Marijuana and Madness
Second Edition
Marijuana and Madness

Second Edition

Edited by

David Castle
St Vincent's Hospital and The University of Melbourne, Victoria, Australia

Sir Robin M. Murray
Institute of Psychiatry and South London and Maudsley NHS Foundation Trust, London, UK

Deepak Cyril D'Souza
VA-CMHC, Schizophrenia Research Clinic, Yale University, New Haven, Connecticut, USA
Contents

List of contributors vii
Preface xi

1 How cannabis works in the brain 1
Leslie Iversen

2 Other cannabinoids 17
Raphael Mechoulam and Lumir Hanus

3 The function of the endocannabinoid system 23
Maria Grazia Cascio and Roger Pertwee

4 Is cannabis becoming more potent? 35
Desmond Slade, Zlatko Mehmedic, Suman Chandra and Mahmoud ElSohly

5 What are the policy implications of the evidence on cannabis and psychosis? 55
Wayne Hall and Louisa Degenhardt

6 Cannabis, endocannabinoids and neurodevelopment 66
Ismail Galve-Roperh

7 The impact of pubertal exposure to cannabis on the brain: a focus on animal studies 82
Miriam Schneider

8 Cannabis and cognition: short- and long-term effects 91
Nadia Solowij and Nicole Pesa

9 Does cannabis cause lasting brain damage? 103
Nadia Solowij, Murat Yücel, Valentina Lorenzetti and Dan Lubman

10 The association between cannabis use and depression: a review of the evidence 114
Louisa Degenhardt, Wayne Hall, Michael Lynskey, Carolyn Coffey and George Patton

11 Cannabis, cannabinoids and bipolar disorder 129
Carol Silberberg, David Castle and Dagmar Koethe

12 Which cannabis users develop psychosis? 137
Marta Di Forti, Cécile Henquet, Hélène Verdoux, Sir Robin M. Murray and Jim van Os

13 Cannabinoids and the cerebellum: a potential role in the development of psychosis 144
Patrick D. Skosnik

14 The neural basis for the acute effects of cannabis on learning and psychosis 160
Sagnik Bhattacharyya and Philip McGuire

15 Does cannabis use cause schizophrenia? The epidemiological evidence 169
Stanley Zammit, Louise Arseneault, Mary Cannon and Sir Robin M. Murray

16 Postmortem studies of the brain cannabinoid system in schizophrenia 184
Suresh Sundram, Brian Dean and David Copolov

17 The endocannabinoid system in schizophrenia 193
Paul Morrison
## Contents

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>The acute effects of cannabinoids in patients with psychotic illness</td>
<td>Cécile Henquet, Andrew Sewell, Rebecca Kuepper, Mohini Ranganathan and Deepak Cyril D'Souza</td>
</tr>
<tr>
<td>19</td>
<td>Cannabis abuse and the course of schizophrenia</td>
<td>Don Linszen and Thérèse van Amelsvoort</td>
</tr>
<tr>
<td>20</td>
<td>Understanding cannabis use in schizophrenia</td>
<td>Leanne Hides, David J. Kavanagh and Kim T. Mueser</td>
</tr>
<tr>
<td>21</td>
<td>Addressing cannabis use in people with psychosis</td>
<td>Wynne James and David Castle</td>
</tr>
</tbody>
</table>

Index 234

*Color plates appear between pages 132 and 133*
Contributors

Louise Arseneault,
MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King’s College, London, UK

Sagnik Bhattacharyya,
Department of Psychosis Studies, Institute of Psychiatry, King’s College, London, UK

Mary Cannon,
Department of Psychiatry, Royal College of Surgeons in Ireland and Beaumont Hospital, Dublin, Ireland

Maria Grazia Cascio,
School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen, Scotland, UK

David Castle,
St Vincent’s Hospital and The University of Melbourne, Victoria, Australia

Suman Chandra,
National Center for Natural Products Research (NCNPR), School of Pharmacy, University of Mississippi, University, MS, USA

Carolyn Coffey,
Centre for Adolescent Health, Murdoch Children’s Research Institute, Parkville, Victoria, Australia

David Copolov,
Professor Monash University, Clayton, Victoria, Australia

Brian Dean,
Mental Health Research Institute, Parkville, Victoria, Australia

Louisa Degenhardt,
National Drug and Alcohol Research Centre, University of New South Wales, Australia

