Cannabis use, schizotypy, and negative priming

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Abstract

The present study examined the effects of frequency of cannabis use, schizotypy, and age on cognitive control, as measured using a location-based negative priming task in a sample of 124 Australians aged 15–24 who had ever used cannabis. This study found that the schizotypy dimension of Impulsive Nonconformity had a significant effect on negative priming such that participants with higher scores on this dimension showed reduced negative priming. Also, higher levels of psychological distress were associated with greater negative priming. Finally, there was a significant age by cannabis use interaction indicating that younger, frequent users of cannabis may be more susceptible to its effects on cognitive control and perhaps at greater risk of developing a disorder on the psychosis dimension.

1. Introduction

There is a well-established association between cannabis use and psychosis (for a review, see Wilkinson et al. (2014)). Longitudinal studies indicate that cannabis use may be a risk factor for the development of symptoms of psychosis (Henquet et al., 2004). Also, studies have shown that people with schizophrenia who used cannabis in adolescence have an earlier age of onset of psychotic illness (Large et al., 2011), with continued use of cannabis following the onset of psychosis resulting in a more severe course of psychotic illness and poorer treatment outcomes (Clausen et al., 2013). Furthermore, administration of tetrahydrocannabinol (THC) to healthy participants has been shown to temporarily induce positive (Barkus et al., 2011) and negative psychosis-like symptoms (Morrison and Stone, 2011).

People who use cannabis regularly display similar cognitive impairments to those typically found in patients with schizophrenia, including deficits in cognitive control (for a review, see Solowij and Michie (2007)). Cognitive control refers to the ability to suppress/inhibit irrelevant or conflicting information (interference suppression) and/or prepotent responses (response inhibition). Deficits in suppressing irrelevant information have long been recognised as a key feature of schizophrenia (McGhie and Chapman, 1961) and have been theorised to underlie core schizophrenia symptoms such as hallucinations and other positive symptoms (Frith, 1979; Kapur, 2003; Howes and Kapur, 2009; Van Os, 2009). However, studies showing that cognitive control deficits are present in first-degree relatives of people with schizophrenia independently of subclinical symptoms (Snitz et al., 2006) suggest that cognitive control deficits may be better understood as reflecting risk for psychotic disorders rather than directly related to the symptoms themselves.

Animal and human research suggests that adolescent exposure to cannabis carries a particularly high risk for psychosis-related outcomes and cognitive impairment (Ehrenreich et al., 1999; Arseneault et al., 2002; Schneider and Koch, 2003). Findings of heightened risk associated with adolescent cannabis use, coupled with research pointing to a role of the endocannabinoid system in regulating neurodevelopmental processes, have led to speculation that adolescent cannabis use may disrupt the normal course of neurodevelopmental processes and result in changes in brain functioning similar to those associated with risk for psychosis (Viveros et al., 2012) or to psychosis itself (Bosson and Niesink, 2010).

The negative priming procedure is a cognitive task that was designed specifically to examine cognitive control (Tipper, 1985; Neill et al., 1995; de Fockert et al., 2010). In this context, cognitive control refers to the use of inhibitory processes to suppress attention and/or responses to distracting stimuli in order to focus cognitive resources on target stimuli that are the focus of current goals. In a typical location-based negative priming task,
participants are repeatedly asked to locate a target stimulus while ignoring a distractor stimulus. In order to perform this task successfully, participants must apply cognitive control in order to inhibit attention and/or responses to the distractor. It is typically found that responses to the target are slower when this target appears in a location that was occupied by the distractor in the previous display. This is referred to as the negative priming effect, and it is taken to suggest that inhibition of the mental representation of the distractor location (or the response to that location) carries over from the previous display (Tipper et al., 1994; Tipper, 2001). On this account, the stronger a person’s ability or tendency to inhibit distracting information, the stronger the negative priming effect will be. Importantly, and consistent with the suggestion that psychosis is associated with a dysfunction in cognitive control, location-based negative priming is reduced in patients with schizophrenia (e.g., Macqueen et al., 2003) as well as first-degree relatives and people with elevated schizotypy (Park et al., 1996), a personality construct that at high levels is thought to indicate a predisposition for psychotic disorders (Nelson et al., 2013).

