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Khat Use and Neurobehavioral Functions: Suggestions for Future Studies

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Abstract

Although there is a rich body of research available regarding the effect of acute and chronic khat dosing in animal models, research on the behavioral and cognitive effects of khat in human subjects is not extensive and several of the available studies have been done only in the context of observational and single-case studies. In light of the absence of a substantial literature on the neurobehavioral deficits associated with khat use and to provide a context that could be used to identify themes for future research we review previous research that has focused on other stimulant drugs. This review highlights multiple areas of neurocognitive deficit that have been identified in previous studies of individuals who have been chronic users of stimulants, such as amphetamines and methamphetamines. The review highlights a substantial body of evidence demonstrating a wide range of learning and memory impairments including deficits that persist during abstinence from active drug use. This review does not imply a similar khat effect, but due to some similarities pharmacologically between the active components of khat (cathinone and cathine) and amphetamines, future studies examining these same domains of cognitive functioning in chronic khat users and abstinent khat users appears to be warranted, if possible using some of the same or similar laboratory measures.

INTRODUCTION

The stimulant leaf khat (Catha edulis Forsk) comes from a tree which grows in countries bordering the Red Sea, along the east coast of Africa and in west Asia (Cox and Rampes, 2003; Balint et al., 2009). Catha edulis is popularly known as "khat" but is also known as "kat", "qat", "qad", "qaad". "jaad", and "miraa". This alkaloid-containing psychostimulant plant is commonly used in East Africa and the Arabian Peninsula (Balint et al., 1991; Banjaw and Schmidt, 2006), as well as by immigrants from these regions who reside in Western countries, primarily Great Britain and the United States (Warfa et al., 2007; Bhui et al., 2003). Khat is chewed habitually by users for its euphoric effects and as a recreational drug, and chewing khat has an important role as well in both traditional and religious ceremonies (Banjaw and Schmidt, 2005; Banjaw and Schmidt, 2006).

Chewing is the most common mode of administration (Cox and Rampes, 2003), although a small number of users use dried leaves to make drinks and an equally small number smoke it

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(Pantelis et al., 1989). The traditional way to consume khat is to pick a few leaves of a young shoot and chew them slowly. Once the leaves are pulped, they are kept in the side of the cheek and the mouth is filled with fresh leaves. The user then chews slowly and intermittently to release the active components of khat that are then swallowed with saliva (Cox and Rampes, 2003), periodically ingesting fresh leaves (Banjaw and Schmidt, 2005).

The psychostimulant component of khat is cathinone, which is released within 15–45 minutes during chewing (Graziani et al., 2008). A khat chewing session, however, may last 3 to 7 hours (Banjaw and Schmidt, 2005). Khat chewing has a social and cultural tradition, and it may occur while in the company of others or alone (Balint et al., 2009). It is highly prevalent in many countries in Africa and Asia, with 75% of men using khat in some countries (Alem et al., 1999). About twenty years ago, it was estimated that around 10 million people commonly used khat in East Africa and Arabian Peninsula countries (Balint et al., 1991), but there is some evidence to suggest that use may be increasing. In 1996, it was estimated that worldwide approximately 6 million individual portions of khat were consumed daily (Kalix, 1996). Recent reports indicate that 80–90% of East African males use Khat on a daily basis and 10–60% of East African females use khat on a daily basis (Numan, 2004; Odenwald et al., 2005; Warfa et al., 2007). In Ethiopia, recent estimates of prevalence (Alem et al., 1999) approach 50%, with 17% self-described as daily users, predominantly men (a reported 5:1 male to female ratio).

While early reports indicated greater prevalence in men than in women, recent reports - including those by members of our group - have shown sharp increases in khat use by women in some countries, including Yemen (Griffiths, 1998; Khalil, 1998). The prevalence of khat use has also been climbing in several communities in Europe and North America (Griffiths, 1998). Interestingly there is evidence to suggest that the gender differences in khat use disappear in Western countries. A recent survey conducted in London, UK, showed that 78% of men and 76% of women of Somali background had used khat, with 76% of participants reporting using more khat in London than they had in Somalia (Griffiths, 1998). Historically, khat is used near where it is grown, but advanced land and air transportation and recent immigrations have allowed a much wider distribution around the world, including distribution in Europe and North America.

Users of khat report feeling as if they are able to think more clearly and more quickly while chewing khat, and also report increased energy, increased confidence, a general sense of wellbeing, decreased hunger and fatigue, and the increased ability to easily converse with others. Other self-reported acute effects of khat include increased levels of alertness, enhanced ability to concentrate, friendliness, contentment and flow of ideas (Cox and Rampes, 2003; Balint et al., 2009). This is usually followed by excessive tension, anxiety, emotional instability, irritability, and restlessness within 2 hours, followed by feelings of low mood, numbness, lack of concentration, sluggishness, and insomnia.

