Arch.gen.Psychiat. 21, 704-709 (1969).

Organicity Measures Following Repeated LSD Ingestion

William H. McGlothlin, PhD; David O. Arnold, PhD; and Daniel X. Freedman, MD, Los Angeles

TWO animal experiments have indicated that relatively large doses of lysergic acid diethylamide (LSD) can produce changes in central nervous system (CNS) function which persist for periods of time considerably longer than are usually estimated as necessary for drug detoxication. Adey[1] reports cats given a single dose of LSD in amounts of 80μg/kg showed disruption of conditioned responses and accompanying electroencephalographic (EEG) changes which persisted for 20 days. Sharpe et al[2] found that two of four squirrel monkeys given daily doses of from 10 to 40μg/kg required four to six months after discontinuing the drug to regain the predrug level of proficiency for difficult visual size discrimination tasks. Otis replicated this experiment using a larger sample and doses of from 10 to 100μg/kg. He found similar impairment of both easy and difficult discrimination lasting for several weeks (L.S. Otis, written communication, March 7, 1969). Single administrations of extremely large doses of LSD (25 mg/kg) have been shown to cause cellular brain damage in rats; however, 1 mg/kg did not produce similar results.[3]

Two studies on humans have examined EEG and performance differences between heavy LSD users and non-using comparison groups. Blacker et al[4] found EEG, test, and interview abnormalities in some chronic LSD users which were suggestive of minimal brain damage; over-all, however, they regarded their findings as inconclusive with respect to LSD-induced CNS damage. Cohen and Edwards[5] administered the Halstead-Reitan battery and other tests to 30 young persons who had used LSD 50 or more times and to a comparison group of the same size. Of the 15 measures recorded, the LSD group showed significantly poorer performance on two tests of visual perception and spatial orientation.

Retrospective studies of this type on humans are subject to several weaknesses: (1) Regardless of how carefully the comparison group is matched with the drug-using sample, there is still no assurance that differences between the groups are not due to predrug factors associated with the willingness to repeatedly ingest potent mind-altering substances. (2) Drug users typically employ a number of substances, so it is difficult to attribute differences to a particular drug.

Submitted for publication July 18, 1969.

From the Department of Psychology, University of California, Los Angeles. Dr. Arnold is at the University of California, Santa Barbara, and Dr. Freedman is now at the University of Chicago.

Reprint requests to Department of Psychology, University of California, 405 Hilgard Ave, Los Angeles 90024 (Dr. McGlothlin).

(3) Unless the subject is institutionalized it is difficult to separate acute from permanent or semipermanent drug effects. (4) Differences in test scores may be due to differences in motivation between the drug-user and comparison samples. The first three of these problems could be resolved by testing before and after a relatively long series of LSD sessions administered in psychotherapy; there is, however, no opportunity for such a study in this country at the present time.

In view of these weaknesses, it is legitimate to question the usefulness of another retrospective study of the relationship, if any, between organicity and LSD. We feel that there are at least two justifications for such an attempt. First, the fairly widespread use of LSD among young people, and the pronounced behavioral changes that frequently accompany heavy use, make it a matter of social concern. It is worthwhile to establish broad limits at least which bracket possible LSD-induced organicity—retrospective studies can accomplish this. Second, if successive studies reveal a consistent *pattern* of impairment, this would provide stronger evidence of drug-related organicity. One of the main purposes of the present study is to further explore Cohen and Edward's finding that deficits in psychological test performance for the LSD sample occurred in specific abilities (visual perception and spatial orientation), but not in other areas.

Methods

Subjects.—Sixteen subjects were selected from a larger follow-up interview study of persons receiving LSD in a medical setting. In the main study, a sample of 300 persons was randomly drawn from a population of 750 who received LSD either in an experimental or psychotherapy setting from one of three physicians in the Los Angeles area during the period 1956 to 1961. The criteria for inclusion in the organicity testing were: (1) 20 or more ingestions of LSD, including any nonmedical use; (2) respondent still living in the Los Angeles area; and (3) no evidence of gross psychopathology prior to the administration of LSD. Twenty-three subjects met the first two criteria; however, three, declined to participate in the testing. Four additional subjects were excluded because of the following preexisting pathology: brain aneurysm with residual bilateral scotoma; a 14-year history of heroin addiction and alcoholism; repeated psychiatric hospitalizations; and a seven-year history of severe emotional disturbance resulting in inability to work.

