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Review

Do hallucinogens cause residual neuropsychological toxicity?

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Abstract

We collected and reviewed studies in which neuropsychological tests were administered to users of LSD or other hallucinogens. Interpretation of the studies is limited by various confounding variables, such as subjects' premorbid cognitive and personality function and prior use of other substances. At present, the literature tentatively suggests that there are few, if any, long-term neuropsychological deficits attributable to hallucinogen use. To better resolve this issue, however, it will be important to study larger samples of chronic, frequent hallucinogen users who have not often used other types of drugs.

Keywords: Neuropsychological tests; Hallucinogens; 5-HT; LSD; Long-term effects

1. Introduction

Hallucinogenic drugs of plant origin, such as psilocybin (*N*,*N*-dimethyl-4-phosphoryloxytryptamine), *N*,*N*-dimethyltryptamine (DMT), and mescaline (3,4,5-trimethoxyphenethylamine) have been used for thousands of years by various peoples around the world (Schultes and Hofmann, 1992; Ott, 1993). In the last 50 years, these naturally occurring hallucinogens have been supplemented by a wide range of synthetic compounds, beginning with the discovery of lysergic acid diethylamide (LSD) in 1943 (Stoll, 1947; Hofmann, 1983), followed by *N*,*N*-dipropyltryptamine (DPT), 2,5-dimethoxy-4-methylamphetamine (DOM), 3,4-methylenedioxy-*N*-ethylamphetamine (MDE), 3,4-methylenedioxy-*N*-methylamphetamine (MDMA), and countless other structural analogs (Shulgin and Shulgin, 1991; 1997). Illicit use of hallucinogenic drugs has become widespread in the United States and elsewhere during the last 30 years, and represents one of the few types of illicit drug use presently increasing among Americans (Hunt, 1997). The 1990s have seen a steady rise in hallucinogen use among 8th, 10th, and 12th graders, as well as college students and young adults. For example, the proportion of high school seniors who had tried a hallucinogenic drug as least once in the prior 12 months climbed from 4.4 to 8.4% between 1985 and 1995 (Johnston et al., 1997). Preliminary results from the 1996 National Household Survey on Drug Abuse suggested that 1.2 million Americans tried a hallucinogen for the first time in the year 1995, which is twice the average annual number reported during the 1980s (SAMHSA, Office of Applied Studies, 1997).

Not surprisingly, a substantial literature has addressed the possibility of residual neuropsychological effects from long-term hallucinogen use, with some reports reaching alarmist tones. For example, a 1971 editorial in Journal of the American Medical Association asserted:

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> The psychedelic plague refers to the morbidity associated with the major psychedelic drugs… it is becoming increasingly more apparent that severe but often insidiously developing personality changes occur in the chronic abuser… Perhaps only a few of those who experience more than 50 'trips' are spared. Which personality profiles are most vulnerable has yet to be established. In any case, present clinical evidence suggests that no longer can it be assumed that these changes are found only in the schizophrenic-vulnerable population, for many pre-abusers possess adaptable personalities and their family histories include no instance of psychosis. The form of the personality deterioration may range from a schizophreniform psychosis to an organic brain syndrome (Donlon, 1971).

Other warnings appeared from investigators who hypothesized that brief psychotic reactions after the consumption of LSD may develop into chronic psychosis in predisposed individuals (Glass, 1973; Vardy and Kay, 1983). By contrast, investigators have also suggested that hallucinogens were unlikely to cause lasting impairment. For example, Cohen (1960) concluded that LSD administration to humans under medical supervision was relatively benign, with psychotic reactions of more than 48 h occurring in only 1.8 per 1000 subjects administered the drug. Strassman (1984), reviewing adverse reactions to hallucinogens, similarly concluded that 'it appears that the incidence of adverse reactions to psychedelic drugs is low when individuals (both normal volunteers and patients) are carefully screened and prepared, supervised, and followed up, and given judicious doses of pharmaceutical quality drug'. As these conflicting reports suggest, the hallucinogens were controversial psychopharmacologic agents from the beginning, with claimed therapeutic potential on one hand and potential for disaster on the other (Barron et al., 1964).

Speculation about the residual effects of hallucinogens continues to the present day (McCann et al., 1997). DSM-IV lists not only Hallucinogen Dependence and Abuse, but also Hallucinogen Intoxication, Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder, and Hallucinogen-Related Disorder Not Otherwise Specified (American Psychiatric Association, 1994). Yet another DSM-IV category, unique to the hallucinogens, is Hallucinogen Persisting Perception Disorder (known also as Post-Hallucinogen Perceptual Disorder or 'flashbacks'). Those with this latter disorder describe brief or lingering recurrences of distorted perceptions reminiscent of hallucinogen intoxication itself. Usually hallucinogen persisting perception disorder spontaneously resolves within weeks or months of cessation of use (Ungerleider and Pechnick, 1994), but it may extend much longer (Abraham, 1983; Abraham and Aldridge, 1993) with one report of symptoms persisting for 26 years (Abraham, 1998). DSM-IV does not comment, however, on whether individuals with this or other hallucinogen-related disorders would be expected to demonstrate residual cognitive impairment, much less an organic brain syndrome, as suggested in the quotation above.

Given the continuing controversy regarding the residual effects of hallucinogens, we conducted a review of available studies in which neuropsychological tests were administered to individuals who had used hallucinogens.

