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*SPECIAL ISSUE ON NOVEL PSYCHOACTIVE SUBSTANCES*

# Why all stimulant drugs are damaging to recreational users: an empirical overview and psychobiological explanation

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**Aims** Stimulant drugs such as nicotine and Ecstasy/3, 4-methylenedioxymethamphetamine (MDMA) are taken for positive reasons, yet their regular use leads to deficits rather than gains. This article outlines the psychobiological rationale for this paradox.
**Methods** The empirical literature on nicotine, cocaine, amphetamine, Ecstasy/MDMA, and mephedrone are reviewed. A theoretical explanation for why they are problematic to humans is then described.
**Results** The acute effects of central nervous system (CNS) stimulants are typically positive, with greater alertness and emotional intensity. However, in the post-drug recovery period, the opposite feelings develop, with lethargy and low moods. All recreational stimulants cause mood fluctuation, although it is most pronounced in drugs with rapid onset and comedown (e.g. nicotine and cocaine), explaining why they are the most addictive. Parallel fluctuations occur across many psychological and neurocognitive functions, with users suffering various off-drug deficits. CNS stimulants also affect the hypothalamic–pituitary–adrenal axis, impairing sleep, disrupting homeostasis, and exacerbating psychiatric distress. Neuroimaging studies reveal altered brain activity patterns in regular users. These problems are related to lifetime usage but commence in novice users.
**Conclusions** Repetitive CNS stimulation is potentially damaging to the organism, both acutely and chronically. The review describes the various psychobiological systems through which recreational stimulant drugs impair human well-being. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—stimulant; nicotine; MDMA; methamphetamine; cocaine; mephedrone

## INTRODUCTION

The word ‘stimulation’ is positive—it denotes activation, alertness, and interpersonal engagement. Hence, any drug with central nervous system (CNS) stimulant properties might be expected to be beneficial to the user. Indeed, it is generally for positive reasons that stimulant drugs are sometimes used for psychosocial purposes. Tobacco smokers state that cigarette smoking leads to greater alertness, with nicotine helping to maintain attention (West and Russell, 1985; Parrott, 1998). Cocaine users report that the drug makes them feel more alert, confident, and powerful (Mello, 2010). Ecstasy/3, 4-methylenedioxymethamphetamine (MDMA) users report feeling more energised and empathetic (Parrott, 2001, 2013a, 2013b; Dumont and Verkes, 2006). Amphetamine, methamphetamine, and mephedrone users give similar reasons, with positive moods being boosted, and increased feelings of confidence (Cruickshank and Dyer, 2009; Schifano *et al.*, 2011; Kirkpatrick *et al.*, 2012; Carvalho *et al.*, 2013). Many of these stimulant drugs are also used at dance clubs and house parties, where they are termed ‘party’, ‘club’, or ‘dance’ drugs (Williams *et al.*, 1998; Winstock *et al.*, 2001; Morefield *et al.*, 2008).

Given these acute psychobiological changes, does the recreational user gain any overall benefits from their drug usage? In order to answer this core question, several issues need to be addressed (Parrott, 2008). Firstly, all the acute drug effects need to be described, because while many acute changes can be quite positive, others may be less desirable. Hence, CNS stimulants can increase feelings of anger or paranoia, and produce acute psychophysiological changes such as cardiac overstimulation, overheating, and death (Schifano *et al*, 2010; Carvalho *et al*, 2013; Kiyatkin, 2013). Secondly, the post-drug psychobiological status needs to be considered, because the recovery period of low mood can be very negative and may indeed be more enduring than the on-drug gains (Parrott and