The 16 subjects tested were all white, twelve male and four female, with a mean age of 40 (range 28 to 51). All but one had attended college; four held bachelors, and four had advanced degrees. Six were currently working in the general area of the arts, and three others had done so in the past. Ten initially received LSD in psychotherapy and six in an experimental setting. Of the latter group, three had psychotherapy in another context, making a total of 13 who had received some psychotherapy.

The median number of medical LSD exposures was 20 (range 1 to 100). Thirteen had subsequently used LSD one or more times under nonmedical conditions; only five, however, had used LSD during the 12 months preceding the testing. The median number of combined medical and nonmedical exposures was 75 (range 20 to 1,100). The usual medical dosage was around 150μg to 200μg; four respondents, however, reported taking doses in excess of 500μg under nonmedical conditions. Most had experimented with various other drugs, especially in the hallucinogen group. Twelve had taken peyote or mescaline and five had done so prior to their initiation to LSD. Six had taken the strong hallucinogens other than LSD (peyote, mescaline, psilocybine, mushrooms, dimethytryptamine [DMT], and dimethoxymethyl-phenylethylamide [STP]) twenty or more times. Six had experimented casually with the opiates. Use of sedatives and stimulants was moderate, with no intravenous injection of methedrine. Twelve had used marihuana, although only eight had done so more than ten times.

A comparison group of 16 was selected from a control group of 60 used in the main study. They were matched for sex, and the means of age and education. Since 13 of the LSD group had received psychotherapy, the same number were obtained from a randomly drawn pool of persons who received non-LSD psychotherapy from the same therapist. This group received psychotherapy during a period when the therapist was not using LSD in therapy and excludes patients for whom LSD would have been counterindicated in the judgment of the therapist. The amount of psychotherapy was somewhat greater for the LSD group; there was a mean of 38 months vs 23 months for the comparison group. Subjects exhibiting serious psychopathology were excluded on the same basis as for the LSD group. The samples were

matched on occupation to the extent of maintaining the same proportion in the art-related professions. Four of the comparison group had used marihuana ten or more times, but none had taken the strong hallucinogens.

Test Battery.—The test battery included the two tests which differentiated the LSD group in Cohen and Edwards study.[5] One (trail-making A) measures the speed with which the subject can scan a series of randomly scattered circles numbered 1 to 25, and connect them in sequence.[6] The second (spatial-orientation test) requires the subject to walk-out a visually presented map which he holds in a constant position with respect to himself.[7] This task is similar to following a street map without orienting the map to match the geographic coordinates. The Porteus maze,[8] Minnesota percept-to-diagnostic test (MPDT),[9] and Witkin's embedded figures[10] were added to explore further possible LSD-related deficits in the visual perception and spatial orientation areas. The Porteus maze is a more complex task of the trail-making test, and has been used to detect brain damage. In this application, the score was the time required to complete the five most difficult mazes from three series without error. The MPDT measures the well-known tendency for CNS-damaged subjects to rotate designs when asked to reproduce simple figures. The score is the amount of rotation in degrees summed for six designs. A 12-item short form of the embedded figures test[11] was used, and failed items were scored as requiring three minutes. In addition to forms A and B of the trail-making test, three other tests from the Halstead-Reitan battery were included: the category, rhythm, and finger oscillation tests.[12] The Shipley-Hartford test was administered as a measure of general intelligence.[13] This test also provides separate scores for verbal and abstract abilities. Finally, Guilford's associational fluency test was included to provide another measure of verbal ability.[14]

Procedure.—The testing was done by an experienced person not involved in the remainder of the study. Subjects were paid $20.00 for their participation. To help control for motivation, a bonus of $2.00 additional was promised and paid for each of five unspecified tests on which they scored above the norm. With the exception of two subjects, control for acute effects of drug use was not a problem. One subject had used LSD on the day prior to the testing, and one was such a chronic user of LSD and other drugs as to make his self-report of pretesting behavior of doubtful validity. Of the remaining 14 subjects, only three had used LSD within the 12-month period preceding the testing. Exclusion of the two subjects with possible acute drug effects did not substantially alter the results. In addition to the psychological testing, a one- to two-hour psychiatric interview (by Freedman) was directed toward detecting any clinical evidence of organic impairment in the behavior of life situation of the LSD group.