Pharmacology of khat

Research initiatives sponsored by the World Health Organization have fostered scientific studies designed to understand the pharmacology of khat. This research has demonstrated that khat leaves contain cathinone, a psychostimulant that is similar in structure and pharmacological activity to amphetamine (Kalix, 1992; Kalix, 1994). Due to these similarities, cathinone has been called a 'natural amphetamine' (Kalix, 1996). Cathinone or more properly S-(−) cathinone has been characterized as an amphetamine-like sympathomimetic amine (Kalix, 1996) with a half-life of approximately 3 hours in humans (Widler et al., 1994; Toennes et al, 2003). Cathinone reaches a maximum plasma level 1–2 hours after oral administration; the effect of cathinone on the user occurs more rapidly than the effect of amphetamine, roughly 15 minutes as compared to 30 minutes (Cho and Kumagai, 1994). In addition to cathinone, cathine or d-norpseudoephedrine has been identified as an additional psychoactive ingredient in khat (Graziani et al., 2008), and cathine has also been noted to have psychostimulant properties. Although cathinone appears to be only half as potent as amphetamine and cathine is roughly 7–10 times less potent than amphetamine, the well-developed scientific literature examining the acute and chronic neurobehavioral effects of amphetamine and methamphetamine may provide a model to guide future research related to the acute and chronic effects of khat use.

Similar to psychostimulants, khat ingestion produces several central nervous system effects, including increased motor stimulation, euphoria, and a sense of excitement and energy (Widler et al., 1994; Kalix, 1996; Nencini et al., 1998). It also results in decreased appetite and increased blood pressure and heart rate. These effects indicate that khat acts through similar central mechanisms as other stimulants. For example, both cathinone and amphetamine increase the activity of the dopaminergic and noradrenergic transmission (Pehek and Schechter, 1990; Pehek et al.,1990; Patel, 2000). While the nature of khat dependence remains under active debate, there is accumulating evidence indicating the existence of a withdrawal syndrome and a low level of tolerance. Withdrawal symptoms usually include inertia, nightmares, trembling, depression, sedation and hypotension (Cox and Rampes, 2003).

Khat use, health and neurological functioning

Over the years epidemiological and case control studies have indicated a clear association between long-term khat use and cardiovascular, respiratory, gastrointestinal, obstetric, metabolic, endocrine, and nervous system dysfunction (Nasher et al., 1995; el-Shoura et al., 1995; Dalu, 2000; Al Habori and Al Mamary, 2004; Al Habori, 2005; Hassan et al., 2000; Hassan et al., 2005). Reviews of research on the relationship between khat use and cardiovascular functions have indicated increased sympathetic activity (Widler et al., 1994; Hassan et al., 2000), increased pulse rate, increased arterial pressure, and increased risk for acute myocardial infarction (Al Motarreb et al., 2002). It has been reported that khat users in Yemen have a higher incidence of esophageal cancer (Balint et al., 2009). Evidence of obstetric problems of khat users indicates that khat use during pregnancy is associated with low birth weight and impaired lactation (Mwenda et al., 2003). Although chronic use of khat associated with brain problems have not been carefully studied, evidence from the study of other similar drugs of abuse suggests that individuals who have been chronically exposed to drugs of abuse show both structural and functional brain changes (Yucel and Lubman, 2007; Yucel et al., 2007). Neurobiological changes due to chronic drug use vary as a function of many factors, however, including the class of drugs and the pattern of use, as well as the complex interplay with pre-existing neurodevelopmental factors. For example, there is some evidence to suggest that primates that have pre-existing lowered D2 receptor densities are at increased risk to use cocaine and become addicted (Nader et al., 2006) and similar results have been reported in the rodent model (Dalley et al., 2007). In similar fashion, humans that are chronic users of cocaine may be more likely to have pre-existing problems in inhibitory control (Bechara, 2005) and impulsivity (Verdejo-Garcia et al., 2008). A similar relationship may well exist between pre-existing conditions and behavior patterns of khat users, which must be considered in future studies.

One primary structure that has been implicated in drug-related deficits across multiple studies is the prefrontal cortex, accounting for various cognitive, behavioral, and emotion regulation deficits. Impairments in these domains may particularly be evidenced in individuals who use multiple drugs, or who are exposed to other high risk environmental conditions.

Cognitive and behavioral deficits associated with khat use

Research on behavioral and cognitive problems following khat use in humans is not extensive and several of the available studies have been done only in the context of observational and single-case studies. Khat users report that they use this substance to improve their performance, stay alert, and to increase their energy (Cox and Rampes, 2003). Preliminary observations suggest that chronic use of khat is associated with various cognitive and mental health impairments, however (Odenwald, 2007; Odenwald et al., 2007; Balint et al., 2009; Odenwald et al., 2009). Central nervous system deficits associated with khat use include impaired concentration, insomnia, headaches, migraine, midriasis, conjunctival congestion, impaired motor coordination, fine tremor, stereotypical behavior (Al-Motarreb et al., 2002).

