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LSD

A Neuropsychological Study of Polydrug Users

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• **The long-term neuropsychological effects of persistent nonmedical drug use are still unknown. In this study, 22 young men, all extensive "polydrug" users, were examined while free from drugs for an average of 60 days by means of the Halstead-Reitan Neuropsychological Test Battery. Their performance was compared to that of age-education-sex-matched neurologically intact medical patients and a similarly matched group of neurologically impaired patients.**

Blind independent ratings of test protocols by two experienced clinicians judged 41% to 64% of the drug users, 11% to 26% of the medical patients, and 84% to 89% of the neurologic patients to be impaired. Interpretation of these results suggests that in some individuals, heavy "polydrug" use may be associated with neuropsychological dysfunction, which persists at least an average of two months beyond cessation of drug use.

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An important and unanswered question in the field of nonmedical drug use is whether long-term exposure to various psychoactive substances causes permanent alteration in brain function. Our relative ignorance applies even to alcohol, the most extensively studied of the substances of abuse. We do know that in a certain minority of very heavy alcohol users, neuropsychiatric impairment develops in the form of Wernicke-Korsakoff syndrome.[1] It is still unclear whether this syndrome is the result of direct alcohol neurotoxicity or of thiamine deficiency.[2,3] More importantly, we do not know whether neuropsychological impairment gradually develops in all alcohol users as a function of their experience with alcohol, or whether such impairment occurs only in certain susceptible individuals. In an extensive review of the neuropsychological literature on alcoholism, Kleinknecht and Goldstein[4] suggest that the majority of investigations to date contain such serious methodologic flaws that their conclusions must be treated with great caution. In the several better-constructed studies, these authors noted that persons with histories of heavy alcohol use for 20 years or more do tend to have impairment in higher intellectual functions such as abstracting ability, even though they might manifest no obvious neurologic or psychiatric disturbance.

Fewer studies have been conducted on possible long-term cerebral effects of marijuana. Several recent, controlled studies have failed to uncover any cerebral dysfunction in marijuana users.[5-8] These negative conclusions are not in accord with several clinical reports of a possible association between marijuana and brain damage.[9-11] Because of various real, research design problems, the latter studies have tended to receive less acceptance than the former.

LSD has received even less extensive study than marijuana. Of five recent investigations that employed similar neuropsychological methods, none found evidence of generalized cerebral impairment. Three of the studies did report that LSD users had moderate difficulty in handling the Halstead category test, a nonverbal measure of abilities to discern abstract principles,[12-14] while a fourth suggested that LSD users might exhibit difficulties in visual-spatial orientation.[15] Another investigation failed to uncover any neuropsychological deficit among 20 youthful users who reported a mean number of 29 LSD exposures.[16] Similarly, the 21 LSD users studied by Blacker et al[17] showed no increase in clinically abnormal electroencephalograms, although these subjects did appear to organize sensory input differently from normal subjects as measured by cognitive tests and EEG visual evoked potential procedures. Lack of knowledge of predrug adaptive abilities, small sample size, inadequate drug use history (particularly history of alcohol intake), and lack of screening for possible acute intoxication represent at least some of the methodologic difficulties that might account for differences in some of these results.

With respect to cerebral consequences of opiate use, several older studies[18,19] and one recent investigation[20] have failed to uncover any deficits among narcotics addicts. Similarly, a review of case reports[21] of medical complications of opiate use fails to mention neurologic sequelae, although rare instances of transverse myelitis[22-24] and pontine myelinolysis[25] following intravenous heroin administration have been recorded. Although the reports to date are negative, the paucity of detailed information leaves open the question of long-term effects of opiates on the brain.

To our knowledge, there exist no reports of investiga-

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tions into possible long-term cerebral and neuropsychological effects of the sedatives, stimulants, and solvents. Even more importantly, to date only one published study[26] has taken into account the possible effects of simultaneous or consecutive use of many different agents by the same individual. This study, which reported negative results, is described in more detail below. A number of polydrug studies are presently underway. This communication may represent one of the first reports of a neuropsychological investigation of such polydrug users.

