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Hyper-priming in cannabis users: A naturalistic study of the effects of cannabis on semantic memory function

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ABSTRACT

Psychotic symptoms have theoretically been linked to semantic memory impairments in patients with schizophrenia. Little is known of the effects of cannabis, the world's most popular illicit drug, on semantic memory and whether they are linked to the psychotomimetic states elicited by the drug. Thirty-six cannabis users were tested whilst under the influence of cannabis. They were then tested again when not intoxicated and compared with 38 non-drug using controls. Semantic memory was assessed using a semantic priming task with a long and short stimulus onset asynchrony (SOA) to differentiate automatic and controlled processing. Under the influence of cannabis, users showed increases in both automatic semantic priming and schizotypal symptoms compared with controls. When abstinent, cannabis users exhibited hyper-priming at long SOAs. Cannabis users did not differ from controls in either trait schizotypy or state schizotypy when not intoxicated. Acute cannabis use increases schizotypyal symptoms and may increase automatic semantic priming in recreational users of this drug. When drug-free, cannabis users did not differ from controls in schizotypy but did show hyper-priming at the long SOA. The acute increase in automatic semantic priming may be one factor contributing to the psychotomimetic effects of cannabis.

1. Introduction

Cannabis is the most widely used illegal recreational drug: amongst all recreational drugs its use is second only to that of alcohol. The British Crime Survey reported that amongst young people (aged 16–24), 30% of men and 18% of women said they had used cannabis during 2004/5 (British Crime Survey, 2006). There have been growing concerns recently over the consequences of long-term cannabis use for cognition and mental health, particularly in light of claims that the drug may induce psychosis in some susceptible individuals (e.g. Di Forti et al., 2007). Acute cannabis intoxication is known to produce memory impairments (for a review, see Ranganathan and D'Souza, 2006). There are many chemical compound constituents of the cannabis plant, the most psychoactively potent of which has been identified as Δ-9-tetrahydrocannabinol (THC). The memory-impairing effects of an acute dose of cannabis are thought to relate to the action of THC at the Cannabinoid 1 (CB1) receptor, which is found at particularly high densities in the hippocampus, cerebellum and basal ganglia. Evidence of memory deficits following long-term cannabis use is less convincing, with verbal memory deficits found in some studies (Dafters et al., 2004; Messinis et al., 2006; Block and Ghoneim, 1993) but not others (Pope et al., 2001; Verdejo-Garcia et al., 2005; Fried et al., 2005). Reasons that have been suggested to account for these discrepancies are time since abstinence, age of onset and extent of use (Di Forti et al., 2007).

Despite numerous investigations of the effect of acute and chronic cannabis administration on what is termed episodic memory, or 'time-locked' memory for events and occurrences, another area of memory has been largely neglected: semantic memory. Semantic memory refers to our memory for facts and general knowledge of the world, including memory for meanings and language. Semantic memory in cannabis users is particularly interesting as semantic memory impairments are suggested to underlie some of the symptoms observed in psychosis such as thought disorder (Spitzer et al., 1993). A recent study found no impairment in speed of semantic processing in cannabis users (Wadsworth et al., 2006), although some previous studies have found evidence for an impairment in category fluency, where participants are required to generate as many category exemplars as they can within a given interval (e.g. Messinis et al., 2006), which is suggestive of a semantic memory impairment.

A more valid method of assessing semantic processing than category fluency is the semantic priming paradigm, a lexical-decision task in which participants must respond to a target word that is preceded by a prime word that is either related to the target or not (Meyer and Schvanevedlt, 1971). Semantic priming is a facilitated by responding to concepts that are semantically related. When a prime word is related to the target word (e.g. chair, table), people generally respond faster than when they are unrelated (e.g. chair, fish), and this decrease in reaction time is the 'priming effect'. The mechanistic explanation for this describes the semantic system as organised in a map-like network of nodes, representing concepts (Neely and Keefe,

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1989). When one node is activated, *spreading of activation* occurs so that connected nodes are also activated. This spreading of activation facilitates faster responding to related nodes in the network.

Semantic priming is a popular methodology for investigating semantic memory as the standard priming task can be manipulated to investigate different semantic mechanisms. Stimulus onset asynchrony (SOA, the time between the onset of the prime and the target) manipulations are used to assess effects on either automatic or controlled processes. SOAs shorter than 250 ms are considered to tap into automatic, pre-attentional processing, whereas controlled processing, which is slower and thought to involve attention, is tapped by SOAs longer than 700 ms.

