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The Effect of LSD on Sleep-Deprived Men

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Abstract. Thirteen young men were tested to determine the motor, attention, physiologic, and behavioral effects of 1.5 μg/kg of LSD taken orally after one or two nights' loss of sleep. Twenty additional subjects were tested in two control categories: 1.5 μg/kg of LSD alone and one night's sleep loss alone.

The major significant results of the study were: the onset of characteristic LSD behavior and attention impairments was more rapid in those men who received LSD after loss of sleep than in the drug-alone group; the sleep-loss-LSD subjects showed inaccuracies in problem solving and vigilance tests not present in the controls; and the men who received LSD after two nights' loss of sleep showed increases in pulse rate, pupil size, and 3-hour plasma levels of LSD when compared with those subject groups which received the drug alone and the drug after one night's sleep loss.

Key-Words: LSD 25 — Sleep Derivation — Attention — Performance — Hallucinations.

I. Indroduction

A careful search of the literature reveals only one prior study on the performance of sleep-deprived individuals who received psychotomimetic drugs. Bliss and coworkers (1959) gave a nonhallucinatory dose of LSD (0.5 μg/kg) to four subjects after they had been without sleep for 48 hours, and all experienced visual hallucinations. Bliss and coworkers' description of this accentuation of drug effect by sleep loss was not part of the main body of their paper, and it was believed that their findings merited more intensive investigation.

This study is a larger, more detailed one, primarily measuring motor, attention, vigilance, and behavioral impairments in sleep-deprived subjects who received LSD. It was completed in 1966[1].

* Formerely Cpt., MC, U.S.A. Edgewood Arsenal, Md., where this work was done.

1 No work with LSD in human subjects has been done since then at U.S.A. Edgewood Arsenal, Md.

II. Methods

A. Subjects. All Subjects were U. S. Army enlisted men who were told at their army posts about the U. S. Army Edgewood Arsenal volunteer program. At this briefing, all those men who chose to enter the program were given group screening tests: a Minnesota Multiphasic Personality Inventory, projective tests, and a social history questionnaire. These were scored and rated. Only those men judged to have very few social and psychological irregularities, approximately 20% of those who volunteered, were accepted. (The primary motivations for volunteering were: duty on the East Coast and 3-day weekend passes).

The men who were chosen for this particular study were selected from the group of accepted volunteers deemed particularly capable of receiving psychochemicals. These men were then placed without bias into one of the test categories.

B. Subject Briefing. At least three days before the drug tests, the subjects were briefed by a physician. Subjects were not told what drug they would receive. They were merely told that they would receive a frequently used drug which in certain doses caused minor to moderate degrees of confusion. The men had the option at that point to choose, without penalty, alternative non-chemical tests.

C. Subject Categories. Thirty-three men were tested in one of the following four categories: 10 (drug alone) received 1.5 μg/kg[2] of LSD; 10 (sleep loss alone) were deprived of one night's sleep and given a placebo; 10 (1N sleep loss-drug) received 1.5 μg/kg of LSD after being deprived of one night's sleep; and three (2N sleep loss-drug) were kept awake two nights and given the drug. An oral dose of 1.5 μg/kg of LSD was used uniformly in this study because it approximates the standard dose of the drug (100 μg).

Data from five subjects who received 2 μg/kg of LSD orally in a prior study[3] were included for purposes of comparison in Tables 1, 3 and 4.

D. Testing Procedures. The subjects were tested in groups of three or four. One group of three was admitted to the medical ward three nights before drug administration and the men remained awake the next two days and nights. The other groups were admitted two nights before drug administration. Baseline measurements were done on the day after admission. That evening, two of the men from these groups were kept awake and the other one or two were allowed to sleep as usual. Those assigned to the sleep loss group were constantly accompanied by an aid man and were not allowed to sleep or doze. At 8 A.M. the next morning,

2 All doses are expressed in terms of the weight of the base.

3 See footnote c, Table 1.

the subjects received either the active drug or saline. Neither the subject nor the nurse or aid man knew whether the solution administered was simply saline or the active chemical.

Each subject had a small cubicle in which he was given psychological and physiological tests 5—15 min every half hour. When the subjects were not being tested, the were permitted to gather in a larger room where they could watch television or play cards.

One nurse and usually one aid man were assigned to attend each subject during testing. The nurse and aid man provided constant observation and kept a clinical record of the patients' responses. The subjects remained on the medical ward until the test was completed and their performance scores returned to their pre-drug level.

