HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2012; **27**: 315–321.
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.2229

Khat use is associated with increased response conflict in humans

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Objective Khat consumption has become a worldwide phenomenon broadening from Eastern Africa and the south west of the Arabian Peninsula to ethnic communities in the rest of the world. Only few studies have systematically looked into cognitive impairments in khat users. We studied whether khat use is associated with changes in the emergence and resolution of response conflict, a central cognitive control function.
Method Khat users (n = 16) and khat-free controls (n = 16) were matched in terms of sex, ethnicity, socio-economical situation, age, alcohol and cannabis consumption, and IQ (Raven's Progressive Matrices). Groups were tested on response conflict, as measured by the Simon task.
Results Khat users performed significantly slower than controls and were more strongly affected by stimulus-induced response conflict.
Conclusions Khat use is associated with specific impairments in behavioral control: general slowing and less efficient resolution of response conflicts, which is likely to impair decision making in everyday life. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—khat; response conflict; Simon task; dopamine

INTRODUCTION

The khat plant (*Catha edulis*) is a flowering evergreen. Its leaves have been chewed in East-Africa and the south west of the Arabian Peninsula since ancient times to ease exhaustion, increase alertness and self-esteem, decrease hunger, and induce euphoria and feelings of well-being (Brenneisen *et al*., 1990; Kalix, 1996). Khat has been used for medical purposes as an appetite suppressant and an anti-ulcer agent (Carrier, 2008) and even for its aphrodisiac effects and to treat premature ejaculation. It is also used for recreational purposes (Krikorian, 1984) during casual meetings (so called khat sessions) in which individuals actively engage in discussions and develop and/or preserve social contact. During those sessions, the leaves and the tender younger stalks of khat are chewed slowly, but intermittently to release the active components, over several hours (Al-Habori, 2005).

However, once the positive acute effects vanish, users undergo feelings of exhaustion, sleeplessness, apathy, depression, lethargy, mental fatigue, and concentration difficulties. In humans, chronic (i.e., daily) long-term use of khat is associated with several adverse effects, such as blood vessel constriction, prolonged malnutrition, increased blood pressure, development of gastrointestinal tract problems, cytotoxic effects on liver and kidneys, and keratotic lesions at the side of chewing (Al-Habori, 2005).

The active ingredients of *C. edulis* are cathine (norpseudoephedrine) and cathinone (benzoylethanamine), the latter is the main contributor of the stimulant effect of khat. These alkaloids are similar in structure and pharmacological activity to amphetamines (Wagner *et al*., 1982): both stimulate the central nervous system and suppress appetite. For this reason, khat is also called a "natural amphetamine." However, cathinone has a more rapid onset (roughly 15 min) and a shorter half life (about 4 h) than amphetamine. Cathinone increases levels of dopamine (DA) and norepinerphrine in the brain by acting on the cathecholaminergic synapses, delaying the reuptake and/or enhancing the release of those neurotransmitters (Wagner *et al*., 1982; Patel, 2000). Nevertheless, it is important to note that the consumption of cathinone in pure form is not entirely comparable with chewing khat leaves. Interestingly, synthetic cathinones, in particular mephedrone, has replaced

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Received 20 October 2011
Accepted 30 March 2012

MDMA (3,4-methylenedioxymethamphetamine or "ecstasy") as one of the favorite recreational drugs among individuals who go clubbing, at least in the UK (Wood, Greene and Dargan, 2011). However, the use of mephedrone has been associated with unpleasant side effects, such as sweating, headache, palpitations, nausea, and vomiting.

The neurobiological underpinnings underlying the acute effect of khat and the long-term cognitive effects of chronic khat use are still unclear and understudied (Hoffman and al'Absi, 2010). However, given the chemical similarity of khat and amphetamine in structure and pharmacological activity, long-term use of khat likely affects the same neurotransmitter and brain structures as the chronic use of amphetamine (Berman *et al*., 2008; Salo *et al*., 2009a). At an anatomical level, one may suspect a lower level of structural connectivity as indication of decreased myelination of the fibers and a lower cortical gray matter volume that might underlie the possible cognitive impairments associated with chronic khat use. At a neuromodular level, instead, chronic khat use is likely to be associated with dopaminergic dysfunctions in prefrontal cortex (PFC) and dorsal anterior cingulate cortex (ACC)—circuits innervated by DA and that have been shown to play major roles in the way we control our thoughts and goal-directed behavior (Miller, 2000).