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Lasky, 1998; Schifano *et al.*, 2011). Thirdly, the effects of repeated drug usage need to be considered. Chronic tolerance is typical of the recreational stimulants and leads to dosage escalation. Furthermore, any drug-related problems tend to increase in parallel with cumulative lifetime usage. In relation to this, there are chronic changes in brain functioning, as revealed through neuroimaging, evoked response potential, and neurocognitive studies (Bolla *et al.*, 1999; Verkes *et al*, 2001; Hester and Garavan, 2004; Cadet *et al*, 2007; Scott *et al.*, 2007; McCann *et al.*, 2008; Cruickshank and Dyer, 2009; Kish *et al.*, 2010; Di Iorio *et al.*, 2012; Schouw *et al.*, 2013; Jasinska *et al.*, 2014; Schifano *et al.*, 2015). Other deficits also occur with the hypothalamic–pituitary–adrenal (HPA) axis, with altered patterns of neurohormonal activity (Gerra *et al.*, 2003; Parrott, 2009; Mello, 2010). In summary, while there can be many acute gains from stimulant drug usage, these need to be balanced against a wide range of potential negative effects. Only when all aspects have been considered (Chapter 15 in Parrott *et al.*, 2004) will it be possible to gauge whether the overall effects of these recreational stimulants are beneficial, neutral, or detrimental.

### *Central nervous system stimulant drugs*

The most widely used CNS stimulant drug is nicotine, because it is the only legal substance in this broad class. Indeed, nicotine is the most extensively researched of all the psychosocial stimulants. Hence, this article will cover the psychobiological effects of nicotine, as revealed through empirical research involving cigarette smokers. It should be noted that caffeine will not be considered in this article, because it is primarily a metabolic activator, with 'stimulant' properties that are comparatively mild and atypical—hence, it is rather different from the true stimulants that mostly affect the monoamine systems directly. The most widely used of the illicit recreational stimulants is cocaine, and many similarities have been noted between the psychophysiological and behavioural effects of cocaine and nicotine (Mello, 2010). The other main stimulants used for psychosocial purposes are amphetamine, methamphetamine, MDMA or Ecstasy, and more recently mephedrone (m-cat or meow-meow). The aim of this article is to summarise the core psychobiological actions of this broad grouping of drugs. It is widely recognised that their regular use leads to chronic problems. However, it is often believed that their novice or light social usage is comparatively safe. Hence, another aim is to explain how and why psychobiological problems can occur with all types of user—because they are a direct psychobiological consequence of drug-induced changes to the CNS (Table 1).

### *Sympathomimetic actions and psychobiological overstimulation*

Central nervous system stimulant drugs *by definition* have sympathomimetic actions, with stimulation being achieved via increases in heart rate, lung functioning, and energetic supplies to the musculature, in order to prepare the body for physical activity (Lovallo, 1997).

Table 1. Psychobiological problems caused by recreational stimulant drugs: general overview

| | Summary of main effects |
|---|---|
| Sympathomimetic overstimulation | Disruption of autonomic balance between the sympathetic and parasympathetic nervous systems. Regular metabolic overstimulation leading to less time for cellular recovery and repair. Cardiac stress. |
| Increased body temperature and oxidative stress | Increased core body temperature with associated acute and chronic problems. Increased oxidative stress, greater likelihood of neural damage, and potential for earlier ageing. |
| Dysfunctional blood brain barrier | Increased susceptibility to bacterial and viral attack, with associated medical problems. |
| Impaired homeostasis | Homeostasis adversely affected, with various effects on the HPA axis. By impairing normal homeostatic balance, a wide range of psychobiological deficits can develop. |
| Repetitive mood fluctuations | Acute mood gains, followed by mood decrements on drug withdrawal. The periodicity of these mood fluctuations is most frequent in drugs with a rapid onset and rapid withdrawal (nicotine and crack cocaine). Drug cravings and dependency/addiction. |
| Chronic mood problems | Regular use of all CNS stimulants can lead to chronic mood deficits. Mood states typically improve following drug cessation. |
| Psychiatric deficits | Recreational stimulants associated with enhanced psychiatric distress. Causation multi-factorial. Prior vulnerability factors interact with drug effects in complex ways. |
| Neurocognitive deficits | Neuroimaging and neurocognitive studies reveal a range of deficits. They may reflect neurotoxicity or neuroadaptive processes. Some recovery may occur on drug cession, while some problems may endure—an important question for future research. |
| Foetal damage | Cocaine and MDMA usage during pregnancy prospectively lead to developmental problems in the emergent children. |

HPA, hypothalamic–pituitary–adrenal; CNS, central nervous system; MDMA, 3, 4-methylenedioxymethamphetamine.