2. Methods

We searched the Medline database (1/1/64 to 1/19/98) for the key terms of hallucinogens ($n = 2189$); LSD, lysergic acid diethylamide ($n = 3430$); Mescaline ($n = 767$); Psilocybin, Psilocybine, Psilocin ($n = 324$); DMT, *N*,*N*-dimethyltryptamine ($n = 313$); and MDMA, *N*-methyl-3,4-methylenedioxymethamphetamine, 3,4-methylenedioxy-*N*-methylamphetamine ($n = 367$). The search results were pooled and cross-referenced with Psychological Tests ($n = 20816$), and Neuropsychological Tests ($n = 11701$). A total of 67 candidate papers were found. These 67 papers included 19 in which neuropsychological tests were actually administered to hallucinogen users. Searching the references of these papers provided an additional 23 references, some prior to 1964, bringing the total number of papers under consideration to 42 investigations. We then applied five exclusion criteria to this group of studies. First, since we were interested in the residual, rather than the acute effects of hallucinogen use, we excluded studies in which testing was performed on subjects acutely intoxicated with these drugs (Landis and Clausen, 1954; Berlin et al., 1955; Silverstein and Klee, 1960; Goldberger, 1966; Duke and Keeler, 1968; Snyder et al., 1968; Wagner et al., 1968; Fischer et al., 1970; Thatcher et al., 1970, 1971; Harrington et al., 1989; Hermle et al., 1992). Second, we excluded studies examining neuropsychological performance in polydrug users (Riley and Jamieson, 1972; Cohen et al., 1974; Nishith et al., 1994), since the contribution of hallucinogens in such cases could not be ascertained. Third, we excluded individual case reports (Glass, 1973) or collections of small numbers of cases (Kleber, 1967; Duncan, 1970; Glass and Bowers, 1970; Hendin, 1973; McCann and Ricaurte, 1991) and considered only those studies examining at least five individuals. Fourth, we excluded studies that commented on the residual effects of hallucinogens but did not include formal neuropsychological testing (Unger, 1963; Klavetter and Mogar, 1967; McGlothlin et al., 1967; Fischer and Scheib, 1971; Mc-

Glothlin and Arnold, 1971; Salzman et al., 1972; Brothers and Gaines, 1973; Jones, 1973; Wackwitz et al., 1974). Fifth, we excluded studies of dissociative agents such as phencyclidine and ketamine (Cosgrove and Newell, 1991). These exclusion criteria reduced the number of studies under consideration from 42 to 9 studies.

3. Results

The nine qualifying studies are summarized in Tables 1 and 2 and discussed in detail in this section.

Blacker et al. (1968) compared 21 LSD users (whom the authors referred to as 'acidheads') with unmatched controls obtained from two sources: 63 male psychiatric inpatients from the United States Naval Hospital and 25 'unselected' normal volunteers. The investigators found subtle electroencephalographic (EEG) changes in the LSD group in comparison to controls, with the former showing increased alpha, beta, delta, and theta activity and increased visual evoked response amplitudes at the dimmer intensities. They considered these findings 'compatible with either drug effects and/or CNS dysfunction', but acknowledged that their results were inconclusive due to lack of premorbid testing. Interpretation of results was further limited by not reporting the total number of episodes of LSD use among the subjects and requiring an abstinence period of as little as 48 h between the last LSD ingestion and the time of testing. Also, the investigators did not systematically assess subjects' current or past use of other illicit drugs, alcohol, or prescription medications, nor did they attempt to exclude subjects who might have been intoxicated with these substances at the time of testing. These limitations are shared by most of the subsequent studies reviewed here (see Table 2).

Cohen and Edwards (1969) reported impaired visuospatial orientation among 30 LSD users in contrast to 30 controls matched for age, sex, years of education, and socio-economic background. The authors also found that performance on the Reitan Trail Making Test A and the Ravens Matrices correlated negatively with extent of LSD use. However, the drug-using group did not differ from the control group on IQ, concept formation, speech perception, time perception, tactual performance, tactual recognition, motor ability, or spatial orientation. Subjects were not excluded for history of psychiatric disorder, but were excluded if hospitalized, under current psychiatric care, or appeared 'obviously mentally disabled'. Again, interpretation is limited by the brief abstinence period and failure to control for current or past use of other illicit drugs.

McGlothlin et al. (1969) selected 300 prospective subjects from a random sample of 700 patients who had received LSD in psychotherapy. Only 19 of these subjects met the authors' three inclusion criteria: (1) history of 20 or more LSD ingestions; (2) residing in the Los Angeles area; and (3) lacking evidence of gross psychopathology predating LSD use. Three additional subjects were excluded for heroin addiction and alcoholism, repeated psychiatric hospitalization, or severe emotional disturbance with an inability to work. Of note, 12 (75%) of these had used other hallucinogens, 6 (38%) had used opiates, 12 (75%) had smoked marijuana, and an unspecified number had engaged in 'moderate' use of oral sedatives and stimulants. The authors chose 16 non-LSD-exposed controls matched for age, sex, and education. Thirteen of the 16 subjects in each group had received psychotherapy from one particular therapist. Four of 16 controls had consumed marijuana more than 10 times; their other drug use, including current or past alcohol use, was not specified. The abstinence period was more than 12 months in 9 subjects, but 2 were reportedly tested under the acute effects of LSD. Neuropsychological tests generally showed no significant differences between groups, and in particular failed to replicate Cohen and Edwards' (1969) finding of poor performance on visuo-perceptual and spatial orientation tests. The only positive finding in this area was that spatial orientation scores in the 16 users correlated negatively with their ranking on the number of LSD ingestions ($P < 0.05$). However, no other visual tests demonstrated a significant relationship between performance and doses consumed. Halstead's category test, a nonverbal test of abstraction, did reveal diminished abstracting ability in the LSD group ($P < 0.01$), but this performance also did not correlate significantly with number of LSD ingestions. Guilford's associational fluency test found the LSD group more proficient in verbal ability than controls, and psychiatric interviewers judged the LSD users more often 'eccentric' in personality structure.

Wright and Hogan (1972) failed to find any impairment of organic brain functioning in subjects who had been taking LSD with unspecified frequency for a mean of 12.2 months. Interpretation of these findings, however, is limited by the usual methodological considerations: pre-LSD functioning was not assessed, past use of other drugs was not documented, and past neurologic or psychiatric history was not reported (although neither group was in psychiatric treatment at the time of testing). In addition, controls were selected from a larger pool of 'normal subjects' experienced with neuropsychological tests from a previous study.