Other indirect observations also indicate long-term effects that range from insomnia, anxiety, irritability, agitation and aggression to major problems such as schizophreniform psychotic disorder, paranoid delusions, mania, and depression, as well as an apparent increase in suicidal depression and an increased relative risk of hallucinations (Yousef et al., 1995; Alem and Shibre,1997; Odenwald et al., 2005; Odenwald, 2007; Balint et al., 2009). These effects are similar to those observed in amphetamine users. Recent evidence suggests a possible synergistic relationship between khat use and post-traumatic stress disorder as a risk factor for paranoia (Odenwald et al., 2007; Odenwald et al., 2009).

While there is no specific neuropsychological data on the acute or chronic effects of khat, research with other stimulants may provide a perspective. Acute d-amphetamine administration improves certain tasks, such as vigilance tasks (Comer et al, 1996; Koelega, 1993) and attention (de Witt et al., 2002; Cami et al., 2000), but impairs performance on visual scanning tasks (Silber et al, 2006). Research has also shown amphetamine to have negative effects on sensorimotor gating (Hutchison and Swift, 1999), reflecting deficits in the ability to filter out irrelevant or intrusive stimuli, which subsequently causes an overload of information (Swerdlow and Geyer, 1998). It is possible that khat produces similar effects on cognitive performance, although perhaps to a lesser extant.

One of the significant implications of these possible khat-related effects is that related to erratic and unstable driving, possibly leading to increased traffic accidents and related fatalities. It is worth noting that Yemen, where khat is widely used by drivers, is ranked among the highest in both the number of vehicular accidents and the number of deaths from these accidents worldwide, despite frequent campaigns for traffic safety sponsored by local and international organizations (Ameen and Naji, 2001). Although khat has a stimulating effect that reportedly enhances attention and performance during the first few hours of use, it may still be a culprit in increasing the risk for road accident fatalities due to increased anxiety and tension that usually appears after several hours of use and due to users engaging in distracting behaviors such as drinking water, smoking, or preparing and cleaning the khat leaves while driving (Ameen and Naji, 2001).

Toennes and Kauert (2004) analyzed the results of 19 forensic vehicular cases in which the use of khat was detected, observing that impaired driving was suggested in 10 of the 19 cases, with observed symptoms by on scene police personnel that were in agreement with effects of indirect sympathomimetic agents including khat-alkaloids (impaired coordination, impaired balance, slow pupil reaction to light, impairment of divided attention, and tremor and balance problems in some cases). They concluded that chronic khat use may lead to a marked deterioration of psychophysical functions, including those relevant to driving vehicles in a safe manner. Presumably, impairments such as this would hamper the operation of heavy machinery, assembly and factory tasks, affect some military operations, and affect many tasks that require vigilance, divided attention, visual scanning, and motor coordination. There is a clear need to further investigate what appears to be a serious potential public safety issue in carefully controlled laboratory experiments,

Effects of long-term khat use

Some limited studies and single case reports suggest long-term effects of khat on behavioral and cognitive functions. These effects range from minor to major psychiatric problems. Minor effects include insomnia, anxiety, irritability, agitation and aggression. Other documented psychiatric effects include a short-lived schizophreniform psychotic illness and mania (Yousef et al, 1995; Odenwald, 2007). Use of excessive amount of khat has also been was found to significantly increase the risk for psychosis or psychotic-like episodes (Alem and Shibre, 1997; Odenwald et al., 2005; Warfa et al, 2007), including paranoid delusions and significant mania. These effects are similar to those observed in amphetamine users. Depression has also been frequently reported to be related to long-term use of khat and seems to be particularly evident during cessation (Odenwald, 2007).

Concurrent use of Khat and Other Drugs of Dependence

Concurrent use of khat and tobacco

During khat chewing sessions, users consume large quantities of tobacco. We have observed that approximately 55% of khat users are also regular smokers, and this is supported by a study with medical students at Aden University showing 42% of khat chewers were heavy smokers, and 9.3% of the participants reported smoking only when they chewed khat (Bawazeer et al.,1999). Griffiths (1998) has shown that 60% of khat chewers also smoked cigarettes. The extent to which concurrent use of khat and tobacco interacts in influencing cognitive or stress-related biobehavioral functions is not known. Studies examining effects of tobacco have shown that long-term smoking contributes to dysregulation of the neurobiological response, and that acutely nicotine affects stress response hormonal and physiological measures. Acutely, nicotine enhances psychomotor performance, such finger tapping (Perkins et al., 1990) and sustained attention (Harakas and Foulds, 2002; Mumenthaler et al., 1998). On the other hand, cognitive deficits have been observed during abstinence from cigarette smoking (al'Absi et al., 2002).