Recent claims have related cannabis use to psychosis, with implications that there may be a causal link between the two (Ferdinand et al., 2005; Fergusson et al., 2005). Disturbance in the organisation and processing of knowledge has long been considered a central feature of schizophrenia and, more broadly, psychosis (Bleuler, 1911/1950). As a result of this, semantic processing tasks are at the forefront of much research on cognitive deficits associated with psychosis and schizophrenia. Whilst normal semantic priming is associated with normal language processing, it is thought that overactive priming (faster and further spreading of activation) may relate to schizophrenic thought disorder and language disruptions. A faster spreading of activation in semantic networks in schizophrenia may result in spurious nodes becoming activated and interfering with the normal train of thoughts. In patients with schizophrenia, research has supported this hypothesis with increased automatic (i.e. at a short SOA) priming or 'hyper-priming' found in some studies (Moritz et al., 2001, 2003). However, the results of research on semantic priming in schizophrenia have been far from consistent. A review of research in this field concluded that hyper-priming was more robustly found in conditions of 'indirect' priming (Minzenberg et al., 2002). Indirect priming refers to priming where, unlike 'direct' priming in which the words are directly semantically related (e.g. lemon-sour), the two words presented have a mediator word that is related to both of them but not presented (e.g. lemon-sweet, not presented mediator = *sour*). We therefore included an indirect as well as a direct priming condition in the current study, which aimed to examine the effects of cannabis, both acutely and sub-acutely, on semantic memory.

The present study set out to compare a naturalistic sample of cannabis users with controls on semantic processing and schizophrenia-like symptoms, both under the influence of the drug and then again when not intoxicated. We investigated semantic priming with a computer-based, lexical-decision task, which manipulated SOA. State schizotypy was assessed using a novel state schizotypy questionnaire (Mason et al., 2008). As little research has investigated the long-term effects of cannabis on semantic memory, this aspect of the study was exploratory. We hypothesised that intoxicated cannabis users would show a pattern of semantic priming similar to one that has been shown in thought-disordered schizophrenic patients, i.e. hyper-priming at a short SOA, and that this would be related to schizophrenia-like symptoms.

2. Method

2.1. Design and participants

An independent groups, repeated measures design was used to compare a sample of 38 non-cannabis-using controls with 36 recreational cannabis users on two separate test occasions 3–5 days apart. Inclusion criteria required that participants were at least 18 years old, had English as a native language, were non-dyslexic and had normal or corrected-to-normal vision, and had no personal history of mental illness. The cannabis-using group were required to be recreational cannabis users (at least once a month, for at least a year). The non-cannabis using group may have tried cannabis in the past but had never been regular users and had not taken cannabis more than 5 times in the previous year. All subjects were recruited using a snowball sampling method (Solowij et al., 1992). All participants gave written, witnessed, informed consent on both occasions. This study was approved by the University College London Graduate School ethics committee and the aims were supported by the U.K. Home Office. In addition, given the ethical issues of studying active cannabis use, the volunteer information sheet stated that researchers did not condone the use of cannabis and participants were provided with a cannabis advice information leaflet (*Home Office*) following testing and a helpline to contact should they wish to talk to someone about their drug use.

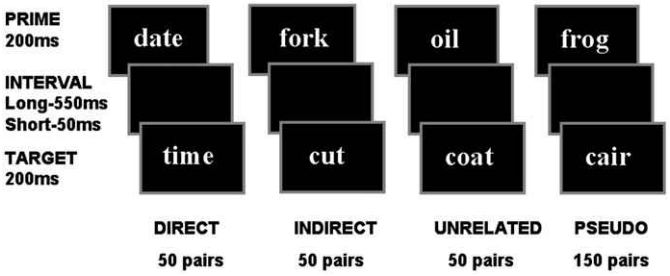

Fig. 1. Schematic of the semantic priming task.