Marta Di Forti,
Institute of Psychiatry, King’s College, London, UK

Mahmoud ElSohly,
National Center for Natural Products Research (NCNPR), School of Pharmacy, University of Mississippi, Mississippi, USA

Ismael Galve-Roperh,
Department of Biochemistry and Molecular Biology I, School of Biology and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Complutense University, Madrid, Spain

Wayne Hall,
School of Population Health, University of Queensland, Herston, Queensland, Australia

Lumir Hanus,
Institute of Drug Research, Department of Pharmacology, Faculty of Medicine, Hebrew University of Jerusalem, Israel

Cécile Henquet,
Department of Psychiatry and Psychology, EURON, Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, Maastricht, and Mondriaan Zorggroep, Division Addiction Care, South Limburg, The Netherlands

Leanne Hides,
Institute of Health and Behavioral Innovation (IHBIU), School of Psychology and Counselling, Queensland University of Technology (QUT), Brisbane, Queensland, Australia

Leslie Iversen,
Department of Pharmacology, University of Oxford, Oxford, UK
## List of contributors

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wynne James</td>
<td>Mental Health Commission, Perth, Australia</td>
</tr>
<tr>
<td>David J. Kavanagh</td>
<td>Institute of Health and Behavioral Innovation (IHBI), School of Psychology and Counselling, Queensland University of Technology (QUT), Brisbane, Queensland, Australia</td>
</tr>
<tr>
<td>Dagmar Koethe</td>
<td>Department of Psychiatry and Psychotherapy, University of Cologne, Germany</td>
</tr>
<tr>
<td>Rebecca Kuepper</td>
<td>EURON, Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, Maastricht, and Mondriaan Zorggroep, Division Addiction Care, South Limburg, The Netherlands</td>
</tr>
<tr>
<td>Don Linszen</td>
<td>Academic Medical Center, University of Amsterdam, The Netherlands</td>
</tr>
<tr>
<td>Valentina Lorenzetti</td>
<td>Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Melbourne, and Orygen Youth Health Research Centre, Centre for Youth Mental Health, University of Melbourne, Parkville, Victoria, Australia</td>
</tr>
<tr>
<td>Dan Lubman</td>
<td>Turning Point Alcohol and Drug Centre, Eastern Health and Monash University, Melbourne, Australia</td>
</tr>
<tr>
<td>Michael Lynskey</td>
<td>Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri, USA</td>
</tr>
<tr>
<td>Philip McGuire</td>
<td>Department of Psychosis Studies, King's College London, Institute of Psychiatry, London, UK</td>
</tr>
<tr>
<td>Raphael Mechoulam</td>
<td>Institute of Drug Research, Department of Pharmacology, Faculty of Medicine, Hebrew University of Jerusalem, Israel</td>
</tr>
<tr>
<td>Zlatko Mehmedic</td>
<td>National Center for Natural Products Research (NCNPR), School of Pharmacy, University of Mississippi, University, Mississippi, USA</td>
</tr>
<tr>
<td>Paul Morrison</td>
<td>Division of Psychological Medicine, Institute of Psychiatry, London, UK</td>
</tr>
<tr>
<td>Kim T. Mueser</td>
<td>Dartmouth Psychiatric Research Center, Concord, New Hampshire, USA</td>
</tr>
<tr>
<td>Sir Robin M. Murray</td>
<td>Institute of Psychiatry and South London and Maudsley NHS Foundation Trust, London, UK</td>
</tr>
<tr>
<td>George Patton</td>
<td>Centre for Adolescent Health, Murdoch Children's Research Institute, Parkville, Victoria, Australia</td>
</tr>
<tr>
<td>Roger Pertwee</td>
<td>School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen, Scotland, UK</td>
</tr>
<tr>
<td>Nicole Pesa</td>
<td>School of Psychology, University of Wollongong, Wollongong, New South Wales, Australia</td>
</tr>
<tr>
<td>Mohini Ranganathan</td>
<td>Psychiatry Service, VA Connecticut Healthcare System, West Haven and Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA</td>
</tr>
<tr>
<td>Miriam Schneider</td>
<td>Central Institute of Mental Health, Mannheim, Germany</td>
</tr>
<tr>
<td>Dan Lubman</td>
<td>Turning Point Alcohol and Drug Centre, Eastern Health and Monash University, Melbourne, Australia</td>
</tr>
<tr>
<td>Andrew Sewell</td>
<td>Psychiatry Service, VA Connecticut Healthcare System, West Haven, CT, USA and Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA</td>
</tr>
<tr>
<td>Carol Silberberg</td>
<td>St. Vincent's Hospital and the University of Melbourne, Victoria, Australia</td>
</tr>
<tr>
<td>Patrick D. Skosnik</td>
<td>Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA</td>
</tr>
</tbody>
</table>
Desmond Slade,
MRI Global, 425 Volker Boulevard, Kansas City, Missouri, USA