E. Performance Measures. The performance measures for the study included the Number Facility (NF) test, which is part of Moran and Mefferd's (1959) repetitive psychometric measures, a manual dexterity test, a vigilance test, an auditory memory span test, and a behavioral rating. The NF is a 3-minute, subject-paced, simple addition task which has multiple forms and is given 25 times before administration of the drug; the average of the five highest pretest scores is used as a baseline. After drug, scores are expressed as a percentage of this baseline (100× number correct/baseline). The percentage of errors (100×errors/number of problems attempted) was also recorded and used as an index of accuracy. The control measurement established for percentage of error was the mean percentage of error on the last five pre-drug NF tests.

Manual dexterity was tested with the Minnesota Manipulation test, a 1 minute peg and formboard test, the results of which (after drug) are scored as a percentage of the average of the last five pre-test scores.

A vigilance test[4], based on the Mackworth apparatus (Mackworth, 1950) was included because vigilance tasks are most sensitive early in sleep derivation (Williams *et al.*, 1959). Visual or auditory cues were presented every 5 sec, and at random intervals their intensity was increased. Each vigilance test lasted 22 min, and during this period the subject was requested to quickly identify the 50 prominent visual or auditory cues from among the approximately 260 stimuli presented. Reaction times, missed vigilance cues, and incorrect responses were recorded. Baselines on vigilance scores were obtained easily because the test was mastered by over 90 percent of the subjects on the first trial. When mastery did not occur then, a second trial always proved adequate.

An auditory memory span (digit recall) test was given to most of the subjects before and during the test.

The same performance tests were given to every group.

4 Constructed by CPT R. Smith, MSC, Edgewood Arsenal, Maryland.

Table 1
Comparison of effects on BCL items of LSD alone and LSD plus sleep loss

BCL category	Reactor fraction[a]			
	Dose of LSD and degree of sleep loss[b]			
	1.5 μg/kg of LSD	1N sleep loss LSD (1.5 μg/kg)	2N sleep loss LSD (1.5 μg/kg)	2.0 μg/kg of LSD[c]
Drowsy	2/10	4/10	1/3	2/5
Restless	4/10	6/10	1/3	2/5
Anxious	2/10	3/10	2/3	2/5
Unduly talkative	1/10	3/10	2/3	—
Hallucinating	3/10	7/10	3/3	4/5
Euphoric	5/10	6/10	1/3	4/5
Contrary	1/10	1/10	1/3	2/5
Short attention span	6/10	9/10	3/3	4/5
Poor coordination	5/10	6/10	3/3	—
Disjointed verbal associations	0/10	4/10	2/3	2/5
Paranoid	0/10	0/10	1/3	2/5
Disoriented	0/10	0/10	1/3	2/5

[a] Subjects were included as reactors only if their behavior was checked on the BCL category more than once during the test period.

[b] Sleep-loss-alone subjects showed few changes on the BCL during the test period: drowsiness (1/10 in the 1N sleep-loss group; 2/3 in the 2N sleep-loss group), and restlessness (2/3 in the 2N sleep-loss subjects).

[c] Unpublished data from a study by G. Aghajanian, Edgewood Arsenal, Md., included for comparison.

F. Behavioral and Physiological Measurements. A behavioral rating measure, a 26-item Behavior Check List (BCL), was scored by experienced nurses before, every half hour during, and after the test. (A partial listing of the BCL items is shown in Table 1). The interrater agreement for the presence or absence of check list items was 72—93 %. An 82-item Symptom Check List, a modification of Abramson's (1960), was completed by the volunteers at the end of the test.

The physiologic measurements included heart rate, blood pressure, pupil size (estimated by disc pupilometer under standard lighting conditions), and rectal temperature. Three baseline measurements of each physiological variable were taken before the test began. Blood levels of LSD were measured 55 min and 3 h after the drug was administered in the manner described by Aghajanian and Bing (1964). Electroencephalograms were recorded from a few men in each experimental group.

III. Results

A. Controls. LSD alone, in the mild dose given, produced surprisingly few changes in motor, behavior, attention, accuracy, and vigilance indices. The differences between the baseline and drug-alone test scores were either insignificant or unimpressive for the percentage error on the NF, the latency time and the corrected perceptual identification on the vigilance test, and the auditory memory span.

The items which were sensitive to the drug alone were the number of correct responses on the NF (Fig. 1), the scores on the Symptom Check List, and to a lesser extent, the scores on the BCL (Table 1).