Khat use in Eastern Africa and in the south west of the Arabian Peninsula has gained popularity during the last 10 years and—mainly because of the Somali diaspora caused by the Somali civil war—has become a worldwide phenomenon broadening to ethnic communities in the rest of the world, such as in North America, Great Britain, and the Netherlands (UNODC, World Drug Report, 2010). The airports of Amsterdam and London have become the main European distribution points (Beckerleg, 2008; Pennings *et al*., 2008). In the Netherlands, the use of the unprocessed plant is legal and unrestricted, which makes this country a suitable platform to investigate the effects of the drug.

Surprisingly, only few studies have systematically looked into cognitive impairments in khat users so far. First, Colzato *et al*. (2011a) reported that khat users exhibit impairments in the inhibition of behavioral responses. Participants were asked to press a left or right button as soon as a green left-pointing or right-pointing arrow appeared (go trials). However, if the color of the arrow suddenly changed to red, the participants were supposed to refrain from responding (stop trials). On go trials, khat users performed just as well as non-users in terms of both accuracy and response speed. However, khat users found it much more difficult than do non-users to inhibit responding on stop trials.

Second, Colzato *et al*. (2011b) showed that khat users performed significantly worse than controls on tasks tapping into cognitive flexibility (the ability to adapt and restructure cognitive representations in response to changing situational demands; cf., Monsell, 1996) as well as monitoring information in working memory.

The current study focused on another key cognitive control function: the ability to deal with and resolve response conflict, that is, the ability to select a correct response in the face of other, competing response tendencies. The arguably purest assessment of response conflict is provided by the Simon task (cf., Hommel, 2011). In this task, participants respond to a non-spatial feature of commonly visual stimuli (e.g., color) by pressing left and right response buttons. Importantly, the location of the stimulus varies randomly so that it can spatially correspond or not correspond with the correct response. As one might expect, performance is better with stimulus–response correspondence than with noncorrespondence—the Simon effect (Simon and Small, 1969). The effect reflects the difficulty of selecting a response in the face of competing response tendencies and can thus be taken as a rather pure measure of (the efficiency of resolving) response conflict (Kornblum, Hasbroucq and Osman, 1990; Hommel, 2011).

Interestingly, the ACC has been considered responsible for the detection of response conflict, and DA has been suggested to play a key role in coding such a conflict (Botvinick, 2007). Holroyd and Coles (2002) argued that response errors or negative feedback induce a dip in DA cell firing, which is transmitted to the ACC, where the drop in DA levels disinhibits the apical dendrites of motor neurons. Indeed, the stimulation of the ACC can transiently inhibit DA release (Jackson, Frost, and Moghaddam, 2001).

To sum up, in the present study, we used the Simon task (Simon and Small, 1969) to test whether khat use produces deficiencies in the resolution of response conflict. Given the aforementioned relation between DA and response conflict and ACC on the one hand, and between DA and khat on the other, we expected increased response conflict (as indicated by a larger Simon effect) in khat users than in khat-free controls.

MATERIALS AND METHODS

Participants

Thirty-two young healthy African adults (28 men and 4 women) were compensated for their participation. They constituted the two groups of 16 khat users and 16 khat-free controls. The sample was drawn from

DOI: 10.1002/hup

40 adults in the Leiden and The Hague metropolitan area, who volunteered to participate in studies of behavioral pharmacology and did not participate in previous studies of Leiden University. Participants were recruited via ads posted on community bulletin boards and by word of mouth. Participants were selected via an interview using the Mini International Neuropsychiatric Interview (Sheehan *et al*., 1998). The Mini International Neuropsychiatric Interview is a well-established brief diagnostic tool in clinical, stress, and psychopharmacology research (Sheehan *et al*., 1998; Elzinga *et al*., 2008; Colzato *et al*., 2009) that screens for several psychiatric disorders including post-traumatic stress disorder, schizophrenia, depression, mania, attention deficit/hyperactivity disorder, and obsessive–compulsive disorder. On the basis of the interview, we excluded 8 of the 40 potential participants because of current medication use or hints to a possible psychiatric disorder (post-traumatic stress disorder) and/or current medication.