Results

The mean test scores for the LSD and comparison groups are presented in the Table, along with the *t*-ratios of the differences. Also shown are the product-moment correlations between the rank-ordered LSD ingestions (highest rank given to largest number ingestions) and the test scores. The tests are ordered such that high scores in the Table are in the favorable direction for the first eight rows, and low scores represent better performance in the last six rows. The square-root transform was applied to the raw scores of the MPDT, the Porteus maze, and the embedded figures to correct for skewness.

The Shipley-Hartford general intelligence estimates have been reduced by seven points —the amount this test has been found to overestimate the full-scale WAIS intelligence quotient (IQ).[13] The estimated mean IQs for the LSD and comparison groups are virtually the same—121 and 122 respectively—which is still quite high, although not exceptionally so for this educational level.

Only one measure, Halstead's category test, yielded a significant difference between the two groups. The mean number of errors made on this test by the LSD group (57.3) was larger than that for the comparison group (39.6) beyond the 0.01 level of confidence. This is a nonverbal measure of ability to discern abstract principles, and also involves memory for a sequence of presentations. The relatively high error scores on this test were fairly uniform for the LSD group—only two subjects scored below the mean for the comparison group. The correlation between category test scores and rank-order LSD ingestions (0.36) was not significant. The LSD group also obtained a lower mean score on the abstract portion of the Shipley-Hartford, which is somewhat similar to the category test, although this difference was not statistically significant.

Mean Test Scores for LSD and Comparison Groups and Correlations of Rank-Order LSD Ingestions With Test Scores

Test	Mean LSD No. = 16	Mean Comparison No. = 16	Mean Difference Comparison — LSD	*t*-ratio	Correlation LSD vs Test Scores
Shipley-Hartford					
Abstract	30.9	33.8	2.9	1.4	−0.07
Verbal	36.1	34.3	−1.8	1.3	0.01
Total	67.0	68.1	1.1	0.4	−0.06
Associational fluency	20.7	18.3	−2.4	0.9	−0.04
Spatial orientation	29.2	31.0	1.8	0.7	−0.53*
Halstead battery					
Finger oscillation (preferred hand)	50.4	51.9	1.5	0.6	0.39
Finger oscillation (nonpreferred hand)	45.7	47.6	1.9	0.9	0.39
Rhythm	27.4	27.0	−0.4	0.4	0.59*
Category (errors)	57.3	39.6	−17.7	2.8†	0.36
Trail making A (seconds)	31.0	26.1	−4.9	1.6	−0.08
Trail making B (seconds)	69.2	71.2	2.0	0.2	−0.28
MPDT ($\sqrt{}$degrees deviation)	4.8	4.1	−0.7	1.1	0.43
Porteus maze ($\sqrt{}$seconds)	21.9	19.1	−2.8	1.3	−0.17
Embedded figures ($\sqrt{}$seconds)	24.9	22.8	−2.1	0.6	0.22

* Significant beyond the 0.05 level of confidence.
† Significant beyond the 0.01 level of confidence.

Neither of the tests which differentiated the LSD and comparison groups in Cohen and Edwards study, trail-making A and spatial orientation, showed significant differences in the current study. Both, however, did show poorer scores for the LSD group, and the difference for trail-making A approached significance. On the other hand, the difference between the means for the quite similar test, trail-making B, was slightly in favor of the LSD group. The results for the other three visual-perception tests (MPDT, Porteus maze, and embedded figures) all showed small differences in favor of the comparison group, but none were significant. In summary, the mean performance for the LSD group was poorer than that for the comparison group on five of the six visual-perception tests, but none of the individual differences was statistically significant. The rank-order LSD ingestions correlated negatively with the spatial orientation score (-0.53, $P < 0.05$). The other five visual tests did not show either significant individual correlations or an over-all trend between LSD ingestions and test scores. In Cohen and Edwards study, the number of LSD ingestions showed a significant positive correlation with trail-making A, but was unrelated to the spatial orientation test.

