Drug and Alcohol Dependence 169 (2016) 134–140

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

A longitudinal examination of the relationship between cannabis use and cognitive function in mid-life adults

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ARTICLE INFO

Article history:
Received 29 July 2016
Received in revised form 12 October 2016
Accepted 17 October 2016
Available online 25 October 2016

Keywords:
Cannabis
Marijuana
Cognitive
Memory
Ageing
Substance abuse

ABSTRACT

Background: The relationship between cannabis use and cognitive function in mid-life has rarely been examined despite verbal learning deficits in young adults.
Method: A longitudinal cohort study of 1,897 Australians recruited at 40–46 years of age and followed up 4 years (94%) and 8 years (87%) later. Random effects regression was used to assess within- and between-person associations between cannabis use and cognitive function across waves of data, and examine whether age-related changes in cognitive performance were modified by cannabis use. The first list of the California Verbal Learning Test (immediate and delayed recall), Symbol Digit Modality Test, Digit Backwards, simple and choice reaction time tasks, were administered at each wave. The Spot-the-Word test was used to assess premorbid verbal ability. Self-reported cannabis use in the past year (no use, < weekly use, ≥ weekly use) was assessed at each wave.
Findings: Participants who used cannabis ≥ weekly had worse immediate recall ($b = -0.68$, $p = 0.014$) and showed a trend toward worse delayed recall ($b = -0.55$, $p = 0.062$) compared to non-users after adjusting for correlates of cannabis use and premorbid verbal ability. These effects were due to between-person differences. There were no significant within-person associations between cannabis use and recall, nor was there evidence of greater cognitive decline in cannabis users with age.
Conclusions: Mid-life cannabis users had poorer verbal recall than non-users, but this was not related to their current level of cannabis use, and cannabis use was not associated with accelerated cognitive decline.

1. Introduction

Understanding the impact of cannabis use on cognitive function in mid-life adults is increasingly important. Cannabis is already consumed by an estimated 178 million people worldwide (United Nations Office on Drugs and Crime, 2015) and 13.1 million people are dependent on the drug (Degenhardt et al., 2013). However, its use is projected to rise significantly in older cohorts (50+ years) with the ageing of the baby-boomer generation (Colliver et al., 2006; Wu and Blazer, 2011). The medicalisation of cannabis is also likely to see increased use in older adults to treat chronic pain (Martin-Sanchez et al., 2009) and as an antiemetic in cancer treatment (Borgelt et al., 2013). For example, Pacula et al. (2015) cite 18 US states where legislation has been established around the medicinal use of cannabis, this trend beginning in California in 1996 with the establishment of medical marijuana dispensaries.

Most research on the relationship between cannabis use and cognitive function comes from studies of young adults (Becker et al., 2010; Block and Ghoneim, 1993; Carlin and Trupin, 1977; Croft et al., 2001; Dafters et al., 2004; Dougherty et al., 2013; Ehrenreich et al., 1999; Fried et al., 2002; Gouzoulis-Mayfrank et al., 2000; Pope and Yurgelun-Todd, 1996; Rodgers, 2000; Solowij, 1995). A meta-analysis of this research found that cannabis use was associated with worse performance on verbal learning and memory (i.e., immediate and delayed recall on the Californian Verbal Learning Test and the Rey Auditory Verbal Learning Test), with effect sizes ranging between 0.21 and 0.27, but not on tasks involving attention, executive function, motor function, reaction time or language ability (Grant et al., 2003). However, more recent research suggests

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http://dx.doi.org/10.1016/j.drugalcdep.2016.10.022
0376-8716/

deficits may also be present in other domains, including attention and concentration and abstract reasoning (Crane et al., 2013). Longitudinal studies have also found deficits relative to premorbid ability (Fried et al., 2005; Meier et al., 2012), including greater cognitive decline into adulthood (Meier et al., 2012). Although some performance decrements recover with cessation of cannabis use (Fried et al., 2005; Tait et al., 2011) full recovery is not always observed (Meier et al., 2012).

Few studies have examined how these cognitive deficits manifest in later adulthood, where they may be exacerbated by cumulative exposure to cannabis, interact with natural age-related declines in processing speed (Anstey et al., 2014; Singh-Manoux et al., 2012), or arise from secondary adverse effects of cannabis on educational and vocational attainment (Horwood et al., 2010)—both of which are protective against age-related cognitive decline (Anstey et al., 2013). Both Solowij et al. (2002) and Pope et al. (2001) found verbal learning deficits in older cannabis users (aged 32–55 years), compared to a non-using control group; however, Pope et al. (2001) found deficits remitted following a 28 day washout period from cannabis use, suggesting that deficits may be restricted to periods of heavy use (Pope et al., 2001).