SUBJECTS AND METHODS

Drug Users

Twenty-two consecutive male admissions to the University of California San Diego–San Diego County residential treatment program for youthful narcotics addicts were enrolled. Twenty of the patients were on a drug-free treatment regimen at the time of testing, while two were in the final stages of methadone detoxification. The criteria for exclusion were: (1) medical history that suggested the possibility of neurologic disease, including birth injuries or obstetrical complications, meningitis or encephalitis as a child, febrile convulsions, idiopathic epilepsy, serious renal, cardiac, hepatic, or endocrinologic disorders; (2) physical examination that was equivocal or positive for neurologic disorder; and (3) current treatment with psychotropic medications. Initially, we also attempted to exclude subjects on the basis of a history suggestive of head injury, overdose with unconsciousness, and withdrawal seizures. Unfortunately, the prevalence of such histories was so high that it proved impractical to reject such individuals. We attempted to control for the possible confounding effects of acute intoxication or of abstinence syndromes by enrolling only those individuals who had been at the facility for at least three weeks (mean length of stay at time of testing, 60.91 ± 36.05 days; range, 19 to 141 days). In addition, all subjects underwent periodic urine screening as a routine part of their treatment. (Substances checked were morphine, codeine, procaine, cocaine, methadone, amphetamines, and barbiturates.) Because the time of urine screening was determined by clinical and not research considerations, only 12 of the 22 patients were tested within 24 hours of neuropsychological examination. The rest were screened between one to four days prior to examination. Only the two subjects receiving methadone showed psychoactive medications in their urine in this period of time.

Medical Comparison Group

Protocols of subjects from a population of medical inpatients that had been tested 10 to 15 years ago by one of us (R.M.R.) as part of another study were selected for comparative purposes. All the medical inpatients had undergone clinical neurologic examinations and had been rated as neurologically clear on the basis of these examinations. The records of these medical inpatients were matched as closely as possible on a case-by-case basis for age, sex, education, and handedness with our drug users.

Neurologic Comparison Group

Similar selection criteria were employed in creating a second comparison group consisting of protocols of subjects who had been previously tested and in whom clinical neurologic examination showed evidence of brain dysfunction. The subjects were matched on a case-by-case basis for age, sex, education, and handedness with our drug users. Mean age of the drug users was 22.3 years (± 2.8; range, 18 to 29); of the medical patients, 24.6 years (± 3.6; range, 19 to 31); and of the neurologic patients, 22.6 years (± 2.9; range, 19 to 29). Mean education of the drug users was 12.0 years (± 1.9; range, 9 to 17); of the medical patients, 11.6 years (± 3.3; range, 8 to 18); and of the neurologic patients, 12.1 years (± 1.4; range, 9 to 16). Because of difficulty in finding left-handed medical and neurologic patients who could match the drug users on age, sex, and education, there are only 19 subjects in each of the comparison groups corresponding to the 19 right-handed drug users. Three of the 22 drug-using subjects went unmatched because they were left handed. These subjects were excluded from some of the data analysis.

We had several reasons for turning to protocols of individuals tested some time ago rather than testing newly admitted medical or neurologic patients. We wanted to select a group of persons who had undergone careful medical and neurologic assessment and who were declared neurologically normal or were abnormal by criteria independent of our test battery. We also needed to match the control groups as closely as possible to the drug users in terms of age, education, sex, and handedness. To satisfy these two considerations with a group of new patients (especially neurologic patients) would have required access to more patients than were readily available to us within the budgetary and temporal constraints of a small pilot study.