There may be a complex interaction between the presumed amphetamine-like effects of khat use and tobacco use. Although both amphetamine and nicotine are dopamine agonists, there are observed differences in their effects on behavioral measures. Amphetamine has been observed to improve performance on cognitive processes such as attention and psychomotor functioning, but appears to impair performance in other areas of cognitive functioning, such as those requiring visual scanning or the ability to filter out irrelevant information (Silber et al., 2006). It is possible that the use of both khat and tobacco presents greater risk than use of khat alone on emotion regulation and cognitive functions. Further investigation in this area is relevant to research focusing on concurrent addictive behaviors in other countries related to the comorbidity of tobacco and alcohol dependence (John et al., 2003; Hurt and Patten, 2003) and the comorbidity of tobacco and marijuana use (Humfleet and Haas, 2004; Lai et al., 2000; Burns et al., 2000).

Concurrent use of khat and alcohol

Due to the acute stimulating effects of khat and its effects on mood and sleep, khat users may also use alcohol as a method to calm down. One early study that investigated alcohol and khat use in Kenya found that more than two thirds of khat users use alcohol and 41% of khat users drank alcohol heavily (Dhadphale and Omolo, 1988). More recently, Kebede et al. (2005) reported that a significant number of their sample of Ethiopian youth between the ages of 15 and 24 used both khat and alcohol. Gelaw and Haile-Amlak (2004) reported that 59% of their sample of adult University workers in Ethiopia used alcohol after chewing khat, primarily to avoid insomnia and to decrease unpleasant feelings and depression. Selassie and Gebre (1996) and Nabuzoka and Badhadhe (2000) have also reported polydrug use in some khat users, primarily the use of alcohol and benzodiazapines.

Effects of Stimulants on Human Performance

In light of the absence of a substantial literature on the neurobehavioral effects of khat on human performance and to provide a context that could be used to identify themes for future research, we next briefly review the available scientific literature regarding the effects of amphetamine on human neurobehavioral functions. This review does not imply a similar khat effect. Rather, in light of some common psychostimulant properties between these substances, previously observed effects of other stimulants should be considered when developing future hypotheses for studies of the neurobehavioral effects of khat.

Neurocognitive Deficits Associated with Acute Amphetamine Use

Acute use of amphetamines and methamphetamines results in a number of effects on the sympathetic branch of the autonomic nervous system including hypertension, tachycardia, hyperthermia, increased breathing rate, and constriction of blood vessels. The acute cognitive and emotional effects of amphetamine use are similar to those reported by khat users including feelings of euphoria, enhanced energy and alertness, feelings of increased physical and mental capacity, and the belief by the user that they are experiencing a surge in productivity (Cretzmeyer et al., 2003; Hart et al., 2001). A sense of elevated self-esteem and increase in libido are also fairly common with acute amphetamine use. These effects may last from 8 to 13 hours, roughly equivalent to the half life of methamphetamine (Busto et al, 1989). Repeated use or binge use of methamphetamines is quite common in chronic users, however, and in these instances methamphetamines may be repeatedly taken over the course of hours or even days. During binge use, users may exhibit an increase in sexual behaviors and repetitive, focused activities such as mechanical work or intense periods of cleaning, very commonly accompanied by sleeplessness (Semple et al., 2003). The progressively higher doses of methamphetamine needed to maintain a drug "high" with binge use can result in heightened anxiety, paranoia, hallucinations, and possibly frank delirium (Harris and Batki, 2000).

As a binge progresses, the positive effects of amphetamines generally become less pleasurable, while toxic effects become more prominent, and individuals eventually experience a phase characterized by increased anxiety, irritability, insomnia, and confusion. A withdrawal syndrome can occur at the termination of binge use and can include dysphoria, depression, irritability, anxiety, poor concentration, hypersomnia, fatigue, paranoia, akathisia, and drug craving (Barr et al., 2002; Zweben et al., 2004). Although a causal relationship has not been adequately demonstrated, methamphetamine use is frequently associated with increased impulsive, violent, and even homicidal behavior, as well as unsafe automobile driving. Clinical studies present a complex picture regarding the acute effects of methamphetamine on cognition. A number of studies have reported an enhancement of cognitive performance with acute administration of therapeutic doses, especially increases in information processing speed, psychomotor functioning, and attention, in both non-drug using volunteers (Johnson et al., 2000; Silber et al., 2006) and stimulant-dependent individuals (Johnson et al., 2005). However, other studies have shown equivocal effects and there is also evidence to suggest that acute doses of methamphetamines lead to deficits in inhibition and the ability to filter out irrelevant information (Comer et al., 2001).

In summary, the existing literature on acute cognitive effects of methamphetamine and amphetamine, combined with qualitative reports regarding use (Soetens et al., 1995), points to some potential increase in attentiveness and speed of processing possibly accompanied by disinhibition and a decrease in the ability to filter information at therapeutic doses.

