

Functional and Structural Brain Imaging

Correlates of Cannabis Use in Young People

with Schizophrenia

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(Medicine)

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## **STATEMENT OF ORIGINALITY**

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## **STATEMENT OF COLLABORATION**

I hereby certify that the work embodied in this thesis has been done in collaboration with other researchers, or carried out in other institutions. I have included as part of the thesis a statement clearly outlining the extent of collaboration, with whom and under what auspices.

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Martin Cohen

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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 brain imaging study investigated the impact of a history of heavy cannabis use on impaired executive function and cerebellar brain structure in first-episode schizophrenia patients. Functional brain imaging data were collected whilst study participants were 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; 7 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 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.

Cerebellar dysfunction has been proposed to lead to “cognitive dysmetria” in schizophrenia via the cortico-cerebellar-thalamic-cortical circuit, contributing to a range of cognitive and clinical symptoms of the disorder, including executive function deficits. In a subsequent study, cerebellar grey and white matter volumes and cerebellar regional grey matter abnormalities was measured in 13 remitted first-episode schizophrenia patients with less than two years’ duration of illness. Patient data were compared to 13 pair-wise age, gender, and handedness-matched healthy volunteers using cortical pattern averaging on high-resolution magnetic resonance images. Total cerebellar volume and total grey matter volumes in first-episode schizophrenia patients did not differ from healthy control subjects, but total cerebellar white matter was increased and total grey to white matter ratios were reduced in patients. Four clusters of cerebellar grey matter reduction were identified: (i) in superior vermis; (ii) in the left lobuli VI; (iii) in right-inferior lobule IX, extending into left lobule IX; (iv) bilaterally in the areas of lobuli III, peduncle and left flocculus. Grey matter deficits were particularly prominent in right lobuli III and IX, left flocculus and bilateral pedunculi. These cerebellar areas have been implicated in attention control, emotional regulation, social functioning, initiation of smooth pursuit eye movements, eye-blink conditioning, language processing, verbal memory, executive function and the processing of spatial and emotional information. Consistent with common clinical, cognitive, and pathophysiological signs of established illness, the findings demonstrate cerebellar pathology as early as in first episode schizophrenia.

The contribution of cannabis use to schizophrenia neuropathology remains controversial. The cerebellum possesses a high density of cannabinoid type 1 receptors involved in the neuronal diversification of the developing brain. Cannabis abuse may interfere with this process during adolescent brain maturation leading to “schizophrenia-like” cerebellar pathology. Hence, magnetic resonance imaging



and cortical pattern matching techniques were used to investigate cerebellar grey and white matter in first-episode schizophrenia patients with and without a history of cannabis use and non-psychiatric cannabis users. In the latter group a lifetime dose dependent regional reduction of grey matter in the right cerebellar lobules was found and a tendency for more profound grey matter reduction in lobule III with younger age at onset of cannabis use. The overall regional grey matter differences in cannabis users were within the normal variability of grey matter distribution. By contrast, the previous study did demonstrate that first-episode schizophrenia subjects had lower total cerebellar grey to white matter ratios and marked grey matter loss in the vermis, pedunculi, flocculi and lobules when compared to pair-wise matched healthy control subjects. This pattern and degree of grey matter loss did not differ from age-matched first-episode schizophrenia subjects with co-morbid cannabis use. The findings indicate small dose-dependent effects of juvenile cannabis use on cerebellar neuropathology but no evidence of an additional effect of cannabis use on cerebellar grey matter pathology in first-episode schizophrenia.

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