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Occasionally, the acute effects of stimulant drug use can be medically dangerous. Bruggisser *et al.* (2010) analysed the stimulant exposure cases reported to the Swiss Toxicology Centre. They noted 667 cases for cocaine, 433 for MDMA, 188 for amphetamine/methamphetamine, and 122 for methylphenidate. They commented that methylphenidate cases had increased in recent years and suggested that research into the non-medical usage of this prescription drug was required. It is widely recognised that repeated sympathomimetic stimulation by recreational drugs is potentially damaging to the organism, because it depletes metabolic energy resources, increases bodily wear and tear, and reduces the time available for parasympathetic nervous system recovery and repair (Selye, 1956; Lovalo, 1997; Parrott, 2009; Clarke *et al*, 2013). CNS stimulant drugs are metabolic activators that increase oxidative stress. Again, this can delay the normal everyday processes of bodily repair. Brown and Yamamoto (2003) noted that all the amphetamine-like stimulants increased oxidative stress and that mitochondrial dysfunction was linked with apoptosis (cell death) and monoaminergic neurotoxicity. When taken repeatedly, the regular use of stimulant drugs may even speed the basic process of ageing, although currently, this remains just a hypothesis. Psychostimulant drugs such as methamphetamine, MDMA, cocaine, and nicotine can also lead to a dysfunctional blood brain barrier (Kousik *et al.*, 2012); this facilitates the invasion of bacteria and viruses into the brain, with a range of adverse health consequences (Table 1).

In a recent review of the thermal effects of CNS stimulants, Kiyakin (2013) noted that stimulant drugs tended to cause acute thermal stress and overheating and that this was often exacerbated by the environmental conditions found during recreational usage: 'These thermal effects differ drastically depending upon the environmental conditions and activity state during drug administration. This state dependency is especially important for drugs of abuse that are usually taken by humans during psycho-physiological activation and in environments that prevent proper heat dissipation from the brain. Under these conditions, amphetamine-like stimulants induce pathological brain hyperthermia (>40 °C) associated with leakage of the blood brain barrier and structural abnormalities of brain cells'. Martin *et al.* (1971) found a significant increase in body temperature with CNS stimulant drugs such as methamphetamine. This has been confirmed with acute MDMA in the quiet laboratory setting (Freedman *et al.*, 2005). When used recreationally, Kiyatkin (2013) noted that stimulant drugs cause even more pronounced increases in core body temperature (Davison and Parrott, 1997; Topp *et al.*, 1999; Parrott, 2012a; Kiyatkin, 2013; Parrott and Young 2014). Australian party-goers on-MDMA demonstrated a group mean body temperature increase of +1.1 °C (Morefield *et al.*, 2009). Young recreational users of cocaine also rated themselves as significantly overheated—than non-user controls at the same party venue (Table 2; Parrott *et al.*, 2011b).

Table 2. Cocaine and Ecstasy/MDMA: mood and neurocognitive effects from three comparative studies of weekend recreational drug users (after Parrott *et al.*, 2011b)

