Psychological and Cognitive Effects of Long-Term Peyote Use Among Native Americans

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Background: *Hallucinogens are widely used, both by drug abusers and by peoples of traditional cultures who ingest these substances for religious or healing purposes. However, the long-term residual psychological and cognitive effects of hallucinogens remain poorly understood.*

Methods: *We recruited three groups of Navajo Native Americans, age 18–45: 1) 61 Native American Church members who regularly ingested peyote, a hallucinogen-containing cactus; 2) 36 individuals with past alcohol dependence, but currently sober at least 2 months; and 3) 79 individuals reporting minimal use of peyote, alcohol, or other substances. We administered a screening interview, the Rand Mental Health Inventory (RMHI), and ten standard neuropsychological tests of memory and attentional/executive functions.*

Results: *Compared to Navajos with minimal substance use, the peyote group showed no significant deficits on the RMHI or any neuropsychological measures, whereas the former alcoholic group showed significant deficits ($p < .05$) on every scale of the RMHI and on two neuropsychological measures. Within the peyote group, total lifetime peyote use was not significantly associated with neuropsychological performance.*

Conclusions: *We found no evidence of psychological or cognitive deficits among Native Americans using peyote regularly in a religious setting. It should be recognized, however, that these findings may not generalize to illicit hallucinogen users.*

Key Words: Hallucinogens, alcoholism, cognition, psychological testing, Native Americans, religion

Illicit use of hallucinogens is widespread and increasing in the United States (Johnston et al 2003); between 1999-2001, more than 2 million Americans tried lysergic acid diethylamide (LSD) for the first time. Despite longstanding concerns about the possible toxicity of these compounds (Halpern and Pope 1999; Halpern et al 2004), knowledge regarding their long-term psychological and cognitive effects remains limited. Studies of the residual cognitive effects of hallucinogens are conflicting and subject to substantial methodological problems (Halpern and Pope 1999). In particular, hallucinogen users in virtually all studies had also used many other illicit drugs, making it difficult to determine which substances contributed to observed deficits. Other possible confounding variables included subjects' premorbid cognitive deficits, current psychopathology, and acute or recent intoxication with alcohol or other drugs (Halpern and Pope 1999; Halpern et al 2004; Parrott 2001).

To assess the residual effects of long-term hallucinogen use, one should ideally examine individuals with extensive exposure to hallucinogens, but minimal exposure to other drugs. To our knowledge, only one large population in the United States offers this opportunity: the 300,000 Native Americans who regularly (and legally) (American Indian Religious Freedom Act Amendments of 1994) ingest the peyote cactus (*Lophophora williamsii*), which contains the hallucinogen mescaline (β-3,4,5-trimethoxyphenethylamine), as a religious sacrament during all-night prayer ceremonies in the Native American Church (NAC) (Aberle 1966; La Barre 1989; Slotkin 1956; Stewart 1987). NAC members accept peyote as a God-given medicine offering spiritual and physical healing for the betterment of all Native peoples. NAC members may attend prayer ceremonies as often as two or three nights in a week or as infrequently as once a year, but most members attend on average one ceremony a month. Many NAC members will therefore ingest peyote hundreds or thousands of times in their lifetime but, in adherence to their faith, strictly abstain from alcohol or other drugs, except for smoking tobacco at times of prayer. Thus, working with these Native Americans offers a unique opportunity to examine the long-term effects of a hallucinogen in isolation from other confounding substances.

Mescaline is a particularly interesting hallucinogen to study, since its structure is partially homologous to LSD (Nichols et al 1977) and it has historically been used as a reference standard in hallucinogen research, with the psychoactive potency of other hallucinogens expressed in "mescaline units" (Shulgin et al 1969; Snyder and Merril 1967). Though mescaline has the lowest potency of the orally active naturally-derived hallucinogens (1:2500 to 1:4000 mescaline:LSD), a full dose (200 to 400 mg) has a long duration of action, with peak effects 2 to 4 hours after consumption, declining over the next 8 hours (Grinspoon and Bakalar 1997; Nichols 2004). The physiological and psychological effects of mescaline are similar to LSD: both are sympathomimetic, profoundly alter perception of self and reality, increase suggestibility, and intensify emotions. With both substances, some users experience a deeply mystical/transcendental state, while others (especially those ill-prepared or with strong histories of mental illness) experience dysphoric symptoms. In comparison to LSD, mescaline is described as more sensual and perceptual and less altering of thought and sense of self (Grinspoon and Bakalar 1997). However, in one double-blind clinical trial, subjects were not able to distinguish mescaline from LSD (Hollister and Sjoberg 1964). A psychoactive dose of mescaline is contained in the amount of peyote typically consumed by an adult member in a NAC ceremony. The mechanism of action of mescaline, like psilocybin and LSD, is hypothesized at the molecular level to result from its effects as a partial agonist of 5-HT2a receptors within the central nervous system (Nichols 2004).

