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Functional magnetic resonance brain imaging of executive cognitive performance in young first-episode schizophrenia patients and age-matched long-term cannabis users

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ABSTRACT

Converging evidence from epidemiological, clinical and neuropsychological research suggests a link between cannabis use and increased risk of psychosis. Long-term cannabis use has also been related to deficit-like ``negative'' symptoms and cognitive impairment that resemble some of the clinical and cognitive features of schizophrenia. The current functional brain imaging study investigated the impact of a history of heavy cannabis use on impaired executive function in first-episode schizophrenia patients. Whilst performing the Tower of London task in a magnetic resonance imaging scanner, event-related blood oxygenation level-dependent (BOLD) brain activation was compared between four age and gender-matched groups: 12 first-episode schizophrenia patients; 17 long-term cannabis users; seven cannabis using first-episode schizophrenia patients; and 17 healthy control subjects. BOLD activation was assessed as a function of increasing task difficulty within and between groups as well as the main effects of cannabis use and the diagnosis of schizophrenia. Cannabis users and non-drug using first-episode schizophrenia patients exhibited equivalently reduced dorsolateral prefrontal activation in response to task difficulty. A trend towards additional prefrontal and left superior parietal cortical activation deficits was observed in cannabis-using first-episode schizophrenia patients while a history of cannabis use accounted for increased activation in the visual cortex. Cannabis users and schizophrenia patients fail to adequately activate the dorsolateral prefrontal

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cortex, thus pointing to a common working memory impairment which is particularly evident in cannabis-using first-episode schizophrenia patients. A history of heavy cannabis use, on the other hand, accounted for increased primary visual processing, suggesting compensatory imagery processing of the task.

1. Introduction

Cannabis is the most commonly used illicit drug and it is generally perceived as being relatively safe. One-third of all Australians over the age of 14 years[1] and 40% of all Americans over the age of 12 years[2] have used it at least once. Recent evidence suggests that cannabis use is a risk factor for schizophrenia, produces cognitive dysfunction in healthy individuals, and exacerbates cognitive and positive symptoms in schizophrenia. Remarkably few brain imaging studies have examined the effects of frequent cannabis use on human brain function and to our knowledge, none have examined the effects in schizophrenia patients.

Acute effects of tetrahydrocannabinol (THC) on executive function are well documented.[3–6] Long-term frequent cannabis use may have specific detrimental effects on frontal lobe function. Deficits in the executive control of cognition and in the organisation and integration of complex information have been detected in recently abstinent cannabis users.[7–9] These findings are of concern as long-term users typically function in an unintoxicated but cognitively impaired state for substantial periods.[10] More controversial is the question as to whether long-term cannabis use can cause irreversible deficits in higher brain function that persist even after drug use stops. Two recent meta-analyses[11,12] concluded that after prolonged abstinence, cannabis related cognitive dysfunction may be almost entirely reversible. However, imaging investigations of brain function in abstinent users have found that regardless of abstinence status, long-term cannabis exposure produces abnormalities in degree and location of brain activation.[13–15] For example, cannabis use alters the neural networks active to a visual-attention task in recently abstinent and currently active users who performed equally well on neuropsychological testing and on the task.[15] In abstinent users, hypoactivity in the left anterior cingulate and lateral prefrontal cortex, and hyperactivity in the hippocampus bilaterally on the Stroop task have been reported,[13] whilst in 28 day abstainers, hyperactivity in the left cerebellum and hypoactivity in the right lateral orbitofrontal and dorsolateral prefrontal cortex were detected on a decision-making task (Iowa Gambling Task).[14] It is unclear whether changes in brain activity detected in neuroimaging studies relate to subtle residual effects where brain activity has adapted to limit impairment or whether the functional neuroimaging and neuropsychological testing evaluate different constructs altogether.[16]

There has been long-standing controversy as to whether heavy frequent cannabis use might precipitate a schizophrenia-like psychosis in people who had not previously shown psychotic symptoms. Four of five recent reviews[17–21] have concluded that adolescent cannabis use is a contributory cause of psychosis. The pooled odds ratio was 2.1 (95% CI: 1.7–2.5), which cannot be explained by confounding factors or reverse causality.[21] A gene–environment interaction, where a functional polymorphism in the catechol-O-methyltransferase (COMT) gene interacts with adolescent-onset cannabis use to predict the emergence of adult psychosis, may help to explain this association.[22] In established schizophrenia, cannabis use may exacerbate psychotic and cognitive symptoms, contribute to poor outcome and increase the likelihood of relapse.[23–25] There is a substantial literature linking impairments in executive control and abnormal activation in several regions of the prefrontal cortex in schizophrenia[26–30] and to dopamine modulation of executive function.[31] Therefore, cannabis may serve to augment pre-existing frontal lobe deficits in schizophrenia. However, to our knowledge, the potential effects of cannabis use in adding to and/or unmasking impaired executive functioning in first-episode schizophrenia have not been systematically investigated using functional brain imaging techniques.

The Tower of London task (TOL) task, an adaptation of the Tower of Hanoi, activates planning related brain regions by requiring subjects to calculate the number of moves necessary to shift a given configuration of coloured balls on pegs presented on a display screen to a goal configuration. TOL performance predominantly engages the prefrontal cortex.[32–34] Previous studies have demonstrated poor TOL performance in patients with frontal brain lesions,[35–38] frontal lobe dementia,[39] and schizophrenia.[38,40–42] Dagher and colleagues[43] used this task in the Single Photon Emission Tomography (SPECT) environment to measure regional cerebral blood flow (rCBF) dependent activation to task complexity in healthy subjects, which was defined as the number of moves required to solve a TOL problem. They found that rCBF in the dorsolateral prefrontal cortex (dlPFC), lateral pre-motor cortex, rostral anterior cingulate cortex and dorsal caudate nucleus increased with task complexity. These findings have been confirmed by our group and others measuring the variation in blood oxygenation level dependent (BOLD) response as a function of task difficulty in the functional magnetic resonance imaging (fMRI) environment.[42,44,45] Dorsolateral prefrontal cortex task-difficulty dependent activation was confirmed when employing a regression model with number of moves required to solve a problem as the independent variable and BOLD signal changes as the dependent variable.[42,44,45] Additional activation related to task demands was reported for the parietal lobes (i.e., precunei and parietal lobules) while superior and middle temporal lobe BOLD contrasts inversely correlated with task demands. Rasser and colleagues[42] found reduced prefrontal cortical activation in first episode schizophrenia despite no significant differences from control subjects in behavioural performance.