2.2. Procedure

All individuals were tested on two separate occasions, with the first session of cannabis users occurring when the participants were under the influence of the drug (day 0) and the second 3–5 days later when drug-free for 24 h (days 3–5). We refer to the second test day as indexing 'sub-acute' rather than chronic effects, as the naturalistic design of the study precluded a 28-day wash-out period in our cannabis-using volunteers. The cannabis users were recruited prior to testing and asked if they intended smoking cannabis over the next few days. If so, a testing time was arranged when participants were going to smoke cannabis and willing to undergo the test battery. Cannabis users smoked their cannabis in front of the investigator and then testing began 15 min post-smoking. The non-cannabis group was drug-free both times. Urine tests were used to confirm the consumption of or abstinence from cannabis and to screen for other drug use (THC, opiates, cocaine, amphetamine, benzodiazepines and other related compounds). Detailed drug use histories were also collected from participants using a structured interview. Participants then completed the test battery below.

2.2.1. Assessments

2.2.1.1. Semantic priming. A computer-based, lexical decision-making task was used to assess semantic priming with relatedness and stimulus onset asynchrony (SOA) manipulations. Participants had to decide whether a target 'word' was a real English word or a pseudo-word. Each target was preceded by a prime word, which varied in its semantic relatedness to the target: directly related, indirectly related, unrelated, or the target was a pseudo-word. In addition, the SOA (time between the onset of presentation of the prime and presentation of the target) varied so that half the word pairs were separated by 250 ms (short SOA) and half by 750 ms (long SOA). Each word in the pair was presented for 200 ms. Participants could respond for 2000 ms after presentation of each prime. Between each word-pair trial there was a 2500-ms gap (see Fig. 1 for a diagrammatic representation of the task).

The stimuli were 450 concrete nouns and 150 pseudo-words arranged in four word-pair conditions: directly related (50 word pairs) indirectly related (50 word pairs), unrelated (50 word pairs) and word-prime, pseudo-target (150 word pairs). The related pairs were co-exemplars of a given category, formed using category norms (Battig and Montague, 1969). Pseudo-words were legally spelled and pronounceable letter strings selected from the ARC non-word database (Rastle et al., 2002). All letters were presented in lower case Times New Roman, 44-point in white in the centre of a black screen on a laptop using DMDX software (Forster and Forster, 2003).

Two matched versions of the word-pair list were created randomly, with the constraint that no condition could appear more than three times consecutively. Ten practice trials preceded three blocks of 100 test trials. Participants received a different list on each occasion, which was counterbalanced across group and day. They were asked to read the first word to themselves and then respond to the second word as quickly and accurately as they could, using a labelled ('word', 'non-word') two-button press. Reaction time (RT) and accuracy data were recorded.

2.2.1.2. Subjective measures

2.2.1.2.1. Psychotomimetic State Inventory (PSI: Mason et al., 2008). The PSI is a 48-item questionnaire designed to assess psychotomimetic states or current (state) schizotypal symptomatology. Participants rate statements that describe their current experience from 0 (not at all) to 3 (strongly). The PSI yields the following six sub-scales: 'delusional thinking', e.g. "You feel that you might cause something to happen just by thinking about it"; 'perceptual distortion', e.g. "You feel more sensitive to light or the colour or brightness of things"; 'negative symptoms', e.g. "You feel rather indifferent about things"; 'manic experience', e.g. "Ideas and insights come to you so fast that you can't express them all"; 'paranoia/suspiciousness', e.g. "You feel that people have it in for you"; 'cognitive disorganisation', e.g. "Your mind jumps a lot from one thing to another". The scale has a test–retest reliability of 0.84 and a Cronbach's alpha overall of 0.94.

2.2.1.2.2. Schizotypal Personality Questionnaire (SPQ). The SPQ is a standard questionnaire assessing trait schizotypy (Raine, 1991).

Table 1
Group means ± standard deviations (ranges) for demographic data of cannabis and alcohol use.