| Study 1 by Lauren Evans: memory and cognition | Control group | Cocaine/MDMA | MDMA |
|---|---|---|---|
| Dysexecutive questionnaire (problem score) | 22.1 | 38.2*** | 37.1** |
| Consonant updating (correct recall) | 3.2 | 3.1 | 2.1 |
| Random letter (number generated—two/seconds) | 98.1 | 83.1*** | 96.6 |
| Supraspan word recall (total words) | 31.1 | 29.9 | 27.9 |
| Study 2 by James Howell: self-rated mood states | Control/alcohol | Cocaine | MDMA |
| Excitement (on-drug) | 3.6 | 4.0 | 4.7* |
| Paranoia (on-drug) | 1.5 | 3.0* | 2.5 |
| Clearheaded (on-drug) | 3.0 | 3.1 | 1.8* |
| Aggression (on-drug) | 2.3 | 3.1 | 1.5 |
| Overheated (on-drug) | 2.5 | 3.5* | 3.9** |
| Depressed (post-drug recovery) | 2.1` | 2.7 | 3.2* |
| Paranoia (post-drug recovery) | 1.6 | 2.6* | 3.6*** |
| Sociable (post-drug recovery) | 3.7 | 3.1 | 2.3** |
| Clearheaded (post-drug recovery) | 3.8 | 3.3 | 2.1** |
| Study 3 by Rebecca Robart: memory and cognition | Control group | Cocaine | MDMA |
| Rivermead behavioural memory (info recalled) | 9.9 | 9.2 | 8.9 |
| Auditory verbal learning task (words learned) | 9.4 | 8.0 | 7.2* |
| Trail making (task completion time) | 15.9 | 19.9 | 21.4** |

MDMA, 3, 4-methylenedioxymethamphetamine.
Tukey paired comparison tests between each drug group and the control group:
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.



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Clarke *et al.* (2013) noted that 'psychostimulants of abuse' such as cocaine, methamphetamine, and Ecstasy could increase neuroinflammation by activating the innate immune response. This natural defence mechanism was designed to protect the body against attacks by noxious stimuli. However, its repeated activation, whether by toxins, microbial agents, or stimulant drugs, may well be implicated in the development of some neurodegenerative diseases (Table 1). Furthermore, 'The data indicate an association of psychostimulant use with Innate Immune Response activation in the brain even at exposures not normally associated with neurotoxicity'.

Repetitive sympathomimetic activation can also lead to cardiac stress. The stimulant effects of nicotine are indicated by the cardiac changes to the first cigarette of the day, which increases heart rate by around +16 bpm, while 4 mg nicotine gum will generate an increase of +5 bpm (Parrott and Craig, 1992). Nicotine also dilates the bronchioles, which is why it used to be medically recommended as a treatment for asthma in the 1930s (before the adverse health effects of tobacco smoking were recognised). When cocaine, methamphetamine, or MDMA are used intensively, they can cause extreme sympathomimetic over-activation. Typically, this occurs when they are 'stacked' (taking several normal doses at one time point) or taken in a prolonged 'binge' (repeated doses over an extended period, from 12 to +48 h without sleep; Topp *et al.*, 1999; Winstock *et al.*, 2001; Parrott, 2005). With MDMA, this hyperactivation generates elements of the serotonin syndrome, because 'hyperactivity, mental confusion, hyperthermia, and trismus (jaw clenching) are typical on-drug experiences for most Ecstasy users' (Parrott, 2002; 2004). At dance clubs, this overstimulation may reflect the combined effects of stimulant drugs and environmental stimulation (Parrott *et al*, 2006). Suy *et al.* (1999) noted that the loud music and dynamic light shows at raves were designed 'to achieve a state of heightened arousal'.

### *Acute mood intensification and post-drug recovery issues*

Recreational drug users typically take stimulants for mood state intensification. These positive moods typically include feelings of alertness and euphoria, although this is then followed by a period of psychophysiological recovery, when the opposite moods predominate. Cigarette smokers report feeling more alert and less stressed after the first cigarette of the day (West, 1993; Wesnes and Parrott, 1992). But in-between cigarettes, they start to feel less alert and more stressed, and report that they *need* a cigarette to feel better. In regular smokers, this craving for more nicotine/tobacco may commence within 20–60 min of extinguishing the last cigarette (Parrott, 1999). The rapidity of this mood fluctuation helps explain the regularity of smoking, with a typical consumption pattern of 10–30 cigarettes each day. These mood fluctuations are illustrated in Figure 1 from Parrott (1994), where smokers rated how they felt immediately before lighting-up a cigarette, then immediately after extinguishing it. They described acute mood gains on smoking—followed by mood deteriorations in-between cigarettes. The essence of nicotine dependency is this repetitive vacillation of mood states.

