ELSEVIER

Schizophrenia Research 48 (2001) 83–92

SCHIZOPHRENIA RESEARCH

www.elsevier.com/locate/schres

Cannabis use is associated with schizotypy and attentional disinhibition

Patrick D. Skosnik[a], Lea Spatz-Glenn[a], Sohee Park[b,*]

[a]*Department of Psychology, Northwestern University, Evanston, IL 60208, USA*
[b]*Department of Psychology, Vanderbilt University, Nashville, TN 37240-0009, USA*

Received 2 February 2000; accepted 19 July 2000

Abstract

While most neurochemical research into the pathogenesis of schizophrenia (SZ) has focused on the dopaminergic, glutamatergic, and serotonergic systems, the exact nature and cause of this disorder have proven intractable. Given the recent discovery and elucidation of the endogenous cannabinioid system, a re-examination of the cannabis-induced exacerbation hypothesis of SZ is warranted. The purpose of the present study was to assess whether current cannabis users exhibit personality correlates and neurocognitive deficits similar to those observed in SZ patients. 15 current cannabis users, 15 drug-free controls, and 10 past cannabis users were assessed on tasks which assess attentional inhibition, spatial working memory, olfactory identification, and schizotypal personality. Current cannabis users demonstrated deficits in attentional inhibition, decreased reaction time, and significantly higher scores on the schizotypal personality questionnaire (SPQ) compared with the non-using and past cannabis using groups. No group differences were found on the working memory or olfactory identification tasks. These results suggest that cannabis use can mimic attentional deficits seen in acute schizophrenia and is associated with schizotypal personality, thus setting the stage for a possible cannabinoid model of SZ.

Keywords: Anandamide; Attention; Cannabis; Inhibition; Schizophrenia; Schizotypy

1. Introduction

Marijuana, or *Cannabis sativa*, has been used for centuries for its euphoriant, psychedelic, and medicinal properties. Whether smoked or eaten, its active ingredient delta-9-tetrahydrocannabinol (THC; Gaoni and Mechoulam, 1964) can cause acute euphoria, altered time perception, dissociation of ideas, paranoia, motor impairment, and occasional hallucinations (Abood and Martin, 1992). In addition, alterations in various cognitive and behavioral abilities such as memory, attention, reaction time, concept formation, motor coordination, and perception have been well documented (Abood and Martin, 1992). Given the similarities between these effects and many of the symptoms of acute SZ, a plethora of past and current research has sought to uncover a possible relationship between cannabis use and the development of psychosis.

The fact that many cannabis users demonstrate acute psychotic reactions has led many researchers to postulate the existence of a specific cannabis-induced psychosis (Spencer, 1970). For example, Chopra and Smith (1974) described SZ-like psychotic episodes in a group of East Indian marijuana users,

* Corresponding author.
E-mail address: sohee.park@vanderbilt.edu (S. Park).

0920-9964/01/$ - see front matter
PII: S0920-9964(00)00132-8

and similar results have been reported by other researchers as well (Beaubrun and Knight, 1973; Bowman and Pihl, 1973; Halikas et al., 1972; Negrete, 1973). However, a specific cannabis-induced psychosis seems unlikely. What is more probable is that certain individuals are genetically or environmentally predisposed to develop SZ, and that cannabis can act as a catalyst for a psychotic episode.

Along these lines there is evidence that cannabis use can act as a specific risk factor for the development of SZ (Andreasson et al., 1987), and that cannabis use can exacerbate SZ symptoms, increase relapse rates, and even attenuate the efficacy of neuroleptic drugs (Breakey et al., 1974; Davidson and Wilson, 1972; Knudsen and Vilmar, 1984; Treffert, 1978; Linszen et al., 1994). Given these data, and the discoveries of the first cannabinoid brain receptors and endogenous neurotransmitters (Devane et al., 1988, 1992), new hypotheses and possible mechanisms can now be examined in relation to the enigma of SZ and cannabinoids.

There is a growing body of evidence suggesting that SZ patients demonstrate varying degrees of neurocognitive impairment (Goldman-Rakic, 1991; Gray et al., 1991; Park and Holzman, 1992; Pantelis and Brewer, 1995; Iwanami et al., 1996; Park et al., 1996). Interestingly, there is also initial evidence that cannabis users show neurocognitive deficits in working memory and selective attention (Solowiji, 1995; Fletcher et al., 1996; Pope and Yurgelun-Todd, 1996), and increased rates of schizotypal personality as assessed by the schizotypal personality questionnaire (Williams et al., 1996). Thus, studies aimed at elucidating the interrelationship between cannabis use, neurocognitive ability, and schizotypal personality may serve to elucidate the role of cannabis in SZ pathogenesis, and may invite new hypotheses into the neurochemical underpinnings of this disease.

The purpose of the present study was to determine if current cannabis users demonstrate SZ-like neurocognitive deficits on tasks which measure hippocampus-dependent attentional inhibition (negative priming; NP) (Venables, 1992), prefrontal cortical-dependent working memory (Goldman-Rakic, 1991), and orbitofrontal cortical-dependent olfactory identification (Potter and Butters, 1980; Jones-Gotman and Zatorre, 1988). In addition, the schizotypal personality questionnaire (SPQ; Raine, 1991) was administered to all participants to determine if schizotypal personality traits are associated with cannabis use. Past cannabis using participants and control subjects were also tested on the same tasks. Past studies show that positive symptomatology is associated with reduced attentional or cognitive inhibition (Gray et al., 1991), whereas working memory deficits tend to be associated with negative symptoms (Carter et al., 1996; Park et al., 1999). Cannabis use has been associated with catalyzing full-blown psychosis with predominantly positive symptoms. Therefore, we expected the current cannabis smokers to display a neurocognitive profile that is associated with the positive symptoms more than the negative symptoms. In other words, we hypothesized that cannabis smokers would show greater deficits in negative priming than on the working memory or the olfactory identification tasks.