Neurocognitive Deficits Associated with Chronic Amphetamine Use

Psychiatric Symptoms—Chronic methamphetamine abusers have high rates of affective distress and psychiatric disorders, which can be especially severe during withdrawal (Newton et al., 2004). Psychosis, including both negative and positive symptoms, is more likely to occur in methamphetamine abusing individuals compared to non-abusing populations, even after adjusting for history of psychotic disorders (Harris and Batki, 2000; Iwanami et al., 1994; McKetin et al., 2006; Srisurapanont et al., 2003). Individuals with a predisposition to psychotic symptoms, including schizotypal or schizoid traits and family histories of psychotic disorders, also have an increased risk of methamphetamine-associated psychosis (Chen et al., 2003, 2005). The presence of psychosis is usually transient, occurring during use or withdrawal and normally abating in a period of days. However, susceptibility to psychotic episodes may persist for years after cessation of methamphetamine use (Ujike and Sato, 2004). Methamphetamine users are also at increased risk of depression and suicidal ideation during active use, withdrawal, and abstinence, and this risk is amplified in women (Kalechstein et al., 2000; Zweben et al., 2004). Methamphetamine users may also have increased rates of antisocial personality disorder (Chen et al., 2003), as well as mania and bipolar disorder (Shoptaw et al., 2003).

Neurocognitive Deficits—A number of studies have suggested that chronic methamphetamine use is associated with mild to moderate neuropsychological impairment, with one current estimate suggesting that approximately 40% of persons with methamphetamine dependence demonstrate some level of global neuropsychological impairment (Rippeth et al., 2004). Significant deficits in several different cognitive processes dependent upon brain fronto-striatal and limbic circuits have been observed in studies of chronic methamphetamine users, including deficits in psychomotor functions, complex information processing speed, attention and working memory, episodic memory, and executive functions, including response inhibition and novel problem-solving (Rogers, et al., 1999a, 1999b; Salo, et al., 2001; Simon, et al., 2000, 2002, [2004]; Ornstein, et al., 2000; Volkow et al. 2001a; Gonzalez et al., 2004; Salo et al., 2002; Woods et al., 2005; Sim et al., 2002; Paulus et al., 2002).

Complex Information Processing Speed: Some chronic methamphetamine users evidence modest visuoconstruction deficits on such tasks as the Rey Complex Figure copy task (Kalechstein, et al., 2003). Some methamphetamine abusers also demonstrate impaired performance on tasks of perceptual speed and information manipulation, and also do very poorly on tasks that combine these skills with visuomotor scanning (Simon et al., 2002). It is unclear whether these seeming deficits are related to perceptual organizational impairment, executive dysfunction, constructional dyspraxia, or some combination of these (Scott, et al., 2007). This area of cognitive functioning has not been examined in the khat user population.

Attention and Working Memory: Clinically, methamphetamine-dependent subjects appear distractible and exhibit difficulties in sustaining attention. This has been reported anecdotally in khat users as well, although this area of cognitive functioning has not been carefully examined in the laboratory setting. Chronic amphetamine users demonstrate impairments on some laboratory tasks involving attention and/or sustained attention. Attentional deficits have been noted in the Stroop Color Word and Trailmaking Tests (Simon et al., 2000; Kalechstein et al., 2003). Chronic methamphetamine users also exhibit deficits on measures of sustained attention and vigilance such as the CPT or Continuous Performance Test (Borgaro et al., 2003). A recent study completed by London and colleagues (London et al., 2005) demonstrated that methamphetamine users made significantly more errors on an auditory version of the CPT than drug-free controls. These investigators noted that the signal detection index was significantly smaller in methamphetamine users than in controls, suggesting impairment in the ability to discriminate targets from non-targets. This suggests that the primary explicit attentional deficits in methamphetamine users may be related to reduced cognitive inhibition (Salo et al., 2002) and an inability to suppress irrelevant task information (Nordahl et al., 2003).

Deficits may also emerge on tasks with more complex processing demands that also involve working memory and decision making, such as an N-back task (London et al., 2005). Individuals with a history of methamphetamine use display working memory deficits in such tasks as the immediate recall component of the auditory verbal learning test (Volkow et al., 2001a) and take 18–30% longer to complete the working memory components of the California computerized assessment package (Chang et al., 2002). Chang et al. (2002) has suggested that this impairment may be directly related to task complexity.

Nordahl et al. (2003) examined the attentional performance of a group of methamphetamine-dependent subjects using a sensitive, computerized battery of selective attention tasks to better understand the nature and specific properties of this cognitive dysfunction (Salo et al., 2001). A single-trial Stroop priming task; a task switching experiment with response conflict trials; a spatial priming task; and a go-no-go task were all used in this assessment. When compared to controls, methamphetamine-dependent subjects displayed more consistent patterns of difficulties in suppressing irrelevant task information. These deficits were reflected in both reaction time measures and accuracy rates. Although the methamphetamine-dependent subjects in this experiment exhibited deficits in the explicit components of these tasks, they had preserved attentional priming.

