Cognition and cannabis: from anecdote to advanced technology

Whether the use of cannabis causes lasting cognitive or behavioural alteration has been controversial for decades. Studies addressing the problem have often been confounded by failure to account for residual acute effects or withdrawal and by failure to measure cognitive function before drug use. Investigative strategies have included neuropsychological testing, brain activation during cognitive tasks, epidemiology and identification of morphological alteration in the brains of cannabis users.

In this issue of Brain, Zalesky et al. (2012) apply a novel strategy—diffusion-weighted MRI and connectivity mapping—to demonstrate microstructural alterations affecting brain axonal pathways in long-term cannabis users. Without predefined regions of interest, thousands of voxel pairs were compared, and impaired axonal connectivity was identified in the fimbria of the hippocampus and the splenium of the corpus callosum. These abnormalities were greatest in subjects who began regular marijuana use during early adolescence and were present in white matter structures in which cannabinoid (CB)1 receptor density is maximal in utero and during childhood. The findings are consistent with the endocannabinoid system playing a key role in brain development, and they provide a plausible explanation for lasting cognitive impairment after disruption of the endocannabinoid system during childhood or adolescence.

Numerous reports have described neuropsychological testing in cannabis users. In a study in which IQ scores were measured at age 9–12 years and again at age 17–20 years, a decline was observed in heavy users compared with former heavy users, but other than ‘no use of marijuana on the day of testing’, there was no defined period of pre-test abstinence (Fried et al., 2002). A study of high school seniors matched for IQ in the fourth grade found impaired memory, mathematical skills and verbal expression in heavy users compared with light users, but testing was performed only 17 h after last use (Block and Ghonheim, 1993). More convincingly, a study of adolescents and young adults matched for IQ and age-identified negative effects of heavy cannabis use on memory, executive function and psychomotor speed after 28 days of abstinence (Bolla et al., 2002).

Similarly confounded are studies using PET or functional MRI to measure brain activation during cognitive testing. Tasks involving attention, recent memory, working memory and motor performance have demonstrated abnormal patterns of activation in prefrontal cortex, hippocampus, basal ganglia or cerebellum after abstinence periods of 24–36 h (Chang et al., 2006). A study of inhibition (the Stroop task) found activation to be abnormally decreased or increased (perhaps reflecting impaired efficiency) in prefrontal and limbic areas after 25 days of abstinence (Eldrith et al., 2004). A study of decision making (the Iowa Gambling Task) found reduced prefrontal activation after 25 days of abstinence (Bolla et al., 2005). Some studies report normal cognitive task performance despite abnormal activation patterns (Jager et al., 2007).

Epidemiological studies offer evidence that cannabis use is a significant risk factor for schizophrenia. A review of such studies concluded that the risk exists independently of several confounders (LeBec et al., 2009). In untreated schizophrenic patients, levels of the endocannabinoid anandamide are increased in CSF (Leweke et al., 1999), and CB1 receptors are upregulated in the anterior cingulate cortex (Zavitsanou et al., 2004). It has been proposed that excessive endocannabinoids (or exogenous delta-9-tetrahydrocannabinol, the principal psychoactive compound in cannabis) disrupt limbic and prefrontal dopaminergic activity, eventually triggering schizophrenic symptoms in genetically or environmentally predisposed individuals (Fernandez-Espejo et al., 2009).

Attempts to identify the effects of in utero exposure to cannabis have had to account for the effects of inadequate prenatal care and exposure to other drugs, including tobacco and ethanol. Several studies have described impaired executive function persisting into late adolescence (Smith et al., 2006). Endocannabinoids play an important role in foetal brain development, with a different distribution of CB1 receptors compared with the adult brain (Harkeny et al., 2007).

Abnormalities on neuropsychological testing and functional MRI activation are consistent with imaging studies demonstrating morphological changes in cannabis users. Some reports have described reduced grey matter in limbic areas (Lorenzetti et al., 2010; Cousijn et al., 2012), and diffusion tensor imaging has identified reduced fractional anisotropy in white matter structures (Ashtari et al., 2009).

The observations by Zalesky et al. provide persuasive evidence of clinically relevant morphological brain abnormalities in cannabis users, especially in view of the absence of predetermined regions of interest, the location of abnormalities in regions that contain abundant cannabinoid receptors during brain development and the identification of the abnormalities in adolescent users, whose brains are continuing to develop. Compared with non-users, users had ‘lower Global Assessment of Functioning scores’ considered ‘typical of the general population of cannabis users’, but formal neuropsychological testing was not performed, and so it remains to be seen whether cognitive impairment parallels the neuropathology. The authors acknowledge that ‘the precise microstructural underpinnings’ of their observations are not well understood, and they do not discount the possibility that abstinence from cannabis might lead to recovery from axonal injury. They emphasize, however, that their findings reflect ‘structural/morphological… abnormalities not functional abnormalities’. Such lesions would be difficult to explain as residual acute effects or withdrawal or as anatomical variations predating cannabis use. Advanced
technology thus adds to ever accumulating evidence that cannabis use by children and adolescents damages the brain.

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