A recent study has found that current cannabis users also display reduced location-based negative priming compared to past users and controls (Skosnik et al., 2001). In this study, however, frequency of cannabis use was not found to be associated with negative priming among regular users. The authors suggested that this might have been due to variability of THC potency across different cannabis strains, which may have masked frequency-related effects. Alternatively, frequency of use may not be related to negative priming after all and other cannabis-related variables, such as age of first cannabis use, may be better predictors. Although, as noted above, cannabis use in early adolescence carries an especially high risk for cognitive impairment and psychosis-related outcomes, no study to date has explored the effects of age of first use on location-based negative priming in regular cannabis users. Another factor that may have contributed to the lack of an association between frequency of use and negative priming in regular cannabis users may be that the impairments in negative priming found in that group were not related to cannabis use directly but rather resulted from their elevated schizotypy (which was noted by Skosnik et al., 2001). As stated above, high levels of schizotypy are themselves considered a risk factor for psychosis and related to deficits in location-based negative priming. Thus, the finding of reduced negative priming among cannabis users by Skosnik et al. (2001) may simply have been a reflection of higher schizotypy among users.

In order to address these gaps in the literature, the current study used a sample of young adults (aged 15–24) to examine the effects of cannabis use and schizotypy on location-based negative priming, and explored whether the effects of cannabis use on negative priming vary according to age. Understanding how cannabis use interacts with age to influence negative priming in adolescents and young adults may provide a greater understanding of the effects of cannabis on neurodevelopmental processes associated with an increased risk of psychosis and related disorders.

2. Method

2.1. Participants

Participants were recruited in Australia via advertisements in national newspapers, websites, community notice boards, and email update lists. Inclusion criteria included being aged between 14 and 24 years and fluent in English. Exclusion criteria included (i) past head injury or neurological disorders, (ii) having ever received a diagnosis of schizophrenia or schizoaffective disorder, and (iii) having a first-degree relative with schizophrenia or schizoaffective disorder. The final sample included 133 participants.

2.2. Procedures

The experiment was run over the internet; all measures were implemented using Inquisit (2012), a software program designed to run experiments and surveys online. Interested participants were emailed information about the study, a screening form, and a consent form. Eligible participants who consented to take part were sent a link via email to complete the assessment. Upon completion of the assessment, participants were emailed a $20 online electronics store voucher. The UNSW Human Research Ethics Committee approved all aspects of this study.

2.3. Measures

2.3.1. Demographic and substance use information

Participants completed a questionnaire asking about demographic information including gender, age, and family history of psychosis-related disorders. The questionnaire asked participants whether they had ever used tobacco, alcohol, cannabis, and other illicit drugs and if so, at what age was their first use. As age of first use can be obtained only from participants who have ever used cannabis and is a variable that we wished to control for, only participants who had ever used cannabis were included in this study.

Participants were asked whether they had used cannabis in the past six months and if so, to what extent they had used it: Less than once a month; About once a month; Once a week or more; or Daily. This was used to categorise participants into two groups, those who used cannabis once a week or more often (frequent users, n = 38) versus those who used cannabis less than once a week, including no use, in the past six months (occasional users, n = 95). For participants who reported past month alcohol and tobacco use, further measures were taken using the relevant items from the brief treatment outcome measure (BTOM; Lawrinson et al., 2005), which assess the number of days of use in the last month, quantity of use per typical day of use, and method of use.

Lastly, participants were asked when they last used cannabis and their responses categorised according to whether they last used cannabis in the past 24 h or more than 24 h ago.

2.3.2. Psychological distress

Participants completed the brief Depression Anxiety Stress Scales (DASS-21; Lovibond and Lovibond, 1995), which contains 21 items assessing depression, anxiety, and stress/tension symptoms. Due to high correlations among the three sub-scales, total scores were used to control for overall psychological distress.

2.3.3. Schizotypy

An adapted version of the short form of the Oxford-Liverpool Inventory of Feeling and Experiences (OLIFE; Mason et al., 2005) was used. This measure comprises four subscales: Unusual Experiences, Introverted Anhedonia, Cognitive Disorganisation, and Impulsive Non-conformity. The Unusual Experiences scale measures deviant perceptual and cognitive experiences related to the positive symptoms of schizophrenia (e.g., “Have you ever thought that you had special, almost magical powers?”), and is often referred to as positive schizotypy. The Introverted Anhedonia scale assesses the inability to experience pleasure, which relates to the negative symptoms of schizophrenia (e.g., “Do you like mixing with people?”). Introverted Anhedonia is often referred to as negative schizotypy. Cognitive Disorganisation items relate to...
disorganised thought and distractibility/inattention (e.g., “Are you easily distracted when you read or talk to someone?”). Lastly, Impulsive Nonconformity items relate to impulsivity (e.g., “Do you often feel the impulse to spend too much money which you know you can’t afford?”).