In an uncontrolled study, Acord (1972) reported impaired abstracting ability (as compared to population norms) in chronic LSD users selected from an inpatient and outpatient neuropsychiatric service. Using the Wechsler Adult Intelligence Scale (WAIS), Halstead Battery, and the Trail Making Test, he reported that 32 of the 40 subjects scored within the 'brain-damaged

Table 1
Studies of the residual neuropsychological effects of chronic LSD and other hallucinogen use: general methods

Study	Subjects	Controls	Mean (range) age in years[b]	No. of doses of LSD or other drugs[c]	Abstinence period[d]	Excluded for psychiatric history[e]	Blinded evaluation[f]	Neuropsychological tests[g]
(Blacker et al., 1968)	13 Males 8 Females	1) 63 NR[a] 2) 25 NR[a]	S: 20 (13–27) 1) C: 32 (19–58) 2) C: 25 (17–44)	Mean 65	48 h	S: Yes C: No	No	G H
(Cohen and Edwards, 1969)	15 Males 15 Females	15 Males 15 Females	S: 21.7 ± 5.46 (NR) C: 21.8 ± 6.18 (NR)	Minimum 50 Median 70	48 h	No See text	Yes	B D E F G Q
(McGlothlin et al., 1969)	12 Males 4 Females	12 Males 4 Females	S: 40 (28–51) C: 40 (NR)	20–1100 Median 75	Varied (1 day–1 year+) Mean 38.9 days	Yes	NR	A B D E F Q
(Wright and Hogan, 1972)	15 Males 5 Females	15 Males 5 Females	S: 20.15 (17–24) C: 19.10 (NR)	5–100 Mean 29.3	4 subj × 1 days	No	No, but some blind scoring	A B D E F G
(Acord, 1972)	40 Males	0	S: 20 (17–24)	'at least 1 hallucinogen'	NR	No	No	A B D E F
(Acord and Barker, 1973)	15 Males	15 Males	S: 21.53 (NR) C: 22.67 (NR)	'at least 1 hallucinogen'	NR	Yes, see text	No	B E F G Q
(Culver and King, 1974)	28 NR[a]	2 groups of 28 NR[a]. See text	S: NR (20–25) C: NR (20–25)	12–28 Median 17	7 days	No	Yes	A D E Q
(Krystal et al., 1992)	7 Males 2 Females	0	S: 34 ± 7 (22–47)	1.9 ± 1.7 doses MDMA/month for 5.1 ± 2.3 years	66 ± 50 days for MDMA. Other ≥21 days. See text	No	No	A B D E G Q
(Grob et al., 1996)	15 Males	15 Males	'Age matched' (NR)	100's est. of DMT[h]	NR	No	NR	B

[a] NR = sex not specified.
[b] S = subjects; C = Controls; mean age ± SD if reported; NR = mean age not reported; (NR), age range not reported.
[c] Number of times that subjects had used a hallucinogen in their lives.
[d] Minimum time from the last personal use of a hallucinogen to baseline testing; NR, not reported/unknown.
[e] Yes = an attempt was made to exclude subjects with a past history of a major psychiatric disorder; No = subjects were included despite significant past or current psychiatric history.
[f] Yes = either the rater was blind to the subject's hallucinogen use or the evaluation was done by machine; No = the raters were aware of subject status.
[g] A = intelligence tests or tests measuring or estimating general intellectual capacity; B = tests of short-term or delayed memory (includes both verbal and visuospatial tests); C = tests of visuo-constructional ability; D = tests of reaction time or psychomotor speed; E = tests of executive or attentional 'frontal functions'; F = tests of visuospatial ability; G = tests of kinesthetic function; H = electrophysiological measures; and Q = other tests.
[h] DMT (*N*,*N*-dimethyltryptamine) from a plant source – see text for details.

Table 2
Studies of the residual neuropsychological effects of chronic LSD and other hallucinogen use: drug screening criteria

Study	Prior use of[a]			Current use of[b]			Attempted exclusion for[c]			Toxic Screen[d]
	Alcohol	Marijuana	Other illicit drugs	Alcohol	Marijuana	Other illicit drugs	Alcohol	Marijuana	Other illicit drugs	
(Blacker et al., 1968)	S: No C: NR	S: 100% C: NR	S: Yes C: NR	NR	NR	NR	No	No	No	No
(Cohen and Edwards, 1969)	NR	S: 100% C: 20%	S: Yes C: No	NR	NR	NR	No	No	Only 'glue sniffers'	No
(McGlothlin et al., 1969)	NR	Yes	Yes	NR	NR	NR	Yes	No	Yes	No
(Wright and Hogan, 1972)	NR	S: 95% C: NR	S: Yes C: NR	NR	S: NR C: No	S: NR C: No	No	S: No C: Yes	S: No C: Yes	No
(Acord, 1972)	NR	98%	NR	NR	NR	NR	No	No	No	No
(Acord and Barker, 1973)	NR	S: 100% C: 'Most'	NR	NR	NR	NR	No	No	No	No
(Culver and King, 1974)	Yes	Yes/No See text	Yes/No See text	Yes	Yes/No See text	No	No	Yes/No See text	Yes	No
(Krystal et al., 1992)	Yes	Yes	Yes	NR	Yes	NR	No	No	No	No
(Grob et al., 1996)	S: Yes C: NR	NR	S: Yes C: NR	S: No C: NR	S: No C: NR	S: No C: NR	No	No	No	No

[a] No = indicates that subjects and controls had not used alcohol, marijuana, or other drugs in the past; Yes = indicates that subjects and controls had used alcohol, marijuana, or other drugs in the past; NR = not reported/unknown; *S*, subjects; *C*, controls. Percentages of past use by subjects and/or controls is listed, when available.
[b] No = indicates that subjects and controls were not actively using alcohol, marijuana, or other drugs; Yes = indicates that subjects and controls were actively using alcohol, marijuana, or other drugs; NR = not reported/unknown; *S*, subjects; *C*, controls. Percentages of active use by subjects and/or controls is listed, when available.
[c] No = indicates that the investigators did not exclude subjects with prior or current use of alcohol, marijuana, or other intoxicating drugs; Yes = indicates some attempt was made to exclude subjects with a history of current use of alcohol, marijuana, or other intoxicating drugs; NR = not reported.
[d] Yes = at the time of testing, subjects gave a urine or blood sample that was screened for psychotropic substances; No = no screen performed.

range' on at least one test, 18 on two, and 4 on all three tests. However, the psychiatric diagnoses of the subjects were not specified, and subjects could qualify for the study with as little as one exposure to LSD.

