleus. The appearance of these waves is similar in the specific nucleus and the sensory cortex, and waves recorded in the thalamic nucleus are abolished by removal of the sensory cortex. Similarly, destruction of the relevant specific nucleus or interruption of thalamocortical connections abolishes the evoked periodic discharges recorded from the projection cortex. On the basis of these observations, Chang postulated that "the specific periodic after-discharges following afferent stimulation represent the activity of the reverberating circuit between the sensory cortex and the thalamus." It is of interest that this periodic after-discharge is so specific that stimulation of a symmetrical point on the cortex of the contralateral hemisphere fails to evoke it, even though the transcallosal evoked response is large. Chang interprets this observation as arguing for the implication of a specific neuronal circuit, rather than representing merely a local discharge of an unorganized aggregate of autorhythmic neurons.

The long period (45-150 msec) of the afferent periodic after-discharges is too great to be accounted for simply by the time necessary for impulses to travel in a loop between the cortex and thalamus. Chang offers the explanation that the surface-positive reverberating waves, like the positive component of the primary response, consist of synchronous discharges of

cortical neurons triggered by the recurrent thalamic volleys but not the afferent impulses themselves (which may not be detectable on the surface of the cortex). Because of variation in speed of transmission and number of interposed synapses, the reverberating impulses may result in a continuous train instead of intermittent pulsed waves. Of the returning waves, only those that arrived at a suitable phase of the cortical neurons' excitability cycle could initiate subsequent discharge of these neurons. Therefore, Chang postulates that the interval between the reverberating waves is probably determined by the state of excitability of the cortical neurons at the time of action, rather than by the conduction time and number of synapses in the cortical-thalamic loop.

SUMMARY

LSD in amounts commonly used to induce major changes in personality, perception, mood, and thinking resulted in a diminished amplitude of certain of the components of the cortical evoked response to light flash in 9 human subjects.

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