Drug Use History

A careful drug use inventory was conducted with each drug user by one of us (M.M.). The same questions regarding use of drugs were asked in various ways of each subject in order to obtain the best possible estimate of drug experience. The drug experience of our drug-using subjects is summarized in Table 1. Because the control groups consist of persons examined 10 to 15 years ago, we cannot report on drug use of these individuals. This represents a deficiency in our data, especially with respect to possible alcohol use by medical and neurologic patients. At the same time, since these individuals belong to an era predating the upswing in recreational drug use (other than alcohol) that began in the mid-1960s, we have made the assumption that polydrug taking was absent or minimal in the two control groups.

Neuropsychological Examination

The neuropsychological battery as assembled by Reitan[27] was administered to all subjects. This battery consists of the Halstead Battery (category test; tactual performance test–total time, memory, localization; rhythm test; speech-sounds perception test; finger oscillation test; and impairment index), trail-making test, Reitan's modification of the Halstead-Wepman aphasia screening test, sensory-perceptual examination (sensory imperception; tactile form recognition), lateral dominance examination, measurement of strength of grip (Smedley hand dynamometer), Wechsler Adult Intelligence Scale, and the Minnesota Multiphasic Personality Inventory (MMPI). A more detailed description of the battery may be found in Reitan,[27] or is available from the authors on request.

Procedures

Drug users who met the various selection criteria described above were approached by one of us (M.M.) to participate in the study. The study was explained to the subjects as a psychological investigation of individuals who had used drugs. Subjects were told that participation was voluntary and that whether they volunteered or not would have no impact on their treatment program. Subjects were also told that they would be compensated $5 for their time. After subjects indicated their understanding of the study and willingness to participate, they were asked to sign an informed consent document as required by the University of California's Human Subjects Committee. Quite to our surprise, we had a 100% volunteer rate, which we have attributed in part to the good rapport established by M.M. as a physician member of the narcotic treatment program, in part to the desire of the subjects to earn a few dollars, in part to the subjects' desire to have their boredom relieved by our "fancy tests," and also to the subjects'

Table 1.—Summary of Drug Experience of 22 Drug Users

Substance	Units	Median	Range
Cigarettes	No. smoked in lifetime	58,400	1,800-233,600
Alcohol	ml/wk at time of heaviest use	1,075	0-5,376
Marijuana	No. "joints" smoked per wk at time of heaviest use	44	2-210
Volatiles	No. of times used in lifetime	8	0-150
Mescaline	No. of times used in lifetime	10	0-500
LSD	No. of times used in lifetime	33	0-2,000+
Cocaine	No. of times used in lifetime	28	0-1,000+
Amphetamines	Grams used in lifetime	10	0-1,125
Barbiturates	Grams used in lifetime	53	0-2,100
Other sedatives	No. of times used in lifetime	5	0-90
Narcotics	No. of "spoons" used in lifetime (1 spoon = approximately $100 expense = approximately 1 gm of material containing 6% to 7% narcotic)	304	1-3,650

Table 2.—Results of Clinical Assessments of Neuropsychological Protocols by Two Raters

Group	Raters Agree		Raters Disagree		% Agreement
	Impaired	Not Impaired	I.G. Not Impaired*, R.M.R. Impaired†	I.G. Impaired*, R.M.R. Not Impaired†	
Neurologic (N=19)	16	2	0	1	95
Medical (N=19)	1	13	4	1	74
Drug (N=22)	9	8	5	0	77

*Rating by Igor Grant.
†Rating by Ralph M. Reitan.

curiosity about the study. The examination took approximately five hours to complete and in almost every case was conducted in a single day. While the actual examinations were carried out by one of the other authors (L.M.) who had no direct knowledge of the drug-use history of the subjects, the final clinical ratings were made by two of us on a blind basis; the protocols from the three groups were intermixed and identifying information removed. The neuropsychological protocols were independently assigned by the two raters to one of two categories: "definitely or probably normal" or "definitely or probably abnormal."

