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Psychotic experiences are linked to cannabis use in adolescents in the community because of common underlying environmental risk factors

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ABSTRACT

Cannabis users are more likely to have psychotic experiences (PEs). The degree to which these associations are driven by genetic or environmental influences in adolescence is unknown. This study estimated the genetic and environmental contributions to the relationship between cannabis use and PEs. Specific PEs were measured in a community-based twin sample (4830 16-year-old pairs) using self-reports and parent-reports. Adolescents reported on ever using cannabis. Multivariate liability threshold structural equation model-fitting was conducted. Cannabis use was significantly correlated with PEs. Modest heritability (37%), common environmental influences (55%) and unique environment (8%) were found for cannabis use. For PEs, modest heritability (27–54%), unique environmental influences (E=12–50%) and little common environmental influences (11–20%), with the exception of parent-rated Negative Symptoms (42%), were reported. Environmental influences explained all of the covariation between cannabis use and paranoia, cognitive disorganization and parent-rated negative symptoms (bivariate common environment=69–100%, bivariate unique environment=28–31%), whilst the relationship between cannabis use and hallucinations indicated familial influences. Cannabis use explains 2–5% of variance in positive, cognitive, and negative PEs. Cannabis use and psychotic experience co-occur due to environmental factors. Focus on specific environments may reveal why adolescent cannabis use and psychotic experiences tend to 'travel together'.

1. Introduction

Psychotic experiences (PEs) are common within the general population (Poulton et al., 2000; Olfson et al., 2002; Polanczyk et al., 2010) and are associated with many negative consequences, including increased risk of suicide (Kelleher et al., 2012). They been found to precede the onset of psychosis amongst some individuals (Kelleher and Cannon, 2011), thus making them an early risk factor for clinical disorder. Examining correlates associated with psychosis may assist in gaining a greater insight into the etiology of PEs. An example of such a correlate is cannabis use.

The relationship between cannabis use and psychotic disorders has been demonstrated amongst adult sub-clinical and clinical populations, with estimates of an approximate 2-fold increased risk of developing psychotic disorder in individuals who regularly use cannabis from an early age, over and above pre-existing vulnerabilities to psychosis (i.e. earlier psychotic symptoms and environmental risk factors such as trauma) (Henquet et al., 2005a, 2005b). Studies amongst adolescent sub-clinical populations have also linked cannabis use with increasing risks for PEs (Fergusson et al., 2003; Henquet et al., 2005a, 2005b; Hides et al., 2009; Van Gastel et al., 2012) (r=0.12–0.23) (Griffith-Lendering et al., 2013). Increased levels of both positive and negative dimensions of PEs have been observed amongst individuals who reported using cannabis in early adolescence (i.e. under 15-years) (Stefanis et al., 2004). This association has been extended to show a dose response effect whereby the risk of PEs was found to increase with the frequency of cannabis use over time (Henquet et al., 2005a, 2005b). Longitudinal investigations into the direction of effect between cannabis use and PEs suggest that cannabis use increases

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individuals' vulnerability for psychotic symptoms (Henquet et al., 2005a, 2005b). This 'vulnerability' directional hypothesis has been reinforced by research in neurophysiology, which has shown that cannabis use can affect brain chemistry. It is proposed that cannabinoids, such as tetrahydrocannabinol (THC) found in cannabis, release the neurotransmitter dopamine (Iversen, 2003), which in turn has been implicated in the neuropharmacology of psychosis (Bowers and Kantrowitz, 2007), thus outlining (albeit briefly here) a biological pathway from cannabis use to psychosis. Furthermore, exposure to THC has also been associated with engaging the endocannabinoid system, which modulates the inhibitory and excitatory synapses in the brain, regulates emotion and motivation and is involved in the formation of habit and implicit learning (Van Winkel and Kuepper, 2014). As disruption of the endocannabinoid system has been associated with symptoms of psychosis (Leweke and Koethe, 2008), it is possible that the endocannabinoid system may be an underlying biological mechanisms contributing to the association between cannabis use and PEs. Furthermore as adolescence has been noted as a sensitive period of time for the development of the endocannabinoid system (Rubino et al., 2012), atypical activity in this system of the brain may hold particular salience for the emergence of psychotic experiences in adolescences. In addition, neuroimaging data suggests that the induction of PEs by THC is mediated by its effects on the prefrontal and the medial cortex (Bhattacharyya et al., 2009, 2012). Using data collected from adolescents within the general population, we tested the hypothesis that ever using cannabis will be associated with PEs.

Although cannabis use is associated with elevated levels of PEs, the majority of cannabis users do not report PEs (Henquet et al., 2008). Differential factors may be present, which increase the risk of PEs amongst some cannabis users but not others. Family studies have shown that the risk for psychosis and psychosis-related outcomes amongst cannabis users is similar within siblings (McGrath et al., 2010) and higher amongst those with first degree relatives with psychosis (Genetic Risk and Outcome in Psychosis (GROUP), 2011), thus suggesting that there may be some familiality shared between cannabis use and psychosis. Familiality can reflect shared genetic vulnerability or shared environment (environmental influences that make children growing up in the same family similar (Plomin et al., 2013)). Investigations into the potential role of genetic factors have shown differences in behavioural and physiological effects of experimentally administered THC to be moderated by variation in genes implicated in neurotransmitter metabolism (Bhattacharyya et al., 2012). Furthermore, gene-environment interaction studies have provided mixed support for a moderating effect of genes (e.g. catechol-O-methyltransferase (COMT) and AKT1 gene) on the association between cannabis use and psychosis (Casadio et al., 2011). It is unknown the extent to which net genetic factors have a role in the relationship between cannabis use and PEs. Furthermore, cannabis use is in part heritable which is not taken into account in G × E analyses, which assume it operates as a purely environmental variable.