Following Colzato *et al*. (2011b), we made sure that the users met the following criteria: (i) khat consumption by chewing route for a minimum of 1 year; (ii) no clinically significant medical disease; and (iii) no use of medication. All khat users met more than four of the seven criteria that according to the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and the World Health Organization (International Classification of Diseases-10) define addiction: tolerance, withdrawal, difficulty controlling the use, negative consequences for job, family and health, significant time or emotional energy spent in searching/consuming the drug, put off or neglected activities because of the use, and desire to cut down the use. None of the khat-free controls reported any history of past or current khat use.

Participants were asked to refrain from taking any psychoactive drugs for at least 24 h before the test, not to consume alcohol on the night before the experimental session, and to have a normal night rest. Participant's compliance with the instruction was encouraged by taking a (not further analyzed) saliva sample test at the beginning of the session (cf. Colzato *et al*., 2004; 2009).

The two groups were matched in terms of ethnicity (100% African), age, sex, IQ, (measured by Raven's Standard Progressive Matrices (SPM); Raven *et al*., 1988), socio-economic situation, and alcohol and cannabis consumption. In the Netherlands, the use of khat is confined to East-African immigrants and is predominantly used by male individuals (Pennings *et al*., 2008). All participants were rated middle socioeconomic status according to the Hollingshead Occupational Status Scale (Hollingshead, 1975). Even though khat was the preferred drug for users, some of them drank alcohol (five) on a weekly base and used cannabis (two) on a monthly base. Khat users and non-users reported to have never used LSD, MDMA, cocaine, amphetamine, barbiturates, ketamine, GHB, or speed. Demographic and drug use information is provided in Table 1. Written informed consent was obtained from all participants after the nature of the study was explained to them. The protocol and the remuneration arrangement of €12 were approved by the institutional review board (Leiden University, Institute for Psychological Research).

Apparatus, stimuli, and task

The Simon task has been previously used to systematically investigate the neurotoxic effects of methylphenidate (Rubia *et al*., 2011). The experiment consisted of a 25-min session in which participants made speeded discriminative button-press responses to the color of a circle. Participants responded left to a green circle and right to a blue circle. Circles were equiprobably presented to the right or to the left of a central fixation point until the response was given or 1500 ms has passed. Intervals between subsequent stimuli varied randomly but equiprobably, from 1750 to 2250 ms in steps of 100 ms. Participants were to ignore the location of the stimulus and to base their response exclusively on its color. Responses were to be given as fast as possible while keeping error rates below 15% on average;

Table 1. Demographic characteristics and self-reported use of khat and other psychoactive drugs. Standard deviations are presented within parentheses

Sample	Khat users	Khat-free controls
N (M:F)[a]	16 (14:2)	16 (14:2)
Age (years)[a]	32.4 (7.2)	28.8 (5.6)
Raven IQ[a]	108 (3.0)	109 (2.9)
Khat exposure (years)*	9.6 (6.0)	0
Khat times in a week*	3.1 (1.8)	0
Bundles used (khat shrubs)*	2.9 (1.2)	0
Bundles used in one session	1.0 (1.9)	0
Hours chewing khat*	5.9 (1.9)	0
Monthly exposure (joints)[a]	0.4 (1.2)	0.5 (1.5)
Monthly drinks (units)[a]	1.5 (2.4)	1.4 (2.2)
Lifetime cocaine (g)[a]	0	0
Lifetime amphetamines (g)[a]	0	0
Lifetime ketamine (g)[a]	0	0
Lifetime speed (g)[a]	0	0

Raven IQ, IQ measured by means of the Raven's Standard Progressive Matrices; bundles used, number of khat bundles consumed in a typical day/session; hours chewing khat, amount of time the users spend chewing khat in a typical day/session; monthly drinks, monthly number of standard alcoholic drinks.
[a]Nonsignificant difference.
Significant group difference;
*$p < 0.01$.