In a subsequent controlled investigation, Acord and Barker (1973) compared 15 LSD users with 15 controls, all recruited from among both patients and staff at a military hospital. LSD users performed inferior to controls on several measures of the Reitan battery, including the Trail Making Test B and the Category test, and localization ability as measured on the Tactile Performance Test. An attempt was made to exclude subjects with 'evidence of psychopathology', except for 'character and behavior disorder with drug abuse as a symptom'. Aside from the addition of a control group, however, this study suffers from methodologic limitations similar to those of the uncontrolled study above. Although the control group denied prior hallucinogen consumption, other drug use was not systematically noted.

Culver and King (1974) matched 3 groups of college seniors for pre-drug use verbal and mathematical Scholastic Aptitude Test (SAT) scores, and Minnesota Multiphasic Personality Inventory (MMPI) results obtained during freshman year. The first group reported no history of marijuana or LSD use, the second group reported marijuana use but no hallucinogen use, and the third reported LSD use approximately once a month for at least 12 months, together with marijuana. Subjects were excluded if they reported illicit drug use prior to college; in-college use of psilocybin, DMT, DOM, or heroin; use of cocaine or intravenous stimulants more than 4 times; and use of 'either pep pills or barbiturates' more than 20 times. A series of neuropsychological tests was performed and repeated on 1-year follow-up. All results fell within the normal range, although the LSD group's performance on the Trail Making Tests A and B was significantly lower at one year than the other two groups. This difference remained significant in an analysis of covariance controlling for alcohol consumption.

In an uncontrolled investigation, Krystal et al. (1992) administered a series of neuropsychological tests to nine self-identified MDMA users. Tests were administered at least 3 h after IV infusion of 7 g of L-tryptophan, as the investigators were also evaluating neuroendocrine and behavioral alterations in those chronically exposed to MDMA (Price et al., 1989). Most tests showed no impairment as compared to population norms, but, on the Wechsler Memory Scale (WMS), several subjects displayed mild to moderate impairment in the Initial Paragraph (44%), Delayed Paragraph (67%), and Delayed Figural (33%) tests, but not in the Initial Figural Test. None of the WMS scores, however, correlated significantly with cumulative lifetime doses of MDMA in this small sample. Once again, prior psychiatric history and current or past use of other drugs represented potential confounding variables.

Grob et al. (1996) assessed 15 members of a legally sanctioned Brazilian religion, the Uniao do Vegetal (UDV), which regularly uses a plant-based hallucinogen, 'hoasca'/'ayahuasca', as a sacrament. This potion contains the powerful indole hallucinogen DMT, which is orally activated by β-carbolines (also present in hoasca) through inhibition of intestinal monoamine oxidase. Fifteen controls with no history of hoasca use were matched for age, ethnicity, marital status, and level of education. The authors also attempted to match for current alcohol consumption, but were not fully successful because the UDV strictly forbids its members from the use of all other psychoactive substances, including alcohol, tobacco, marijuana, cocaine, and amphetamines. This limitation may explain why the hoasca users performed better than controls on recall of words on the fifth learning trial of the WHO-UCLA Auditory Learning Verbal Memory Test. In contrast to prior reports of increased novelty-seeking (Kleckner, 1968) and aggression (Brickman, 1968; Edwards et al., 1969) among chronic LSD users, the members of the UDV scored significantly lower than controls in the novelty-seeking and harm-avoidance domains in the Tridimensional Personality Questionnaire.

4. Discussion

We reviewed nine studies assessing residual neuropsychological effects in chronic hallucinogen users. The general impression to emerge from these studies is that such effects, if present, are modest; the dire predictions of the 1971 editorial, quoted at the beginning of this article, appear unjustified.

Admittedly, several of the studies have tentatively reported impairment on certain neuropsychological measures in hallucinogen users as compared to controls. These findings include changes in evoked potentials (Blacker et al., 1968), visuo-spatial impairment (Cohen and Edwards, 1969), deficits on the Trail Making Tests (Acord, 1972; Acord and Barker, 1973; Culver and King, 1974), and memory deficits (Krystal et al., 1992). However, several other studies have failed to replicate these results (McGlothlin et al., 1969; Wright and Hogan, 1972; Grob et al., 1996).

Importantly, all of these findings are subject to substantial methodologic limitations, as illustrated in the two tables presented above. First, most studies failed to control for premorbid attributes of hallucinogen users versus controls; indeed some studies included subjects known to have a history of psychiatric disorders prior to any hallucinogen ingestion. Second, virtually all of the studies failed to control for use of other illicit drugs and alcohol, both in the past and at the time of

evaluation. In fact, none of the nine studies included a toxic screen to exclude subjects with evidence of illicit drug use at or near the time of testing. Third, the studies varied widely in the abstinence period required between the most recent hallucinogen use and the time of test administration. In some cases, this abstinence period may have been very short, thus causing the effects of acute hallucinogen intoxication to confound evaluation of residual effects.