		Cannabis users	Controls
	Age	26.37 ± 9.63 (19–55)	26.24 ± 10.73 (18–55)
	SPQ	16.74 ± 11.97 (1–49)	13.03 ± 8.35 (0–37)
	HADS anxiety	5.74 ± 3.75 (0–17)	5.14 ± 3.11 (0–14)
	HADS depression	2.57 ± 2.65 (0–14)	2.41 ± 2.48 (0–11)
Cannabis use	Years used	7.6 ± 5.8 (2–30)	–
	Days/month	12.8 ± 5.1 (1–30)	–
	Joints/session	2.3 ± 1.3 (1–5)	–
	Last used (days)	2.2 ± 1.1 (1–7)	414.12 ± 495.12[a] (30–1825)
Alcohol use	Years used	11.3 ± 9.2 (2–39)	9.9 ± 9.9 (1–38)
	Days/month	12.0 ± 8.5 (1–30)	10.1 ± 7.0 (1–30)
	Units/session	7.5 ± 5.8 (1–25)	6.2 ± 5.0 (1–22)
	Last used (days)	5.5 ± 11.6 (1–90)	10.7 + 32.7 (1–180)

[a] $n = 17$ controls who had used cannabis.

2.2.1.2.3. Subjective Effects Scale (SES). The SES comprises eight subjective effects of cannabis rated on 10-cm visual analogue scales (Curran et al., 2002) and is sensitive to state change.

2.2.1.2.4. Hospital Anxiety and Depression Scale (HADS). This brief assessment was used to tap trait anxiety and depression (Zigmond and Snaith, 1983).

2.2.2. Statistical analyses

For the semantic priming task, RTs faster than 250 ms and slower than 1500 ms were excluded. Participants were also excluded from analysis if their mean RTs were consistently more than 2 standard deviations away from their group mean (1 control) and if they made over 20% errors (1 cannabis user). All data are reported without these participants. For the semantic priming task, a 2 × 2 × 3 × 2 repeated measures analysis of variance (ANOVA) with one between-subjects factor of Group (cannabis user, control) and three within-subjects factors of Day (0, 3–5), Relatedness (directly, indirectly, unrelated), and SOA (short, long) was performed on both the RT and error data. Results were checked for a main effect of relatedness in RT data, indicating that priming has occurred. For parsimony, priming effects (conducted by subtracting the RT for related or indirectly related word pairs from the RT to unrelated pairs, see Spitzer et al., 1993) were computed, and direct and indirect priming effects were analysed separately using repeated measures ANOVA with one between- subjects factor of Group and two within-subjects factors of Day and SOA. When significant interactions occurred, post-hoc simple effects tests were conducted using Bonferroni correction. Correlations between priming and other variables were conducted using Pearson's correlation coefficient.

3. Results

3.1. Demographics

One-way ANOVAs showed no significant group differences in age, anxiety or depression (Table 1). There were no group differences in total scores on the trait schizotypy measure (SPQ), but the cannabis users did score more highly on one of the nine sub-scales: 'loss of concentration' ($P = 0.003$). Chi-square analysis showed no significant group differences of gender (Control group: 22 males, 15 females; Cannabis group 21 males, 14 females). Most participants were university students or graduates and there were no group differences in the highest educational level achieved.

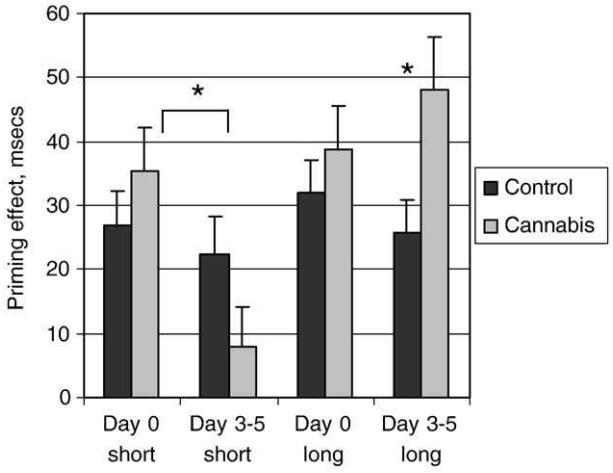

Fig. 2. Direct priming effects across Day, SOA (short or long) and Group.

3.2. Drug use

All cannabis users smoked cannabis on day 0. All controls gave THC-negative urine samples. Three cannabis users also tested positive for other drugs (2 MDMA and 1 amphetamine). Removing these individuals did not change the outcomes of analyses so these were not excluded. There were no significant differences in reported occasional drug use between the groups [n controls, n cannabis = ecstasy 4, 6; cocaine 3, 4; lysergic acid diethylamide (LSD), 3,6; amphetamine 0, 2]. None were regular users of this drug, i.e. >once per month.