2. Methods and materials

2.1. Participants

All subjects were recruited by placing advertisements from the university community as well as from the local Evanston and Chicago areas. Individuals tested [50% male; mean age = 23.3 (S.E. = ±1.05); mean years of education = 14.8 (S.E. = ±0.28)] were screened for a history of mental illness in themselves or in their families, head injury, and the use of any drugs other than cannabis. Each individual was paid for participation in the study, written informed consent was obtained from each, and a full debriefing was given at the conclusion of the study.

The inclusion criteria for the *current cannabis using* group [$n = 15$; 60% male; mean age = 22.3 (S.E. = ±0.91); mean years of education = 14.6 (S.E. = ±0.41)] was a pattern of cannabis consumption which included regular use at least once per week (mean use = 1.3 times per week) without taking any other drugs. No subject in this group was tested within 48 h of smoking cannabis and therefore nobody was acutely intoxicated at the time of testing. Inclusion into the *past cannabis using* group [$n = 10$; 70% male; mean age = 23.6 (S.E. = ±1.59); mean years

of education = 15.2 (S.E. = ±0.47)] included the consumption of cannabis at least once in the past, with no use in the 45 days prior to the experiment. The *control* group [$n = 15$; 30% male; mean age = 24.1 (S.E. = ±2.5); mean years of education = 14.6 (S.E. = ±0.56)] had no history of any drug use prior to the experiment. An ANOVA indicated that the three groups did not differ in age [$F(2,37) = 0.297$; $P > 0.25$] or years of education [$F(2,37) = 0.413$; $P > 0.34$].

All subjects participated in three experimental tasks: negative priming (NP), working memory, and olfactory identification (UPSIT). In addition, all subjects filled out the 74 item schizotypal personality questionnaire (SPQ). The tasks are described below, and the order of presentation of each task was counterbalanced across all subjects.

2.2. Negative priming (NP)

All stimuli were presented on a Macintosh computer. The stimuli were presented at each of the four corners of the computer screen (Fig. 1). The visual angle between the vertical and horizontal positions was 7.8°. The target stimulus consisted of the symbol (o) while the distractor consisted of the symbol (+). The stimuli (o or +) subtended 0.6° by 0.6° of visual angle. Subjects sat 45 cm from the computer screen and indicated the location of

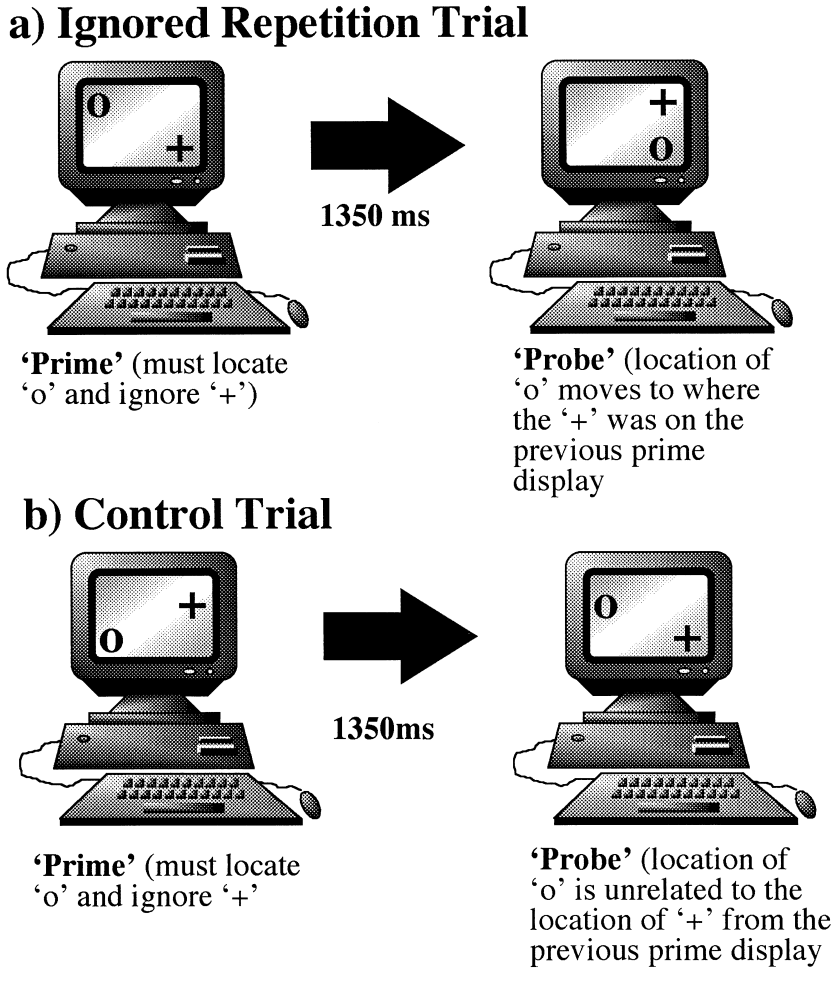

Fig. 1. Schematic diagram of the negative priming procedure. Neutral (N) trials without a distractor stimulus are not shown.

the target by pressing the corresponding key on the keyboard.