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Peyote is also of interest because it is reputed to be an effective treatment for alcoholism when used in the NAC religious context (Albaugh and Anderson 1974; Bergman 1971; Blum et al 1977; Calabrese 1997; Garrity 2000; Menninger 1971; Roy 1973). Of course these reported benefits might be primarily attributable to participation in the NAC religion, rather than to peyote itself. Notably, however, the efficacy of hallucinogens for treating substance dependence is also supported by anthropological reports from other traditional societies (de Rios et al 2002), by animal studies using the botanical hallucinogen ibogaine (Glick and Maisonneuve 2000), and by human studies using LSD (Halpern 1996). Thus it seems possible that peyote and other hallucinogens might have specific pharmacological properties of potential value for treating substance dependence. Before further investigating any such possible clinical effects, however, it would seem important to establish whether hallucinogens produce adverse residual effects of their own – a possibility that has dampened enthusiasm for research in this area over the last few decades (Grob 1994).

In light of these considerations, we approached members of the Navajo Nation to perform psychological and neuropsychological evaluations of NAC members. This group represented a large group of potential study participants: among 255,000 enrolled members of the Navajo tribe, about one third are NAC members, and almost all of these individuals live on tribal land or close by. We also recruited two comparison groups of Navajos – one reporting virtually no peyote or other substance use, and one reporting past alcohol dependence – since alcohol represents a serious problem among many Native Americans (Lamarine 1988; Mail and Johnson 1993; Manson et al 1992). We included the former alcoholic group not only because of its public health importance, but also to assess the sensitivity of our test battery.

Methods and Materials

With the assistance of a Navajo case finder, we recruited three groups of Navajos aged 18–45: 1) NAC members who had ingested peyote on at least 100 occasions (the peyote group); 2) a former alcoholic group reporting at least five years of drinking more than 50 12-ounce beers (or equivalent) per week, but currently sober at least 2 months; and 3) a comparison group reporting minimal use of any substance.

We performed all evaluations off the reservation of Navajo Nation. After complete description of the study to the subjects, written informed consent (approved by the McLean Hospital Institutional Review Board) was obtained. At a baseline evaluation, a trained psychiatrist recorded demographic information, medical history, comprehensive substance use history, and lifetime history of psychiatric disorders as determined by semi-structured questions. We then administered the Rand Mental Health Inventory (RMHI; Davies et al 1988; Veit and Ware 1983) and the Tan Reading Subtest of the Wide Range Achievement Test-3 (WRAT-3; Jastak Associates 1993). In addition, we administered a breathalyzer (Alco-Sensor IV, Intoximeters, Inc., St. Louis, Missouri) to candidates for the former alcoholic group and interviewed a close contact of each candidate to confirm duration of sobriety. A formal neurological assessment was not conducted.

We excluded participants reporting 1) a history of head injury or other medical condition that might affect cognitive function; 2) current use of psychoactive medications; 3) lifetime use of cocaine, stimulants, opioids, sedative-hypnotics, hallucinogens other than peyote, or hydrocarbon inhalants more than 10 times, or cannabis more than 100 times; 4) for the former alcoholic and comparison groups, lifetime use of peyote more than 5 times; 5) for the peyote and comparison groups, consumption of more than 5 alcohol-containing beverages per day continuously for one month or more at any time, or any other alcohol consumption qualifying for a diagnosis of alcohol dependence in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association 1994); 6) English reading skills below the third-grade level, as indicated by a score of less than 30 on the WRAT-3; and 7) evidence of a current DSM-IV Axis I disorder (American Psychiatric Association 1994) other than simple or social phobia.

