Institution: King's College London

Unit of Assessment: UoA4 – Psychology, Psychiatry & Neuroscience

Title of case study: 12: Increasing public awareness of Cannabis use and psychosis

1. Summary of the impact

Research at King's College London (KCL) showed that use of cannabis, especially high potency types such as 'Skunk', increases the risk of psychosis. The work has demonstrated that adolescents who start early and carry some genetic vulnerability are at highest risk and that experimental cannabis administration alters brain function and induces transient psychosis. KCL research has led to increased public awareness of the adverse effects of cannabis use on mental health, in the UK and abroad, and sparked a public debate in the UK on the legal status of the drug ending with the Government reclassifying cannabis from Category C to Category B. KCL research on brain function has facilitated a collaboration with industry to develop new psychiatric medication.

2. Underpinning research

Until recently, the relevance of cannabis use to the aetiology of psychotic disorders was uncertain and controversial. Research at Institute of Psychiatry, King's College London (KCL) has been carried out to elucidate this relationship by Prof Sir Robin Murray (1998-present, Professor of Psychiatric Research), Prof Avshalom Caspi (1997-present, Chair in Social/Personality Psychology), Prof Terrie Moffitt (1997-present, Professor of Social Behaviour and Development), Prof Philip McGuire (1992-present, Professor of Psychiatry and Cognitive Neuroscience), Dr Louise Arseneault (1998-present, Reader in Developmental Psychology), Dr Marta Di Forti (2003-present, Clinical Research Worker), Dr Paul Morrison (2006-present, Clinical Senior Lecturer) and Dr Sagnik Bhattacharyya (2006-present, Clinical Senior Lecturer).

KCL researchers find links between early cannabis use, genetic factors and psychosis risk: While a number of cross-sectional studies had demonstrated that patients with schizophrenia were more likely to smoke cannabis than the general population, it was believed that this was a form of self-medication. However, in 2002 KCL researchers carried out a unique prospective study in a large cohort of 759 New Zealand children followed into adulthood (age 26) and demonstrated that teenage cannabis use (of at least three times by age 15 or 18) increased the incidence of later psychosis. Starting cannabis earlier than 15 years had the greatest impact on psychosis risk and introduced the idea that the brain may be most vulnerable while it is still maturing (1).

KCL researchers used genetic information from this New Zealand cohort to show that carriers of a variation of the gene COMT were more likely to exhibit psychotic symptoms and develop schizophreniform disorder if they used cannabis (2). This had a major scientific impact as it was the first report of a gene-environment interaction in the aetiology of psychosis, something that is fundamental to contemporary models of the disorder. A subsequent report, using data from 489 first-episode psychosis patients and 278 control participants, found a variation of the gene AKT1 conferred more than a twofold increase in the chance of a psychotic disorder (OR 2.18) in people with any history of cannabis use, while for people who were using cannabis daily there was a sevenfold increase in the chance of psychosis (OR 7.23) (3). Both these genes are involved in brain dopamine function, which is known to be abnormal in psychosis.

Elucidation of cannabis-related factors that may contribute to psychosis risk: Cannabis has two main constituents: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). KCL research with healthy adults has demonstrated that while THC is pro-psychotic and anxiolytic (4), CBD can reduce anxiety and has no effect on psychotic symptoms or cognition (5). The latter study also found that pre-treatment with CBD diminishes the psychotic symptoms induced by THC. Over the past 20 years, a higher potency variety of cannabis, Skunk, has appeared in the UK. Home Office figures show that Skunk contains around 16.2% THC and almost zero CBD, compared to cannabis resin, which contains 5.9% THC and 3.9% CBD. It was therefore postulated that it was the high THC/CBD-devoid Skunk that carried a greater psychosis risk. As such, KCL researchers investigated 280 cases presenting with a first episode of psychosis to a south London hospital compared to 174 healthy controls. While there was no difference between cases and controls in whether they had ever taken cannabis, or age at first use, the group presenting with psychosis were far more likely to be current daily users (Odds ratio [OR] 6.4) and, compared to the controls who smoked cannabis, were almost seven times more likely to have used Skunk (OR 6.8) (6).