2.3.4. Negative priming

A location-based negative priming task was used, adapted from the procedure used by Skosnik et al. (2001) (Fig. 1). Each trial consisted of two stimulus displays: a prime display followed by a probe display. In each stimulus display, stimuli appeared in two of the four corner positions of the screen (each corner position was equidistant from the screen centre). One of these stimuli was a target (a black circle frame), and the other was a distractor (a black diamond frame). The screen background colour was light grey. Stimuli were set to appear at 20% of screen size. Upon presentation of each display, participants were required to indicate whether the target stimulus appeared on the left or right side of the screen by pressing a corresponding key as quickly as possible. They were told to ignore the diamond, which is a distractor. In the probe display of a control trial (middle), the target appears in a location that was not occupied in the prime display. On positive priming trials (bottom), the target appears in the same location across prime and probe displays.

![Fig. 1. Schematic of the negative priming procedure. (A) Temporal sequence of trial events. For each stimulus display, participants are required to indicate whether the target stimulus (the circle) is on the left or right of the screen by pressing a corresponding key as quickly as possible. They are told to ignore the diamond, which is a distractor. (B) Examples of trial types. In the probe display of a negative priming trial (top), the target circle appears in the location that the distractor had occupied in the prime display. In the probe display of a control trial (middle), the target appears in a location that was not occupied in the prime display. On positive priming trials (bottom), the target appears in the same location across prime and probe displays.](image)

Response times were recorded for the probe display of each trial type. Negative priming scores were calculated by subtracting the mean response time for probe displays of negative priming trials from the response time for probe displays of control trials. A slower response on negative priming trials compared to control trials (resulting in a more negative score) reflects the negative priming effect (Tipper et al., 1990). In calculating any score, incorrect responses and responses under 150 ms and over 2000 ms were excluded. Participants with more than 10 timing exclusions or less than 70% correct responses on any one trial type were excluded (n=9, leaving 124 participants in the final analysis). Participants who were excluded did not differ from included participants on age, gender, or cannabis grouping (all p’s > 0.05).

2.4. Data analysis

Multiple linear regression was used to explore the effects of cannabis use, age, their interaction, and schizotypy on negative priming scores (which were approximately normally distributed). The following variables were also entered into the model to adjust for their influence: gender, whether first use of cannabis was before the age of 16 (yes/no), past month alcohol use (number of days), past month tobacco use (number of days), total number of other types of illicit drugs ever used, psychological distress (DASS-21 total score), and cannabis use in the previous 24 h. These variables were entered into the model regardless of group differences, since prior research indicates their possible influence on negative priming or cognition in general (Ehrenreich et al., 1999;...
Braunstein-Bercovitz, 2000; Curran et al., 2002; Verdejo-García et al., 2005; Lisdahl et al., 2014). Age was centred around the mean to avoid multicollinearity. No correlations above 0.6 were found among any of the independent or control variables included in the model.

To explore the significant age \( \times \) cannabis use interaction effect (see below), a follow-up multiple regression analysis was run on each cannabis use group separately using the same variables as above (omitting the cannabis use group and age \( \times \) cannabis use terms).

3. Results

Participants had a mean age of 20.3 years (S.E.=2.5), and 58% were female. Independent samples \( t \)-tests (two tailed) examined group differences on schizotypy dimensions and psychological distress. Mann–Whitney U tests were used to examine differences on age, alcohol use, tobacco use, and other drug use, which were non-normally distributed. Chi square tests examined differences between groups on gender, first cannabis use before 16 years of age, and use in the past 24 h. These are presented in Table 1. Cannabis use groups differed on levels of tobacco use, \( U=922.5, z=3.88, p=0.001 \), other drug use, \( U=753.5, z=4.80, p<0.001 \), Unusual Experiences, \( t(122)=2.75, p=0.007 \), Impulsive Nonconformity, \( t(122)=2.27, p=0.025 \), psychological distress, \( t(122)=2.11, p=0.037 \), first use before 16, \( X^2(1, n=124)=6.59, p=0.010 \), and use in the past 24 h, \( X^2(1, n=124)=25.5, p<0.001 \).