Table 1. Demographic Features of the Peyote Group, Former Alcoholic Group, and Comparison Group

Demographic Feature[a]	Peyote Group (n = 61)	Former Alcoholic Group (n = 36)	Comparison Group (n = 79)	Peyote vs. Comparison Group p Value[b]	Alcohol vs. Comparison Group p Value[b]
Sex, Male	15 (25)	20 (56)	14 (18)	.40	.004
Age	31 [23, 37]	34 [30, 40]	29 [23, 37]	.94	.003
Ever Married	38 (62)	26 (72)	47 (59)	.86	.22
Education, High School or Less	26 (46)	26 (72)	44 (56)	.56	.43
Middle or Upper Middle Class[c]	30 (50)	7 (21)	33 (42)	.26	.05
Telephone in Home	46 (75)	21 (58)	55 (70)	.57	.21
Lifetime Episodes of Peyote Use	300 [150, 500]	0 [0, 2]	0 [0, 2]	<.001	.98
Lifetime Episodes of Cannabis Use	0 [0, 2]	10 [1, 45]	0 [0, 2]	.23	<.001
Lifetime Alcoholic Drinks	10 [4, 175]	48200 [33400, 88750]	75 [5, 788]	.067	<.001
Years of Substance Use[d]	21 [15, 28]	9.1 [6.0, 13.8]	—	—	—
WRAT-3 Score	46 [43, 50]	44.5 [41, 48.75]	45 [41, 51]	.41	.86
WAIS-R Vocabulary Score	28 [20, 37]	27 [20, 37]	28 [22, 37]	.58	.59
Days between Last Substance Use and Testing[d]	35 [17, 92]	247 [146, 365]	—	—	—

[a]Shown as n (%) for proportions and median [interquartile range] for continuous variables. See text for definitions of terms.

[b]Differences between peyote group and comparison group and between former alcoholic group and comparison group completed separately by Fisher's exact test for categorical variables and by Wilcoxon rank sum test for continuous variables.

[c]Hollingshead-Redich classes 2 or 3 (there were no participants in class 1). Note that n = 60 for peyote group, 33 for former alcoholic group and 78 for comparison group because of missing data.

[d]"Substance" refers to peyote in the case of the peyote group and alcohol in the case of the former alcoholic group.

We specifically screened the 80 potential participants (Figure 1) in the peyote group for a history of hallucinogen persisting perception disorder ("flashbacks") (Halpern and Pope 2003); none reported this condition. We did not formally ask members of the peyote group about tolerance to peyote, as we are aware of no evidence that tolerance develops with the intermittent pattern of use that described most NAC members; we also did not hear any anecdotal descriptions of individuals requiring progressively larger doses.

Participants satisfying all criteria were invited to return for a battery of neuropsychological tests, chosen to assess particularly for impairment in memory and attentional/executive functions. The test battery was similar to the batteries administered in our previous studies of cannabis users (Pope et al 2001a) and MDMA users (Halpern et al 2004), as well as in published studies of alcoholism (Grant 1987). For the present study, however, we focused almost entirely on nonverbal measures, because we doubted the reliability of Western verbal tests in Navajo participants, many of whom had grown up speaking Diné (the Navajo language) rather than English. This problem is illustrated by participants' performance on the vocabulary subscale of the Wechsler Adult Intelligence Test-Revised (WAIS-R; Wechsler 1981), where the three study groups achieved similar mean scores – but all fell about 1.3 standard deviations below average scores for normative Western populations (Table 1). By contrast, participants' performance was generally comparable to Western norms on nonverbal tests (see Results below) – suggesting that these tests were less vulnerable to linguistic or cultural bias.

Peyote group participants were asked to perform these tests at least seven days after their most recent peyote meeting; all others were tested within four weeks of the baseline evaluation. On the day of testing, an investigator, blinded to group status, first administered a breathalyzer test to ensure that participants were alcohol-free. She then administered a battery of neuropsychological tests that included the 1) Vocabulary Subtest of the WAIS-R (as already noted above); 2) WAIS-R Digit Span Subtest; 3) WAIS-R Digit Symbol Subtest; 4) WAIS-R Block Design Subtest; 5) Rey-Osterreith Complex Figure Test (ROCF; Osterrieth 1944); 6) Wisconsin Card Sort Test (WCST; Heaton 1981); 7) Nonverbal portions of the Wechsler Memory Scale (WMS; Wechsler 1945); 8) Stroop Test (Stroop 1935; MacLeod 1991); 9) Ravens Progressive Matrices (Burke 1985); and 10) Trail-Making Tests A and B from the Halstead-Reitan Battery (Trails A and B; Reitan and Wolfson 1993).