Evidence from epidemiological studies suggests that the risk of psychotic symptoms is higher amongst individuals who use cannabis and have a family history of schizophrenia. There is also evidence to support that a genetic vulnerability to psychosis increases the risk amongst cannabis users to develop psychotic symptoms (Arseneault et al., 2002; Verdoux et al., 2003), thus suggesting that a shared genetic propensity may underlie the association between cannabis use and psychotic experiences. Furthermore, additive genetic influences explain a proportion of variance in both cannabis use (40–59%) (Verweij et al., 2011) and PEs (33–58%) (Polanczyk et al., 2010; Ericson et al., 2011; Hur et al., 2012; Zavos et al., 2014); hence they may covary because the same common genetic influences underlie both of these phenotypes. Cannabis use and PEs are also influenced by environmental factors, thus questioning whether similar environmental correlates of cannabis use and PEs contribute to their covariation. For example peer victimization has been associated with emerging psychotic symptoms (Arseneault et al., 2011) and substance use (Tharp-Taylor et al., 2009) amongst adolescents. Similarly there is also some evidence to support the association between socioeconomic disadvantage with emerging psychotic symptoms (Morgan et al., 2009) and substance use (Daniel et al., 2009), thus alluding to the potential for environmental factors to act as explanatory mechanisms underlying the association between cannabis use and PEs. Cannabis use has also been found to increase the risk of trauma (i.e. maltreatment) based vulnerabilities for psychosis (Shevlin et al., 2009), thus identifying trauma as a potential 'environmental' risk factor which contributes towards the association between cannabis use and psychotic experiences. However it is important to note that psychotic experiences are not the same as clinical psychosis and therefore inferences from studies investigating psychosis should be undertaken with caution.

The role of genetic and environmental influences on the covariation between cannabis use and PEs has not been tested formally and is done for the first time here. Our aims for this study were twofold, first to examine if cannabis use is associated with specific PEs (including the range of positive, cognitive and negative experiences) in adolescence. Second, to estimate the extent to which genetic and environmental factors influence the association between cannabis use and PEs.

2. Methods

2.1. Sample

The Longitudinal Experiences And Perceptions (LEAP) study (Ronald et al., 2014) involves participants from the Twins Early Development Study (TEDS), a community sample of monozygotic (MZ) and dizygotic (DZ) twins born in England and Wales between 1994 and 1996. Zygosity of participants was assigned using a parent-reported questionnaire of physical similarity, which is over 95% accurate when compared to DNA testing (Price et al., 2000). For cases where zygosity was unclear, DNA testing was conducted.

On average 93% of participating families were White Caucasian, 38% had parents with A-levels (UK advanced educational qualification) or higher educational qualifications, 45% had mothers who were employed and 92% had fathers who were employed (Haworth et al., 2013). This is representative and equivalent to UK population percentages for this generation, being 93% White Caucasian; 32% for A-levels or higher; 49% for mother employed; and 89% for father employed (Walker et al., 2001). TEDS has full ethical approval and written consent was obtained at point of contact.

10,874 families from TEDS were invited to take part in the LEAP study. Parent reports for 5076 (47%) families and twin reports for 5059 (47%) pairs were obtained. Adolescents involved in the LEAP project had a mean age of 16.32 years. Individuals were excluded ($N=327$ families) if they did not provide consent at first contact (when TEDS was started), if they had a severe medical disorder, had experienced severe perinatal complications or if their zygosity was unknown. After exclusions, the sample reported on in this study comprised of 4830 families (45% male, 36% MZ twin pairs). In the sample 94% was White Caucasian and 16% had mothers with one or more A-levels (UK advanced educational qualification) as highest qualification. Amongst those who did not participate 91% of the sample was White Caucasian and 12% had mothers with one or more A-levels as highest qualification. Data was collected using postal questionnaires, where participants and their parents were asked to answer questions on participants' perceptions and experiences.

2.2. Measures

2.2.1. Cannabis use

We assessed cannabis use by asking participants "*Have you ever tried cannabis*", to which they responded "*Yes*"(1) or "*No*"(0). Participants were informed of other names often used to describe cannabis such as "*hash*", "*weed*", "*dope*", and "*pot*", to ensure that all instances of cannabis use were captured.

2.2.2. Psychotic experiences

Psychotic experiences (PEs) were assessed at age-16 using the Specific Psychotic Experiences Questionnaire (*SPEQ*) (Ronald et al., 2014). SPEQ assesses specific PEs as quantitative traits and includes five self-report subscales: paranoia (15 items), hallucinations (9 items), cognitive disorganisation (11 items), grandiosity (8 items),