Across all participants, the mean negative priming score was \(-25.7\) (S.E.=40.3). A one-sample \( t \)-test revealed that this was significantly below zero, \( t(123)=7.11, p<0.001 \). This shows that, on average, participants responded more slowly to probe displays on negative priming trials than control trials; in other words, we found evidence of negative priming across all participants. Table 2 presents the results from the overall multiple regression, which assessed the relationship between negative priming scores and schizotypy, cannabis use and age. The total variance explained by the model was \( R^2=0.21 \), \( F(14, 109)=2.07, p=0.019 \). There was a significant effect of Impulsive Nonconformity (Beta=0.237, p=0.040), indicating that higher Impulsive Nonconformity scores were associated with reduced negative priming scores. There was a significant interaction between age and cannabis use (Beta=-0.263, p=0.024), which we explored further by conducting a separate regression on each cannabis use group (see below). There was also a significant effect of psychological distress (Beta=-0.303, p=0.019), with higher psychological distress associated with greater negative priming.

The follow-up multiple regression model for the frequent cannabis use group accounted for 71% of variance in this group, \( F(12,22)=4.42, p=0.001 \). Again, Impulsive Nonconformity was significantly associated with negative priming (Beta=0.500, p=0.017) as was psychological distress (Beta=-0.760, p=0.002). Importantly, there was a significant effect of age (Beta=-0.445, p=0.035), indicating that, among frequent users, younger participants showed reduced negative priming compared with older participants. There was also a significant effect of Unusual Experiences, with higher scores being associated with greater negative priming (Beta=-0.521, p=0.006).

No significant associations were found for any of the predictors in the occasional users group (highest Beta=0.172, p=0.27).

4. Discussion

This study explored the relationship between negative priming and levels of cannabis use, schizotypy, and age. Negative priming essentially provides a measure of the extent to which a person is able to use inhibitory control processes to suppress the processing of distracting information and hence focus cognitive resources on goal-relevant target stimuli. The stronger the inhibitory control that is exerted on trial \( T \), the more it will carry over to influence responding on trial \( T+1 \), and hence the greater the negative priming effect that will be observed. The schizotypy dimension of Impulsive Nonconformity was found to have a significant association with negative priming such that higher levels of Impulsive Nonconformity were associated with reduced negative priming,
implying weaker cognitive control in more impulsive participants. The results also showed a significant interaction between age and cannabis use, with further analyses indicating that younger participants showed reduced negative priming compared with older participants but only if they used cannabis frequently.

The schizotypy dimension of Unusual Experiences was associated with negative priming among frequent cannabis users such that higher Unusual Experiences scores predicted stronger negative priming than did lower scores. This finding is in contrast to what would be expected based on findings from the general population of higher positive schizotypy being associated with impaired location-based priming (Park et al., 1996). A recent study by Bloomfield et al. (2014) might help in explaining how Unusual Experiences might be differentially related to negative priming in frequent cannabis users. Specifically, Bloomfield et al. (2014) found that among chronic users of cannabis prone to positive psychosis-like effects in response to cannabis, frequency of use correlated significantly with reduced dopamine synthesis capacity in the striatum. THC has been shown to increase striatal dopamine transmission in rats (Ton et al., 1988) and humans (Bossong et al., 2009). However, as Bloomfield et al. (2014) suggest, chronic use of cannabis in humans (assuming no other risk factors are present) may lead to a downregulation of dopaminergic activity in the striatum. Thus, it might be the case that people prone to experiencing psychosis-like symptoms are more sensitive (initially) to the dopaminergic effects of cannabis and thereafter, assuming no other risk factors are present, undergo greater downregulation of striatal dopamine activity with frequent chronic use. Therefore, as a result of this downregulation, frequent cannabis users prone to experiencing positive psychosis-like symptoms will have chronically lowered striatal dopamine activity. Given evidence that reduced striatal dopamine activity is associated with enhanced negative priming (Beech et al., 1990), this could explain why frequent users of cannabis prone to unusual experiences showed enhanced negative priming in the current study. Further, as this downregulation of striatal dopamine activity is consequent to chronic, frequent use of cannabis (Bloomfield et al., 2014), it would not typically be in effect among people who use cannabis less frequently, regardless of positive schizotypy levels. This explains the absence of a negative effect of Unusual Experiences on negative priming among occasional cannabis users in our sample.