DOI: 10.1002/hup

feedback was provided at the end of a trial block. The task consisted of six blocks of 60 trials (with all conditions being equiprobable), the first of which served as a practice block.

Procedure and design

All participants were tested individually. Individual IQs were determined by means of a 30-min reasoning-based intelligence test (SPM). The SPM assesses the individual's ability to create perceptual relations and to reason by analogy independent of language and formal schooling; it is a standard, widely used test to measure Spearman's g factor and of fluid intelligence in particular (Raven *et al.*, 1988). Participants provided a saliva sample, completed the SPM, and subsequently performed the behavioral tasks measuring response conflict. Participants were allowed to take a short break (maximum of 5 min) between task blocks. The experiment was controlled by a PC attached to a 17-inch monitor with a refresh rate of 120 Hz.

Statistical analysis

Independent *t*-tests were performed to test age, IQ, alcohol, and cannabis consumption differences between the groups. In the Simon task, mean reaction times (RTs) and (square-rooted) error percentages[1] were analyzed by means of analyses of variance (ANOVAs) using spatial stimulus–response correspondence (versus noncorrespondence) as a within-participant factor and group as a between-participant factor. Moreover, Pearson correlation coefficients were computed between the degree of exposure to khat and cognitive performance to test whether the magnitude of cognitive impairments is proportional to the amount of khat consumed. Effect magnitudes were assessed by calculating partial eta squared (η_p^2) for repeated-measures ANOVAs. A significance level of $p < 0.05$ was adopted for all tests.

RESULTS

Participants

No significant group differences were obtained for age, $t(30) = 1.51$, $p = 0.13$, intelligence, $t(30) = 0.71$, $p = 0.48$, alcohol consumption, $t(30) = 0.15$, $p = 0.88$, or cannabis consumption, $t(30) = 0.56$, $p = 0.80$. Table 1 shows drug-use profiles for the two groups.

[1] Error percentages were transformed into square-rooted values to account for the problem that percentages are not normally distributed—which is a precondition for ANOVAs (Winer, 1971).

Simon task

The RT analysis showed evidence of a group effect, $F(1, 30) = 7.02$, $p < 0.05$, mean squared error (MSE) = 8637.81, $\eta_p^2 = 0.19$: khat users were in general slower than khat-free controls. The RT and error rates analyses showed a main effect of correspondence, $F(1, 30) = 158.81$, $p < 0.0001$, $MSE = 159.58$, $\eta_p^2 = 0.84$ (RTs) and $F(1, 30) = 51.90$, $p < 0.0001$, $MSE = 11.63$, $\eta_p^2 = 0.63$ (errors), which was modified by group in RTs but not in errors, $F(1, 30) = 7.27$, $p < 0.05$, $MSE = 159.58$, $\eta_p^2 = 0.19$ (RTs) and $F < 1$ (errors). To verify whether the overall RT increase in khat users may have confounded this outcome, we ran another ANOVA with overall RT level as covariate; however, the crucial 3-way interaction remained significant: $F(1, 29) = 5.71$, $p < 0.05$, $MSE = 165.08$, $\eta_p^2 = 0.16$.

Both groups showed a significant main effect of correspondence, $F(1, 15) = 140.87$, $p < 0.0001$, $MSE = 55.57$, $\eta_p^2 = 0.90$ (RTs) and $F(1, 15) = 24.71$, $p < 0.0001$, $MSE = 8.70$, $\eta_p^2 = 0.62$ (errors); $F(1, 15) = 70.85$, $p < 0.0001$, $MSE = 263.60$, $\eta_p^2 = 0.82$ (RTs) and $F(1, 15) = 27.71$, $p < 0.0001$, $MSE = 14.57$, $\eta_p^2 = 0.65$ (errors), for khat-free controls and khat users, respectively. These main effects indicated that responses were faster and more accurate with stimulus–response correspondence (431 ms and 2.9%) than with non-correspondence (471 ms and 9.0%, respectively). As expected, however, the RT correspondence effect was reliably increased in khat users as compared with khat-free controls, and the error rates followed the same pattern (Table 2).

