Persistent neurocognitive deficits after marijuana use

Bolla et al. report that very heavy use of marijuana is associated with persistent decrements in neurocognitive performance (i.e., memory, executive functioning, psychomotor speed, and manual dexterity) even after 28 days of abstinence.

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Heavy marijuana use: The price of getting high

Commentary by Barbara S. Koppel, MD

Marijuana use is common, and often accepted as "normal," as any parent of teenagers knows. My own children, a sophomore and a senior in high school, estimate that 50% to 65% of their peers often use marijuana. The percent would be higher if marijuana was as easy to obtain as alcohol. National surveys of households and of 6th to 12th grade students concur (Table). The neurologic effects of heavy alcohol use are well known. Should we be less concerned about marijuana? Does marijuana use have measurable long-term adverse effects on the brain?

It is in this context that the paper by Bolla et al. is important. Although previous work suggested deleterious short-term effects on cognitive function, a report in 2001 concluded that residual effects were reversible after 1 week of abstinence and related to recent, not cumulative, drug use.[1] Bolla et al. studied 22 volunteers without comorbid psychiatric conditions, neurologic disorders, or heavy alcohol or other illicit drug use who had smoked marijuana at least three times weekly for 2 years. The investigators assured abstinence by admitting subjects to the Clinical Inpatient Research Unit at the National Institute on Drug Abuse for 30 days. At 28 days, a neuropsychologic test battery was performed, and the results were correlated with the amounts of marijuana consumed: on average, 10, 42, and 94 joints/week. Duration was not considered, as the average age of the volunteers was only 22 years. After data analysis by linear regression, a dose-response effect was found for tests of verbal memory, visual learning and memory, executive function, psychomotor speed, and manual dexterity. These functions require participation of prefrontal, cerebellar, and hippocampal brain regions, and all of these areas contain cannibinoid receptors.[2,3]

Despite the strong relationship between neurocognitive test scores and marijuana use, subjects' performance in the great majority of tests remained within the normal range. This makes drawing inferences about the possible effects of such findings on human behavior especially difficult, but a recent survey of adolescent girls correlated the presence of marijuana metabolites in urine and sexually transmitted diseases.[4] Executive dysfunction related to marijuana use may contribute to poor judgment.

An important question that must still be addressed is whether continued heavy use of marijuana results in progressive declines in cognitive performance and test scores that would be unambiguously abnormal. Such data will likely be needed if teenagers and young adults are to be persuaded that heavy and sustained marijuana usage is harmful to brain function. A search of the web yields many responses rebutting earlier studies purporting to show negative effects of marijuana on brain function. Common criticisms included testing "too early," while latent marijuana was still on board; withdrawal effects making participants "too grumpy" to perform well; and concurrent use of other illicit drugs or alcohol. The study by Bolla et al. was well designed to eliminate these confounding effects. While more needs to be done, their results are an important and convincing piece of evidence that heavy marijuana use affects the brain in ways that cause learning difficulties in school, problems in performing daily tasks, and premature aging of cognitive function.

Table *Frequency of marijuana use*

Grade level	Rapid response	Not responding	Daily use, %	Weekly use, %	Monthly use, %	Annual use, %
6th	13,719	335	0.8	1.2	1.7	2.9
7th	14,583	414	1.3	3.0	4.3	7.7
8th	18,603	372	1.9	4.8	7.2	12.7
9th	14,491	376	4.2	9.9	13.9	22.1
10th	16,966	332	5.3	12.6	18.7	29.8
11th	10,618	197	6.1	13.9	20.8	32.6
12th	10,686	190	7.5	15.2	21.9	35.7
JrHS	46,905	1,121	1.4	3.2	4.7	8.3
SrHS	52,761	1,095	5.6	12.7	18.5	29.4
Total	99,666	2,216	3.6	8.2	12.0	19.5

Data are from the *Pride Questionnaire Report*, 2001–02 National Summary, Grades 6–12.