Most of these methodologic problems would be expected to increase the risk of a type I error; namely to show a residual effect of hallucinogens when none existed. Despite such biases, these studies generally found few residual effects. It therefore seems unlikely that hallucinogens produce major residual neuropsychiatric impairments, which have been missed in the studies to date. This impression echoes the conclusions of the earlier review by Strassman (1984): 'The question of organic brain damage as well as permanent changes in personality, attitudes, and creativity in patients and normals who have repeatedly ingested psychedelic drugs is controversial, but tends to point to subtle or nonsignificant changes'.

On the other hand, the possibility of a type II error – failure to detect a true residual hallucinogen effect – cannot be excluded. One possible source of a type II error is small sample size: the nine neuropsychological studies assessed only 9–40 hallucinogen users each. With these numbers, it is possible that subtle toxic effects were missed. Such effects, even if modest, might still be significant from a population perspective. Another possible source for a type II error is the lack of older subjects in most studies. Younger individuals might exhibit little toxicity, whereas impairment might become more obvious with increasing age. Further, several of the studies investigated subjects who had used hallucinogens only a single occasion, and a majority of all subjects studied had used hallucinogens fewer than 50 times. Thus, a neurotoxic effect after several hundred hallucinogen exposures cannot be excluded. Finally, the tests employed in available studies may have failed to 'tap' specific areas of cognitive deficits.

Indeed, there are theoretical reasons to suspect that hallucinogens might produce neurotoxicity after long-term exposure. First, LSD and mescaline have been shown to produce vasospasm in isolated canine cerebral arteries at drug concentrations equivalent to those required to produce intoxication in humans (Altura and Altura, 1980). Thus, these agents might produce repeated hypoxic events. Second, hallucinogens bind to some of the same neuroreceptors involved in the expression of neurodegenerative psychotic disorders. In particular, the indolalkylamine (e.g. LSD, psilocybin) and phenethylamine (e.g. mescaline) hallucinogens are potent partial agonists at 5-HT$2_{a/c}$ (serotonin $2_{a/c}$; 5-hydroxytryptamine $2_{a/c}$) receptors (Winter, 1978; Sloviter et al., 1980; McCall, 1986; Jacobs, 1987; Sanders-Bush et al., 1988; Winter and Rabin, 1988; Glennon, 1990; Krebs and Geyer, 1994; Fiorella et al., 1995a,b; Marek and Aghajanian, 1996), whereas the atypical antipsychotic medications are thought efficacious in part from an opposite effect: potent antagonism at 5-HT$2_{a/c}$ (He and Richardson, 1995; Maurel-Remy et al., 1995; Gleason and Shannon, 1997). Further, it has been noted that selective serotonin reuptake inhibitors (SSRIs) attenuate or block intoxication (Bonson et al., 1996), and may ameliorate hallucinogen persisting perception disorder (Young, 1997), suggesting that hallucinogens may cause a reversible or irreversible neurotoxic impingement upon central serotonergic systems. Much research is also being directed upon *N*-methyl-D-aspartate (NMDA) glutamate receptors (Coyle, 1996), since NMDA antagonists (notably including PCP and ketamine) can induce psychotic-like intoxications in man (Javitt and Zukin, 1991; Krystal et al., 1994) and also cause pathomorphological alterations in rat brain cerebrocortical neurons (Olney et al., 1989; Corso et al., 1997). While traditional and atypical antipsychotic agents have proven neuroprotective to such damage in preclinical models, LSD and DOM have counterintuitively proven similarly protective due to the very same 5-HT2_a agonism as mentioned above (Farber et al., 1998). In short then, while there may be shared neuroreceptor dysregulation between psychotic illness and hallucinogen use, knowledge of the precise biochemical effects of hallucinogens is clearly limited by our rudimentary understanding of the pathogenesis of psychosis at the molecular level, despite evolving advances in our understanding of signal transduction pathways.

5. Conclusion

Returning to the clinical question of the neuropsychological toxicity of hallucinogen use, future studies should take care to address the various methodological problems reviewed above. A particular concern is the difficulty of securing a population of hallucinogen users who are free of concomitant psychopathology and/or other psychoactive drug use. To minimize this problem, it will be important to match user and nonuser groups on as many of these potentially confounding variables as possible, and also to assess the correlation between lifetime hallucinogen exposure and degree of neuropsychological impairment. Such assessments will require a large sample of subjects with extensive hallucinogen exposure, as hallucinogens might have subtle neurotoxic effects not detectable with smaller samples or with individuals with lesser exposure.

Also, the existing literature essentially fails to illuminate which potentially confounding variables would form the basis for exclusion in an 'ideal' study and

which neuropsychological tests would be the most sensitive. For this reason alone, any re-evaluation of the neuropsychological toxicity of hallucinogens should incorporate a broad set of exclusion criteria with an extensive neuropsychological battery in order to maximize the sensitivity and specificity of the findings. In addition to traditional neuropsychological batteries, timed information processing tasks might yield further evidence of functionally significant deterioration.

'Pure' hallucinogen users (those with extensive hallucinogen exposure and minimal exposure to other drugs) are difficult to find; this problem may account for the inclusion of polydrug abusers into most studies of hallucinogens. However, there exist indigenous populations, outside of Western industrialized culture, where hallucinogens are used for religious purposes, as in the Uniao de Vegetal studied by Grob et al. (1996). Such groups provide a natural 'laboratory', in that they use hallucinogens extensively but rarely use other drugs. In particular, the iboga cults of Gabon (Pope, 1969; De Smet, 1996), the Huichol of Mexico (Dorrance et al., 1975), and the Tarahumara of Mexico (Bye, 1979) all potentially offer such opportunities for study. Also, in the United States, the 250000 members of the Native American Church ingest the hallucinogenic cactus, Peyote (Lophophora williamsii), as a religious sacrament (Bergman, 1971; Albaugh and Anderson, 1974). These Native Americans often have a good command of English and may therefore be suitable candidates for standard neuropsychological tests. Such testing can be augmented with non-verbal assessments to further control for cultural and language differences. Studies of non-Western cultures will also yield important information about the social, cultural, and medical ramifications of chronic use of botanical hallucinogens, and these data may provide important prognostic implications for the growing numbers of hallucinogen users in Western societies.