Table 1 details cannabis and alcohol use across the groups. There were no significant group differences in years of alcohol use, days used per month or units per session. Seventeen controls reported having tried cannabis but no more than 5 times and not in the previous year.

Five cannabis users and three controls reported having used alcohol on day 0 (max 2 units). One of these cannabis users and two of the controls also consumed alcohol on days 3–5. In the interim (including the evening of day 0) nine cannabis users reported having consumed cannabis, and 13 cannabis users and 22 controls reported having consumed alcohol during the interim. None of the participants reported cannabis use on the day of follow-up testing.

3.3. Semantic priming

3.3.1. Reaction time data (Table 2)

A 2 × 2 × 3 × 2 (Group × Day × Relatedness × SOA) repeated measures multivariate analysis of variance (RMANOVA) revealed a significant main effect of Relatedness ($F_{2,140} = 72.54$, $P < 0.001$) with shorter RTs for

Table 2
Mean reaction times (S.D.) across group, day, word-pair type and condition.

		Cannabis		Controls	
Relation	SOA	Day 0	Days 3–5	Day 0	Days 3–5
Direct	Short	657 (113)	623 (112)	612 (105)	577 (65)
	Long	680 (115)	612 (96)	628 (82)	592 (78)
Indirect	Short	659 (116)	615 (110)	606 (100)	582 (72)
	Long	685 (127)	632 (128)	622 (82)	593 (73)
Unrelated	Short	692 (125)	630 (106)	639 (104)	600 (71)
	Long	719 (121)	661 (118)	660 (89)	618 (70)
Pseudo	Short	771 (121)	725 (113)	724 (88)	681 (74)
	Long	767 (139)	703 (108)	708 (85)	660 (72)

Table 3
Mean percentage errors (S.D.) across group, day, word-pair type and condition.

		Cannabis		Controls	
Relation	SOA	Day 0	Days 3–5	Day 0	Days 3–5
Direct	Short	3.09 (3.55)	1.50 (2.26)	1.55 (2.56)	1.50 (2.26)
	Long	3.2 (3.64)	1.93 (4.08)	1.63 (2.73)	1.89 (2.56)
Indirect	Short	3.22 (4.26)	1.76 (3.44)	3.08 (4.34)	2.57 (2.84)
	Long	1.99 (3.00)	1.15 (2.46)	1.39 (2.64)	1.77 (3.02)
Unrelated	Short	6.61 (3.30)	6.65 (3.73)	6.45 (3.35)	6.44 (3.45)
	Long	5.32 (6.22)	5.19 (5.33)	4.95 (5.42)	4.19 (4.44)
Pseudo	Short	11.45 (8.18)	9.23 (7.17)	12.42 (15.88)	9.74 (8.93)
	Long	8.61 (7.19)	6.36 (5.97)	8.31 (6.38)	6.97 (6.16)

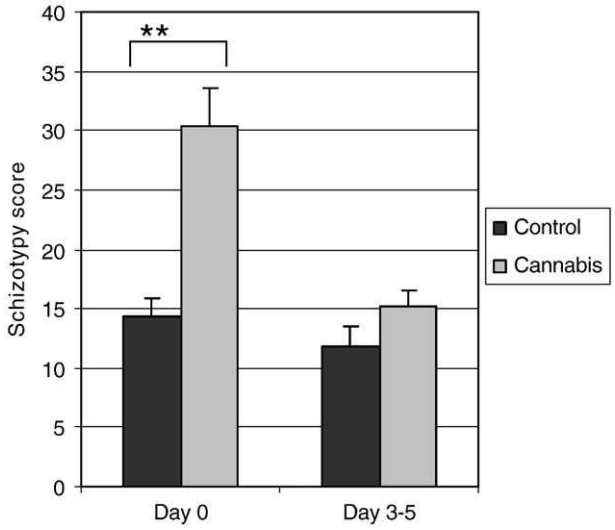

Fig. 3. State schizotypy scores across Day and Group.

related word pairs, indicating priming had occurred; direct and indirect priming effects were calculated (direct RT − unrelated RT/indirect RT − unrelated RT) for both Day and SOA conditions and analysed separately (Spitzer et al., 1998). There was no main effect of Group, indicating groups did not differ on reaction time (Table 2).

3.3.2. Indirect priming

A RMANOVA showed no significant effects of group or interactions on indirect priming, only a main effect of day ($F_{1,69} = 5.41$, $P = 0.023$) whereby participants demonstrated less priming on days 3–5 than on day 0.