References

1. Pope HG, Gruber AJ, Hudson JI, et al. Neuropsychological performance in long-term cannabis users. Arch Gen Psych 2001;58:909–915.
2. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor localization in brain. Proc Natl Acad Sci 1990;87:1932–1936.
3. Davies SN, Pertwee RG, Riedel G. Functions of cannabinoid receptors in the hippocampus. Neuropharmacology 2002;42:993–1007.
4. Liau A, Diclemente RJ, Wingood GM, et al. Associations between biologically confirmed marijuana use and laboratory-confirmed sexually transmitted diseases among African American adolescent females. Sex Transm Dis 2002;29:387–390.

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Wine and dementia

Truelsen et al. studied the association between amount and type of alcohol consumption and risk of dementia in 1,709 Danish subjects. A moderate (weekly/monthly) intake of wine was associated with a decreased risk of dementia. Certain substances in wine may reduce the occurrence of dementia.

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The accompanying editorial by Brust reviews the evidence that alcohol-containing beverages are associated with dementia, whereas wine, particularly red wine, prevents stroke. Noting that the Truelsen et al. data are consistent with a protective effect [? of flavonoids] in wine.

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An enriched environment enhances cognitive function in young animals

Faverjon et al. found that both in normal rats and in rats after status epilepticus, environmental enrichment during early development improved cognitive outcome. Furthermore, the enriched environment increased neurogenesis and pCREB, a transcription factor critical for hippocampal learning and memory.

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The accompanying editorial by Greenwood and Parent notes that this study adds important information to previous observations that environmental enrichment improves function and enhances brain development in normal and brain-injured animals. The Faverjon et al. paper points to specific mechanisms for enhancing recovery after brain injury. Reviewing putative mechanisms whereby an enriched environment may facilitate repair, Greenwood and Parent note that an enriched environment increases neurogenesis in developing rats suggesting a treatment strategy that may be particularly useful for toddlers.

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Effects of subthalamic deep brain stimulation (DBS) on mood and behavior

Mania

Kulisevsky et al. report three patients with Parkinson's disease who developed manic behavior after receiving bilateral implantation of electrodes for DBS targeted to the subthalamic nucleus.

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Aggressive behavior with stimulation of the posteronmedial hypothalamus

Bejjani et al. report a parkinsonian patient treated by subthalamic stimulation who developed an acute and transient aggressive behavior during intraoperative stimulation.

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Depression and suicide risk

Berney et al. found that 6 of 24 PD patients prospectively studied significantly worsened in their mood state, becoming depressed within 6 months after STN-DBS: three of the six were transiently suicidal.

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The accompanying editorial by Mayberg and Lozano links these three papers while noting the growing literature on neuro-behavior changes associated with DBS. Changes in mood, motivation, and other behavior occur in PD—often early. The occurrence of DBS-related depression and euphoria suggests strategies for the better understanding and treatment of not only behavior disorders of PD but also those of other neuropsychiatric syndromes.

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Sleep deprivation: Effects on seizures during inpatient monitoring

Malow et al. assigned 84 patients with medically refractory partial epilepsy undergoing inpatient video-EEG monitoring to sleep deprivation every other night or to normal sleep. The sleep-deprived and non-sleep-deprived patients had similar rates of seizures during monitoring.

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Creutzfeldt-Jakob disease (CJD) in Australia: 1970 to 1999

The Collins et al. comprehensive national surveillance program confirmed 387 persons as developing a transmissible spongiform encephalopathy (TSE) within Australia during the 30-year period 1970 to 1999. Annual TSE gradually increased over the 3 decades. Death certificates were a useful but imperfect method of case detection. Variant CJD was not identified.

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Homocysteine and cognitive function

Prins et al. studied 1,077 non-demented elderly in a population-based study. They found that elevated plasma homocysteine levels were associated with lower cognitive function. This association was independent of the presence of cerebral infarcts, white matter lesions, and generalized brain atrophy on MRI.

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DWI of stroke does not predict outcomes

The Wardlaw et al. prospective, blinded study of diffusion imaging in stroke highlights why stroke-imaging studies must account for the strong, non-linear association between stroke severity and functional outcome. When compared with clinical predictors, diffusion lesion volume did not predict outcome independently of other measures in all severities of stroke.

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Effects of intratympanic gentamicin injections for Meniere disease on the vestibular hair cells

Horizontal vestibular hair cells may regenerate after intratympanic gentamicin injections for Meniere disease. de Waele et al. showed that galvanic-evoked myogenic potentials are a good predictive marker for successful outcome of the treatment.

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