In the visuospatial NP task, pairs of prime and probe displays are presented on a computer screen (Fig. 1). First, a 'prime' display is presented in which a target stimulus must be located while a distractor stimulus is ignored. Immediately following the 'prime' display, a 'probe' display is presented, in which a target stimulus is presented at the *ignored distractor position* from the *previous* prime display (i.e. *ignored repetition*. Thus, subjects are required to select the location that they had just ignored. Typically, when a 'prime'–'probe' pair involves such an *ignored repetition*, the reaction times (RTs) to locate the target on the 'probe' displays are *longer* owing to inhibitory processes associated with the ignored location, and such an increase in RT as a result of a previous exposure is called the negative priming effect (Tipper, 1985). In the ignored repetition condition, the negative priming effect depends on the degree of selective attention achieved on the prime display. Hence, the greater the attentional inhibition exhibited during the prime display, the slower the RT to locate the target on the subsequent probe display. When the 'prime'–'probe' pairs do not involve an *ignored repetition* of a location, such increases in RTs to locate the target on the probe displays do not occur. In other words, when the location of the distractor in the 'prime' display and the location of the target in the 'probe' display do not overlap, there is no NP effect.

There were three types of trial involving the 'prime'–'probe' display pairs: (1) *ignored repetition trials* (IR) which represented the condition in which the RTs to locate the target on the probe were expected to be slowed; (2) *control trials* (C) in which the target position on the probe display was unrelated to the distractor position in the prime display (Fig. 1b); and (3) *neutral trials* (N) characterized by the absence of a distractor in the prime displays (not shown). N trials were utilized to assess the simple RT to detect a visual target. Each subject received 24 of each type of trial. The dependent measure will be the reaction time to locate the target on the probe trials. NP scores were calculated by subtracting the IR probe RTs from the C probe RTs. Thus, longer RTs in the IR trials compared with those from the C trials resulted in more *negative* NP scores, and indicated a greater NP effect (greater attentional inhibition).

Subjects were seated at the computer and were asked to read the instructions on the screen. They were instructed to indicate the location of the target (o) as accurately and quickly as possible while simultaneously ignoring the distractor (+). Subjects indicated the location of the target by pressing a key on the keyboard, which corresponded to the location of the target on the screen. When ready, the subjects pressed the spacebar to initiate a block of trials. A trial began with a prime display which remained on until a response was made. After a 1350 ms delay, the probe display appeared and the subjects again had to respond to the target location. This constituted one trial, and a mask screen of at least 6.4 s separated each trial. At this point, the subjects were asked if they are ready to move on to the next trial, which could be initiated by again hitting the space bar. The 6.4 s intertrial interval with the mask screen is necessary because Tipper et al. (1991) showed that NP can last up to about 7 s, thus any chance for residual priming was minimized. Subjects received 24 of each type of trial (IR, C, and N) in randomized order.

2.3. Spatial working memory

All stimuli were presented on a Macintosh computer. The target was a small black dot (2° of visual angle) appearing in one of eight possible positions, each separated by 45°, along the circumference of an imaginary circle. The fixation point was a small black crosshair (0.5° of visual angle) appearing in the center of the screen. The distance between the fixation point and any target location was 12° of visual angle. Subjects sat 45 cm from the computer monitor. The remembered target location was chosen utilizing a computer mouse and the target locations were presented in a completely random order.

After receiving instructions, subjects focused on the fixation point in the middle of the screen. When ready, the subjects clicked the mouse, and a black target flashed in one of the eight locations for 200 ms. After the target disappeared, subjects were presented with an intervening task for 10 s in order to prevent any rehearsal of the target location. This intervening task involved reading a series of words on the computer screen, deciding whether the words were in the

same semantic category or not. After this delay period, the eight possible target positions were presented and the subjects touched the location where the target had been presented. Subjects performed three blocks of 16 trials, and were allowed to rest between blocks. A sensory control task was also administered. It was identical to the working memory task except that the target remained on the screen during the intervening task. Subjects performed 16 trials of the control task. The per cent correct was calculated for both the memory and sensory tasks.

2.4. Olfactory identification

Olfactory identification was assessed using the University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al., 1984). The UPSIT is a standardized multiple choice scratch-and-sniff test consisting of four books of 10 items each. Subjects were asked to scratch the scent-impregnated area with a pencil and to identify the particular smell from the four choices for each item. If the subjects could not identify a particular smell, they were encouraged to make the best possible guess. The dependent measure was the number of correct choices out of 40 (% correct).

2.5. Schizotypal personality questionnaire

All subjects were given the schizotypal personality questionnaire (SPQ) developed by Raine (1991). The SPQ consists of 74 yes/no questions with nine subscales based on the features of schizotypal personality in *DSM-III-R* (American Psychological Association, 1987). The dependent measure was the number of affirmative answers chosen on the questionnaire. Thus, higher scores indicate an increased tendency toward schizotypy. There are nine subscales in the SPQ corresponding to the nine syndromes of schizotypal personality as specified by the DSM.

2.6. Data analysis

Groups were compared using the analysis of variance (ANOVA) and Pearson product moment correlation (level of significance $P < 0.05$, two-tailed unless otherwise noted).

