Challenges of marijuana research

The use of any drug ideally represents a decision based on objective, scientifically based cost–benefit analyses that factor in both the short and long-term effects of that exposure. Pharmacological, toxicological, pharmacokinetic and pharmacodynamic investigations that are deemed to be essential for the rational use of any therapeutic agent are therefore part of the usual drug approval process. With regard to marijuana, sociopolitical factors have intervened in this scientific process. Three major lay perspectives appear to dominate the societal view of marijuana—the ‘reefer madness’ camp holding the view that there are no redeeming attributes to the ‘evil weed’, the ‘innocuous’ camp who consider it to be a harmless recreational substance and the ‘medical marijuana’ camp that believes marijuana to be a panacea for a multitude of aches, pains and chronic diseases with, of course, every shade of opinion in-between. On the scientific front, three trends preface nearly every recent journal article concerning marijuana—the significant prevalence of marijuana use, the changes in age of first use (Kohn et al., 2005; Monshouwer et al., 2005) and the increasing strength of the drug, leading to higher acute and chronic exposures (National Institute on Drug Abuse, 2005; Pijlman et al., 2005). For example, in 2004 ~96.8 (40.2%), 25.5 (10.6%) and 14.6 (6.1%) million Americans aged 12 and older were considered to have used marijuana within their lifetime, the last year, and the last month, respectively (Office of National Drug Control Policy, 2006). However, in the 3 of the 11 states in which medical use of marijuana is legal, and for which statistics are available, 0.05% of the population are registered, i.e. legal, users (General Accounting Office, 2002). Even though marijuana is available from pharmacies in the Netherlands, 80% of users secure their drug via illicit channels (Erkens et al., 2005). Therefore, large numbers of people—adults, pregnant women, adolescents and children—acutely and/or chronically inhale/ingest imprecise dosages of marijuana of unknown purity via pharmaceutically inelegant dosage forms without the complement of knowledge concerning the pharmacological actions, the toxicological risks and the pharmaceutical quality of the product that would be required for the approval and use of any other drug.

Cogent, scientifically based research into marijuana is essential but is also very difficult for a number of important reasons. Firstly, there are logistical issues inherent in studying any substance that is illegal in most countries. Specifically, there are numerous hurdles that must be surmounted to secure a Schedule I substance approval for acute studies; there are problems with subject memory and honesty in determining recent and chronic exposures; and there is a heightened need for confidentiality and non-disclosure agreements in order to legally protect study participants. Second, marijuana is a natural product, inherently variable in its strength and composition, even when acquired through legitimate channels (Pearson, 2004). Investigations of the acute response require a standardized drug product and administration utilizing standardized methods. In spite of these methodological controls, consistent Δ⁹-tetrahydrocannabinol (THC) plasma levels between or within subjects may not be achieved (Ponto et al., 2004), making determination of the dose–response relationship from a single smoked dose potentially problematic. The variability in potency (due to time and non-existent product quality assurance) coupled with the unpredictable route of administration (i.e. smoking) will potentially result in unreliable assessments of immediate and lifetime exposures. Therefore, estimates of the lifetime number of ‘joints’ or cumulative THC exposure are critical pieces of information but represent only crude approximations of actual exposures. Third, the pharmacokinetics and pharmacodynamics of marijuana do not lend themselves to easy examination. Pharmacokinetically, marijuana has a long half-life due to accumulation in body fat and extensive enterohepatic recirculation, and it exhibits user-dependent bioavailability. Pharmacodynamically, tolerance is known to develop to various pharmacological effects (e.g. cardiovascular effects: Grotenhermen, 2003; Gonzalez et al., 2005) and the relationship between THC plasma concentrations and psychotropic effects are generally described by a hysteresis over time (Grotenhermen, 2003). Furthermore, ascertaining the time frame of acute, chronic and withdrawal effects, and the onset of a true abstinent state, requires a kinetic/dynamic sophistication beyond a positive or negative urine test. For example, urine tests generally are positive for 3–5 days after a single exposure but THC may remain detectable for up to 12 days. More troubling, urine levels of metabolites may fluctuate between positive and negative results for days, the duration of which is dependent on the previous magnitude and frequency of use (Ellis et al., 1985; Grotenhermen, 2003). Fourth, studying a potential drug of abuse entails various ethical dilemmas. Ideally, the comparison group should be completely drug naive. For acute response studies, it is considered to be unethical to introduce a potential drug of abuse to a naive subject or to reintroduce the agent to an
abstinent user. As a result, comparative groups are generally 'occasional' users. Hence, the nature of the comparison group is highly dependent on definition of the user group. Additionally, for studies of chronic users, the investigator is placed in the position of potentially 'encouraging' the on-going use of an illicit substance. Finally, in examining the effects of an exogenous agent that has endogenous counterparts, there will always be questions regarding any alterations in brain structure and function of the 'chicken or egg' type, i.e. did the altered functioning create the need for enhanced cannabinoid stimulation or did the enhanced cannabinoid stimulation create the altered functioning? Baseline data (i.e. before marijuana use), especially brain structure/function information, are essentially non-existent and impossible to obtain ethically in any prospective manner. Limited amounts of pre-exposure neuropsychological testing data (e.g. standardized school-based tests: Block and Ghoneim, 1993) when available may prove to be a valuable resource (Fried et al., 2005) in characterizing pre-exposure states. Furthermore, specific effects may not be tied to the dichotomous user/non-user state or to the continuum of dosage but may be related to the specific timing of exposures (e.g. neurodevelopmental effects: Viveros et al., 2005). Therefore, information on all aspects of marijuana use—how much, how long and when—must be secured from the subject, making the quality of the data highly dependent on reliability of memory and honesty of the research subjects.