3.3.3. Direct priming

A RMANOVA revealed a significant 3-way Group × Day × SOA interaction [$F_{1,70} = 6.71$, $P = 0.012$], a Day × SOA interaction ($F_{1,70} = 5.55$, $P = 0.021$) and a main effect of SOA ($F_{1,70} = 7.43$, $P = 0.008$).

Post-hoc tests demonstrated a significant difference between cannabis users' priming on day 0 and day 3 at the short SOA ($t_{34} = 3.12$, $P = 0.004$) reflecting greater priming in the cannabis users on day 0 than day 3. There were no differences from controls between day 0 and day 3 at either SOA or the cannabis users at the long SOA across days. To further explore the 'chronic' effects of cannabis, group differences on day 3 were examined. A significant difference between controls and cannabis users at the long SOA emerged ($F_{1,70} = 5.62$, $P = 0.02$) with significantly greater priming in the cannabis users compared with controls (Fig. 2).

3.3.4. Errors

No group differences were found (Table 3). There was a 2-way Relatedness × SOA interaction ($F_{2,70} = 5.13$, $P = 0.007$) and main effects of both Relatedness ($F_{2,70} = 110.55$, $P < 0.001$) and SOA ($F_{1,70} = 10.06$, $P = 0.002$). Fewer errors occurred the more directly semantically related were the pairs, and the longer the SOA.

3.3.5. Psychotomimetic State Scale

A 2 × 2 RMANOVA of total state schizotypy scores found a significant Day × Group interaction ($F_{1,70} = 15.07$, $P < 0.001$) and significant main effects of Day ($F_{1,70} = 29.99$, $P < 0.001$) and Group ($F_{1,70} = 15.84$, $P < 0.001$). As can be seen from Fig. 3, the cannabis group scored significantly higher on schizotypy on the night of drug use ($P < 0.001$), but 3–5 days later there were no group differences (individual sub-scales are not reported).

3.4. Subjective effects

Seven scales showed significant Day × Group interactions (stoned, tipsy, dizzy, dry mouth, impaired memory, loss of concentration, increased heart rate: see Table 4). All of these scales showed the cannabis group scoring higher than controls on day 0 and no group differences on days 3–5.

3.5. Correlations

No significant correlations occurred between cannabis use (frequency in days per month or years used), change (between day 0 and days 3–5) in the cannabis users in schizotypy (total score on the Oxford-Liverpool Inventory of Feelings and the Experiences questionnaire and change in semantic priming (priming effects for long and short SOA).

4. Discussion

This study investigated semantic priming in cannabis users both under the influence of the drug and when they had abstained for 3 to 5 days. The main finding was of an increase in priming, or 'hyper-priming' in cannabis users at the short SOA when they were under the influence of the drug versus when they were drug-free. In addition, un-intoxicated cannabis users showed a pattern of greater priming at the long SOA compared with non-cannabis-using controls. Although the two groups did not differ in trait schizotypy, on the night of drug use there was a marked increase in schizotypal symptoms in cannabis users.

As far as we are aware, this is the first study to examine semantic priming in cannabis users. Our results imply that cannabis use is associated with semantic abnormalities. Acutely, cannabis use was associated with an increase in automatic semantic priming, compared with the lower level shown when drug-free. The classic theories of semantic priming dysfunction and its relationship to schizophrenic symptoms suggest that it is an increase in automatic spreading of activation (i.e. manifest as hyper-priming at a short SOA) that accounts for symptoms such as thought disorder. This is supported by some research showing hyper-priming at a short SOA in patients with thought disorder (Moritz et al., 2001; Spitzer et al., 1993;