Nicotine has a rapid time profile of action—and hence a rapid cycle of mood changes (Figure 1). Mood fluctuations also occur with stimulant drugs displaying longer time profiles. MDMA may have the longest time profile of any of the recreational stimulants. Its peak acute effects occur around 1.5 to 3 h post-administration, while the post-drug recovery period may last for several days. Figure 2 shows the pattern of prospective mood changes over a week, as reported by young recreational users who had taken Ecstasy/MDMA at the weekend. The positive moods on-drug were followed by heightened feelings of sadness/depression, unpleasantness, and unsociability 2 days later (Parrott and Lasky, 1998). Curran *et al.* (2004) found increased feelings of aggression and depression, 4 days after acute recreational Ecstasy/MDMA. Parrott *et al.* (2008) reported significantly lower excitement and greater tiredness 4 days after weekend Ecstasy/MDMA. In these studies, mood states returned to baseline values after 7 days (Parrott and Lasky, 1998;

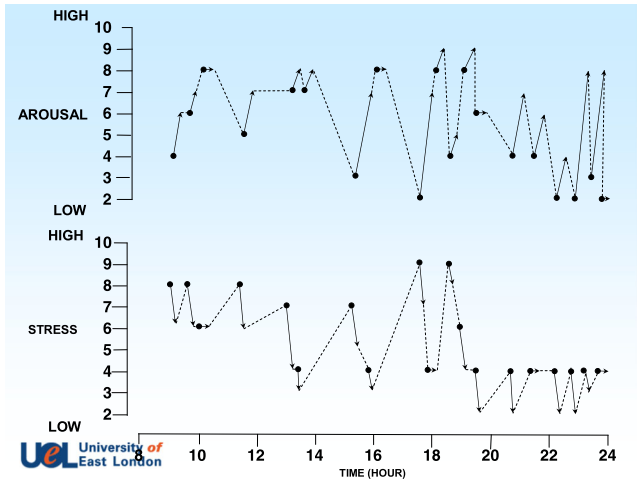


Figure 1. Self-rated feelings of arousal and stress in 1 day of a regular smoker. Mood states were rated immediately prior to each cigarette, then immediately afterwards. Each arrow represents the mood effects of a single cigarette. The dotted lines show the mood change in-between each cigarette (after Parrott, 1994)



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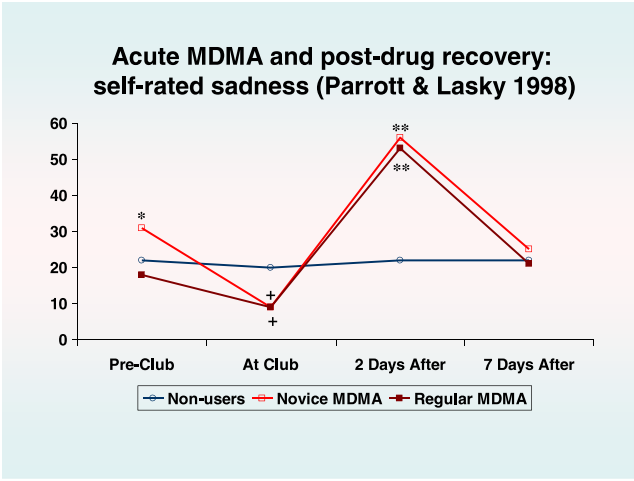


Figure 2. Self-rated feelings of sadness in weekend dance clubbers, before, during, and after clubbing, in recreational Ecstasy/3, 4-methylenedioxymethamphetamine (MDMA) users and non-user controls (after Parrott and Lasky, 1998)

Curran *et al.*, 2004). This long time profile helps explain why Ecstasy/MDMA is taken only intermittently, with many users taking Ecstasy/MDMA once a week or less frequently (Parrott, 2005). Furthermore, they only report drug cravings just before their intended time of next taking it. Hence, if they were planning to take MDMA on a Friday evening, their self-rated levels of craving started to increase around midday, then built-up over that afternoon until they took it (Hopper *et al.*, 2006); on all the other 'non-usage' days, they reported near-zero craving.