The current study also found that the effects of cannabis use on negative priming interacted with age. Specifically, younger frequent users of cannabis showed reduced negative priming compared to older frequent users. This finding is in line with animal studies that show adolescent rats that are more susceptible to the negative effects of THC on learning and memory than are adult rats (Cha et al., 2006). The current finding of reduced negative priming in younger frequent cannabis users might be interpreted as reflecting an age-related sensitivity to cannabis-induced striatal dopamine transmission. Striatal dopamine hyperactivity has long been implicated in mediating information-processing abnormalities seen in schizophrenia (see Braff and Geyer (1990) for a review) and, recently, implicated in disrupting negative priming (Amitai et al., 2013). As noted above, THC increases levels of dopamine in the rat striatum (Ton et al., 1988) and though administration of THC may not reliably increase striatal dopamine transmission in healthy control participants, it has been shown to do so in patients with psychosis and unaffected first-degree relatives (Kuepper et al., 2013). Adolescents may similarly be more sensitive to the dopaminergic effects of cannabis in the striatum. Indeed, animal studies have shown that rats have the highest dopamine receptor levels in striatal areas during puberty, with excessive receptors in striatal areas then being eliminated by the time they reach adulthood (Tarazi and Baldessarini, 2000). Thus, the current finding may reflect an adolescent sensitivity to cannabis-induced striatal dopamine activity, possibly due to an age-limited overexpression of dopamine receptors in striatal areas. Assuming there are no other risk factors present, this sensitivity may lessen over time due to downregulation processes (occurring with chronicity, as described in the previous paragraph) or the maturation of other brain systems, such as prefrontal brain areas, which develop later (Sowell et al., 1999) and are involved in inhibiting striatal activity (Kolachana et al., 1995).

The current study also found that higher levels of psychological distress were significantly associated with enhanced negative priming. To the extent that our measure of psychological distress (DASS-21; Lovibond and Lovibond, 1995) gauges general negative affect (Henry and Crawford, 2005) or a propensity towards it, a relevant body of literature comes from Gray's concept of anxiety proneness (e.g., Gray, 1990). On this view, anxiety proneness is a dimension of personality characterised as reflecting sensitivity to an aversive motivational system, the behavioural inhibition system (BIS), which underlies the experience of negative feelings, including fear, anxiety, and sadness. Importantly, several lines of evidence have recently come together to support the idea that BIS sensitivity is associated with greater cognitive control. For instance, people with high BIS sensitivity show a stronger neural response indicative of cognitive control during a response inhibition task (Amadio et al., 2008) and trait anxiety (closely related to BIS sensitivity) is associated with better performance on cognitive control tasks (Sehlheimer et al., 2010). The present finding of enhanced negative priming in participants with higher levels of psychological distress is therefore quite in line with current evidence that anxiety proneness is related to greater cognitive control.

Unlike previous studies (Skosnik et al., 2001), the current study did not find frequent users of cannabis in general to have impaired negative priming. A possible reason for the difference between the current study and the study conducted by Skosnik et al. (2001) is that the latter did not control for the confounding influence of high schizotypy, particularly Impulsive Nonconformity. The current study suggests that, at least in people who have ever used cannabis, Impulsive Nonconformity may be especially important for understanding impairments in negative priming over and above other schizotypy dimensions. In addition, compared with similar studies (e.g., Ehrenreich et al., 1999), we did not find age of first use to have a significant effect on negative priming. This may also be related to our examining the effect of age of first use in the presence of Impulsive Nonconformity, which better accounted for variance in negative priming. Research has pointed to impulsivity predicting an earlier initiation of substance use in adolescence (Ernst et al., 2006) as well as being associated with risk for psychosis (Lee et al., 2013) and so it could be argued that past findings of an association between age of first cannabis use and cognition may have been driven, in part, by higher impulsivity among early initiation to cannabis use.

In summary, the current study investigated the relationship between cannabis use, schizotypy, age, and negative priming. Negative priming provides a well-validated measure of the effectiveness of inhibitory cognitive control mechanisms in suppressing processing of potentially distracting information, and hence targeting cognitive resources towards goal-relevant target stimuli (Tipper, 1985; Neill et al., 1995; de Fockert et al., 2010). Our data revealed that higher scores on the Impulsive Nonconformity dimension of schizotypy were related to reduced negative priming, suggesting that more impulsive participants show greater deficits in cognitive control compared with less impulsive participants. Consistent with previous findings regarding anxiety proneness and cognitive control, higher psychological distress was found to be associated with greater negative priming, suggesting a greater degree of inhibitory cognitive control among more distressed
participants in this study. The current study further found that cannabis use interacted with age to influence negative priming, implying that the effectiveness of inhibitory cognitive control processes was impaired in younger cannabis users compared with older cannabis users if they used cannabis frequently. Longitudinal research examining changes in negative priming over time among frequent adolescent cannabis users would be useful to determine the factors involved in the maintenance of, as opposed to improvement in, changes in priming with age. On the whole, these findings highlight the potential location-based negative priming as a useful paradigm in understanding how various factors may interact throughout adolescence and young adulthood to increase risk for psychiatric disorders.

Author contributions

The authors declare that there are no conflicts of interest in this study.

References


Conflict of interest

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