RESULTS

Clinical Examination of Neuropsychological Protocols

The judgments of the raters are summarized in Table 2. Depending on the rater, 41% to 64% of polydrug users, 11% to 26% of medical patients, and 84% to 89% of neurologic inpatients were judged to have definite or probable impairment.

The more experienced of the two raters judged more cases to have impairment (Table 2). Dr Reitan has had many years of experience in the evaluation of neuropsychological test results and has done much research; Dr Grant has had independent experience in evaluation of results obtained from drug users and has also received training at Dr Reitan's laboratory.

Statistical Analysis of Test Results

Neuropsychological test results for the three groups are presented in Table 3. Analysis of variance shows between-group differences on a large number of measures. The data were analyzed further using the t statistic (two-tailed) for means of two samples. These results show that the drug users performed less well than the medical comparison group on five of 29 measures at the $P < .05$ level of confidence, whereas the drug users performed better on one test. The differences between drug users and the medical comparison group are highlighted further when the 19 age- and education-matched individuals in each group are compared on a case-by-case basis by means of the paired t test. The drug users performed less well than medical patients on seven of 29 measures (performance intelligence quotient [IQ], full-scale IQ, picture completion, object assembly, category, nondominant time on tactual performance test [TPT], and both hands time on TPT) and better on one of 29 (rhythm test). The test that most significantly differentiated the drug users from the medical comparison group was the category test ($P < .002$, N (pairs) = 19; $df = 18$).

Although the drug users appear to be clinically and statistically deviant on neuropsychological testing, they nevertheless perform considerably better than do neurologic patients. As illustrated in Table 3, the drug users are superior to neurologic patients on 16 of 29 measures at the $P < .05$ level. Medical patients are superior to neurologic patients on 15 of 29 measures at the $P < .05$ level.

Relationship of Drug Use to Neuropsychological Results

Although our sample of drug users was small (N = 22), we attempted to look for possible associations of various types, extent of drug use, and tendency toward abnormal test results. In one analysis, we rank-ordered our subjects according to amount of substance use in each category of drugs. We then employed the χ^2 statistic to determine whether that half of the subjects that had most experience with any particular substance tended to have more protocols rated clinically as abnormal by both raters than subjects who had relatively less experience with that particular substance. We were able to find no associations

Table 3.—Comparison of Neuropsychological Test Results of Drug User, Medical, and Neurologic Groups

