For the **National Haemoglobinopathy Registry** see http://www.nhr.nhs.uk

Whether the financial resources for future randomised trials of transfusion management of surgery in individuals with sickle-cell disease will be available is uncertain. Therefore, lower-quality evidence, such as that obtained by registries, might offer the best data with which to address unanswered questions. The UK National Haemoglobinopathy Registry has been set up to improve treatment services through the collection of data on the demographic characteristics, treatment, and disease complications of patients with haemoglobinopathies. Support by the National Heart, Lung and Blood Institute for a US registry with a biorepository (by consent) is being preceded by a surveillance pilot study (Registry and Surveillance System for Hemoglobinopathies [RuSH]). This effort responds to the National Heart, Lung and Blood Institute Strategic Plan, which aims to further understanding of the clinical mechanisms of diseases and thereby improve prevention, diagnosis, and treatment. Both of these national initiatives could provide important information about potential predictors of surgical outcomes, including genomic features that affect responses to sepsis,[8] prediction of renal failure,[9] and links to asthma, to help determine future transfusion practices.

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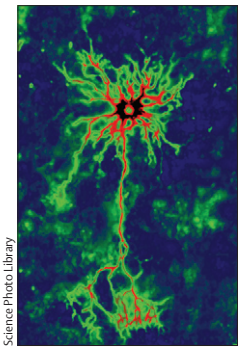
Teenage kicks: cannabis and the adolescent brain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In the past decade or so, research with MRI and functional MRI has revolutionised what we know about how the human brain develops. We now understand that the brain undergoes protracted development, continuing throughout adolescence and beyond.[1] Adolescence is defined as the period starting with the physical and hormonal changes associated with puberty and ending when an individual attains a stable, independent role in society.[2] Although the point marking the end of adolescence varies with culture, the end of the teenage years represents a working consensus in developed countries. One brain region that develops substantially during the teenage years is the prefrontal cortex, which is involved in executive functions, such as decision making, inhibitory control, and planning,[3,4] and in social understanding and self-awareness.[5]

A key finding from structural MRI studies is that the volume of grey matter, which contains brain cell bodies and synapses, changes between childhood and adulthood. In the prefrontal cortex, grey matter increases in volume during childhood, peaks in early adolescence, and then declines in adolescence and throughout the 20s.[1] The loss of grey matter during adolescence is thought to be due, at least partly, to synaptic pruning—the process by which excess synapses are eliminated. Supporting this notion, findings from studies of post-mortem human brain tissue have shown a decline in the number of synapses in the prefrontal cortex during adolescence.[6] Synaptic pruning is partly dependent on environmental input: synapses that are used are strengthened; synapses that are not used are pruned away.[7] In this way, synaptic pruning sculpts neuronal circuitry according to the environment during sensitive periods of brain development.

Although a great deal of evidence supports early periods of sensitivity to sensory information,[7] less is known about the existence of later sensitive

periods. Meier and colleagues' study[8] provides some evidence that adolescence might represent a period of brain development that is particularly sensitive to environmental input. The researchers investigated the association between self-reported persistent cannabis use and changes in cognitive ability in 1037 participants of the Dunedin longitudinal study, which has followed this cohort in Dunedin, New Zealand, from birth to their current age of 38 years. Cognitive ability was assessed from IQ and various neuropsychological measures, including working memory, processing speed, perceptual reasoning, and verbal comprehension. Cannabis use over the past year was reported at five timepoints between 18 and 38 years. A major strength of this study was that cognitive ability had already been tested at the age of 13 years, before first cannabis use, so the researchers had a baseline measure with which to compare the results of a second test in the same individuals 25 years later.

The findings showed, first, that persistent cannabis use is associated with a statistically significant decline in cognitive ability. That is, the more persistent the cannabis use, the greater the cognitive decline. Second, the association between persistent cannabis use and cognitive decline was significantly greater for people who began using cannabis before, compared with after, 18 years. Third, if cannabis use started in adolescence (before 18 years), the cognitive deficit remained significant when people had stopped using for at least 1 year before testing.

These findings provide prospective evidence from a large cohort that adolescent cannabis use is more damaging to cognitive abilities during adulthood than is adult use. The results remained significant after adjustment for other possible confounding factors, including alcohol and so-called hard-drug dependence (eg, heroin, cocaine, or amphetamines), years of education, and diagnosis of schizophrenia. But we still have to be cautious about interpreting the correlation between cannabis use and reduced cognitive ability as a direct causal relation. Perhaps a third factor—for example, decreased motivation or a psychiatric disorder developed in adolescence, such as anxiety or depression—leads people to smoke cannabis and perform poorly on IQ and neuropsychological tests.

Nevertheless, this study is important because it suggests that adolescence is a period of brain development that is sensitive to environmental factors. Cannabis seems to have long lasting negative consequences on a broad spectrum of cognitive abilities, perhaps because persistent cannabis use during adolescence affects how brain circuitry develops.[9] Could training and rehabilitation programmes reverse the decline in cognitive ability associated with cannabis use in people younger than 18 years? This is a question for future research. People can relearn sensory information that has been lost because of lack of sensory input in early sensitive periods of brain development, but only via fairly intensive training and under certain conditions.[10]

The implications of this study are far reaching. Other environmental influences—for example, alcohol, tobacco, and drug treatments—might also negatively affect the developing brain in the long term. Conversely, if the adolescent brain is particularly malleable, this might be a key time for positive effects of the environment, such as teaching, rehabilitation, and training. As highlighted in a recent Series in *The Lancet*,[11] global health and education policy should include a greater focus on adolescence, when the brain is still highly adaptable and can be shaped by the environment.

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