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References

Abraham, H., 1998. Hallucinogens persisting perception disorder. Practical Rev. Psychiatry 22, 1–2.

Abraham, H.D., 1983. Visual phenomenology of the LSD flashback. Arch. Gen. Psychiatry 40, 884–889.

Abraham, H.D., Aldridge, A.M., 1993. Adverse consequences of lysergic acid diethylamide. Addiction 88, 1327–1334.

Acord, L.D., 1972. Hallucinogenic drugs and brain damage. Mil. Med. 137, 18–19.

Acord, L.D., Barker, D.D., 1973. Hallucinogenic drugs and cerebral deficit. J. Nerv. Ment. Dis. 156, 281–283.

Albaugh, B.J., Anderson, P.O., 1974. Peyote in the treatment of alcoholism among Native Americans. Am. J. Psychiatry 131, 1247–1250.

Altura, B.T., Altura, B.M., 1980. Phencyclidine, lysergic acid diethylamide, and mescaline: cerebral artery spasms and hallucinogenic activity. Science 212, 1051–1052.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, IV. American Psychiatric Press, Inc., Washington, D.C.

Barron, F., Jarvik, M.E., Bunnell, S. Jr., 1964. The hallucinogenic drugs. Sci. Am. 210, 29–37.

Bergman, R.L., 1971. Navajo peyote use: its apparent safety. Am. J. Psychiatry 128, 695–699.

Berlin, L., Guthrie, T., Weider, A., Goodell, H., Wolff, H.G., 1955. Studies in human cerebral function: the effects of mescaline and lysergic acid on cerebral processes pertinent to creative activity. J. Nerv. Ment. Dis. 122, 487–491.

Blacker, K.H., Reese, J.T., Stone, G.C., Pfefferbaum, D., 1968. Chronic users of LSD: the "acidheads". Am. J. Psychiatry 125, 341–351.

Bonson, K.R., Buckholtz, J.W., Murphy, D.L., 1996. Chronic administration of serotonergic antidepressants attenuates the subjective effects of LSD in humans. Neuropsychopharmacology 14, 425–436.

Brickman, H.R., 1968. The psychedelic "hip scene": return of the death instinct. Am. J. Psychiatry 125, 78–84.

Brothers, R., Gaines, R., 1973. Perceptual differences between hippies and college students. J. Soc. Psychol. 91, 325–335.

Bye, R.A. Jr., 1979. Hallucinogenic plants of the Tarahumara. J. Ethnopharm. 1, 23–48.

Cohen, G.H., Collins, H., Susmilch, C., 1974. Personality characteristics and social background of the lysergic acid diethylamide user. In: Singh, J.M. and Lal, H. (Eds.), Drug Addiction. Stratton, New York, pp. 263-271.

Cohen, S., 1960. Lysergic acid diethylamide: side effects and complications. J. Nerv. Ment. Dis. 130, 30–40.

Cohen, S., Edwards, A.E., 1969. LSD and organic brain impairment. Drug Depend. 2, 1–4.

Corso, T.D., Sesma, M.A., Tenkova, T.I., Der, T.C., Wozniak, D.F., Farber, N.B., Olney, J.W., 1997. Multifocal brain damage induced by phencyclidine is augmented by pilocarpine. Brain Res. 752, 1–14.

Cosgrove, J., Newell, T.G., 1991. Recovery of neuropsychological functions during reduction in use of phencyclidine. J. Clin. Psychol. 47, 159–169.

Coyle, J.T., 1996. The glutamatergic dysfunction hypothesis for schizophrenia. Harvard Rev. Psychiatry 3, 241–253.

Culver, C.M., King, F.W., 1974. Neuropsychological assessment of undergraduate marijuana and LSD users. Arch. Gen. Psychiatry 31, 707–711.

De Smet, P.A.G.M., 1996. Some ethnopharmacological notes on African hallucinogens. J. Ethnopharm. 50, 141–146.

Donlon, P.T., 1971. The psychedelic plague and polypsychotropia. J. Am. Med. Assoc. 215, 475–476.

Dorrance, D.L., Janiger, O., Teplitz, R.L., 1975. Effect of peyote on human chromosomes. Cytogenic study of the Huichol Indians of Northern Mexico. J. Am. Med. Assoc. 234, 299–302.

Duke, R.B., Keeler, M.H., 1968. The effects of psilocybin, dextro-amphetamine and placebo on performance of the trail making test. J. Clin. Psychol. 24, 316–317.

Duncan, D.F., 1970. LSD and intelligence: an exploratory study. Psychology 7, 6–7.

Edwards, A.E., Bloom, M.H., Cohen, S., 1969. The psychedelics: love or hostility potion. Psychol. Rep. 24, 843–846.

Farber, N.B., Hanslick, J., Kirby, C., McWilliams, L., Olney, J.W., 1998. Serotonergic agents that activate 5HT(2A) receptors prevent NMDA antagonist neurotoxicity. Neuropsychopharmacology 18, 57–62.

Fiorella, D., Rabin, R.A., Winter, J.C., 1995a. The role of the 5-HT2A and 5-HT2C receptors in the stimulus effects of hallucinogenic drugs. I: antagonist correlation analysis. Psychopharmacology (Berlin) 121, 347-356.

Fiorella, D., Rabin, R.A., Winter, J.C., 1995b. The role of the 5-HT2A and 5-HT2C receptors in the stimulus effects of hallucinogenic drugs. II: reassessment of LSD false positives. Psychopharmacology (Berlin) 121, 357-363.

Fischer, R., Scheib, J., 1971. Creative performance and the hallucinogenic drug-induced creative experience or one man's brain-damage is another's creativity. Confin. Psychiatr. 14, 174–202.