Test	Drug (N = 22) Mean	Drug (N = 22) SD	Medical (N = 19)* Mean	Medical (N = 19)* SD	Neurologic (N = 19)* Mean	Neurologic (N = 19)* SD	F Ratio	P	Medical-Drug†	Drug-Neurologic†	Medical-Neurologic†
Wechsler Adult Intelligence Scale											
Verbal IQ	103.09	12.81	108.42	15.21	98.42	17.77	2.04	NS	1.19	.95	1.81‡
Performance IQ	101.41	11.43	113.05	13.35	96.84	16.11	7.17	.01	2.93§	1.03	3.29§
Full-scale IQ	102.50	12.31	111.68	14.81	97.74	15.72	4.72	.025	2.11§	1.06	2.74§
Information	10.18	3.03	10.58	2.69	9.42	2.39	.88	NS	.43	.86	1.37‡
Comprehension	11.36	2.38	11.95	2.51	9.21	3.34	5.25	.01	.75	2.34§	2.78§
Arithmetic	10.14	2.68	9.95	4.88	9.53	4.77	.11	NS	.15	.50	.26
Similarities	11.14	2.68	11.74	2.23	9.68	4.07	2.25	NS	.75	1.34‡	1.88‡
Digit span	9.77	3.18	10.00	3.43	8.00	2.52	2.45	NS	.22	1.91‡	1.99‡
Vocabulary	10.41	2.94	10.26	2.79	9.16	2.79	1.14	NS	.16	1.36‡	1.18
Digit symbol	10.14	1.98	10.95	2.92	8.21	2.84	5.65	.01	1.03	2.49§	2.85§
Picture completion	10.59	1.65	12.53	2.09	9.90	2.51	8.11	.01	3.24§	1.03	3.42§
Block design	11.23	3.60	12.53	2.53	10.05	3.61	2.67	NS	1.29	1.02	2.39§
Picture arrangement	9.68	2.44	11.26	2.79	9.58	3.20	2.19	NS	1.89‡	.11	1.68‡
Object assembly	9.91	2.35	11.74	2.66	10.21	3.31	2.45	NS	2.28§	.33	1.53‡
Trail-making											
A	27.05	6.94	29.00	12.76	47.26	43.22	3.70	.05	.60	2.11§	1.72‡
B	75.55	28.48	69.63	32.38	135.21	101.82	6.52	.01	.61	2.57§	2.60§
Total	102.59	31.81	98.63	42.78	182.47	141.90	5.94	.01	.33	2.50§	2.40§
Category	51.14	20.27	24.42	10.39	73.84	26.79	28.23	.01	5.06§	3.01§	7.30§
Actual performance test (TPT)											
Dominant time	5.36	1.66	5.13	2.03	10.24	3.98	21.81	.01	.39	5.09§	4.82§
Nondominant	4.09	1.79	3.18	1.38	8.00	3.63	20.93	.01	1.76‡	4.32§	5.24§
Both hands	2.31	.81	1.94	.50	5.21	4.08	11.20	.01	1.68‡	3.17§	3.37§
Total	11.76	3.35	10.26	2.89	23.46	9.58	27.95	.01	1.49‡	5.21§	5.58§
Memory	8.18	.80	7.32	1.64	6.11	1.97	9.36	.01	2.12‖	4.38§	1.98‡
Localization	4.64	1.73	4.47	2.14	2.67	2.30	5.36	.01	.27	3.01§	2.40§
Seashore rhythm	4.00	3.61	6.00	2.94	7.11	2.77	5.14	.01	1.88¶	2.98§	1.17
Speech perception	6.09	2.60	6.63	4.39	9.47	6.50	2.97	NS	.48	2.19§	1.54‡
Tapping											
Dominant	49.14	5.23	50.94	6.98	46.90	7.21	1.83	NS	.91	1.12	1.68‡
Nondominant	45.73	4.21	46.25	4.89	42.00	6.48	1.97	NS	.28	2.14§	1.59‡
Impairment index	.36	.18	.29	.20	.71	.24	21.79	.01	1.13	5.13§	5.54§

*For medical group, N = 18 for impairment index and for tapping (dominant); N = 8 for tapping (nondominant); and N = 17 for TPT total time. For neurologic group, N = 18 for TPT (both hands, time, memory, localization), tapping (nondominant), and impairment index; N = 17 for TPT nondominant hand; and N = 16 for TPT total time.

†*t* tests (two-tailed) for mean values of two samples.

‡Trend for first to be better than second group ($P<.2$).

§First group better than second group ($P<.05$).

‖Second group better than first group ($P<.05$).

¶Trend for second group to be better than first group ($P<.2$).

between impairment and total amount of use of any particular drug. In a second analysis, we rank-ordered all the drug users by means of their category test scores (the category test is perhaps the most sensitive single test for cerebral dysfunction)[27] and extent of use of each drug. A series of Spearman rank-order correlations showed no associations between category test ranks and drug use ranks.