3. Results

A summary of the results is presented in Table 1. Fig. 2 shows the effects of the NP experiment for the three groups. The accuracy in locating the target was near 100% for almost all subjects, and there was no difference in accuracy between the groups. An ANOVA showed that the three groups

Table 1
Data summary for per cent negative priming, mean RT (ms), working memory (% correct), UPSIT (% correct) and SPQ scores

	THC users	Past users	Controls
NP scores	4.5 ± 7.1	−17.0 ± 4.9	−13.9 ± 5.1
RT (ms)	402.0 ± 10.9	461.0 ± 8.9	464.6 ± 18.1
Working memory	93.1 ± 1.8	94.8 ± 1.3	91.2 ± 2.0
UPSIT (%)	94.5 ± 1.3	95.5 ± 0.9	92.3 ± 2.0
SPQ scores	30.7 ± 2.6	17.6 ± 1.4	12.6 ± 2.4
Suspiciousness	2.5 ± 0.58	1.7 ± 0.59	1.3 ± 0.47
Magical thought	3.3 ± 0.53	1.3 ± 0.37	0.67 ± 0.23
Perceptual distortion	2.9 ± 0.55	1.6 ± 0.31	1.1 ± 0.27
Odd behavior	4.1 ± 0.47	2.7 ± 0.52	0.47 ± 0.27
Odd speech	0.45 ± 0.52	1.3 ± 0.34	1.9 ± 0.36
Reference	3.9 ± 0.57	1.7 ± 0.34	1.8 ± 0.59
Anxiety	1.8 ± 0.54	3.5 ± 0.67	2.6 ± 0.51
Constricted effect	2.1 ± 0.5	1.8 ± 0.47	1.7 ± 0.5
No close friends	1.7 ± 0.51	2.1 ± 0.55	1.2 ± 0.41

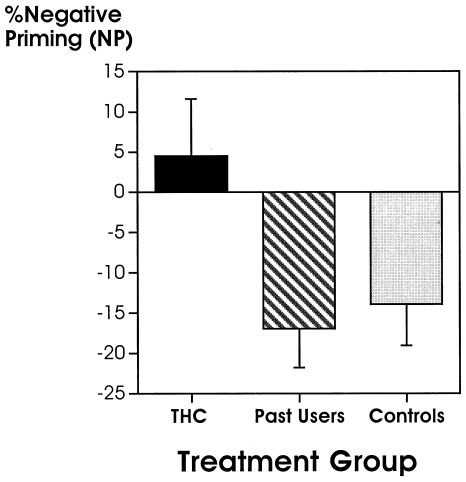

Fig. 2. Mean (SEM) % negative priming scores for the current cannabis users (THC), past users, and controls. Only the THC group shows abolition of negative priming as indicated by the positive score.

differed significantly on the negative priming. [$F(2,37) = 3.72$, $P < 0.035$]. As can be seen from Fig. 2, the current cannabis group showed a more positive NP score (disinhibition or absence of NP), while the past cannabis group and control group demonstrated negative NP scores (normal NP). No sex differences were found. Focused comparisons revealed that the current cannabis group demonstrated more positive NP scores compared with both the past cannabis group [$F(1,23) = 3.64$, $P < 0.035$, one-tailed] and the control group [$F(1,28) = 3.41$, $P < 0.04$, one-tailed]. There was no difference in the NP scores between the past cannabis group and the control group [$F(1,23) = 0.17$, $P > 0.68$]. There was no significant correlation between the NP scores and the amount of marijuana consumed per week (as indicated by self-report) in the cannabis using group ($r = 0.15$, $P > 0.42$).

Fig. 3 shows the baseline RT data obtained from the N trials (no distractor) in the NP experiment. There was a difference among the three groups on the RT [$F(2,37) = 6.5$, $P < 0.004$]. The current cannabis group demonstrated faster reaction time compared with the past cannabis group [$F(1,23) = 15.0$, $P < 0.001$] and the control group [$F(1,28) = 8.8$, $P < 0.006$]. There was no difference between the past cannabis group and the control group in the RT [$F(1,23) = 0.023$, $P > 0.12$], nor was there any correlation between RT and the amount of marijuana consumed per week ($r = 0.03$, $P > 0.74$). There was no sex difference.

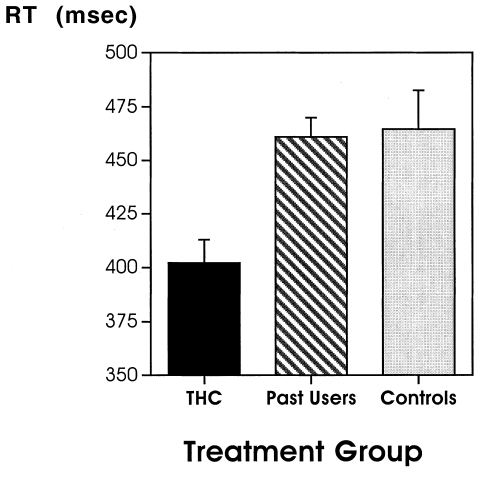

Fig. 3. Mean (SEM) reaction times (ms) for the current cannabis users (THC), past users, and controls.