Correlations

To test whether the magnitude of cognitive impairments is proportional to the amount of khat consumed,

Table 2. Performance on the Simon task as a function of correspondence (correspondent versus noncorrespondent) and group (khat users versus khat-free controls). Standard errors of reaction times and error rates are presented in parentheses

Variables	Khat users	Khat-free controls
Simon task		
Correspondence		
Reaction times (ms)	458 (16.5)	405 (16.5)
Error rates (%)	2.6 (0.8)	3.1 (0.8)
Noncorrespondence		
Reaction times (ms)	506 (16.6)	436 (16.6)
Error rates (%)	9.7 (1.6)	8.3 (1.6)
Simon effect		
Reaction times (ms)*	48	31
Error rates (%)	7.1	5.2

Significant group difference;
*$p < 0.05$.

DOI: 10.1002/hup

we computed Pearson correlation coefficients between the individual lifetime khat exposure, hours chewing, and number of bundles used in a khat session and Simon effects in RT and accuracy. Hours chewing positively correlated with Simon effect, $r(16) = 0.62$, $p = 0.01$, whereas khat exposure, peak and number of bundles used in a khat session did not, even though the direction of the associations was similar. Hence, longer chewing is associated with increased response conflict (Figure 1).

DISCUSSION

This study tested, for the first time, whether long-term khat use is associated with a detectable selective impairment in cognitive control to resolve response conflict. As expected, khat users were slower than khat-free controls in selecting the correct response when an alternative response was simultaneously activated. Moreover, the size of this deficit corresponds to the hours spent in chewing khat. Hence, the longer the chewing, the more active compounds are released, the greater the magnitude of the loss in selecting the correct response. We suggest that this impairment may be due to the long-term use of cathinone, the active ingredient of khat, which is associated with dysfunctions in PFC and a reduced DA level—the neurotransmitter that plays a key role in resolving response conflict (Cools, 2006; Botvinick, 2007). Taking into account the chemical resemblance between cathinone and amphetamine, our results are also in line with those of previous studies in humans showing impairments in response conflict as consequences of long-term amphetamine and methamphetamine use (Salo *et al*., 2009b; Rubia *et al*., 2011; 2009c; 2009b). Alongside all those studies, we found no group differences in accuracy, presumably reflecting the fact that error rates are not normally distributed and therefore less sensitive.

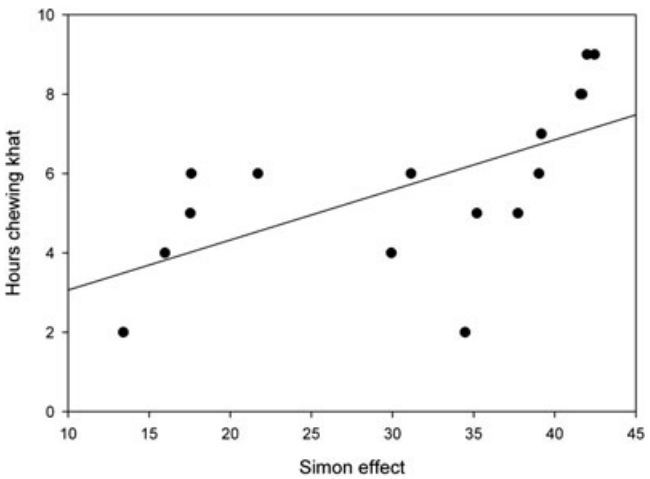

Figure 1. Scatter diagram of individual hours chewing khat against Simon effect (in ms)

As our participants were screened for several psychiatric disorders, we can rule out an alternative account in terms of pre-existing psychiatric disorders (such as posttraumatic stress disorder and psychosis) that have been associated with khat-consuming populations such as Somali refugees (Kroll *et al*., 2011). Particularly important was the matching of the age range: the ability to resolve response conflict is known to decline with increasing age (Mager *et al*., 2007).