Table 4

	Cannabis	Control	Cannabis	Control	Day × Group	Day	Group
	Day 0	Day 0	Days 3–5	Days 3–5	*F, P*	*F, P*	*F, P*
Stoned	6.80 (2.05)**	0.22 (0.85)	0.22 (0.71)	0.06 (0.23)	180.9, 0.001	569.4, 0.001	116.2, 0.001
Tipsy	3.20 (3.3)**	0.27 (0.84)	0.14 (0.49)	0.27 (1.17)	15.1, 0.001	44.6, 0.001	11.8, 0.001
Dizzy	3.43 (2.3)**	0.16 (0.56)	0.49 (1.44)	0.38 (1.21)	25.3, 0.001	59.5, 0.001	20.8, 0.001
Dry mouth	4.43 (2.82)**	0.84 (1.61)	0.49 (1.44)	0.51 (1.33)	25.7, 0.001	104.1, 0.001	13.3, 0.001
Impaired memory	3.60 (2.29)**	0.68 (1.54)	0.74 (1.22)	0.65 (1.58)	24.1, 0.001	77.3, 0.001	11.4, 0.001
Loss of concentration	4.37 (2.72)**	1.59 (2.03)	1.00 (1.41)	1.05 (1.49)	14.0, 0.001	72.6, 0.001	6.8, 0.002
Increased heart rate	4.06 (3.00)**	0.30 (0.90)	0.43 (1.09)	0.35 (1.18)	28.2, 0.001	81.2, 0.001	17.2, 0.001
Hunger	3.63 (2.91)*	1.62 (2.08)	2.03 (2.08)	1.51 (2.09)	3.1, 0.050	11.4,0.001	4.0, 0.022

Manschreck et al., 1988). In the current study, the increase in automatic semantic priming was not correlated with the increase in schizophrenic-like symptoms reported under the influence of cannabis. However, the similarity between the effects observed here and those observed in some studies with schizophrenic patients suggests that increased automatic semantic priming may reflect the cognitive basis of some of the psychotomimetic effects of cannabis. These findings are in accordance with the acute effects of THC (Curran et al., 2002) and with the chronic effects of cannabis observed in some (Messinis et al., 2006) but not all (Pope et al., 2001) previous studies which used more primitive and less process-pure semantic tasks, such as category fluency. Given that hyper-priming at a short SOA has been suggested by some to be only present in acute psychosis (Gouzoulis-Mayfrank et al., 2003), these findings are also in accordance with the acute cannabis model of psychosis (D'Souza, 2007).

The mechanism underpinning this pattern of semantic abnormalities in cannabis users is as yet unclear. Neurochemically, the semantic processing changes observed in the current study could be mediated by a variety of mechanisms. Acutely, cannabis has been shown to increase dopaminergic neuronal firing and increase the release of dopamine at terminal fields in the striatum and prefrontal cortex (Lupica and Riegel, 2005), and following an acute dose of the dopamine agonist levo-dopa automatic semantic priming has been found to be increased (Kischka et al., 1996). Therefore it is possible that the acute increase in semantic priming observed in this study was dopaminergically mediated. Another way in which cannabis might evoke changes in semantic priming is via CB1 receptors found on excitatory terminals in areas important in memory such as the hippocampus. It has been suggested that CB1 receptors on excitatory terminals may act as a 'safety mechanism' preventing network excitability (Di Forti et al., 2007). Changes in network excitability could theoretically cause increases in semantic priming acutely, which may explain the increases in priming we observed in cannabis users under the influence of the drug.

Long-term cannabis users exhibited elevated levels of controlled semantic processing. As controlled semantic processes are related to attentional mechanisms under conscious control, it is perhaps difficult to imagine how long-term cannabis use might enhance these processes. It is possible that these are pre-existing differences between cannabis users and controls that draw them to use the drug. Long-term increases in controlled processing may reflect a compensatory process for this depression in automatic semantic processing. However, the long-term semantic abnormalities observed in the current study may not necessarily have negative implications. The link between creativity and semantic priming has been alluded to in one previous study (Spitzer et al., 1996). Future research should address whether the enhanced controlled semantic priming observed in regular cannabis users, rather than a pathological effect, is in fact producing beneficial effects such as enhanced creative processes. An alternative explanation may be that semantic activation is less efficient in cannabis users and thus semantic nodes take longer to activate and this is what is reflected here in our findings of enhanced processing at the long SOA.

There were no group differences in errors, indicating that cannabis users were not different from controls in their ability to perform the task, their concentration or their motivation. This is important to note as it suggests that priming differences are not related to any general performance decrements, as has been suggested to be the case in some studies with patients with schizophrenia. Further, there were no differences in indirect priming, despite the suggestion that hyper-priming is more robustly elicited by indirect priming tasks. However, this may well stem from having indirect and direct conditions within the same task. It has been suggested that combining conditions in this way induces a bias to perceive indirectly related words (e.g. fork-cut) as unrelated given the stronger semantic associations of the directly related pairs (e.g. date-time) (Shelton and Martin, 1992).