3. References to the research

1. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 2002;325(7374):1212-13. Doi: http://dx.doi.org/10.1136/bmj.325.7374.1212 (509 Scopus Citations)
2. Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene. Biol Psychiatry 2005;57(10):1117-27. Doi: 10.1016/j.biopsych.2005.01.026 (560 Scopus Citations)
3. Di Forti M, Iyegbe C, Sallis H, Kolliakou A, Falcone MA, Paparelli A, Sirianni M, La Cascia C, Stilo SA, Marques TR, Handley R, Mondelli V, Dazzan P, Pariante C, David AS, Morgan C, Powell J, Murray RM. Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. Biol Psychiatry 2012;72(10):811-6. Doi:10.1016/j.biopsych.2012.06.020 (8 Scopus Citations)
4. Morrison PD, Zois V, McKeown DA, Lee TD, Holt DW, Powell JF, Kapur S, Murray RM. The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. Psychol Med 2009;39(10):1607-16. Doi: 10.1017/S0033291709005522 (47 Scopus Citations)
5. Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, Nosarti C, O' Carroll CM, Seal M, Allen P, Mehta MA, Stone JM, Tunstall N, Giampietro V, Kapur S, Murray RM, Zuardi AW, Crippa JA, Atakan Z, McGuire PK. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 2010;35(3):764-74. Doi: 10.1038/npp.2009.184 (66 Scopus Citations)
6. Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, Handley R, Luzi S, Russo M, Paparelli A, Butt A, Stilo SA, Wiffen B, Powell J, Murray RM. High-potency cannabis and the risk of psychosis. Br J Psychiatry 2009;195(6):488-91. Doi: 10.1192/bjp.bp.109.064220 (80 Scopus Citations)

Grants

- Terrie Moffitt, Medical Research Council (2002-2007) £1.2million: Life-course persistent antisocial behaviour
- Murray, RM, Morrison, Pand Di Forti M, Psychiatry Research Trust (2003-6) £41,000: The effects of ∆-9-THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol) on cognitive and emotional function: a functional magnetic resonance imaging study
- Morrison P and Murray RM, Medical Research Council (2006-9) £230,244: Neurocognitive and genetic basis of the effects of cannabis
- Bhattacharyya, S and McGuire P, Guy's & St Thomas's Charitable Foundation (2008-12) £340,000: Estimating risks of schizophrenia across genetic and environmental factors
- Murray RM, Morgan C, Di Forti M, Fisher H, Dazzan P, Psychiatry Research Trust (2008-11) £325,000: The impact of early adverse experiences on the vulnerability for psychosis
- Van Os R, Selten JP, Arango C, Khan R, Morgan C, Murray RM Di Forti M, European Union (2009-14) £12m: EU-GEI: European network of national schizophrenia networks studying Gene-Environment Interactions

4. Details of the impact

KCL research on the role of cannabis use in the aetiology of psychotic disorders has led to public awareness of the connection between patterns of cannabis use and mental health and to the UK Government considering and incorporating the issues surrounding cannabis use into policy and information. KCL research has also had industry impact by helping to advance the development of new medicines that act on the brain endocanniboid system to ameliorate psychiatric symptoms.

Public awareness: KCL research has had a major impact on the public's perception of the risks of cannabis use on mental health and has helped in the understanding of why the drug can have adverse effects in some users but not others. These studies generated a high level of media interest and KCL experts have conveyed the importance of their findings in a number of interviews in high profile UK television programmes, e.g. BBC1 Horizon (1a), BBC3 How Drugs Work (1b)

and Should I Smoke Dope? (1c), BBC News on Cannabis and IQ (1d); radio programmes, e.g. The Life Scientific (1e) and newspaper articles, e.g. The Daily Mail (1f), The Independent (1g) and The Guardian (1h).