Episodic Memory: Extensive use of methamphetamines has also been repeatedly associated with deficits in episodic memory. This area of cognitive functioning has not been examined in the khat user population. The deficits seen in chronic methamphetamine users are most evident as impairment in word recall tasks, which measure recall at specific times after stimulus presentation (Thompson et al., 2004; Volkow et al., 2001a; Simon et al., 2000). Memory impairment in chronic amphetamine users appears to be related to self-reported severity of drug use (McKetin and Mattick, 1998). The marked deficits in episodic memory seen with chronic methamphetamine use are also among the most susceptible cognitive functions to methamphetamine relapse (Simon et al., 2004). Chronic use of amphetamines appears to have a larger negative effect on learning as compared with delayed recall, suggesting that impairment in learning (and perhaps retrieval) rather than consolidation or retention difficulties underlies the overall episodic memory deficit.

Woods et al., 2005 recently demonstrated impairment in overall learning, free recall, utilization of semantic clustering strategies, repetitions, and non-semantically related intrusion errors in 87 persons with methamphetamine dependence, who were nonetheless normal in retention and recognition discrimination. Woods and colleagues have demonstrated that, although there is an episodic memory deficit seen in methamphetamine users on the Hopkins Verbal Learning Test, it is of a strategic nature (executive, planning and organizational) and is not purely mnemonic (Woods et al., 2005). Moreover, Volkow (2001b, 2001c) showed associations between reduced striatal dopamine terminal function and deficits in list learning and recall in a sample of methamphetamine users. Taken together, these data support the notion that methamphetamine use may disrupt the organizational and technical components of memory encoding and retrieval that are dependent upon brain fronto-striatal pathways. It is not clear whether other aspects of learning and memory that depend upon these same pathways are similarly affected, such as the prospective memory component of episodic memory or non-declarative (procedural) memory (Scott, et al., 2007).

Executive Functions: A recent meta-analysis (Scott, et al., 2007) noted the presence of significant executive dysfunction in chronic methamphetamine users across several studies, with observed Wisconsin Card Sorting Test perseverations, Stroop Color-Word interference, and reduced performance on Part B of the Trailmaking Test. This area of cognitive functioning has not been examined in the khat user population.

Impairments in executive function, which include the cognitive domains of abstract reasoning, planning, and behavioral flexibility, are evident in methamphetamine users on the Stroop Interference Task (Kalechstein et al., 2003) as well as the Behavioural Assessment of the Dysexecutive Syndrome – BADS test (Verdejo-Garcia and Perez-Garcia, 2007a). These deficits may reflect underlying episodic memory deficits or might indicate problems with response inhibition and/or cognitive set shifting. Moderate language impairment has been demonstrated in chronic methamphetamine users, which may be partially explained by information processing speed deficits and executive function impairments. This language impairment is apparent on measures of verbal fluency which require rule-guided generation of words under time constraints, such as the Controlled Oral Word Association Test (COWAT). This verbal fluency deficit may reflect executive dyscontrol of search and retrieval strategies or generally slowed information processing speed (Scott, et al., 2007).

There is a growing body of evidence to also suggest that chronic methamphetamine users evidence significant problems with impulsivity and impaired decision-making capabilities. Methamphetamine dependent individuals exhibit risky decision-making and impulse control problems as demonstrated by their sensitivity to immediate versus delayed rewards (Hoffman et al., 2006; Monterosso et al., 2006), selection of impulsive choices when compared to normal controls (Gonzalez et al., 2007), and self-report of impulsive behavior patterns (Semple et al., 2004, 2005). Several investigators (Bechara et al., 2001; Grant et al., 2000, Pirastu et al., 2006; Verdejo-Garcia and Perez-Garcia, 2007b) have noted that chronic amphetamine users have an increase in the use of disadvantageous decision-making strategies on the Iowa Gambling Task (Bechara et al., 1997). Similar results have been found with performance on the Cambridge Gamble Task (Rogers et al., 1999a, 1999b), in that chronic amphetamine users showed disadvantageous decision-making and selected a likely small reward option less frequently than controls (85% of trials versus 95%), which may reflect an impairment in correctly estimating outcome probabilities (Ersche and Sahakian, 2007). Comparable results have been reported by Ersche et al. (2005) regarding the performance of chronic amphetamine abusers on the Risk Task (Rogers et al., 1999a). These seeming decision-making deficits may be related to the executive functioning aspects of working memory deficits (Bechara and Martin, 2004).