The LSD group scored somewhat higher than the comparison group on verbal ability as measured by the Shipley-Hartford and associational fluency tests. The significant positive correlation (0.59) between LSD ingestions and score on the rhythm test may be an artifact related to the occupations of those with the largest number of LSD ingestions. Six of the eight highest users are, or had been, in art-related professions, although only one was a musician.

The psychiatric interviews did not reveal clinically significant signs of organic impairment in behavior or life situations. For some, there were characterlogical and psychological features which were somewhat eccentric; but, over-all, the ability to judge, to acquire competence and new learning, to focus attention and concentrate, to recall and retrieve relevant information appeared intact. Where unusual personality traits were encountered, they seemed to have been present in the pre-LSD life history, style, and subculture of the subjects.

Comment and Conclusions

The weaknesses of the between-group design limit the confidence of any conclusion concerning a causal relation between LSD use and differences in group scores, although the present study is probably less vulnerable

to uncontrolled variables than was the case for the two previous studies with humans (Blacker et al and Cohen and Edwards). The method of forming the sample was not dependent on volunteers, and the subjects were considerably more removed from the immediate emotional upheavals and other long-lasting, but nonpermanent effects of LSD and the drug-using milieu, than were the younger samples. On the other hand, while subjects exhibiting gross pre-LSD psychopathology were excluded, we still cannot eliminate the possibility that between-group differences are due to prior factors associated with the decision to use LSD repeatedly.

In terms of over-all results, our study agrees with those of Blacker et al and Cohen and Edwards, ie, there is no generalized evidence of organicity in the LSD group. Certainly, any deficit that may exist does not approach that shown by subjects with neurologically proven brain lesions. Even on the category test, on which the LSD group showed the poorest performance, the mean number of errors (57) is considerably short of the mean-score norms of around 80 obtained by persons with proven brain damage.[15]

On the other hand, the relatively poor performance on the category test, coupled with high scores on the verbal measures, is consistent with an interpretation of a lesser degree of organicity. It is well established that abstract abilities are more impaired by CNS damage than are verbal abilities, and the category test has been found to be the most sensitive subtest in the Halstead-Reitan battery for detecting organicity.[14] A high verbal—low abstract score combination is a clinical indicator of possible organicity, and the Shipley-Hartford was initially designed to provide an index derived from the ratio of abstract to verbal ability (conceptual quotient). While the conceptual quotient is no longer considered to be more than a warning indicator of possible organicity, it is of interest to note that six of the LSD group, including the three heaviest users, obtained quotients below 85—a score level Shipley[16] considered "moderately suspicious" with respect to brain pathology. Only one in the comparison group scored below this value.

Arguing against an LSD-related interpretation of the lower scores on abstract ability is the fact that neither the category test nor the abstract portion of the Shipley-Hartford correlated significantly with the number of LSD ingestions. Also, Cohen and Edwards found no difference between LSD and comparison groups on the category test among a sample with a mean age of 22.

The failure of the present study to find more than minimal support for the impaired performance on visual-perceptual and spatial-orientation tests reported by Cohen and Edwards may indicate that such effects persist for a relatively long time following the use of LSD, but are not permanent. Cohen and Edwards subjects were asked not to use LSD or other drugs for a period of 48 hours prior to the testing, but the majority were fairly regular LSD users at the time of the testing. By contrast, most of the subjects in the present study had not used LSD within one year of the testing. The one subject who did use LSD on the day preceding the testing performed quite poorly on all the visual tests. The animal studies mentioned earlier also support this interpretation. Visual size discrimination in monkeys was impaired for periods of weeks or months following repeated administration of LSD, but eventually recovered to the original level (Sharpe et al[2] and L.S. Otis, written communication, March 7, 1969). Similar findings with respect to EEG measures in cats were reported by Adey.[1]