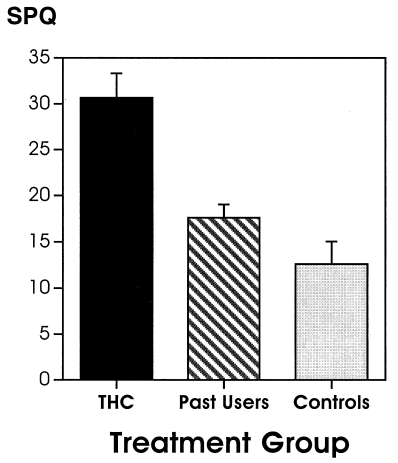

Fig. 4. Mean (SEM) schizotypal personality questionnaire (SPQ) scores for the current cannabis users (THC), past users, and controls.

The results of the SPQ can be seen in Fig. 4. An ANOVA revealed that the three groups differed significantly in total SPQ scores [$F(2,37) = 16.5$, $P < 0.0001$]. Again, no sex differences were found. Focused comparisons revealed that the current cannabis group showed significantly elevated SPQ scores compared with the past cannabis group [$F(1,23) = 14.5$, $P < 0.0009$] and the control group [$F(1,28) = 25.4$, $P < 0.0001$]. There was no significant difference in SPQ scores between the past cannabis and control groups, even though the past group showed slightly higher scores than the control group [$F(1,23) = 2.4$, $P > 0.13$]. There was no correlation between the amount of marijuana smoked and SPQ scores in the current cannabis group ($r = 0.078$, $P > 0.22$). There were significant differences between the three groups on the subscale scores of magical thought [$F(2,37) = 12.7$, $P < 0.0001$], perceptual distortion [$F(2,37) = 5.9$, $P < 0.006$], ideas of reference [$F(2,37) = 5.4$, $P < 0.009$], odd behavior [$F(2,37) = 22.1$, $P < 0.0001$], and odd speech [$F(2,37) = 15.7$, $P < 0.0001$]. Magical thought, perceptual distortion, ideas of reference are the subscales that contribute to the positive syndrome. The three groups did not differ on the subscales of suspiciousness [$F(2,37) = 1.6$, $P > 0.775$], anxiety [$F(2,37) = 0.61$, $P > 0.452$], constricted effect [$F(2,37) = 0.18$, $P > 0.165$], or no close friends

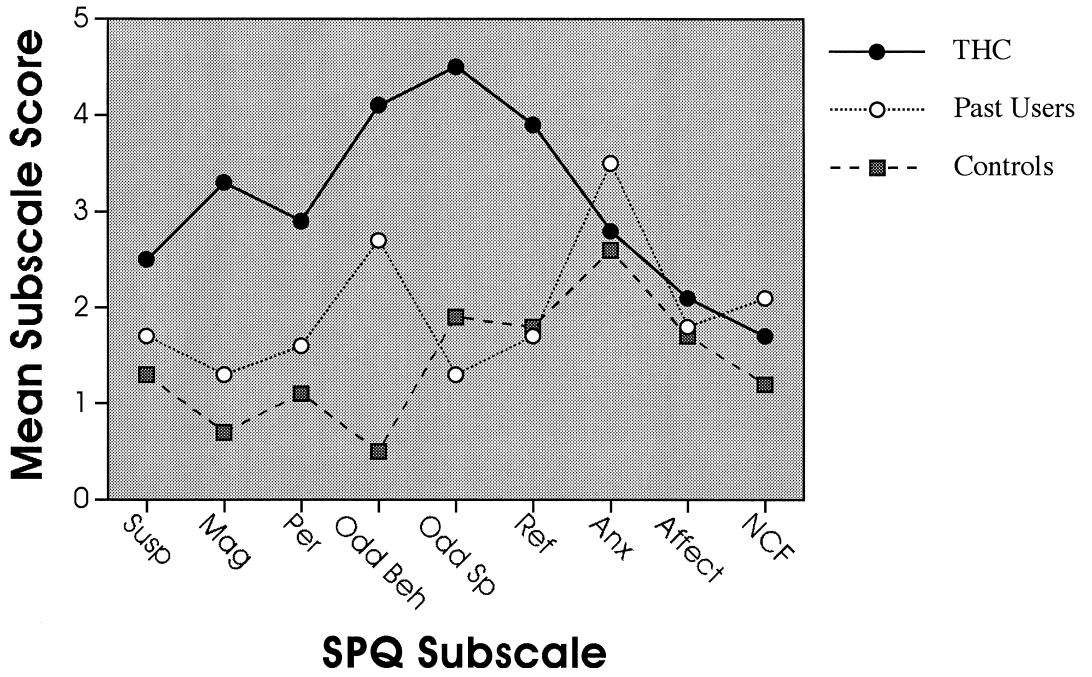

Fig. 5. Profile analysis of the three groups on the subscales of the schizotypal personality questionnaire (SPQ).

[$F(2,37) = 0.82$, $P > 0.551$]. These are the subscales that contribute to the negative syndrome. A profile of the individual subscale scores is represented in Fig. 5. There was no correlation between the amount of marijuana smoked and any of the SPQ subscale scores; correlation coefficients ranging from -0.18 to 0.15).

There was, however, a significant correlation between SPQ scores and NP scores ($r = 0.34$, $P < 0.017$). In other words, those with more positive NP scores (disinhibition or no NP) tend to exhibit higher SPQ scores (Fig. 6). But there was no significant correlation between NP scores and any of the SPQ subscale scores. There was also no significant difference between any of the groups on the working memory [$F(2,37) = 0.91$, $P > 0.59$] or olfactory identification tasks [$F(2,37) = 0.98$, $P > 0.62$].