The CNS stimulant with the most rapid hit is crack cocaine, because it generates an intensive mood rush, followed by rapid mood deterioration. This rapidity helps explain why crack cocaine is so addictive, although similar patterns of repetitive mood fluctuation are found with every other recreational stimulant. They all induce an acute rush or hit on drug ingestion, followed by a post-drug recovery period of low moods. Crack cocaine users describe this recovery period as 'crashing out'. Some heavy cocaine users take the drug for several days with any sleep, becoming increasingly jittery and paranoid, before crashing out and sleeping for an extended period of time. Nasal cocaine infusers tend to follow a less intensive pattern of regular cocaine hits for a period, followed by a drug recovery—again dominated by feelings of lethargy and anhedonia (Parrott *et al.*, 2011b).

Mood fluctuation is also noted with another class of stimulant drugs—the cathinones. In the horn of Africa, they are often obtained by chewing leaves of the Khat bush. Aden *et al.* (2006) reported that Khat chewers in Kenya experienced intensive moods when chewing Khat, followed by negative moods and withdrawal symptoms afterwards. Some heavy users spent more than half their domestic budget on purchasing Khat leaves, indicating its strong addiction potential (Parrott, 2007). Methcathinone or m-cat is comparatively stronger than cathinone, and users report a similar pattern of intense moods on drug, followed by negative moods afterwards. Schifano *et al.* (2011) noted that many of the adverse effects of mephedrone 'were similar to amphetamine, methamphetamine, and MDMA'. To summarise, one of the core paradoxes of the recreational stimulants is that users take them for their positive mood effects, yet they experience low moods during the post-drug recovery period (Table 1). Every known CNS stimulant causes this repetitive mood fluctuation.

### *Chronic mood effects of stimulant drugs*

Given that stimulant drugs cause mood states to fluctuate acutely, what are the long-term consequences for regular drug users? In respect to nicotine, prospective studies have found that taking up smoking during adolescence leads to a range of adverse mood state deficits. Wu and Anthony (1999) prospectively investigated a large cohort of 8–14-year-old schoolchildren. Taking up smoking was associated with an increased risk of developing feelings of depression later, whereas depressed mood at baseline did not increase the risk of becoming a smoker in later years. In another large prospective study, Johnson *et al.* (2000) monitored cigarette use and anxiety ratings over the adolescent period. Heavy cigarette smoking at 16 years of age led to significant increases in generalised anxiety, agoraphobia, and panic disorder, 5 years later, whereas higher levels of anxiety at age 16 years did not lead to an increase in later smoking. Steuber and Danner (2005) prospectively studied 14 000 teenagers over time and found that cigarette smoking led to more depression in both genders, although the increase was more pronounced in females. McGhee *et al.* (2000) found that smoking at age 18 years 'elevated the risk of anxiety/depressive disorder' 3 years later. In summary, these and many other studies have shown that taking up smoking leads to increased stress and depression (Parrott, 2006b). Tobacco smoking is also associated with other psychological problems, including low self-esteem, low self-efficacy, and suicidal behaviours. Oquendo *et al.* (2004) reported that cigarette smoking was one of 'the three most powerful predictors' of suicidal acts, in a subgroup suffering from major depression. Indeed, disadvantaged subgroups are most at risk from developing smoking-related psychobiological/psychiatric problems (Parrott, 2006b).