Using statistical methods similar to those of our previous study of cannabis users (Pope et al 2001a), we compared the

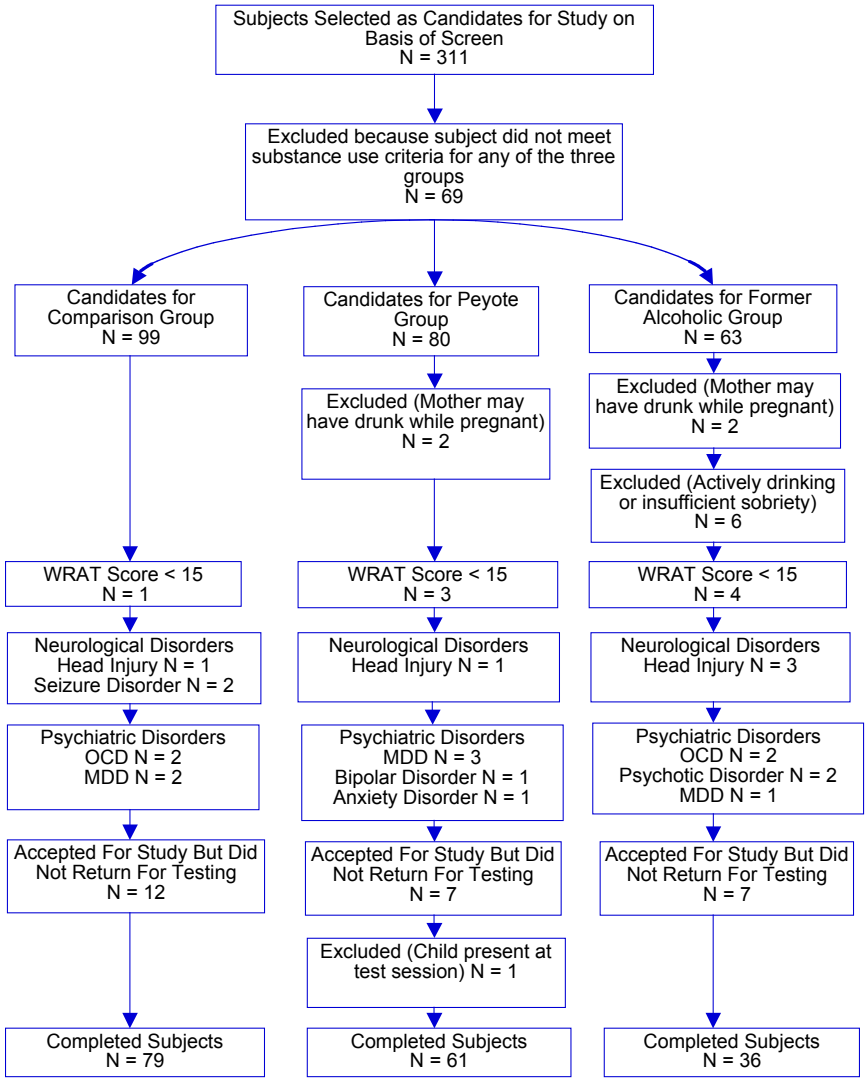

Figure 1. Flow chart showing subjects screened and withdrawn (1999-2003). WRAT, Wide Range Achievement Test-3; OCD, obsessive compulsive disorder; MDD, major depressive disorder.

peyote group with the comparison group, and the former alcoholic group with the comparison group, separately using multivariate linear regression, adjusting for age and sex. We also repeated the analyses while restricting the sample to the 152 participants reading at least at an eighth-grade level (WRAT-3 scores of at least 40). Finally, within the peyote group, we assessed the association between log-transformed lifetime episodes of peyote use and scores on all test measures.

Because of correlations between many test measures, it was difficult to calculate an appropriate correction for multiple comparisons. Accordingly, the significance levels of findings are shown without correction. Thus some of the differences, especially those with modest levels of significance, might represent chance associations. We address this issue further in the Discussion section below.

Results

We performed baseline interviews on 311 Navajos, of whom 135 were excluded or failed to return for the neuropsychological testing visit, leaving final samples of 61 participants in the peyote group, 36 in the former alcoholic group, and 79 in the comparison group (Figure 1). The groups differed somewhat in age and gender distribution, but were similar in level of education, reading skills, and English vocabulary (Table 1) – although all groups displayed lower mean English vocabulary scores than the fiftieth percentile of Western populations, as discussed above.

On the RMHI, the former alcoholic group reported significantly greater pathology than the comparison group on all 9 of the mental health scales, whereas the peyote group showed no significant differences from the comparison group on most scales and scored significantly better on 2 (Table 2).

The neuropsychological tests yielded no significant differences between the peyote and comparison groups on any measure, whereas the former alcoholic group showed poorer performance on the immediate condition of the ROCF and on total perseverations on the WCST (Table 3). On the ROCF, the former alcoholic group showed greater deficits when compared directly to the peyote group (for example, on the immediate condition, the estimated difference [SE] was −4.0 [1.3]; $p = .002$).