Studies with current amphetamine/methamphetamine users have shown marginal to severe impairment on tests of cognitive flexibility, such as the Wisconsin Card Sorting Test (Simon et al., 2002; Ornstein et al., 2000) and the intra-dimensional/extra-dimensional (IDED) set-shifting task of the CANTAB test battery (Downes et al., 1989; Rogers et al., 2000). There is recent evidence which suggests that the impaired cognitive flexibility in methamphetamine users, however, may be associated with male, but not female, gender (Kim et al., 2005). Although these deficits were seen in active, chronic amphetamine/methamphetamine users (Ersche et al., 2006; Ornstein et al., 2000; Simon et al., 2000), there is some evidence to suggest that these deficits may not be present in abstinent amphetamine/methamphetamine users (Hoffman et al., 2006). Growing evidence indicates that inhibitory cognitive control on

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such tasks as the Stroop test (Stroop, 1992) is compromised in amphetamine users (Salo et al., 2002, 2007; Simon et al., 2002). Some studies, however, have not found impaired interference control in recently abstinent methamphetamine users (Chang et al., 2002; Hoffman et al., 2006; Kalechstein et al., 2003), which may represent partial recovery of brain function following abstinence from methamphetamine (Ersche and Sahakian, 2007).

Monterosso et al., 2005 have reported that chronic methamphetamine users demonstrate deficits in behavioral inhibition on the Stop-Signal Reaction Time task (Dougherty et al., 2003; Evenden, 1999; Hom et al., 2003; Logan, 1994). Methamphetamine users have a significantly longer stopping process than controls and a significantly longer stop-signal reaction time, suggesting that response inhibition is compromised in these psychostimulant users independent from attentional processing. Inhibition failure on the Stop-Signal task appears to be associated with the previous amount of methamphetamine consumed (Monterosso et al., 2005), and may reflect dose-dependent neuroadaptive changes underlying poor behavioral inhibition in chronic users of methamphetamine.

Strategic planning and the ability to think ahead and actively search for an appropriate solution to a given problem or to mentally organize behavior to achieve a goal through a series of intermediate steps appears to be impaired in chronic amphetamine users. Amphetamine users, regardless of current drug status, solved significantly fewer problems correctly on the one-touch Tower of London test (Owen et al., 1995), and therefore needed more attempts in order to generate correct answers compared to controls (Ersche et al., 2006; Ornstein et al., 2000). Amphetamine users also struggled to generate solutions for the relatively easy three-move Tower of London test (Ersche et al., 2006). The first 1–3 stages of the Tower of London require little true planning ability, since they can be easily solved by a visual matching-to-sample strategy (Owen, 1997), so it is conceivable that the poor performance of amphetamine users at this low level of difficulty may represent either an over-confident approach to the solution of the problem or an inefficiency in concentrating on the task demands (Ersche and Sahakian, 2007). Amphetamine users have also shown marked impairment on similar but more complicated tasks requiring complex spatial working memory function and visuo-spatial strategy generation (Ornstein et al., 2000).

Persistent Cognitive Deficits in Abstinent Amphetamine-Dependent Subjects

Marked impairment in some areas of neurocognitive functioning of methamphetamine-dependent patients may persist into abstinence, be slow to normalize, and may actually worsen initially (Meredith et al., 2005). Methamphetamine-dependent individuals in early abstinence (5 to 14 days) perform markedly worse than controls on measures of attention and psychomotor speed (Trailmaking Test Part A, Symbol Digit Modalities Test, Stroop Color), and measures of verbal learning and memory (Rey Auditory Learning Test, WMS III Logical Memory) and figural memory (Rey Complex Figure 30 minute delay), as well as on fluency-based measures of executive function that included set shifting and inhibition (Kalechstein et al., 2003). There is evidence that verbal memory performance improves following protracted drug abstinence, however (Wang et al., 2004). Decrements in performance on psychomotor and verbal memory tasks lessen in methamphetamine-dependent subjects after 3 to 14 months of abstinence (Volkow et al., 2001b), but these individuals continue to perform significantly worse on working memory tasks after 6–10 months of abstinence compared to controls (Chang et al., 2002). Also, despite two months of abstinence, methamphetamine abusers consistently demonstrate errors in selective attention and priming (Salo et al., 2002). After three months of abstinence, recovering methamphetamine abusers score worse on word recognition tests and tests of episodic memory than do individuals who continue to use methamphetamines, who themselves do worse than methamphetamine-naïve controls (Simon et al., 2004).

Suggested Future Neurocognitive Research with Chronic Khat Users

Multiple areas of neurocognitive deficit have been identified in previous studies of individuals who have been chronic users of stimulants, such as amphetamines and methamphetamines, including deficits that persist during abstinence from active drug use. A substantial body of evidence has demonstrated a wide range of learning and memory impairments in chronic amphetamine and methamphetamine users (Ersche et al., 2006; Gonzalez et al., 2004; Hoffman et al., 2006; Kalechstein et al., 2003; Moon et al., 2007; Ornstein et al., 2000; Rippeth et al., 2004; Simon et al., 2002; Woods et al., 2005). Recent evidence from rodent research implicates a similar association between daily khat use and spatial learning and memory (Kimani and Nyongesa, 2008) as well as behavioral sensitization with repeated dosing (Kimani et al., 2008). Due to some similarities pharmacologically between the active components of khat (cathinone and cathine) and amphetamines, future studies examining these same domains of cognitive functioning in chronic khat users and abstinent khat users appears to be warranted, if possible using some of the same or similar laboratory measures.