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Quitting smoking has been prospectively shown to lead to psychological gains in adults. Cohen and Lichtenstein (1990) monitored 211 cigarette smokers who were planning to quit. Those who failed to stop smoking reported high stress at baseline and continuing high levels of stress over the duration of the study, whereas those who quit reported similarly high levels of stress at baseline, but a gradual and significant reduction in stress over time—with continued cessation. This was confirmed by Carey *et al.* (1993), who found that 6 months of smoking cessation led to a significant reduction in self-rated stress. Parrott (1995) replicated this in another prospective study, where stress was significantly reduced after 3 and 6 months after biochemically confirmed smoking abstinence, while environmental 'life-stressors' remained constant over time in both quitters and relapsers. Hughes (1992) noted that the immediate period of smoking cessation can be very difficult, with negative moods and high cravings during the first few days and weeks of cessation. Yet, when abstinence was maintained over successive months, a wide spectrum of mood states improved over those found at baseline. Hence, smoking cessation can lead to a wide range of mood state benefits (review: Parrott, 2006b). Shahab and West (2012) found that current smokers were significantly less happy than either non-smokers or former smokers, whereas the former smokers reported similar levels of happiness to non-smokers. In a meta-analysis of 26 prospective smoking-cessation studies, Taylor *et al.* (2014) found that smoking cessation led to reduced stress, anxiety, and depression, improved positive mood states, and better quality of life, in comparison with continued smoking.

In their review of Khat and cathinone, Feyissa and Kelly (2008) concluded that 'Khat chewing can induce a substantial degree of mood disturbances, particularly depression in healthy subjects'. They further noted that 'Other mood disorders such as khat-induced behavioural syndrome described as hypomania have been reported by several authors… There are similar reports of mood disorders secondary to repeated amphetamine use'. Amphetamine may be seen as the archetypal recreational stimulant (Parrott *et al.*, 2004), and its chronic usage is associated with a range of adverse mood consequences; similarly, the adverse mood effects of chronic methamphetamine and chronic cocaine are well documented (reviews: Williamson *et al.*, 1997; Cruickshank and Dyer, 2009; Panenka *et al.*, 2013). Typically, these negative moods include restlessness, anxiety, and anger, often accompanied by physical tremors or dyskinesias. Fasano *et al.* (2008) noted the repetitive stereotypical movements of chronic cocaine users, while similar patterns of physical restlessness and nervous irritability have been noted with amphetamine and methamphetamine users. Psychiatric problems such as major depression, schizophrenia, paranoid psychosis, and aggression can also develop —particularly in those with prior susceptibility factors (Cruickshank and Dyer, 2009; Vearrier *et al.*, 2012; Panenka *et al.*, 2013; Glaser-Edwards and Mooney, 2014). MDMA/Ecstasy is also associated with adverse moods such as stress, anger, and depression, along with psychiatric problems in the more susceptible (Schifano *et al.*, 1998; Soar *et al*, 2001; MacInnes *et al.*, 2001; Reid *et al.*, 2007; Scholey *et al.*, 2011; Parrott *et al.*, 2011, 2013a, 2014b). In a prospective study of disadvantaged Canadian schoolchildren, Brière *et al.* (2012) found that youngsters who commenced taking recreational MDMA reported significantly higher depression 1 year later. They reported a similar increase in depression in a different subgroup of youngsters who started taking methamphetamine, while a third subgroup who took both drugs reported the largest increase in depression. Verheyden *et al.* (2003) noted that quitting Ecstasy was associated with improved self-ratings of mental health. While in a prospective study, Turner *et al.* (2014) found that Ecstasy/MDMA cessation led to significantly lower depression scores 18 months later.

### *Arousal and optimal performance: the Yerkes–Dodson inverted U function*

Given the close association between physiological arousal and psychological performance, it might be expected that any increase in alertness would lead to a parallel improvement in performance. However, this presumes that the arousal–performance relationship is linear, and it is well established that the relationship is curvilinear rather than liner—making any performance change difficult to predict. In one of the classic studies of early psychological research, Yerkes and Dodson (1908) demonstrated that performance was optimal at a slightly raised level of arousal and declined when arousal increased further. The Yerkes–Dodson inverted U function was empirically confirmed in Parrott (1975), where normal volunteers were administered a range of sedating and alerting drugs. Arousal was increased by three CNS stimulant drugs, with a statistically borderline increase for methylphenidate ($p < 0.10$) and larger significant increases for pemoline ($p < 0.0001$) and dexamphetamine ($p < 0.0001$). Performance under placebo was on the left arm of the curvilinear function, just below the peak. Performance was increased slightly under methylphenidate—to near the optimal peak of the inverted U function, while performance under the two stronger CNS stimulant drugs was comparatively lower and on the declining arm of



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the inverted U function (see Figure 1 in Parrott and Hindmarch, 1975).