However, it is important to bear in mind that the causal relation between chronic use of khat and cognitive impairments is not necessarily clear-cut. We cannot rule out that pre-existing genetic or neurodevelopmental factors may play a modulating role. For instance, individuals with a genetic predisposition that hampers response conflict functions might be drawn to chewing khat more strongly so that what looks like an effect of drug use might actually represent a form of self-selection.

It is also important to note that we cannot exclude that pesticides as DDT, which are still used in khat-growing countries, may have partially contributed to the adverse cognitive effects of chewing khat (Daba *et al*., 2011). Moreover, two other factors may be associated with our results of increased response conflict: First, long-term khat users are known to undergo withdrawal symptoms during the first days of abstinence, such as mental fatigue, sleeplessness, and apathy. Second, since cathine lasts longer than one day in the system, it cannot be ruled out that our findings may be due to possible acute effects potentially masking or potentiating longer term effects (Al-Habori, 2005).

Even though positron emission tomography studies on DA receptors availability still need to be carried out, we may speculate that in khat users, the inputs from midbrain dopaminergic nuclei are drastically reduced. Such nuclei are fundamental in driving the ACC, which is assumed to bias response-selection mechanisms toward the correct response (Botvinick, 2007).

The current findings raise the issue whether long-term khat use, as in the case of methamphetamine (Salo *et al*., 2009a), decreases the plasticity of the white matter (the structural connections between regions based on known axonal projections) underlying the cognitive control system in PFC and ACC. Of particular interest would be to investigate the acute effect of khat on cognitive functions. Given that the acute administration of amphetamine enhances inhibitory mechanisms involved

DOI: 10.1002/hup

in visual search (Fillmore, Rush and Abroms, 2005), it is possible that the acute administration of khat improves rather than impairs the ability to inhibit irrelevant information and to select correct responses in the face of conflict.

Moreover, given the chemical similarity of khat and synthetic cathinones in structure and pharmacological activity, the long-term use of these so called designer drugs, such as mephedrone, is likely to be associated with similar cognitive deficits such as in the case of the chronic use of khat. Given that the use of mephedrone has increased in recent years, because of the fall in the use of MDMA, it seems of societal relevance to devote more research on the functional significance of possible deficits associated with the use of designer drugs.

CONCLUSION

Together with previous demonstrations of khat-related impairments in working memory updating, flexibility, and inhibitory control (Colzato *et al.*, 2011a, 2011b), the present finding that long-term khat use is associated with general slowing and a more specific decrement in the ability to resolve response conflict suggests an extensive and wide-ranging impact of khat use on human cognition. Therefore, using khat can be expected to have a negative effect on a broad range of everyday behavior. For instance, impairments in the selection of correct actions in the presence of less appropriate alternatives is fundamental in driving behavior, which is likely to account for the increasing number of traffic accidents in Eastern Africa and the south west of the Arabian Peninsula countries linked to khat-chewing habits (Toennes and Kauert, 2004). Moreover, even though general slowing by 62 ms and a specific conflict-induced delay of 17 ms seems negligible at first sight, these numbers correspond to a 12.8% and 35.4% slowing of general response speed and decision-making time, respectively. Moreover, the task we used to assess response conflict was incredibly simple in using minimalistic stimulus and response sets related by only two stimulus–response rules. Considering the much greater complexity of many everyday life decisions, together with the fact that decision-making time increases with the number of stimuli and responses involved (Hick, 1952), it is easy to imagine that even a small-looking impairment can have considerable consequences on real-life decision making.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interests.

ACKNOWLEDGEMENTS

We thank Lucy Chadota for her enthusiasm and invaluable assistance in recruiting the participants of this study.

The research of Lorenza S. Colzato, Bernhard Hommel, and Wery van den Wildenberg is supported by NWO (Netherlands Organization for Scientific Research).

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DOI: 10.1002/hup