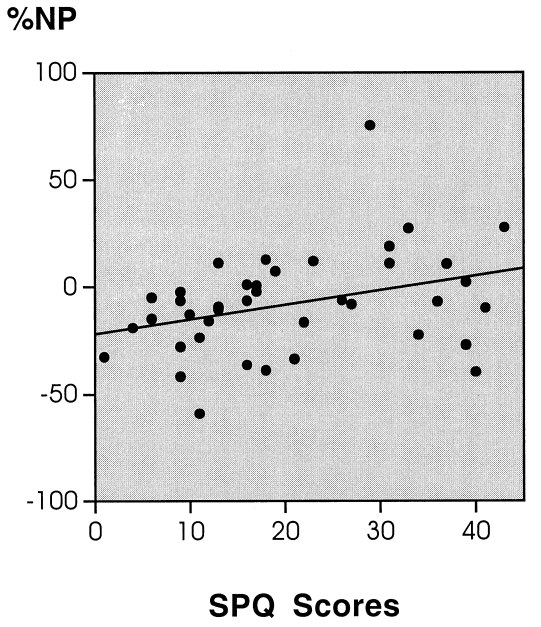

Fig. 6. Correlation between % negative priming score and schizotypal personality questionnaire (SPQ) scores.

4. Discussion

The results of the present study provide evidence that current cannabis use can mimic the attentional inhibition dysfunction seen in SZ. Specifically,

individuals currently using cannabis at least once per week had increased NP scores (increased disinhibition) than did past users or controls. This effect did not stem from an overall deficit in visual attention, since cannabis users actually had significantly faster RTs when they were performing a simple detection task. Furthermore, we found that the current cannabis users showed increased scores on the positive syndrome of the SPQ but not on the negative syndromes, suggesting that the cannabis may affect behaviors related to the positive symptoms but not the negative symptoms. This result is interesting in the context of negative priming, because it has been demonstrated that acutely psychotic but not chronic SZ patients perform poorly on the spatial negative priming task (Park et al., 1996). However, further study is needed to test this hypothesis.

Schizophrenia patients show deficits in working memory and olfactory identification tasks utilized in the current experiment (Park and Holzman, 1992; Pantelis and Brewer, 1995), but interestingly the current cannabis smokers showed no deficits. One possible reason for the lack of any working memory deficits is that cannabis-induced memory changes may occur only after years of chronic use. Given that the sample population utilized in the current study were all college-aged students, it is possible that the period of cannabis use was too short to visibly interrupt working memory systems. A second possibility is that cannabis use impairs behavior associated with the positive symptoms of schizophrenia but not those related to negative symptoms. Working memory and olfactory identification are associated with negative symptoms and prefrontal function (Carter et al., 1996; Park et al., 1999; Pantelis and Brewer, 1995). It is also possible that THC may even improve negative symptoms and prefrontal functions. In any case, THC may not disrupt prefrontal function at low doses. In the case of the olfactory identification function, the key region for this task, the orbitofrontal cortex (Potter and Butters, 1980; Jones-Gotman and Zatorre, 1988), contains a lower density of cannabinoid receptors compared with other structures (Herkenham et al., 1990). Therefore cannabis use may not greatly affect olfactory identification function.

Given the plethora of past and present research which has shown a link between cannabis use and variables related to SZ, it seems a logical next step to examine the possible points of crossover between what is known about the neurobiology of SZ and the recently discovered endocannabinoid system. For example, there seems to be a close interaction between the endocannabinoid system and the dopaminergic system (Chen et al., 1989, 1990; Ng Cheong Ton and Gardner, 1986; Ng Cheong Ton et al., 1988; Taylor et al., 1988; Souilhac et al., 1995; Sanudo-Pena et al., 1996; Giuffrida et al., 1999). Additionally, central cannabinoid (CB1) receptors appear to be localized in such brain areas as prefrontal cortex, basal ganglia, and hippocampus (Herkenham et al., 1990), structures which have been repeatedly implicated in the pathogenesis of SZ (Andreasen et al., 1992; Frith, 1992; Funahashi et al., 1993; Gray et al., 1991; Morice, 1990; Swerdlow et al., 1986; Weinberger et al., 1986). Finally, it has been shown that SZ patients demonstrate abnormal activity in arachidonic acid (AA) metabolism (Yao et al., 1996). Given that AA is the molecular precursor of the endocannabinoid neurotransmitter anandamide (Devane et al., 1992), it could be hypothesized that SZ patients have an alteration in the normal levels of this transmitter. Indeed, a recent study by Leweke et al. (1999) has provided initial evidence that SZ patients have elevated levels of anandamide in cerebral spinal fluid, thus providing the first direct evidence of a specific dysregulation of cannabinoid dynamics in SZ.

Several other questions stemming from the current study also need to be addressed. The lack of significant correlations between the amount of marijuana consumed and NP or SPQ scores is somewhat surprising. However, it is possible that no correlation was found because of the differential potencies of cannabis strains used by the participants. For example, one individual may consume a less potent strain of cannabis 10 times per week, whereas another individual may smoke a stronger strain but less often, making the circulating levels of THC in these two individuals near equal. Therefore, a dose- and strain-controlled laboratory study is much needed. In addition, our sample size may have been too small to detect weak correlations. Hence, future studies need to be performed using a larger sample size with actual blood or urinary levels of THC assayed in order to determine how these compounds affect cognition and schizotypy.