In summary, three conclusions may be made from the present study. First, the results confirm the findings of earlier studies in that there is no evidence of generalized brain damage related to the amounts of LSD ingested by this sample. Second, the results provide only minimal support for earlier findings suggesting that performance on visual perception and spatial orientation tests may be permanently impaired by the repeated use of LSD. Third, there is evidence of moderate impairment of abstract abilities among the present LSD group which is suggestive of minimal brain damage, although the experimental design does not permit the establishment of a causal relationship. Should the opportunity arise to obtain pre-LSD and post-LSD measures on a group receiving a long series of LSD

treatments in psychotherapy, it would appear profitable to further investigate both the visual-perception deficits reported by an earlier study and the question of possible deficit in abstract ability suggested by the present study. It would probably also be advisable to investigate further possible temporary vs permanent effects by conducting post-LSD testings shortly after the termination of the series of treatments, and again after longer time intervals.

This research was supported by Public Health Service grant No. MH-13484 from the National Institute of Mental Health. Dr. Arthur Chandler, Dr. Sidney Cohen, and Dr. Oscar Janiger provided the initial list of respondents; Dr. Alan Edwards made a number of helpful suggestions based on his earlier work in this area; Mr. John Williams performed the psychological testing; and Miss Kay Jamison and Mrs. Judith Bernstein aided in the analysis.

References

1. Adey, W.R.: Neurophysiological Action of LSD, proceedings of the Fifth Annual Meeting of the American College of Neuropharmacology, San Juan, Puerto Rico, Dec 7-9, 1966, to be published.

2. Sharpe, L.G.; Otis, L.S.; and Schusterman, R.J.: Disruption of Size Discrimination in Squirrel Monkeys (*Saimiri sciureus*) by LSD-25, *Psychon Sci* 7:103-104, 1967.

3. Denber, H.C.B.; Charipper, H.A.; and Roizen, L.: Cytological Effects of Lysergic Acid Diethylamide (LSD-25) in Rat Brain and Liver, *Fed Proc* 23:147, 1964.

4. Blacker, K.H., et al: Chronic Users of LSD: The "Acidheads", *Amer J Psychiat* 125:341-351, 1968.

5. Cohen, S., and Edwards, A.E.: LSD and Organic Brain Damage, *Drug Dependence*, to be published.

6. Reitan, R.M.: Validity of the Trail-Making Test as an Indicator of Organic Brain Damage, *Percept Motor Skills* 8:271-276, 1958.

7. Semmes, J., et al: Spacial Orientation in Man After Cerebral Injury: I. Analysis by Locus of Lesion, *J Psychol* 39:227-244, 1955.

8. Porteus, S.D.: *Porteus Maze Test: Fifty Years Application*, Palo Alto, Calif: Pacific Books, 1965.

9. Fuller, G.B., and Laird, J.T.: The Minnesota Percepto-Diagnostic Test, *J Clin Psychol* 19:1-35, 1963.

10. Witkin, H.A.: Individual Differences in Ease of Perception of Embedded Figures, *J Personality* 19:1-15, 1950.

11. Jackson, D.N.: A Short Form of Widkin's Embedded Figures Test, *J Abnorm Soc Psychol* 53:254-255, 1956.

12. Reitan, R.M.: Investigation of the Validity of Halstead's Measures of Biological Intelligence, *Arch Neurol Psychiat* 73:28-35 (Jan) 1955.

13. Watson, C.G., and Klett, W.G.: Prediction of WAIS I.Q.'s From the Shipley-Hartford, The Army General Classification Test and the Revised Beta Examination, *J Clin Psychol* 24:338-341, 1968.

14. Guilford, J.P.: *Nature of Human Intelligence*, New York: McGraw-Hill Book Co., Inc., 1967.

15. Vega, A., and Parsons, O.A.: Cross Validation of the Halstead-Reitan Test for Brain Damage, *J Consult Psychol* 31:619-625, 1967.

16. Shipley, W.C., and Burlingame, C.C.: A Convenient Self-Administering Scale for Measuring Intellectual Impairment in Psychotics, *Amer J Psychiat* 97:1313-1325, 1941.