In this paper we use an alternative approach to previous research by examining within-person changes in cognitive function that co-occur with changes in cannabis use in a longitudinal cohort. Within-person effects estimate the average change in an outcome (i.e., cognitive test performance) during time periods when an individual is exposed to a particular risk factor (i.e., cannabis use) relative to when they are not exposed (i.e., not using cannabis). This approach provides superior control for time-invariant factors (e.g., heritable traits, personality, sex) than statistical adjustment, and also reduces confounding by unmeasured time-invariant confounds (Gunasekara et al., 2014). It has been used to strengthen evidence for a causal relationship between substance use and various health and social outcomes (Fergusson et al., 2002; Livingston, 2011; McKetin et al., 2013). Time-varying factors still need to be adjusted for because they can confound these types of analyses.

We assessed the relationship between current levels of cannabis use and cognitive functioning across three waves of data in a population-based longitudinal cohort of adults in their forties and examined whether deficits were related to current levels of cannabis use by testing within-person changes in cognitive performance during periods of cannabis use. We hypothesised (a) that heavy cannabis users would perform more poorly on tests of verbal recall; and (b) that this effect would be due to a significant within-person association between cannabis use and cognitive function, indicating worse cognitive function during periods of more frequent cannabis use relative to periods of no use. We also explored whether cannabis use modified age-related changes in cognitive performance, which could indicate early cognitive decline.

2. Material and methods

2.1. Participants and procedure

Participants were 2,530 people aged 40–46 years, who were recruited from the Personality and Total Health (PATH) through life cohort in 2000–2001. Participants were randomly drawn from the electoral roll of the Australian Capital Territory and Queanbeyan in Australia (Anstey et al., 2012). Voting is compulsory in Australia and therefore electoral roll samples provide a good reflection of the adult general population. The response rate was 64.6%. A comparison with the Australian census data show that the final cohort was representative of the general population in terms of their marital and employment status, but that they were more educated (Anstey et al., 2012). Participants were followed up every four years, with 2,354 (93%) re-interviewed at wave 2, and 2,182 at wave 3 (86%).

For this study, participants were excluded if they reported a history of head injury (n = 321), stroke or transient ischemic attack (n = 62) or epilepsy (n = 21). Similar to previous studies on cognitive function in this cohort (Tait et al., 2011), we excluded participants for whom English was a second language (n = 210), because this was related to poor performance on verbal recall. A further 18 participants were excluded because they reported illicit psychostimulant use at either wave 2 or 3 (this was not assessed at wave 1), and one participant was excluded because they were missing data on cannabis use at all three waves. This left 1,897 participants in the final sample, with 1,774 followed up at wave 2 (94%) and 1,653 followed up at wave 3 (87%). Data on cannabis use was missing at seven observation points, giving a total of 5,317 observations across all three waves.

All participants were volunteers who provided informed consent prior to participation. The study was approved by the Australian National University's Human Research Ethics Committee.

2.2. Measures

2.2.1. Cannabis use. Past year cannabis use was assessed using the question "Have you used marijuana/hash in the past 12 months?" followed by the question "How often do you use marijuana/hash?" (once a week or more, once a month, every 1–4 months, once or twice a year, less often/no longer use). Based on these questions, participants were classified as either not using cannabis within the past year (non-users), using cannabis less than weekly use, or using cannabis weekly or more often.

2.2.2. Cognitive tests. All cognitive tests were administered at each wave. Immediate and delayed recall was assessed with components of the California Verbal Learning Test (Delis et al., 1987). Participants were read a list of 16 words from 4 taxonomic categories (e.g., fruits, tools), presented in unblocked order, and asked to immediately recall as many words as possible (immediate recall). This list was read once only. Following a short interval (i.e., completing a grip strength task), participants were again asked to recall as many words as possible (delayed recall).Working memory was assessed using the Digits Backwards subtest of the Wechsler Memory Scale, which involves reading a series of digits to the participant who is then required to recall them in reverse order (Wechsler, 1945). The Symbol-Digit Modalities Test (Smith, 1982) requires participants to substitute digits (1–9) with a corresponding symbol as fast as possible within a 90-s period; it involves attention, visual scanning and motor speed (Sheridan et al., 2006) and is sensitive to changes in cognitive function following mild head injury (Hinton-Bayre et al., 1997). Simple and choice reaction time was measured by getting the participant to press one of two buttons on the top of a small box (held in both hands), with their index fingers, in reaction to a red stimulus light located on the front of the box under each button. A green get-ready light was centred beneath these. The mean simple reaction time was taken from four blocks of 20 trials and the mean choice reaction time from two blocks of twenty trials. For simple reaction time participants used their right hand regardless of dominance. Premorbid verbal ability was assessed using the Spot-the-Word Task (Baddeley et al., 1993). This test involves presenting the participant with 60 consecutive word pairs, each of which contains one real word and one word that is not real ('flonty—xylophone'). The participant is required to point to the real word in the pair. The Spot-the-Word test is a robust measure of verbal intelligence which is resilient to deterioration with age