Relationship of History of Head Injury to Neuropsychological Results

Although the subject selection procedure called for exclusion of any subject with a history suggestive of neurologic disease or serious medical illness, none of the volunteers needed to be dropped on this basis. Ten of our drug users did have histories of head injury, the usual causes being traffic accidents, sports injuries, and falls. Nine of the subjects reported lapses of consciousness lasting from 30 seconds to three hours. Among the 17 drug users for whom the two raters agreed regarding their neuropsychological status, the relationship of head injury history and neuropsychological status results were as follows: head injury, neuropsychological impairment, five; head injury, neuropsychological status not impaired, three; no head injury, neuropsychological impairment, four; no head injury, neuropsychological status not impaired, five. Although such judgments are difficult to make on the basis of subjective reports by patients, it did not appear that the severity of injury was related to impairment. Thus, it seems that head injury history alone cannot explain why approximately half the drug users are judged as neuropsychologically abnormal.

Relationship of Psychopathologic Factors to Neuropsychological Results

An analysis of variance was performed to compare the mean scores of each of the three groups on the four validity and nine clinical scales of the MMPI (the scale of [Si] was not available on the medical and neurological groups who had been tested many years earlier). The drug users differed from the other two groups on F, Pd, Mf, Pa, Sc, and Ma ($P < .025$ or better). One estimate of the degree of the drug users' disturbance is given by their mean Goldberg (psychotic) Index[28] of 68 (index for medical patients = 40; for neurologic patients = 47). Although it should not be interpreted to mean that most of the drug users are psychotic, this finding does suggest considerable psychological chaos and deviance. The neuropsychological evaluations of the 11 most disturbed subjects were compared with those of the 11 least deviant ones. No differences could be found, suggesting that in this group, at least, psychiatric disturbance was not influencing neuropsychological performance.

COMMENT

Our study shows that approximately half of 22 young men, all of them polydrug users, and all of them abstinent at time of examination, show abnormalities in adaptive abilities when subjected to an extensive series of neuropsychological tests. Those individuals who demonstrate neuropsychological abnormality, according to our evaluation of these tests, would be said to have mild, generalized cerebral dysfunction.

How certain can we be that the differences observed in our judgments of our neuropsychological protocols imply cerebral dysfunction and that influences other than drug use might not account for the findings?

It is true that our study is small and that such small studies must be doubly careful to ensure that chance results are not misinterpreted as positive findings. Even given this caution, it seems to us improbable, given two groups of subjects matched for age, sex, and education (drug users and medical patients), that chance alone could account for the drug using group's exhibiting deficit twice as often as the comparison medical group.

We cannot conclude that polydrug use caused these subjects' test impairments because we do not know for certain that the polydrug users might not have shown impairment even before their first drug experience. In fact, it might be argued that mild cerebral deficit might drive individuals toward self-medication. The MMPI results also suggest that the polydrug users are different psychiatrically from the medical and neurologic groups. A case could be made that individuals with severe psychiatric disorders might have difficulties in handling the neuropsychological battery for reasons other than cerebral dysfunction. Although the question of the effect of psychopathologic factors on neuropsychological performance is not fully settled, the bulk of the evidence from the literature seems to us to suggest that this battery is a valid measure of those adaptive abilities whose disruption correlates with brain damage (reversible or irreversible). The battery results are not much influenced by functional psychiatric illness, with the possible exception of chronic schizophrenia.[29-33] In brief, the inference for cerebral dysfunction rests on past correlative studies.

A further argument that might be advanced is the motivational one. It could be said that drug users are a notoriously carefree and unreliable group and that they might not have tried as hard to do their best on a long series of neuropsychological examinations as did medical or neurologic patients. First, we should point out that the medical and neurologic groups had been examined routinely (10 to 15 years ago) as part of their overall evaluation while hospitalized and with no special incentives having been mentioned. In contrast, it is our firm impression that the polydrug users were, in fact, interested in undergoing testing on the grounds of curiosity, good rapport with two of the investigators (the initial interviewer, M.M., and the examiner, L.M.), and out of a desire to earn money. The fact that the project was strictly voluntary and that 100% of subjects who were approached agreed to participate further suggests to us that the polydrug users were an interested group. We also had the impression that at least some of the subjects had an investment in "proving" that their drug use caused them no difficulty whatsoever. Because of these various observations we feel moderately confident that the polydrug users did not perform less well simply because they were unmotivated.