As has been reported, the loss of a night's sleep caused no consistent impairment of performance except on the vigilance (watchkeeping) task. The sleep-loss-alone subjects consistently showed an increase in missed perceptual cues over their baseline performance.

B. One Night's Sleep-Loss-Drug. The men deprived of one night's sleep and given the set dose of LSD did not have as impressive a decrement in performance (compared with the drug-alone men) as was expected. In fact the scores on the auditory memory span, the Minnesota Manipulation Test, the BCL, the Symptom Check List, and the latency time on the vigilance test were not significantly different between these two groups. Likewise, pupil size, blood levels of LSD, and pulse changes did not differentiate the groups. EEG's[5] showed more of the increased low voltage activity characteristic of LSD in the 1N sleep-loss-drug subjects than in the drug-alone subjects, but this was not prominent or consistent enough to enable one to distinguish the two groups by this criterion.

Differentiating the 1N sleep-loss-drug group from its drug-alone controls were: the percentage error on the NF, the percentage correct on the NF, and the number of misidentified perceptual cues on the vigilance task. The 1N sleep-loss-drug men showed significantly greater impairment on the NF (percent correct) at 0030, 0055, and 0130 hours experimental time than the drug-alone men, even correcting for their slight deficit immediately prior to receiving the drug (Fig. 1). The NF (percent error) also significantly differentiated these two groups at 0100 and 0130 hours (Fig. 2).

Analysis of the vigilance test data revealed that the 1N sleep-loss-drug subjects had more frequent perceptual misidentifications then did either control group (Table 2). The 1N sleep-loss-drug men scored a median of 11 incorrect perceptual responses during each test period compared with a median of 3 ($P < 0.05$) for the sleep-loss-alone and 2

5 M. A. Goldberg, CPT, MC, Edgewood Arsenal, Maryland, interpreted the EEG's.

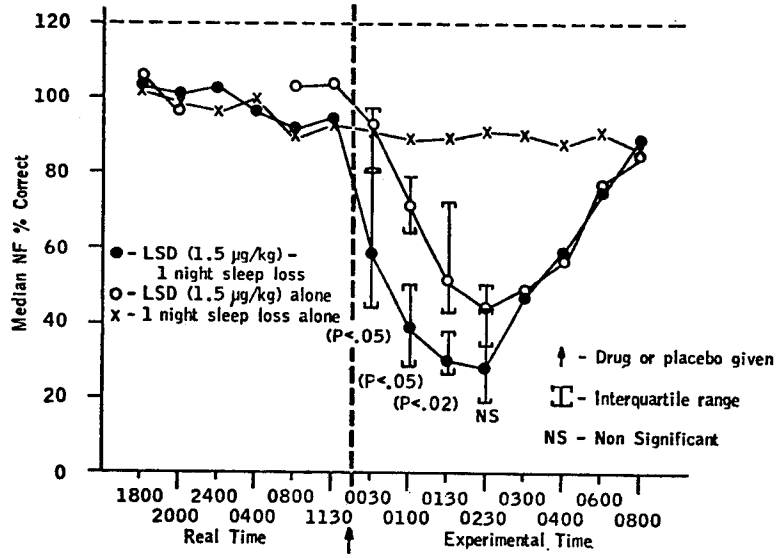

Fig. 1. NF scores for sleep-Loss-LSD group and controls

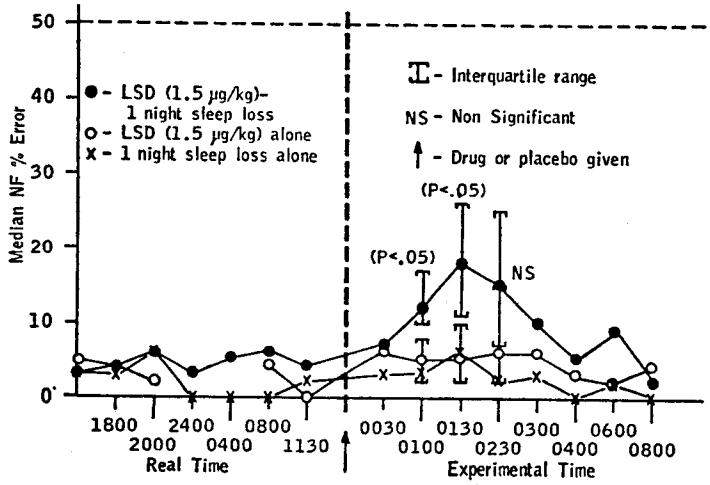

Fig. 2. NF percent error for the sleep-loss-LSD group and controls

($P < 0.02$) for the drug-alone group [Mann Whitney U Test (Siegal, 1956), two-tailed]. Missed perceptual cues, characteristic of sleep-deprived subjects, were as prominent for the 1N sleep-loss-drug men as for the sleep-loss-alone subjects. Reaction times were so variable for all the groups that they are not particularly useful.