Nadia Solowij,
School of Psychology, University of Wollongong, Wollongong and Schizophrenia Research Institute, Sydney, Australia

Deepak Cyril D’Souza,
VA-CMHC Schizophrenia Research Clinic, Yale University, New Haven, USA

Suresh Sundram,
Mental Health Research Institute, Parkville, Victoria, Australia Thérèse van Amelsvoort, Academic Medical Center, University of Amsterdam, The Netherlands

Thérèse van Amelsvoort,
Academic Medical Center, University of Amsterdam, The Netherlands

Jim van Os,
Maastricht Medical Centre, Maastricht, The Netherlands

Hélène Verdoux,
Department of Psychiatry, University Victor Segalen, Bordeaux, France

Murat Yücel,
Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Melbourne, and Orygen Youth Health Research Centre, Centre for Youth Mental Health, University of Melbourne, Victoria, Australia

Stanley Zammit,
Department of Psychological Medicine, Cardiff University and Academic Unit of Psychiatry, University of Bristol, Bristol, UK
Preface

Since the first edition of *Marijuana and Madness* in 2004, interest in the topic has continued to grow. For example, in the seven years since the first edition in 2004, almost as many papers have been published on this topic (400) as in the time period between 1962 and 2004 (462). This interest has been driven by a number of factors, including advances in our understanding of the brain cannabinoid system, and recognition that cannabinoids other than Δ⁹-tetrahydrocannabinol (THC) may be important. The second edition of this book provides an opportunity to update the core chapters and to add several entirely new chapters that focus on these advances.

The book begins with an overview by Iversen on how cannabis works in the brain, followed by reviews of cannabinoids other than THC (Mechoulam *et al.* and of the cannabinoid system (Cascio and Pertwee). ElSohly and colleagues consider the evidence as to whether cannabis is increasing in potency, an important issue that has often been obscured by the debate about the legal status of cannabis. Then Hall and Degenhardt discuss the implications of the negative effects of cannabis on mental health services, health education and public policy.

These chapters set the scene for a detailed discussion of the most pressing issues in the field of cannabis and psychiatric disorders.

If exposure to cannabis being associated with negative health consequences is to have biological plausibility, there needs to be a biological mechanism(s) to explain the association. Galve-Roperh reviews the evidence that the endocannabinoid system constitutes a novel extracellular signaling system involved in the regulation of nervous system formation, and the possible effects of perturbation of this system at crucial periods of brain development. Schneider presents the animal research showing that pubertal development, during which the endocannabinoid system appears to be very active, seems to represent the period most susceptible toward possible lasting negative cannabinoid effects. Solowij and Pesa review the evidence suggesting long term effects of cannabis on brain structure and neuropsychological function in humans. Skosnik proposes the cerebellum as a point of convergence through which alterations in the cannabinoid system may mediate processes involved in the generation of psychosis.

One of the vexing clinical conundrums is the discrepancy between the “benefits” of cannabis reported by users, and the negative consequences on the course and expression of schizophrenia observed by clinicians. Henquet *et al.* review the acute effects of cannabis and cannabinoids in people with psychotic illness, whereas Di Forti *et al.* explore genetic factors that may moderate the psychomometric effects of cannabis and Bhattacharyya and McGuire address the effects of cannabis on learning and psychosis. Turning to other psychiatric disorders, Silberberg *et al.* review the literature on cannabis and bipolar disorder, and Degenhardt *et al.* do likewise for depression.

The rest of the book concentrates on the impact of cannabis on schizophrenia, with a review of the evidence as to whether cannabis might be a causal factor in schizophrenia (Zammit *et al.*), studies of the cannabinoid system in schizophrenia (Sundram *et al.*, and Morrison), and of the impact of cannabis on the course of schizophrenia (Linszen *et al.*). The concluding chapters address the motives that maintain cannabis use among people with schizophrenia (Hides *et al.*) and treatment interventions for cannabis use in schizophrenia (James and Castle).

As editors, we are excited at the richness of the material provided to us by the contributors, all leaders in their field. We hope that readers will be likewise impressed at the progress that has been made in our understanding of the relationship between marijuana and madness.