Fischer, R., Kappeler, T., Wisecup, P., Thatcher, K., 1970. Personality trait dependent performance under psilocybin. Dis. Nerv. Sys. 31, 92–101.

Glass, G.S., 1973. Psychedelic drugs, stress, and the ego. J. Nerv. Ment. Dis. 156, 232–241.

Glass, G.S., Bowers, M.B. Jr., 1970. Chronic psychosis associated with long-term psychotomimetic drug abuse. Arch. Gen. Psychiatry 23, 97–103.

Gleason, S.D., Shannon, H.E., 1997. Blockade of phencyclidine-induced hyperlocomotion by olanzapine, clozapine and serotonin receptor subtype selective antagonists in mice. Psychopharmacology (Berlin) 129, 79–84.

Glennon, R.A., 1990. Do classical hallucinogens act as 5-HT2 agonists or antagonists? Neuropsychopharmacology 3, 509–517.

Goldberger, L., 1966. Cognitive test performance under LSD-25, placebo and isolation. J. Nerv. Ment. Dis. 142, 4–9.

Grob, C.S., McKenna, D.J., Callaway, J.C., Brito, G.S., Neves, E.S., Oberlaender, G., et al., 1996. Human psychopharmacology of hoasca, a plant hallucinogen used in ritual context in Brazil. J. Nerv. Ment. Dis. 184, 86–98.

Harrington, A., Oepen, G., Spitzer, M., 1989. Disordered recognition and perception of human faces in acute schizophrenia and experimental psychosis. Compr. Psychiatry 30, 376–384.

He, H., Richardson, J.S., 1995. A pharmacological, pharmacokinetic and clinical overview of risperidone, a new antipsychotic that blocks serotonin 5-HT2 and dopamine D2 receptors. Int. Clin. Psychopharmacol. 10, 19–30.

Hendin, H., 1973. College students and LSD: who and why? J. Nerv. Ment. Dis. 156, 249–258.

Hermle, L., Funfgeld, M., Oepen, G., Botsch, H., Borchardt, D., Gouzoulis, E., Fehrenbach, R.A., Spitzer, M., 1992. Mescaline-induced psychopathological, neuropsychological, and neurometabolic effects in normal subjects: experimental psychosis as a tool for psychiatric research. Biol. Psychiatry 32, 976–991.

Hofmann, A., 1983. LSD: My Problem Child – Reflections on Sacred Drugs, Mysticism, and Science. J.P. Tarcher, Inc., Los Angeles, CA.

Hunt, D., 1997. Rise of hallucinogen use. NCJ 166607. National Institute of Justice, Washington, D.C., pp. 1-12.

Jacobs, B.L., 1987. How hallucinogenic drugs work. Am. Sci. 75, 386–392.

Javitt, D.C., Zukin, S.R., 1991. Recent advances in the phencyclidine model of schizophrenia. Am. J. Psychiatry 148, 1301–1308.

Johnston, L.D., O'Malley, P.M., Bachman, J.G., 1997. National Survey Results on Drug Use from the Monitoring the Future Study, 1975–1995: Vol. II, College Students and Young Adults. NIH 98-4140. U.S. Government Printing Office, Washington, D.C.

Jones, A.P., 1973. Personality and value differences related to use of LSD-25. Int. J. Addict. 8, 549–557.

Klavetter, R.E., Mogar, R.E., 1967. Peak experiences: investigation of their relationship to psychedelic therapy and self-actualization. J. Humanistic Psychology 7, 171–177.

Kleber, H.D., 1967. Prolonged adverse reactions from unsupervised use of hallucinogenic drugs. J. Nerv. Ment. Dis. 144, 308–319.

Kleckner, J.H., 1968. Personality differences between psychedelic drug users and nonusers. Psychology 5, 66–71.

Krebs, K.M., Geyer, M.A., 1994. Cross-tolerance studies of serotonin receptors involved in behavioral effects of LSD in rats. Psychopharmacology (Berlin) 113, 429–437.

Krystal, J.H., Karper, L.P., Seibyl, J.P., Freeman, G.K., Delaney, R., Bremner, J.D., Heninger, G.R., Bowers, M.B. Jr., Charney, D.S., 1994. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch. Gen. Psychiatry 51, 199–214.

Krystal, J.H., Price, L.H., Opsahl, C., Ricaurte, G.A., Heninger, G.R., 1992. Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: effects on mood and neuropsychological function? Am. J. Drug Alcohol Abuse 18, 331–341.

Landis, C., Clausen, J., 1954. Certain effects of mescaline and lysergic acid on psychological functions. J. Psychol. 38, 211–221.

Marek, G.J., Aghajanian, G.K., 1996. LSD and the phenethylamine hallucinogen DOI are potent partial agonists at 5-HT2A receptors on interneurons in rat piriform cortex. J. Pharmacol. Exp. Ther. 278, 1373–1382.

Maurel-Remy, S., Bervoets, K., Millan, M.J., 1995. Blockade of phencyclidine-induced hyperlocomotion by clozapine and MDL 100,907 in rats reflects antagonism of 5-HT2A receptors. European J. Pharmacol. 280, R9–11.

McCall, R., 1986. Effects of hallucinogenic drugs on serotonergic neuronal systems. Pharmacol. Biochem. Behav. 24, 359–363.

McCann, U.D., Lowe, K.A., Ricaurte, G.A., 1997. Long-lasting effects of recreational drugs of abuse on the central nervous system. Neuroscientist 3, 399–411.

McCann, U.D., Ricaurte, G.A., 1991. Lasting neuropsychiatric sequelae of (+)-methylenedioxymethamphetamine ('ecstasy') in recreational users. J. Clin. Psychopharmacol. 11, 302–305.

McGlothlin, W.H., Arnold, D.O., 1971. LSD revisited, a ten-year follow-up of medical LSD use. Arch. Gen. Psychiatry 24, 35–49.

McGlothlin, W.H., Arnold, D.O., Freedman, D.X., 1969. Organicity measures following repeated LSD ingestion. Arch. Gen. Psychiatry 21, 704–709.

McGlothlin, W.H., Cohen, S., McGlothlin, M.S., 1967. Long lasting effects of LSD on normals. Arch. Gen. Psychiatry 17, 521–532.

Nishith, P., Mueser, K.T., Gupta, P., 1994. Personality and hallucinogen abuse in a college population from India. Personality and Individual Differences 17, 561–563.

Olney, J.W., Labruyere, J., Price, M.T., 1989. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science 244, 1360–1362.

Ott, J., 1993. Pharmacotheon: Entheogenic Drugs, Their Plant Sources and History. Natural Products Co., Kennewick, WA.

Pope, H.G. Jr., 1969. Tabernanthe iboga: an African narcotic plant of social importance. Economic Botany 23, 174–184.

Price, L.H., Ricaurte, G.A., Krystal, J.H., Heninger, G.R., 1989. Neuroendocrine and mood responses to intravenous L-tryptophan in 3,4-methylenedioxymethamphetamine (MDMA) users. Arch. Gen. Psychiatry 46, 20–22.

Riley, D.N., Jamieson, B.D., 1972. Personality pathology and student drug use: an empirical study. N. Z. Med. J. 76, 252–255.

Salzman, C., Lieff, J., Kochansky, G.E., Shader, R.I., 1972. The psychology of hallucinogenic drug discontinuers. Am. J. Psychiatry 129, 755–761.

SAMHSA (Substance Abuse and Mental Health Services Administration), Office of Applied Studies, 1997. Trends in initiation of drug use. In: Preliminary Results From the 1996 National Household

Survey on Drug Abuse. DHHS (SMA) 97-3149. National Clearinghouse for Alcohol and Drug Information, Rockville, MD, pp. 23-25.

Sanders-Bush, E., Burris, K.D., Knoth, K., 1988. Lysergic acid diethylamide and 2,5-dimethoxy-4-methylamphetamine are partial agonists at serotonin receptors linked to phosphoinositide hydrolysis. J. Pharmacol. Exp. Ther. 246, 924–928.

Schultes, R.E., Hofmann, A., 1992. Plants of the Gods: Their Sacred, Healing, and Hallucinogenic Powers. Healing Arts Press, Rochester, VT.

Shulgin, A., Shulgin, A., 1991. Pihkal: A Chemical Love Story. Transform Press, Berkeley, CA.

Shulgin, A. and Shulgin, A., 1997. Tihkal: The Continuation. Transform Press, Berkeley, CA.

Silverstein, A.B., Klee, G.D., 1960. The effect of lysergic acid diethylamide on digit span. J. Clin. Exp. Psychopathol. and Q. Rev. Psychiatry Neurol. XXI, 11-14.

Sloviter, R.S., Drust, E.G., Damiano, B.P, Connor, J.D., 1980. A common mechanism for lysergic acid, indolealkylamine and phenethylamine hallucinogens: serotonergic medication of behavioral effects in rats. J. Pharmacol. Exp. Ther. 214, 231-238.

Snyder, S.H., Faillace, L.A., Weingartner, H., 1968. DOM (STP), a new hallucinogenic drug, and DOET: effects in normal subjects. Am. J. Psychiatry 125, 357–364.

Stoll, W.A., 1947. Lysergsäure-diäthylamid, ein phantastikum aus der mutterkorngruppe [Lysergic acid diethylamide, a phantasticon of the ergot group]. Scheizer Archiv fur Neurologie und Psychiatrie 60, 1–45.

Strassman, R.J., 1984. Adverse reactions to psychedelic drugs: a review of the literature. J. Nerv. Ment. Dis. 172, 577–595.

Thatcher, K., Wiederholt, W.C., Fischer, R., 1971. An electroencephalographic analysis of personality-dependent performance under psilocybin. Agents Actions 2, 21–26.

Thatcher, K., Kappeler, T., Wisecup, P., Fischer, R., 1970. Personality trait dependent performance under psilocybin. Part II. Dis. Nerv. Sys. 31, 181–192.

Unger, S.M., 1963. Mescaline, LSD, psilocybin, and personality change. Psychiatry 26, 111–125.

Ungerleider, J.T., Pechnick, R.N., 1994. Hallucinogens. In: Galanter, M., Kleber, H.D. (Eds.). The American Psychiatric Press Textbook of Substance Abuse Treatment. American Psychiatric Press, Inc., Washington, D.C., pp. 141-148.

Vardy, M.M., Kay, S.R., 1983. LSD psychosis or LSD-induced schizophrenia? A multimethod inquiry. Arch. Gen. Psychiatry 40, 877–883.

Wackwitz, J.H., Pelfrey, M.C., Stenmark, D.E., 1974. The relationship of social and personality characteristics to hallucinogen use among college females. Addictive Dis. Int. J. 1, 189–202.

Wagner, J.G., Aghajanian, G.K., Bing, O.H.L., 1968. Correlation of performance test scores with "tissue concentration" of lysergic acid diethylamide in human subjects. Clin. Pharmacol. Ther. 9, 635–638.

Winter, J.C., 1978. Stimulus properties of phenethylamine hallucinogens and lysergic acid diethylamide: the role of 5-hydroxytryptamine. J. Pharmacol. Exp. Ther. 204, 416–423.

Winter, J.C., Rabin, R.A., 1988. Interactions between serotonergic agonists and antagonists in rats trained with LSD as a discriminative stimulus. Pharmacol. Biochem. Behav. 30, 617–624.

Wright, M., Hogan, T.P., 1972. Repeated LSD ingestion and performance on neuropsychological tests. J. Nerv. Ment. Dis. 154, 432–438.

Young, C.R., 1997. Sertraline treatment of hallucinogen persisting perception disorder. J. Clin. Psychiatry 58, 85.