Dissemination of information: In addition to increasing public awareness of the potential effects of cannabis use on psychosis, KCL has also disseminated the effects of the increasing strength of cannabis being sold on the street and its specific detrimental effects. Although it cannot be certain that KCL research has had a direct effect on cannabis use, Home Office figures show that use has declined by about 15% in the last decade. In 2012 the Schizophrenia Commission, established by Rethink Mental Illness, published a report in which they recommended several changes "that need to be made to transform the lives of those with schizophrenia or psychosis," one of which was the need for "a stronger focus on prevention including clear warnings about the risks of cannabis." This utilised evidence provided by Di Forti et al, 2009 and a review paper (2a) that widely cites the KCL research discussed above (2b). Dissemination has also been through continued professional development (CPD) activities aimed at psychiatrists. For instance, a CPD podcast for the Royal College of Psychiatry features Prof Murray discussing his research (2c).

Changes in the law: In 2007-9, the UK Government re-considered the issue of the legal categorisation of cannabis, following its 2004 downgrading from Category B to Category C. One of the main reasons given by the Prime Minister during his announcement was that this was "because of concerns about stronger strains of the drug, particularly Skunk, and the potential mental health effects they can have." Evidence from KCL researchers to the Advisory Council on the Misuse of Drugs resulted in their 2005 and 2008 reports accepting the effect of cannabis on psychosis and emphasising that education concerning the risks of cannabis was important. The 2008 report utilises Arsenault et al. 2002 and Caspi A et al. 2005 and was compiled with the help of written evidence by Prof Murray and verbal evidence from Dr Paul Morrison. Although these reports did not recommend re-classification, in 2009 the evidence given by KCL researchers formed part of the 2009 government decision to alter the legal classification of cannabis from a Category C drug to Category B, which holds greater legal penalties for someone caught holding the drug (3a).

Government Information: Initially Government information on cannabis on their website 'Talk to Frank' contained no information on the adverse effects of cannabis on mental health. However, as a result of KCL research, in 2009 the Department of Health launched a major TV, radio and online campaign to demonstrate the role cannabis can play in the development of mental health problems. The 'Talk to Frank' television adverts, aimed at young people who might not be aware of possible dangers, illustrated how cannabis can contribute to paranoia and damage mental health. Launching the campaign, the then Home Office Minister Alan Campbell said: "We are extremely concerned about the use of stronger cannabis and the harm it can cause to mental health" (3b).

Recognition of KCL research beyond the UK: A number of countries have utilised KCL expertise with regard to the relationship between cannabis and psychosis; for instance, both public and government sources in Canada. The Controlled Substances and Tobacco Directorate for the government organisation Health Canada produced an information summary of the potential therapeutic uses and harmful effects of cannabis that utilised the majority of the KCL research papers discussed above (4a). Additionally, a set of 'Knowledge Notes' distributed by the Canadian group Alberta Addiction & Mental Health Research Partnership Program cites Arsenault et al. 2002 and Caspi A et al. 2005 when discussing current research on cannabis use and its association with psychosis (4b). Prof Murray provided a direct contribution to a 2010 documentary for the Canadian Broadcasting Corporation investigating the link between Skunk use and schizophrenia (4c).

Industry sponsored clinical trial: By studying the effects of cannabidiol (CBD) on healthy volunteers, KCL work has facilitated the development of new medicines that act on the brain's endocanniboid system that have the potential to ameliorate psychiatric symptoms. In partnership with GW Pharmaceuticals, the main manufacturer of medicines from the cannabis plant, KCL researchers have piloted the effectiveness of CBD as an antipsychotic medication, and have recently been appointed as Chief Investigator for a Phase II trial of CBD as an adjunctive antipsychotic in patients who have not responded to conventional treatment (5a). Similar trials are

being carried out by the University of Cologne (5a). GW Pharmaceuticals are also sponsoring a trial of the role of CBD and another cannabinoid (THCV) on preventing weight gain in patients taking antipsychotic medication (5b). Weight gain is a serious side effect of taking anti-psychotic medication and often leads to other conditions such as Type 2 Diabetes. The new drug has the potential to reduce these side effects which are implicated in the early mortality of people with a diagnosis of schizophrenia.