Of the cautionary notes raised above the most serious to a cross-sectional study of this kind relates to the premorbid condition of the drug users' brains. It seems unlikely, yet it is impossible to rule out categorically, that people who become substantial drug users might have neuropsychological deficits to start with. These subjects were not polydrug users at large, but "selected" in that they somehow arrived in a residential treatment situation. Only a prospective study designed to assess adaptive abilities prior to onset of substantial drug use can evaluate adequately this premorbid factor. For purposes of the discussion that follows, and in order to examine more closely what clues might be offered by our data, we have chosen purposely to set aside this objection.

We have noted already that about half our polydrug users were judged to have mild neuropsychological deficit, a finding that, if supported, represents one of the only bits of experimental evidence to support the frequently expressed concern that polydrug use might be associated with cerebral dysfunction. This dysfunction does not appear to represent the effects of acute intoxication or of abstinence syndrome since our subjects had spent a mean of 60 days in a residential treatment facility at time of testing. One direction for further research should be to determine whether these deficits do, in fact, clear after a considerably longer period of time, for example, six months. Such clearing would suggest that cessation of polydrug use is followed by a moderately prolonged reversible "intermediate range" neuropsychological deficit. Further testing of abstinent subjects even beyond six months after detoxification would also help determine whether any of these deficits become permanent.

The only other neuropsychological investigation dealing

specifically with the issue of polydrug use has reported negative results.[26] While these contradictory conclusions might represent population or experimental design differences, we suspect that differing strategies of inferring deficit might equally well be responsible. Bruhn and Maage[26] selected several neuropsychological tests, each of which reportedly has some power to discriminate between neurologically impaired and intact subjects. They then tested four groups of prisoners, ranging from a group with minimal drug experience to one with a history of heavy, multiple drug use, and found they could not separate the groups statistically on the basis of any of the tests. In our study, if only statistical differences between groups on individual tests are considered, then drug users fare worse than medical patients on seven measures and better on one. It could be argued that such differences are chance results and that our findings do not differ from those of Bruhn and Maage. We believe, however, that the judgments of our experienced clinicians, whose inferences were based on a detailed case-by-case inspection of the totality and patterning of test results (including some that are not easily quantifiable), represent valid and reliable statements concerning the neuropsychological status of our subjects. In brief, had the Bruhn and Maage subjects been evaluated clinically by means of the more extensive standardized battery, it is possible that a proportion of them might have been judged to be impaired as well.

In the present study, we were unable to establish an association between the use of any particular agent and impairment. Small sample size accounts for part of our difficulty, but another potentially more serious impediment is the unrealiability of the drug use history. Although we made a concerted effort to get drug use information that could be reduced to a quantitative estimate of total drug experience, it became clear very quickly that some subjects simply did not remember as well as others, while other subjects could not be any more specific than to make statements such as "all day every day" with respect to marijuana use. As Cisin[34] has pointed out, there is no absolute answer to this dilemma; emphasis on obtaining information in the context of good rapport coupled with a combination of structured and open-ended inquiry is perhaps the best that can be done.

The problem of alcohol use represents yet another confounding influence in polydrug research. As we have illustrated in Table 1, most of our drug users drink considerable amounts of liquor, and it is well established that in at least some individuals, excessive alcohol intake is related to cerebral dysfunction. Any future neuropsychological investigation should, therefore, attempt to control for potential alcohol effects. One way of doing so might be to study a control group of alcohol users who are not greatly experienced with other drugs.

In summary, we have presented data that might, in a preliminary way, be interpreted to indicate that polydrug use is associated with neuropsychological dysfunction. Many methodologic and theoretical problems make it impossible to deduce cause and effect relationships. Nevertheless, such findings represent clues to possible polydrug effects, clues that we hope will stimulate further substantive and methodologic research.

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