Table 2. *Vigilance test: perceptual misidentifications*

A) Sleep loss alone

Hours without sleep	Baseline	26	29	33	36	50
No. of subjects	13		10		3	
Median no. of visual misidentifications	1	2	5	4	3	5
Median no. of auditory misidentifications	1	2 (27.5 hr)		3 (30.5 hr)	1	1

B) Drug alone

Experimental time (hr)	Baseline	0100	0230	0400
no. of Subjects		10		
Median no. of visual misidentifications	1	2		2
Median No. of auditory misidentifications	1		2	

C) Drug and sleep loss

Hours without sleep	0	26	29	33	55	59
Experimental time (hr)	Baseline		0100	0400	0100	0400
No. of subjects	13		10		3	
Median no. of visual misidentifications	1	2	12	9	21	[a]
Median no. of auditory misidentifications	0	2	11 (31 hr)		[a]	

[a] Subjects too affected to remain in testing booth.

C. Two Night's Sleep-Loss-Drug. The effect of 1.5 μg/kg of LSD given orally to men deprived of two nights' sleep was far more striking than those effects resulting from that dose of drug after one night's loss of sleep. After 50 h without sleep, the three subjects then given LSD showed significant and impressive decrements in all performance parameters tested, which included the previously unimpaired Minnesota Manipulation Test and the auditory memory span.

The clinical reaction produced by 2N sleep-loss-drug stress was also more pronounced than that of the drug-alone and the 1N sleep-loss-drug groups (Table 1) and was significantly more rapid in onset (Table 3).

Table 3. *Onset of behavioral signs*

Experimental condition	Number of subjects	Median number of 12 selected behaviors (BCL Items) present			
		Baseline (Immediately before drug)	0030 hr	0100 hr	0130 h
2N sleep loss-drug	3	1	5[a]	5[a]	4
1N sleep loss-drug	10	0	2	2	4
Drug alone (1.5 μg/kg)	10	0	0	1	2
Drug alone (2.0 μg/kg)[b]	5	0	1	2	4

[a] Significantly different (with correction for the sleep-loss effect prior to drug) from same dose, drug-alone group; $P < .05$ (Mann Whitney U, two-tailed).
[b] Data from an earlier study, for comparison.

Specifically, as recorded on the BCL, all three of the 2N sleep-loss-drug men were anxious and poorly coordinated at 0030 hours experimental time, and two of the three were hallucinating and had a shortened attention span. Of the 10 drug-alone men, only one was hallucinating at 0030 hours, none had a shortened attention span, and none were reported to be anxious.

The performance changes which distinguished the 1N sleep-loss-drug effect from the drug-alone response were again notable and even more pronounced for the 2N sleep-loss-drug response. The percentage correct on the NF was much lower for the 2N sleep-loss-drug men than for the 1N sleep-loss-drug group. As in Fig. 2, the percentage error on the NF was markedly increased for the 2N sleep-loss-drug volunteers. The perceptual misidentifications in vigilance testing were again prominent (Table 2). However, vigilance testing could not be performed more than once with these subjects because they became too perplexed to complete this extended task.

Unlike the 1N sleep-loss-drug reaction, certain adrenergic changes characteristic of LSD were accentuated by the 2N sleep-loss-drug stress. Accentuation of the drug-induced pupillary dilation and tachycardia by two nights of sleep loss occurred for the most part early in the drug period (Table 4).

IV. Discussion

LSD given to mildly sleep-deprived men caused a more rapid onset of behavioral and performance decrements and a somewhat more profound degree of these impairments than in the drug-alone group. The combination of drug and sleep deprivation also elicited some performance impairments that were not seen in the control groups.

