Functional and Structural Brain Imaging

Correlates of Cannabis Use in Young People

with Schizophrenia

A thesis submitted to the

University of Newcastle, NSW, Australia

for the degree of

Doctor of Philosophy

(Medicine)

Martin Cohen

M.B.B.S.; F.R.A.N.Z.C.P.

July 2014

STATEMENT OF ORIGINALITY

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

Martin Cohen

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.

Martin Cohen

ACKNOWLEDGEMENT

There can be no doubt that the nurturing of junior colleagues is pivotal in the career directions and professional choices that we make. I am fortunate to have had two very wonderful supervisors and mentors who have encouraged, cajoled and educated me over many years. Professor Vaughan Carr took me under his wing and gave me opportunities to explore the wonderful research world, rich with collaborations and exchanges of ideas and techniques whilst I was an advanced trainee and junior consultant. Professor Ulrich Schall welcomed me into his labs and introduced me to the world of neuroimaging and was always exceptionally generous with his time, his expertise and his patience. His nurturing and development of young researchers is astounding as is his sharp mind and enormous capability for tolerating wayward ideas and helping them become refined and testable. I have no doubt that this thesis is completed only because of your support and generosity- Danke.

Prof. Schall introduced me to Professor Philip Ward, who had been mentored by a wonderful person and exceptional researcher, Professor Patricia Mitchie. This obviously rubbed off on Prof. Ward, as he is genuinely one of the kindest people and outstanding researchers that I have met, thank you Phil for being so inclusive of me from the time I met you, as a very junior researcher. Dr Patrick Johnson thank you for sharing your image processing knowledge with me and for just being so very much fun to be around. Pat, doing this work was never the same after you left and thanks for introducing me to Paul Rasser. Paul has a remarkable maths brain and astounding capacity to develop new techniques and solve complex issues and run databases and be so very patient, which is a rare and wonderful coalition of capabilities to work with. Thank you Paul for the time you have taken with me and in being so perpetually helpful, this work is a product of your collaboration and

capabilities. Professor Nadia Solowij, who when I met her was already an international expert in cannabis research. Nadia, thank you for your collaboration in the review article, I greatly valued your opinions and astounding knowledge in the area. Professor Paul Thompson, who is a giant of imaging research, thank you for your generosity and support in assisting us to deploy the techniques you have developed.

Dr Ross Fulham thank you for bringing your exceptional analysis expertise to the study, your advice on image processing and cleaning up data and analysis technique was invaluable. Tim Ehlkes and Dr Greg Peck, thank you for your contribution to this work, you are great guys to work with and your contribution cannot be underestimated. I would also like to express my gratitude to Dr Renate Thienel and all of the researchers who gave of their time to be a part of these studies. Thank you also to all of the great people I have met along the way at international conferences and at the University of Newcastle and of the Centre for Brain and Mental Health Studies. I have been fortunate to have met so many talented and generous people in this journey.

To my wonderful wife Kate, who has supported me through attaining my specialist qualifications and now this further journey, thank you. Without your patience encouragement and interest, this thesis would never have been completed. Finally, to my two special boys Max and Charlie, thanks for being so very delightful and making everyday so much more enjoyable.

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.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES