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No additive effect of cannabis on cognition in schizophrenia

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ABSTRACT

Background: We aimed to examine the association between lifetime cannabis use and estimates of both premorbid and current cognitive function in psychotic disorders in an Australian cohort.
Methods: In an Australian multicenter cohort, 1237 participants with an established ICD-10 diagnosis of psychotic disorder were categorised according to history of lifetime cannabis use (non-users, n = 354; cannabis users, n = 221; cannabis dependency, n = 662). Groups were analyzed according to available indices of cognitive ability: the National Adult Reading Test — Revised (NART-R) for ability prior to illness onset; and the Digit Symbol Coding Test (DSCT) for current ability. Two-way analysis of variance was conducted without any covariate, followed by a two-way analysis of covariance (using age, age at onset of psychiatric illness, premorbid IQ and the Socio-Economic Index for Areas (SEIFA) rankings).
Results: Whilst there appeared to be a significant association between cannabis use and mean DSCT (higher DSCT scores in cannabis using groups) $F(2,1080) = 9.478$, $p < 0.001$, $\eta 2 = 0.017$), once covariates were used in the analysis there were no significant differences between groups in mean DSCT scores ($F(2,1011) = 0.929$, $p = 0.395$, $\eta 2 = 0.002$). Similarly there were no differences between groups in mean NART scores once, age, age at illness onset and SEIFA rankings were used as covariates ($F(2,1032) = 1.617$, $p = 0.199$, $\eta 2 = 0.003$).
Conclusions: Confounding variables underpin the association between cannabis use and cognitive function in psychotic disorders. Taken together, it would appear that cannabis use or dependence has no additive effect on cognitive dysfunction in these disorders.

1. Introduction

Whilst the association between cannabis use and cognitive ability has received much attention in the literature, there appears to be a discrepancy between studies examining this association in healthy controls and studies examining the combined effects on cognition of schizophrenia and cannabis use. Indeed the findings in schizophrenia remain controversial and complex, and warrant further investigation.

1.1. Cannabis use in Australia

Globally, Australia has one of the highest rates of cannabis use (Teesson et al., 2012). Recent data suggests that cannabis is the most prevalent illicit substance used in Australia, with 34.3% of people aged 12 or older having used cannabis, with the average age at initiation of 18.5 years; whilst use declined from 1998 to 2007, recent use (reported as use in the previous 12 months) increased from 9.1% in 2007 to 10.3% in 2010 (Australian Institute of Health and Welfare, 2011). A recent study indicated a trend towards an increase in the concentration of Δ9-tetrahydrocannabinol (THC) and dominance of THC in contemporary cannabis in Australia, consistent with values reported in Europe and the United States (Swift et al., 2013). The use and cultivation of cannabis remains illegal in Australia.

1.2. Population studies investigating the association between cannabis use and cognition

Studies in healthy individuals suggest that persistent cannabis use beginning in adolescence is prospectively associated with global cognitive decline, with more severe and prolonged neuropsychological impairment in those who use cannabis earlier, more frequently and for prolonged periods (Bolla et al., 2002; Messinis et al., 2006; Solowij and Battista, 2008; Gruber et al., 2011; Solowij et al., 2011; Meier et al., 2012). Further, in a prospective study of 1307 individuals followed

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from birth to age 38, Meier et al. (2012) found that those who ceased or reduced heavy cannabis exposure over the study still showed cognitive decline. Some authors have hypothesized that exposing the vulnerable adolescent brain to cannabis leads to brain changes that underpin neuropsychological decline (Jager and Ramsey, 2008; Jager et al., 2010; Ashtari et al., 2011; Meier et al., 2012). Rogeberg (2013) however, argues that the causal interpretation of the findings of Meier et al., 2012 is based on the erroneous assumption that intelligence quotient (IQ) trajectories would be equal for their cannabis using cohort in the absence of cannabis use. Rogeberg suggests that perhaps the association between substance use and cognitive decline may be better explained by residual confounding of socio-economic status, based on the Flynn–Dickens model of a two-way causality between IQ and the environment (Dickens and Flynn, 2001; see Rogeberg, 2013).

An additional consideration is the potential for cannabis to affect male and female cognitive performance differently; as reviewed by Crane et al. (2013) a small body of literature suggests there are sex differences which appear to be domain specific (Pope et al., 1997; Clark et al., 2009; King et al., 2011; Solowij et al., 2011).

1.3. Studies investigating the combined effect on cognitive ability of schizophrenia and cannabis use

There is conflicting data regarding the association between cannabis use and performance on cognitive testing in participants with schizophrenia, with studies suggesting cannabis use is associated with either inferior performance (Pencer and Addington, 2003; D'Souza et al., 2011; Ringen et al., 2010), or with superior performance (Kumra et al., 2005; Stirling et al., 2005; Jockers-Scherübl et al., 2007); some studies report that there are no differences (Sevy et al., 2007; Scholes and Martin-Iverson, 2010). Methodological limitations in and differences between such studies have been explored by Coulston et al. (2007a) (see the Discussion section). Recent meta-analyses, however, report that patients with schizophrenia who have a history of cannabis use have superior cognitive functioning when compared with patients with schizophrenia without a history of cannabis use (Potvin et al., 2008; Rabin et al., 2011; Yücel et al., 2012). A number of hypotheses have been put forward in light of the findings. Some authors have supported a causality argument (i.e., that cannabis may have a neuroprotective effect, and lead to improved cognitive performance in some patients) (Coulston et al., 2007a,b; Rabin et al., 2011; Yücel et al., 2012) whilst other authors have favoured a reverse causality argument (i.e., that cannabis-using patients represented a sub group with superior cognitive ability, with superior social skills and hence are more able to access illicit substances) (Solowij and Michie, 2007; Potvin et al., 2008). It may also be prudent to consider that residual confounding (i.e., other variables that are also associated with cannabis use, such as age or premorbid socio-economic status) may better explain the association observed between cannabis use and cognition in participants with psychotic disorders, as argued by Rogeberg (2013) in healthy populations. Indeed the meta analyses by Rabin et al. (2011) and Yücel et al. (2012) included only a small number of studies, characterized by modest sample sizes and inconsistent methodologies limiting the consideration of potential confounding variables (see Table 1). It may be that any such observed association between cannabis use and cognition in schizophrenia in a large cohort may be lost when the identified confounding variables are controlled for in the statistical analyses.

1.4. Aims and hypotheses

Responding to conflicting findings regarding the premorbid effect of cannabis use on cognitive function in psychotic disorders, we sought to investigate whether an association existed between cannabis exposure (either cannabis use or dependence across the lifetime) and both premorbid and current cognitive function in participants with psychotic disorders, and further, to explore the impact of confounding variables. We hypothesized that confounding variables, such as age or socio-economic status, may underpin an observed association.

2. Experimental/materials and methods

2.1. Participants

Participants had been interviewed as part of the Survey of High Impact Psychosis (SHIP), a large two-phased multi-centre study involving recruitment from seven sites across Australia, previously described in detail (Morgan et al., 2012, 2014; Stefanis et al., 2013, 2014; Power et al., 2014). In phase 1, screening for psychosis covered people aged 18–64 who were in contact with public mental health services and those non-government organisations who were supporting people with mental illness. Of the 7955 who screened positive for psychosis, 1825 were randomly selected for further assessment in phase 2. All participants provided written informed consent prior to participation. In phase 2 a total of 1642 participants had an established ICD-10 diagnosis of a psychotic disorder (schizophrenia, schizoaffective, delusional and other non-organic psychotic disorder, bipolar disorder, depressive disorder with psychotic features). This study included in the analysis the 1242 participants with an ICD-10 diagnosis of schizophrenia (F20), schizoaffective disorder (F25) and delusional disorder (F22).

The geographical regions covered by the SHIP were the catchment areas of the following sites: (i) Hunter New England and (ii) Orange services in New South Wales; (iii) West Moreton in Queensland; (iv) Northern Mental health in South Australia; (v) North West Area Mental Health and (vi) St Vincent's Mental Health Service in Victoria; and (vii) Fremantle, Peel and Rockingham-Kwinana in Western Australia. Ethics approvals for the study were obtained from relevant institutional human research ethics committees.

2.2. Diagnostic algorithm and definition of cannabis use and dependence

Participants in phase 2 were assessed using the DIP (Diagnostic Interview for Psychosis; Castle et al., 2006). The DIP interview was administered by mental health professionals who had undergone extensive training prior to the data collection phase of the survey. The DIP is comprised of a number of modules (demography and social functioning, diagnostic, service utilization). The diagnostic module (DIP-DM) follows the structure of the Operational Criteria for Psychosis (OPCRIT) (McGuffin et al., 1991), a 90-item checklist which allows the examiner to rate symptoms in a number of domains (present state, past year, and lifetime). Diagnostic classification of cases was made using the OPCRIT diagnostic computer algorithm (McGuffin et al., 1991).

The DIP also includes items relating to cannabis use, including frequency of use and diagnosis of dependency (using DSM-IV criteria) throughout the lifetime of the participant. In this study, participants were categorized as either cannabis non-users (CN; if they reported never having used cannabis in their lifetime), cannabis users (CU; if they reported any frequency of cannabis use in their lifetime, ranging from 'daily use' to 'used less frequently than once per month', but never satisfied the criteria for cannabis dependence), and cannabis dependency (CD; if they satisfied the criteria for cannabis dependency at any point in their lifetime). We did not have data to indicate the length of time the participants were using cannabis, or at which time in their life they satisfied the criteria for cannabis dependence.

2.3. Cognitive assessment

Two cognitive assessments were administered at the time of DIP interview. The National Adult Reading Test — Revised (NART-R) can be used to estimate premorbid IQ and, given the stability of NART-estimated IQ over the course of schizophrenia (Morrison et al., 2000) it therefore provides a reliable estimate of cognitive ability prior to illness onset (Nelson and Willison, 1991). The Digit Symbol Coding

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