Finally, it would be interesting to examine whether cannabis use may further exacerbate the neurocognitive deficits in SZ patients, and if this exacerbation can be reversed with neuroleptic treatment. By performing these and similar studies examining the interaction of cannabis, the endocannabinoid system, and SZ, much knowledge will be accrued with regard to both one of the most debilitating mental disorders, and the system that subserves one of the most prevalent drugs of abuse.

Acknowledgements

This work was supported in part by the NIMH and NARSAD. We are grateful to Michael Paulin, Kelly Minor, and Christine Hooker for their valuable input throughout this project and to Jeffrey Yao, Wendi Gardner, and Robert Chatterton Jr. for their helpful comments.

References

Abood, M.E., Martin, B.R., 1992. Neurobiology of marijuana use. Trends Pharm. Sci. 13, 202–207.

Andreasen, N.C., et al., 1992. Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Arch. Gen. Psych. 49, 943–958.

Andreasson, S., Allebeck, P., Engstrom, A., Rydberg, U., 1987. Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. The Lancet 2, 1483–1485.

Beaubrun, M.H., Knight, F., 1973. Psychiatric assessment of 30 chronic users of cannabis and 30 matched controls. Am. J. Psych. 130, 309–311.

Bowman, M., Pihl, R.O., 1973. Psychological effects of chronic heavy use. A controlled study of intellectual functioning in chronic users of high potency cannabis. Psychopharm. 29, 159–170.

Breakey, W.R., Goodell, H., Lorenz, P.C., McHugh, P.R., 1974. Hallucinogenic drugs as precipitants of schizophrenia. Psychol. Med. 4, 255–261.

Carter, C., Robertson, L., Nordahl, T., Chaderjian, M., Kraft, L., O'Shora-Celaya, L., 1996. Spatial working memory deficits and their relationship to negative symptoms in unmedicated schizophrenia patients. Biol. Psych. 40 (9), 930–932.

Chen, J., Paredes, W., Li, J., Smith, D., Gardner, E.L., 1989. In vivo brain microdialysis studies of delta-9-tetrahydrocannabinol on presynaptic dopamine efflux in nucleus accumbens of the Lewis rat. Soc. Neurosci. Abstr. 15, 1096.

Chen, J., Paredes, W., Li, J., Smith, D., Lowinson, J., Gardner, E.L., 1990. Delta-9-tetrahydrocannabinol produces naloxone-blockade enhancement of presynaptic dopamine efflux in nucleus accumbens of conscious, freely moving rats as measured by intracerebral microdialysis. Psychopharm. (Berlin) 102, 156–162.

Chopra, G.S., Smith, J.W., 1974. Psychotic reactions following cannabis use in East Indians. Arch. Gen. Psych. 30, 24–27.

Davidson, K., Wilson, C.H., 1972. Psychosis associated with cannabis smoking. Br. J. Addict. 67, 225–228.

Devane, W.A., Dysarz III, F.A., Johnson, M.R., Melvin, L.S., Howlett, A.C., 1988. Determination and characterization of a cannabinoid receptor in rat brain. Mol. Pharmacol. 34, 605.

Devane, W.A., Hanus, L., Breur, A., Pertwee, R.G., Stevenson, L.A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A., Mechoulam, R., 1992. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258, 1946–1949.

Doty, R.L., Shaman, P., Dann, W., 1984. Development of the University of Pennsylvania Smell Test: standardized microencapsulated test of olfactory function. Physiol. Behav. 32, 489–502.

Fletcher, J.M., et al., 1996. Cognitive correlates of long-term cannabis use in Costa Rican men. Arch. Gen. Psych. 53 (11), 1051–1057.

Frith, C.D., 1992. The Cognitive Neuropsychology of Schizophrenia. Lawrence Erlbaum Associates Ltd., Hove, UK.

Funahashi, S., Bruce, C.J., Goldman-Rakic, P.S., 1993. Dorsolateral prefrontal lesions and oculomotor delayed response performance: evidence for mnemonic 'scotomas'. J. Neurosci. 13, 1479–1497.

Gaoni, Y., Mechoulam, R., 1964. Isolation, structure, and partial synthesis of an active constituent of hashish. J. Am. Chem. Soc. 86, 1646–1647.

Giuffrida, A., Parsons, L.H., Kerr, T.M., Rodriguez de Fonseca, F., Navarro, M., Piomelli, D., 1999. Dopamine activation of endogenous cannabinoid signaling in dorsal striatum. Nat. Neurosci. 2 (4), 358–363.

Goldman-Rakic, P.S., 1991. Prefrontal cortical dysfunction in schizophrenia: the relevance of working memory. In: Carroll, B. (Ed.). Psychopathology and the Brain. Raven Press, New York.

Gray, J.A., Feldon, J., Rawlins, J.N.P., Hemsley, D.R., Smith, A.D., 1991. The neuropsychology of schizophrenia. Behav. Brain Sci. 14, 1–20.

Halikas, J.A., Goodwin, D.W., Guze, S.B., 1972. Marijuana use and psychiatric illness. Arch. Gen. Psych. 27, 162–165.

Herkenham, M., Lynn, A.B., Little, M.D., Ross Johnson, M., Melvin, L.S., De Costa, B.R., Rice, K.C., 1990. Cannabinoid receptor localization in brain. Proc. Natl. Acad. Sci. USA 87, 1932–1936.

Iwanami, A., Kanamori, R., Isono, H., Okajima, Y., Kamijima, K., 1996. Impairment of inhibition of unattended stimuli in schizophrenic patients: event-related potential correlates during selective attention. Neuropsychobiol. 34, 57–62.