A recent meta-analysis of the neurocognitive deficits associated with users of methamphetamines (Scott, et al 2007) indicates that the largest (medium to large) effect sizes are seen in the domains of executive functions, learning, and memory. Medium effect sizes were seen in this same meta-analysis in the domains of motor skills and speed of information processing. This is consistent with other contemporary reviews of the neuropsychological effects of amphetamines and methamphetamines in humans (Nordahl et al, 2003; Ersche and Sahakian, 2007). Although numerous laboratory studies with animals have suggested that cathinone has a potential for abuse perhaps greater than amphetamine and causes persistent dependence with minimal withdrawal (Feyissa and Kelly, 2008), cathinone is nonetheless 50% less potent than amphetamine and this may also reduce the effect size seen in proposed future laboratory studies of human khat consumption. For this reason, it is recommended that initial human laboratory studies of the neurocognitive deficits associated with khat use focus on the domains of learning, memory, and executive functions.

It is therefore recommended that future studies consider specific examination of the neuropsychological domains of learning and episodic memory, working memory, set shifting/cognitive inhibition, cognitive flexibility, inhibitory control, strategic planning, and decision-making, with some potential for subsequent studies examining attention/ psychomotor speed, sustained attention, visuoconstruction, verbal fluency, and nonverbal fluency (see Table 1). Suggestions for possible measures are listed in Table 1.

It should be noted, however, that many of these psychological and neuropsychological measures do not currently have adequate normative information for non-English speaking populations and there may be cultural barriers as well to their use.

Care should be taken in future khat research studies to account for the confounding factors of inadequate sample size and appropriate control for age, gender, education, measured intelligence, and polydrug use that have plagued previous studies on stimulant drug use in human subjects (Jovanowski et al., 2005). Careful screening of research subjects will be needed to identify those subjects in particular that concurrently use tobacco and/or alcohol, as well as drugs of abuse, especially benzodiazapines. It is recommended that studies of the relationship of neurocognitive functioning to khat use be carried out in a carefully controlled laboratory environment. There is a particular need for well designed human studies investigating the neurocognitive effects of acute khat dosing.

Several other areas of investigation should also be considered in the proposed future research agenda for human khat studies. Although the reported gender differences in khat use prevalence might be attributable to cultural roles or the availability of sufficient time to use khat, it would be worthwhile to investigate the potential role of hormones (particularly estrogen) as mediating factors. A number of recent studies in both humans (Munro et al, 2006) and non-human primates (Czoty et al, 2009) suggest that changes in DA receptor availability may be involved in the variation in symptoms of various neuropsychiatric disorders across the menstrual cycle, including differences in sensitivity to the abuse-related effects of stimulants.

Another emerging area of considerable interest in stimulant research and addiction is the role of pharmacogenetics related to drug response and human molecular genetics as an intervening variable in characterizing the response to addictive substances, including opiates, cocaine, and stimulants (Kreek et al., 2005b; Kreek et al., 2005a; Kendler et al., 2003). Particularly salient for khat researchers is the role that genetic influences may play in the neurocognitive domains of impulsivity, risk taking, and stress responsivity (Kreek et al., 2005a) which are central to the investigation of stimulant drugs such as khat.

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Table 1

Potential Areas of Neurocognitive Deficit in Chronic Khat Users, Based Upon Studies Completed with Chronic Users of other Stimulant Drugs

Domain of neuropsychological functioning	Potential measures
Learning and Episodic Memory	RAVLT (Trials 1–5)
	RAVLT Delayed Recall
	WMS IV Logical Memory (30 min delay)
	Rey Complex Figure Recall (30 min delay)
	Hopkins Verbal Learning Test
Working Memory	Letter-Number Sequencing
	Visual Memory Span – Backwards
Set shifting/cognitive inhibition	Trailmaking Test, Part B
	Stroop Interference
Cognitive Flexibility	Wisconsin Card Sorting Test
	CANTAB set-shifting task (IDED)
	Behavioural Assessment of the Dysexecutive Syndrome – BADS test
Inhibitory Control	Stop-Signal task
	Go-Nogo Task
Strategic Planning	Tower of London Test
	One-Touch Tower of London Test
Decision-Making	Iowa Gambling Task
	Cambridge Gamble Task
	Risk Task
Attention/Psychomotor Speed	Trailmaking Test Part A
	Symbol Digit Modalities Test
	Stroop – Color
Sustained attention	Continuous Performance Test (CPT)
Visuoconstruction	Rey Complex Figure
Verbal Fluency	Controlled Oral Word Association Test
Nonverbal Fluency	Ruff Figural Fluency Test