Table 4. *Onset of changes in heart rate and pupil size*

Experimental condition[a]	Number of subjects	Median increase of heart rate over baseline rate (bpm)				
		0030 hr	0100 hr	0130 hr	0200 hr	0230 hr
2N sleep loss-drug	3	11[b]	23	23[b]	23[b]	19
1N sleep loss-drug	10	3	11	7	11	11
Drug alone: 1.5 μg/kg	10	3	6	5	4	6
Drug alone: 2.0 μg/kg[c]	5	6	9	—	—	12
Experimental condition[a]	**Number of subjects**	**Median increase in pupil diameter over baseline size (mm)**				
		0030 hr	0100 hr	0130 hr	0200 hr	0230 hr
2N sleep loss-drug	3	2.5[e]	3.0[d]	3.0[d]	3.0[d]	3.0
1N sleep loss-drug	10	0.8	1.8	1.9	1.8	2.1
Drug alone: 1.5 μg/kg	10	0.5	1.3	2.0	2.4	2.2
Drug alone: 2.0 μg/kg[c]	5	0.5	1.8	—	2.5	2.4

[a] Sleep-loss-alone controls showed no median increase over their baseline rate or size.

[b] Significantly different from the same-dose comparison groups, $P < 0.05$, Mann Whitney U, two-tailed.

[c] Data from an earlier study, for comparison.

[d] Significantly different from the same dose comparison groups, Mann Whitney U Test, two-tailed. — [d] $P < 0.05$. — [e] $P < 0.02$.

The rapid onset of the behavioral effects of the drug when given to sleep-deprived subjects clearly paralleled the rapid onset of the performance impairments and the physiologic effects of the drug. This finding is at variance with the author's results with scopolamine hydrobromide given to sleep-deprived men (Safer, 1970). Sleep deprivation did not increase the rapidity of onset of any of the effects of scopolamine. This lack of uniformity in effects on onset may be explained by the fact that LSD is a stimulant whereas scopolamine is not classified as such.

The sleep-loss-drug men showed errors in their problem solving and perceptual recognition tests that were not present or impressive for the drug-alone or the sleep-loss-alone control groups. Inaccuracy on the NF beyond the baseline range did not occur with either LSD alone or sleep loss (one and two nights' deprivation), but was prominent and significant for both groups of sleep-loss-drug men.

Likewise, perceptual misidentification on the vigilance tests, which was prominent for the sleep-loss-drug men, was barely increased over baseline scores for the drug-alone and sleep-loss-alone men (Table 2). On rank order correlation (Underwood, 1954), the NF and vigilance inaccuracies co-existed [$P < 0.01$ [visual]; $P < 0.05$ (auditory)] thereby

Table 5. *Blood level of LSD*

Experimental condition	Number of subjects	Median blood level of LSD	
		0055 hr ng/kg	0300 hr ng/kg
Drug alone	10	1.79	1.11
1N sleep loss-drug	10	1.80	0[a]
2N sleep loss-drug	3	3.15	1.60[b]

[a] The level of precision of the test becomes poor below 1 ng/kg, so that traces and questionable levels are registered as 0.

[b] Significantly different from the two comparison groups, Mann Whitney U Test, two-tailed, $P < 0.05$.

supporting the likelihood that they reflect the same CNS impairment. However, neither inaccuracy measure showed a relationship to clinically noted hallucinations.

The records of five men who were not deprived of sleep and who were given 2.0 μg/kg of LSD orally[6] were reviewed to compare the effects of sleep loss and 1.5 μg/kg of LSD with those impairments caused by the higher dose of LSD alone. Analysis of the data revealed that the intensity of the clinical reaction to 1.5 μg/kg of LSD given after two nights without sleep was much like that caused by 2.0 μg/kg of LSD (Table 1). However, as was the case with the 1.5 μg/kg drug-alone men, the 2.0 μg/kg LSD subjects showed no increase in inaccuracies of the NF beyond the baseline range.

Blood levels of LSD after a dose of 1.5 μg/kg were measured from samples taken twice during the test and showed no clear relationship to NF performance. This is contrary to the findings of Aghajanian and Bing (1964), but it must be remembered that they gave 2.0 μg/kg intravenously, so that their test blood levels were much higher. A notable finding on blood levels of LSD was that the median blood level at 0300 hours experimental time for the 2N sleep-loss-drug group was significantly higher than that of the other two groups (Table 5). The reason for this finding is unclear. Of note in this regard is Mandell's (1964) finding of a fluorescent indole compound (SRIS) in the urine of subjects deprived of sleep for over 36 hours. However, although the maximum activity wavelengths of SRIS (Mandell, 1964) and LSD (Aghajanian and Bing, 1964) are similar, their fluorescent wavelengths are appreciably different.

6 Data from a previous study by George Aghajanian, M. D., formerly CPT, MC, Edgewood Arsenal, Maryland.

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