The restricted sample of participants with WRAT-3 scores of at least 40 (comprising 56 [92%] of the participants in the peyote group, 32 [89%] in the former alcoholic group, and 64 [81%] in the comparison group) yielded little change in the estimated differences between the peyote and comparison groups on any measures. The former alcoholic group, however, showed slightly greater deficits relative to the comparison group on virtually all of the measures in Tables 2 and 3. For example, on the WAIS-R Block Design subtest, the estimated difference between the alcoholic group and the comparison group widened to −4.5 [1.9], $p = .017$; on the Digit-Symbol Subtest, the difference became −4.9 [2.6], $p = .062$.

Finally, within the peyote group, no associations between log-transformed lifetime peyote use and any neuropsychological test measure approached significance ($p \geq .1$ in all cases; see Table 4). On the RMHI measures, however, greater lifetime peyote use was associated with significantly better scores on five of the nine scales, including the composite Mental Health Index (see Table 5 for details).

Discussion

The residual psychological and cognitive effects of long-term hallucinogen use are poorly understood, in part because most previous studies have evaluated hallucinogen users who were also heavy users of other illicit drugs – making it difficult to identify any effects specific to hallucinogens themselves. These effects deserve further study – first, because illicit hallucinogen use is widespread and growing in Western cultures, and second, because many members of traditional cultures, including some 300,000 Native Americans, regularly use hallucinogens as religious sacraments.

We administered the RMHI and a battery of nonverbal neuropsychological tests to 61 Navajo longstanding participating members of the NAC. We compared this group to 79 Navajos reporting minimal lifetime use of peyote or any other substance,

Table 2. Scores on Psychological Measures in the Peyote Group, Former Alcoholic Group, and Comparison Group

				Peyote vs. Comparison Group		Alcohol vs. Comparison Group	
Measure[a]	Peyote Group ($n = 61$)[b]	Former Alcoholic Group ($n = 36$)[b]	Comparison Group ($n = 79$)[b]	Estimated Mean Difference[c] (SE)	p Value	Estimated Mean Difference[c] (SE)	p Value
Rand Mental Health Inventory							
Anxiety	18.0 (6.4)	24.1 (7.7)	18.6 (6.2)	.7 (1.2)	.55	6.1 (1.5)	<.001
Depression	7.1 (2.5)	10 (3.6)	7.3 (2.8)	.3 (.5)	.60	2.8 (.7)	<.001
Loss of Behavioral/Emotional Control	15.7 (5)	21.8 (7.3)	17.2 (6)	−1.4 (1.0)	.18	5.2 (1.4)	<.001
General Positive Affect	48.2 (6.5)	41.1 (9.6)	44.6 (7.3)	3.6 (1.4)	.008	−3.6 (1.8)	.045
Emotional Ties	10.4 (2.1)	8.4 (2.6)	10 (2.0)	.4 (.4)	.30	−1.4 (.5)	.006
Life Satisfaction	4.8 (0.9)	4.4 (1.2)	4.7 (0.9)	.05 (.2)	.77	.4 (.2)	.05
Psychological Distress	45 (14.1)	61.7 (19.6)	47.8 (15.2)	−2.9 (2.8)	.31	15.4 (3.7)	<.001
Psychological Well-Being	68.1 (9.5)	57.9 (13.5)	63.3 (10.3)	4.8 (1.9)	.015	−5.3 (2.6)	.041
Mental Health Index	189.0 (21.7)	162.3 (31.4)	181.7 (23.3)	7.3 (4.4)	.10	−21 (5.9)	<.001

[a]Higher scores indicate more of the construct; for the overall Mental Health Index, higher scores indicate better mental health. All scores are shown as mean (SD) for each group.

[b]Because of missing responses on some of the questions, the number of participants used to compute mean scale scores ranges from 56 to 61 in the peyote group, 33–35 in the former alcoholic group, and 71–79 in the comparison group.

[c]Differences represent peyote group minus comparison group and former alcoholic group minus comparison group, respectively, by linear regression adjusted for age and sex (see text).