Jones-Gotman, M., Zatorre, R.J., 1988. Olfactory identification deficits in patients with focal cerebral excision. Neuropsychol. 26, 387–400.

Knudsen, P., Vilmar, T., 1984. Cannabis and neuroleptic agents in schizophrenia. Acta Psych. Scand. 69, 162–174.

Leweke, F.M., Giuffrida, A., Wurster, U., Emrich, H.M., Piomelli,

D., 1999. Elevated endogenous cannabinoids in schizophrenia. Neuroreport 10 (8), 1665–1669.

Linszen, D.H., Dingemans, P.M., Lenior, M.E., 1994. Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch. Gen. Psych. 51 (4), 273–279.

Morice, R., 1990. Cognitive inflexibility and pre-frontal dysfunction in schizophrenia and mania. Br. J. Psych. 157, 50–54.

Negrete, J.C., 1973. Psychological adverse effects of cannabis smoking: a tentative classification. Can. Med. Assess. J. 108, 195–202.

Ng Cheong Ton, J.M., Gardner, E.L., 1986. Effects of delta-9-tetrahydrocannabinol on dopamine release in the brain: intracranial microdialysis experiments. Soc. Neurosci. Abstr. 13, 135 p.

Ng Cheong Ton, J.M., Gerhardt, G., Friedemann, M., Etgen, A.M., Rose, G.M., Sharpless, N.S., Gardner, E.L., 1988. The effects of delta-9-tetrahydrocannabinol on potassium-evoked release of dopamine in the rat caudate nucleus: an in vivo electrochemical and in vivo microdialysis study. Brain Res. 451, 59–68.

Pantelis, C., Brewer, W., 1995. Neuropsychological and olfactory dysfunction in schizophrenia: relationship of frontal syndromes to syndromes of schizophrenia. Schizophr. Res. 17, 35–45.

Park, S., Holzman, P.S., 1992. Schizophrenics show spatial working memory deficits. Arch. Gen. Psych. 49, 975–982.

Park, S., Lenzenweger, M.F., Puschel, J., Holzman, P.S., 1996. Attentional inhibition in schizophrenia and schizotypy: a spatial negative priming study. Cognit. Neuropsychiat. 1 (2), 125–149.

Park, S., Püschel, J., Sauter, B.H., Rentsch, M., Hell, D., 1999. Spatial working memory deficits and clinical symptoms in schizophrenia: a 4-month follow-up study. Biol. Psychiat. 46 (3), 392–400.

Pope Jr., H.G., Yurgelun-Todd, D., 1996. The residual cognitive effects of heavy marijuana use in college students. J. Am. Med. Assoc. 275 (7), 521–527.

Potter, H., Butters, N., 1980. An assessment of olfactory deficits in patients with damage to prefrontal cortex. Neuropsychol. 18, 621–628.

Raine, A., 1991. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr. Bull. 17 (4), 554–564.

Sanudo-Pena, M.C., Patrick, S.L., Patrick, R.L., Walker, M., 1996. Effects of intranigral cannabinoids on rotational behavior in rats: interactions with the dopaminergic system. Neurosci. Lett. 206, 21–24.

Solowiji, N., 1995. Do cognitive impairments recover following cessation of cannabis use? Life Sci. 56 (23/24), 2119–2126.

Souilhac, J., Poncelet, M., Rinaldi-Carmona, M., Le Fur, G., Soubrie, P., 1995. Intrastriatal injection of cannabinoid agonists induced turning behavior in mice. Pharmacol., Biochem. Behav. 55 (1), 3–7.

Spencer, D.J., 1970. Cannabis induced psychosis. Br. J. Addict. 65, 369–372.

Swerdlow, N.R., Braff, D.L., Geyer, M.A., Koob, G.F., 1986. Central dopamine hyperactivity in rats mimics abnormal acoustic startle response in schizophrenics. Biol. Psych. 21, 23–33.

Taylor, D.A., Sitaram, B.R., Elliot-Baker, S., 1988. Effect of delta-9-tetrahydrocannabinol on the release of dopamine in the corpus striatum of the rat. In: Chesher, G., Consroe, P., Musty, R. (Eds.), Marijuana: An International Research Report. Australian Government Publishing Service, Canberra.

Tipper, S.P., 1985. The negative priming effect: inhibitory priming by ignored objects. Q. J. Exp. Psychol. 37A, 571–590.

Tipper, S.P., Weaver, B., Cameron, S., Brehaut, J., Bastedo, J., 1991. Inhibitory mechanisms of attention in identification and localization tasks: time course and disruption. J. Exp. Psychol.: Learn., Mem. Cognit. 17, 681–692.

Treffert, D.A., 1978. Marijuana use in schizophrenia: a clear hazard. Am. J. Psych. 135, 1213–1215.

Venables, P.H., 1992. Hippocampal function and schizophrenia: experimental psychological perspective. Ann. N.Y. Acad. Sci. 658, 111–127.

Weinberger, D.R., Berman, K.F., Zec, R.F., 1986. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenics. I. Regional cerebral blood flow evidence. Arch. Gen. Psych. 43, 114–124.

Williams, J.H., Wellman, N.A., Rawlins, J.N., 1996. Cannabis use correlates with schizotypy in healthy people. Addiction 91 (6), 869–877.

Yao, J.K., van Kammen, D.P., Gurklis, J.A., 1996. Abnormal incorporation of arachidonic acid into platelets of drug-free patients with schizophrenia. Psych. Res. 60, 11–21.