Cannabis users showed a marked increase in schizophrenia-like symptoms when intoxicated, during cannabis use. This suggests that cannabis users do encounter a number of unusual, psychotic-type experiences compared with non-users, an effect that may possibly be a risk factor for individuals prone to psychosis. The absence of group differences in trait schizotypy is unlike previous studies (Schiffman et al., 2005; Nunn et al., 2001; Williams et al., 1996; Skosnik et al., 2001), but as those had large sample sizes this may reflect a lack of power in the current study. However, it is possible that, when answering trait questionnaires, cannabis users find it difficult to disentangle their experiences on cannabis from experiences in their 'drug-free' life. As participants in this study answered a state schizotypy questionnaire under the influence of cannabis, it may be that when they come to answer the same (or similar trait schizotypy) questionnaires whilst not under the influence of the drug, it is easier for them to separate the two experiences. This is in line with recent research comparing users' experiences both on and off cannabis (Barkus et al., 2006).

The finding of hyper-priming at a long SOA in abstinent cannabis users is intriguing from the perspective of psychosis. The pattern of semantic priming when acutely intoxicated is similar to that observed in patients with schizophrenia, but when un-intoxicated it is very different. It does, however, look similar to the pattern of results observed in a study of semantic priming in high schizotypes, or people scoring highly on a trait schizotypy scale (Morgan et al., 2006a). In the latter study, scoring high on a schizotypy scale showed reduced priming at the short SOA and increased priming at the long SOA. However, there were no trait differences in schizotypy. As priming effects are essentially differences in *reaction time*, it has been suggested that studies of priming in patients with schizophrenia are confounded by factors such as medication, generalised psychomotor slowing and attentional dysfunction (Moritz et al., 2001). Studies of high scorers on schizotypy scales may allow us to look more purely at the cognitive underpinnings of schizophrenia-like symptoms without such confounds. Given the suggestion of the link between psychosis and cannabis use, that these cannabis users demonstrate a similar pattern of priming to individuals who are exhibiting high levels of schizophrenia-like symptoms may highly tentatively suggest their early cognitive origins. Future research should examine whether and how such priming abnormalities relate to degree of use of the drug – whether they are progressive or whether tolerance develops – by examining the effects on experienced versus naive cannabis users.

Both the acute and 'chronic' effects of cannabis on semantic priming observed in this study differ from acute and chronic effects of another psychotomimetic drug – ketamine – on priming (Morgan et al., 2006b). In the latter study priming was found to be decreased at the long SOA both acutely and chronically. The differences between the effects on priming of these two drugs are interesting in that, although there are many overlapping memory deficits (Fletcher and Honey, 2006), they suggest these two psychotomimetic drugs may have different semantic memory profiles, which may possibly be linked to the different symptoms they produce. This highlights the usefulness of sensitive paradigms such as this in teasing apart the cognitive profiles of different drugs.

This was a naturalistic study and therefore subject to several limitations common to studies of this kind, such as not knowing the dose and purity of cannabis ingested and not being able to accurately verify abstinence. Physiological measures such as horizontal nystagmus, tandem gait and/or expired air CO obtained would have helped verify acute drug use. Although urine screens allowed us to objectively assess drug use, the long half-life of cannabis made confirming abstinence in cannabis users problematic and quantitative urinalysis was beyond the resources of the current study. On the other hand, a strength of this research is its ecological validity: our participants were taking cannabis in the form and quantity that they would normally take it in a usual setting. A further limitation of this cross-sectional study is the possibility that semantic abnormalities observed

when un-intoxicated pre-dated cannabis use and may possibly even represent a vulnerability factor. Prospective studies are the only way to address this issue. In addition, whilst we recorded the number of years participants had spent in education and most were university level students, pre-morbid verbal IQ was not formally assessed.

In summary, cannabis users showed increased state schizotypy and increased automatic semantic priming when under the influence of the drug. Cannabis users did not differ from controls in trait or state schizotypy when drug-free, but did show hyper-priming at the long SOA. The acute increase in automatic semantic priming may be one contributory factor in the psychotomimetic effects of cannabis.

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