Table 3. Non Verbal Neuropsychological Test Scores for Peyote, Former Alcoholic, and Comparison Groups

Score[a]	Peyote Group ($n = 61$)	Former Alcoholic Group ($n = 36$)	Comparison Group ($n = 78$)	Peyote vs. Comparison Group: Estimated Mean Difference[f] (SE)	Peyote vs. Comparison Group: p Value	Alcohol vs. Comparison Group: Estimated Mean Difference[f] (SE)	Alcohol vs. Comparison Group: p Value
Auditory Continuous Performance Test[b]							
Inattention Errors	.9 (1.4)	.7 (1.5)	.9 (1.7)	.0 (.3)	.95	−.2 (.4)	.57
Impulsivity Errors	.6 (.9)	.7 (1.1)	.4 (.7)	.2 (.1)	.21	.3 (.2)	.13
Total errors	1.5 (1.9)	1.4 (1.9)	1.4 (2.1)	.2 (.3)	.82	.1 (.4)	.85
Ray-Osterreith Complex Figure:							
Copy Condition	33.9 (2.1)	33.0 (2.8)	33.6 (2.1)	.3 (.4)	.42	−.5 (.5)	.21
Immediate recall	23.6 (6.1)	20.1 (5.6)	22.2 (5.9)	1.2 (1.0)	.22	−2.6 (1.3)	.03
Delayed recall	22.9 (5.7)	19.9 (8.0)	21.5 (5.3)	1.2 (.9)	.19	−2.0 (1.2)	.09
Halstead-Reitan Battery:							
Trails A time, sec.	23.9 (8.3)	27.1 (13.7)	23.9 (7.0)	−.5 (1.4)	.74	1.1 (1.8)	.55
Trails A errors	.2 (.5)	.2 (.4)	.2 (.4)	.0 (.1)	1.0	−.1 (.1)	.51
Trails B time, sec.	63.6 (20.6)	71.6 (30.5)	61.6 (16.9)	1.1 (3.5)	.76	1.7 (4.5)	.70
Trails B errors	.4 (1.0)	.6 (.8)	.5 (.7)	−.1 (.1)	.43	.0 (.2)	.94
Stroop Test:[c]							
Color Naming Time, sec.	62.8 (10.4)	61.1 (11.7)	62.0 (10.7)	.6 (1.9)	.73	−1.7 (2.4)	.50
Color Naming, errors	2.1 (1.5)	1.8 (1.5)	2.2 (1.7)	−.1 (.3)	.78	−.3 (.3)	.36
Word Reading Time, sec.	51.1 (9.8)	48.3 (8.4)	48.4 (8.8)	2.6 (1.6)	.10	.4 (2.1)	.83
Word Reading, errors	1.3 (1.3)	1.0 (1.1)	.9 (1.2)	.4 (.2)	.10	.2 (.3)	.55
Color Interference Time, sec.	115.1 (22.6)	116.8 (23.4)	114.7 (23.2)	.1 (4.0)	.99	3.3 (5.2)	.53
Color Interference, errors	4.6 (3.7)	4.8 (3.7)	5.0 (4.1)	−.4 (.7)	.53	.0 (.9)	.97
Wechsler Adult Intelligence Scale, Revised:							
Digit Span, forward	6.2 (1.7)	6.8 (1.8)	6.4 (2.0)	−.3 (.3)	.38	.3 (.4)	.54
Digit Span, backwards	6.1 (1.9)	6.0 (1.5)	6.2 (2.0)	−.1 (.3)	.71	.0 (.4)	.91
Digit Span, total	12.3 (3.1)	12.8 (2.6)	12.6 (3.4)	−.4 (.5)	.47	.5 (.7)	.43
Block Design	35.0 (8.5)	35.5 (8.3)	35.5 (8.1)	−1.9 (1.3)	.16	−3.1 (1.7)	.08
Digit-Symbol	63.3 (9.7)	59.0 (13.5)	86.1 (11.5)	−2.1 (1.6)	.26	−3.9 (2.4)	.10
Ravens Progressive Matrices:	42.4 (5.2)	41.1 (8.0)	42.2 (7.2)	.3 (1.3)	.80	−.2 (1.7)	.91
Wechsler Memory Scale:							
Figures, immediate	11.3 (1.9)	11.4 (2.1)	11.3 (2.0)	−.1 (.3)	.57	.2 (.4)	.63
Figures, delayed	12.2 (1.4)	11.9 (1.7)	11.9 (1.9)	.3 (.3)	.30	.0 (.4)	.91
Wisconsin Card Sort Test:[d]							
Categories, Deck 1	2.8 (1.4)	2.8 (1.4)	2.7 (1.5)	.1 (.2)	.75	−.1 (.3)	.70
Categories, Deck 2	3.3 (1.7)	3.1 (1.7)	3.3 (1.8)	.1 (.3)	.64	.1 (.4)	.82
Total categories	6.1 (2.8)	5.7 (2.7)	6.0 (2.9)	.1 (.5)	.77	.0 (.8)	.96
Perseverations, Deck 1	2.5 (.6)	2.4 (.5)	2.3 (.8)	.2 (.1)	.17	.2 (.2)	.14
Perseverations, Deck 2	1.8 (.8)	1.9 (.9)	1.7 (.7)	.1 (.1)	.43	.1 (.2)	.57
Total perseverations[e]	2.8 (.6)	2.9 (.5)	2.7 (.8)	.2 (.1)	.10	.3 (.2)	.04