In this issue, Chang and colleagues (page 1906) report on what appears to be a neuroadaptive state in chronic marijuana users. These investigators utilized BOLD fMRI to examine the brain activation patterns in chronic marijuana users \( N = 24 \) and matched control subjects \( N = 19 \) during a set of visual attention tasks with graded levels of difficulty. In addition, neuropsychological testing was performed. The chronic marijuana users were divided into two groups, active users \( N = 12 \) and abstinent users \( N = 12 \), based on results of urine testing. Three hypotheses were investigated. Firstly, that marijuana users would show an altered attention network when compared with the control group; this altered network would entail decreased activation in the normal attention network and enhanced activation in compensatory brain regions. Second, active users when compared with abstinent users would show greater use of these compensatory regions with increasing attentional load. Third, both user groups would exhibit normal cognitive function, providing evidence for neuroadaptation to the chronic marijuana status. Three additional pieces of information were determined for each user subject, specifically the age of first use, the cumulative THC exposure and the duration of abstinence. As expected, all three groups had similar neurocognitive function and task performance, but altered patterns of brain activation. Marijuana users exhibited less activation in significant portions of the normal attention network and greater activation in several smaller, assumed to be compensatory, regions. There was an inverse correlation between BOLD signal changes and estimated lifetime THC exposure in the cerebellum, potentially indicative of a down-regulation of CB1 receptors. On the other hand, there was a positive correlation between the duration of abstinence and the BOLD signal in parts of the normal attentional network. 'Age of first use' was related to the activation patterns observed, with subjects initiating use earlier in adolescence exhibiting greater activation in compensatory regions and those initiating use later in adolescence showing greater activation in the normal attention network. Cumulative THC exposure and 'age of first use' interacted significantly whereas 'abstinence status' did not.

There are a number of inevitable limitations associated with this study arising from the difficulties outlined above. First and foremost is the reliance on urine-testing results to classify marijuana-user subjects into the 'active' and 'abstinent' groups. Active users were asked to abstain from marijuana use for at least 4 h but without monitored abstinence or [THC], so the actual pharmacological influences (i.e. acute or chronic effects) cannot be ascertained. Abstinent users had negative urine tests with the range of 'abstinence' from 0.5 to 156 months but with the majority of subjects only assessed within the first 2 months. Rather than a group of truly drug-free subjects, this group may reflect a mixture of subjects with low and residual [THC], those undergoing withdrawal and individuals truly free of THC-mediated effects.

From these results, the brain, in response to chronic marijuana exposure, appears to undergo neuroadaptation by accessing compensatory processes in order to maintain normal cognitive performance. Important questions remain concerning the ability of these processes to accommodate tasks of greater cognitive demand or the impact of taping into reserves prior to the advent of aging processes that depend on such reserves to maintain cognition. The average age in this study was \( \sim 30 \) years, not that of the 'baby-boomers' now confronting age-associated cognitive declines. The degree of the compensation necessary appears to be related to the age of initial use and the cumulative exposure. The demographic trends in use and the enhanced potency of marijuana highlight the importance of verifying these relationships. Abstinence appears potentially to 'normalize' brain activation patterns; however, only serial imaging during monitored abstinence will reliably determine the role of reversible and non-reversible changes.

The work of Chang et al. (2006) sheds light on a potential mechanistic explanation (i.e. neuroadaptation) of the incongruity (i.e. how can the brain be altered without an apparent change in cognition?) that fuels the attitudinal schism of society on using marijuana. Replication of these results with careful subject classification, exposure and abstinence documentation, a variety of tasks and a broader age range should further enhance our understanding of the risks and benefits. Marijuana, with its therapeutic potentials and public health consequences, warrants scientific scrutiny and the acquisition of objective information regarding all aspects of the substance itself and the cannabinoid system more
generally—difficult as that may be, unencumbered by the burdens of sociopolitical pressures and biases.

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References