5. Sources to corroborate the impact

1) Public awareness

a. BBC1/2: Horizon – Cannabis: The Evil Weed?
- Interviews with KCL researchers Dr Cathy Fernandes from 31:15; Dr Zerrin Atakan from 38:35. Aired 3rd and 14th Feb, 2009: http://www.youtube.com/watch?v=Iv4n5MSRFY4

b. BBC3: How Drugs Work – Cannabis http://www.bbc.co.uk/programmes/b00x9ddq
- Interview with Prof Robin Murray from 35:28. Aired 6.Jan.2011: http://vimeo.com/18561901

c. BBC3: Should I Smoke Dope? http://www.bbc.co.uk/programmes/b009nyxf
- Interview with Prof Robin Murray from 40:49. Aired 26.Mar.2008: http://www.youtube.com/watch?v=4gGhOAc-aV4 (Over 120,000 hits on this website alone)

d. BBC News 28.8.2012: Young cannabis smokers run risk of lower IQ, report claims. http://www.bbc.co.uk/news/health-19372456 (includes interview with Prof Moffitt)

e. BBC Radio 4. The Life Scientific: Robin Murray. 7.Feb.2012: http://www.bbc.co.uk/programmes/b01bwmvt

f. The Daily Mail. Cannabis causes mental illness: http://www.dailymail.co.uk/health/article-205447/Cannabis-causes-mental-illness.html

g. The Independent. Is this the 'tobacco moment' for cannabis? 26.Nov.2012: http://www.independent.co.uk/life-style/health-and-families/health-news/is-this-the-tobacco-moment-for-cannabis-8349054.html

h. The Guardian: A clear danger from cannabis. Robin Murray. 29.Oct.2009: http://www.guardian.co.uk/commentisfree/2009/oct/29/cannabis-schizophrenia-classification

2) Dissemination of information

a. Casadio P, et al. Cannabis use in young people: the risk for schizophrenia. Neurosci Biobehav Rev 2011;35(8):1779-87. Doi: 10.1016/j.neubiorev.2011.04.007

b. Abandoned Illness. A report by the Schizophrenia Commission: http://www.rethink.org/media/514093/TSC_main_report_14_nov.pdf

c. Royal College of Psychiatry CPD podcast: the nature and history of psychosis – Cannabis: http://www.psychiatrycpd.co.uk/podcasts/crowandmurraythenaturean/crowandmurraypart3/crowandmurraycannabis.aspx

3) Government impacts

a. Advisory Council on the Misuse of Drugs: Cannabis Classification and Public Health. 2008: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/119174/acmd-cannabis-report-2008.pdf

b. Talk to Frank Website: http://www.talktofrank.com/drug/cannabis
- What long-term damage does cannabis cause?: http://www.talktofrank.com/faq/what-long-term-damage-does-cannabis-cause

4) Recognition of KCL research beyond the UK

a. Information for Health Care Professionals. Cannabis and the cannabinoids. Health Canada. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf

b. Alberta Addiction Partnership: http://www.mentalhealthresearch.ca/Publications/Documents/Knowledge%20Notes09-Cannabis%20use-Addington.pdf

c. CBC Canada: The Downside of High
- http://www.cbc.ca/documentaries/natureofthings/2010/downsideofhigh/index.html
- http://www.youtube.com/watch?v=MQyO3YmS4Gk

5) Industry sponsored clinical trial

a. Details of funding and clinical trial available on request.

b. University of Cologne: http://www.clinicaltrials.gov/ct2/show/NCT00628290?term=Cannabidiol&rank=10

c. GW Pharmaceuticals: http://www.gwpharm.com/Partnering.aspx