[a]Represents raw score unless otherwise stated. All scores are shown as mean (SD) for each group.
[b]$n = 76$ in the comparison group.
[c]$n = 60$ in the peyote group.
[d]$n = 80$ in the peyote group, 35 in the former alcoholic group, and 75 in the comparison group.
[e]Log-transformed values because of skewed distribution.
[f]Differences represent peyote group minus comparison group, former alcoholic group minus comparison group, respectively, by linear regression adjusted for age and sex (see text).

and 36 Navajos reporting at least 5 years of alcohol dependence, but currently sober at least 2 months. The peyote group showed no significant differences from the comparison group on most scales of the RMHI and scored significantly better on 2 scales. We also found no significant differences between the peyote group and comparison group on any of the neuropsychological measures. Moreover, within the peyote group, log-transformed lifetime episodes of peyote use showed no significant associations with neuropsychological measures and were associated with significantly better scores on several RMHI measures. These findings suggest that long-term use of this hallucinogenic substance, at least when ingested as a bona fide sacrament, is not associated with adverse residual psychological or cognitive effects.

By contrast, we found highly significant psychological deficits and a few significant neuropsychological deficits in the former alcoholic group. The latter findings (decreased visuospatial memory on the ROCF and increased perseverations on the WCST) suggest that some deficits in frontal lobe functions may persist long after alcohol consumption has ceased. Although these deficits were modest, it should be noted that the former alcoholic participants were young individuals, reporting a median of 8 months of abstinence from alcohol, and screened to exclude cases with major neurological or psychiatric disorders or

Table 4. Association Between Log-Transformed Lifetime Peyote Use and Neuropsychological Test Scores

	Estimated Mean Difference[c] (SE)	*p* Value
Auditory Continuous Performance Test:		
Inattention Errors	.1 (.2)	.80
Impulsivity Errors	−.1 (.1)	.27
Total errors	−.1 (.3)	.75
Rey-Osterreith Complex Figure:		
Copy Condition	.2 (.3)	.44
Immediate recall	.5 (.8)	.53
Delayed recall	.1 (.8)	.87
Halstead-Reitan Battery:		
Trails A time, sec.	.9 (.9)	.31
Trails A errors	.0 (.1)	.74
Trails B time, sec.	.8 (3.0)	.79
Trails B errors	.0 (.1)	.94
Stroop Test:[a]		
Color Naming Time, sec.	1.4 (1.8)	.38
Color Naming, errors	.1 (.2)	.59
Word Reading Time, sec.	2.2 (1.4)	.12
Word Reading, errors	−.1 (.2)	.57
Color Interference Time, sec.	3.5 (3.3)	.30
Color Interference, errors	.0 (.5)	.93
Wechsler Adult Intelligence Scale, Revised:		
Digit Span, forward	.0 (.2)	.92
Digit Span, backwards	−.1 (.3)	.54
Digit Span, total	−.2 (.4)	.73
Block Design	.2 (1.2)	.85
Digit-Symbol	−2.2 (1.3)	.08
Ravens Progressive Matrices:	.3 (1.2)	.82
Wechsler Memory Scale:		
Figures, immediate	.2 (.3)	.40
Figures, delayed	−.1 (.2)	.47
Wisconsin Card Sort Test:[a]		
Categories, Deck 1	.0 (.2)	.98
Categories, Deck 2	.3 (.3)	.31
Total categories	.3 (.4)	.54
Perseverations, Deck 1	−.1 (.1)	.27
Perseverations, Deck 2	.0 (.1)	.66
Total perseverations[b]	−.1 (.1)	.22

[a] $n = 60$ participants.
[b] Log-transformed values because of skewed distribution.
[c] Represents estimated change in score for every increase of 1 in log (episodes of peyote use) (SE), by linear regression, adjusted for age and sex. $n = 61$ participants unless otherwise stated.

a history of any other substance abuse. A less rigorously selected group of former alcoholic individuals might have performed more poorly. Notably, the former alcoholic participants reported more cannabis consumption than the other two groups (see Table 1), although by design no participant exceeded 100 lifetime episodes of cannabis use. However, cannabis use seems unlikely to explain the neuropsychological and psychological deficits in the former alcoholic group, since we have shown in a previous study that even individuals reporting a median of 20,000 lifetime episodes of cannabis use displayed virtually no detectable neuropsychological test deficits after a 28-day washout (Pope et al 2001a).

Several limitations of our study should be considered. First, selection effects likely influenced our recruitment efforts; for example, individuals with severe cognitive deficits might have been less likely to volunteer for the study. However, selection bias would not occur unless there were differential effects across groups – a less likely possibility, since all groups were recruited in the same manner. A related consideration is that we excluded a few candidates from each group on screening because of current psychiatric disorders (see Figure 1). However, these exclusions were infrequent and similar across groups, so that differential effects across groups were again likely minimal. Second, we cannot exclude the possibility of residual confounding, either due to unmeasured confounders or inadequate adjustment for measured confounders. For example, participants in the three groups might have differed in terms of baseline cognitive ability prior to ever ingesting peyote or alcohol. Third, participants' histories were obtained by self-report without external validation, except as indicated above. However, participants were screened without knowledge of the "right" answers needed for acceptance into the study, thus reducing the chances of false responses. These three limitations are inherent to all naturalistic studies of the long-term effects of substance use; we have discussed these methodological issues in detail in previous publications (Pope et al 2001b, Pope 2002).

Fourth, as noted earlier, it is difficult to calculate an appropriate correction for multiple comparisons in the present study, because many of the measures – such as, for example, the subscales of the RMHI, or scores on various cognitive tests of memory – were very closely correlated with one another. Therefore, a simple Bonferroni correction, dividing the alpha level by the total number of comparisons, would tend to over-correct, possibly causing many type II errors (failing to reject the null hypothesis when in fact a genuine difference exists). Given these considerations, we have presented the findings without correction for multiple comparisons; readers should therefore recognize that some findings of modest significance (e.g., *p* values between .01 and .05) may represent chance associations. However, we would note in passing that all significant differences between the former alcoholic group and the comparison group were in the same direction, arguing that the findings cannot easily be ascribed to chance.

Fifth, the cross-sectional study design limits our ability to draw causal inferences. For example, the superior psychological functioning of the peyote group and inferior psychological functioning of the former alcoholic group are probably not exclusively due to pharmacological effects of peyote or alcohol

Table 5. Association Between Log-Transformed Lifetime Peyote Use and Rand Mental Health Inventory Scores

	Estimated Mean Difference[b] (SE)	*p* Value
Rand Mental Health Inventory:[a]		
Anxiety	−2.5 (.9)	.005
Depression	.8 (.3)	.017
Loss of Behavioral/Emotional Control	−1.9 (.7)	.010
General Positive Affect	1.0 (1.0)	.32
Emotional Ties	.1 (.3)	.67
Life Satisfaction	.07 (.1)	.59
Psychological Distress	−5.7 (1.9)	.005
Psychological Well-Being	1.4 (1.4)	.31
Mental Health Index	7.1 (3.1)	.024

[a] Higher scores indicate more of the construct; for the overall Mental Health Index, higher scores indicate better mental health. Because of missing responses on some of the questions, the number of participants used to compute mean scale scores ranges from 58 to 61.
[b] Represents estimated change in score for every increase of 1 in log (episodes of peyote use) (SE), by linear regression, adjusted for age and sex.

themselves, but also due to sociocultural or psychological factors.

Sixth, it is possible that our test battery was not sensitive enough to detect residual deficits from peyote use. Arguing against this possibility is that our tests readily detected significant psychological and cognitive deficits in the former alcoholic group, despite the lower statistical power of comparisons involving this smaller group. Thus, although we cannot exclude a type II error with the peyote group, it seems unlikely that we would have missed a psychological or cognitive deficit of major clinical significance. Of course, more complicated tasks, not performed in this study, might yet reveal differences in functioning not detected by the instruments that we used.

Our findings have public health importance for several reasons. Most important, for the Native Americans who use peyote as a religious sacrament, it appears that this practice does not cause residual psychological or neuropsychological deficits detectable in the battery of tests that we administered. These observations also offer reassurance regarding the more than 10,000 NAC members who serve in the United States Armed Services; we find no evidence that a history of peyote use would compromise the psychological or cognitive abilities of these individuals.

It is not clear whether our findings with peyote would apply to other types of hallucinogens. Although mescaline resembles other hallucinogens in certain respects, it may differ in other respects; for example, it does not appear to produce "flashbacks" (hallucinogen persisting perceptual disorder) in the manner of LSD. Therefore, we cannot exclude the possibility that long-term use of chemically different hallucinogens (such as LSD or psilocybin) might produce adverse residual effects, even if peyote does not. In any event, further studies of the residual effects of these substances—especially in populations with minimal exposure to other types of drugs—are warranted.

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