The performance gains following a small dose of a CNS stimulant were demonstrated by Ramaekers *et al.* (2006). They found a significant improvement in car tracking accuracy (less weaving), following acute oral doses of 75 mg MDMA and 20 mg methylphenidate, although with MDMA, the tracking gain was accompanied by an element of impaired performance, namely a significant overshoot in responding to deceleration by the car ahead. This latter deficit was not found with methylphenidate so that the overall performance gain was consistent with the position for 20 mg methylphenidate found in Parrott (1975)—namely the peak of the arousal–performance function (see previous paragraph). Physiological overstimulation can however impair performance, and this has been empirically found with recreational Ecstasy/MDMA users. Parrott and Lasky (1998) found significant impairments on a simple visual scanning task following Ecstasy/MDMA at a dance club, with this performance deficit being greater in the subgroup who had taken more drugs. Brookhuis *et al.* (2004) tested recreational MDMA users in a driving simulator after drug self-administration and found some performance deficits following acute self-administration. The level of performance deficit was much greater in those who had partied all night and combined MDMA with other recreational drugs; here, their severely impaired driving skills were described as 'extremely dangerous'. This may have reflected a combination of high polydrug consumption, prolonged overstimulation, and fatigue–tiredness. Whatever the combination of explanatory factors, it illustrated the practical dangers of taking recreational stimulant drugs in the real world.

Inverted U performance functions have also been empirically demonstrated with nicotine. In Parrott and Craig (1989), psychological task performance showed a mixture of monotonic and curvilinear functions. On some measures, performance was at its peak following the low dose of 2 mg nicotine gum, whereas on other assessment measures, it was at its peak following higher doses of nicotine. This was further confirmed in Parrott (1992), where a mixture of linear and curvilinear functions was empirically generated (see Figures 2 and 3 in Parrott, 1992). This can make the performance effects of nicotine difficult to predict. Cognitive skills are certainly better in nicotine-replete smokers than in nicotine-deprived smokers (Parrott *et al*, 1996; Parrott and Garnham, 1998). Yet, smokers do no seem to gain many real advantages from nicotine, because when non-smokers were compared with active smokers, their cognitive skills were broadly similar. This suggests that smokers need nicotine to function normally and may suffer from psychological performance deficits without it (Parrott, 1998, 2006b; Parrott and Kaye, 1999). In particular, the performance skills of smokers seem to fluctuate more than non-smokers, due possibly to the benefits of smoke inhalation, being followed by deficits in-between cigarettes (Ashton *et al.*, 1972; review: Parrott, 1998). Heffernan *et al.* (2005) found that the memory skills of cigarette smokers were significantly worse than non-smokers, possibly because information storage and retrieval were being undertaken against constantly fluctuating levels of nicotine.

The regular uses of cocaine, amphetamine, methamphetamine, and MDMA are associated with a range of neurocognitive impairments (Table 1). Cruickshank and Dyer (2009) commented that 'Methamphetamine use is associated with moderate impairment in neuropsychological performance corresponding with frontostriatal and limbic abnormalities (Scott *et al.*, 2007). Principal neurocognitive impairments appear to occur in domains of executive function, learning, episodic memory, speed of information processing, motor skills, working memory and perceptual narrowing'. Soar *et al.* (2012) noted several higher brain regions that were dysfunctional in regular cocaine users, further noting that 'Cocaine dependence and abuse has been frequently associated with neuropsychological and cognitive deficits (e.g. Bolla *et al.*, 1999; Hester and Garavan, 2004: Verdejo-Garcia and Perez-Garcia, 2007)'. Vonmoos *et al.* (2013) found that dependent cocaine users were significantly impaired in cognitive tasks for attention, working memory, declarative memory, and executive functions, in comparison with non-user controls. Recreational cocaine users were broadly intermediate between the other two groups, with significant cognitive impairments in some domains. In a follow-up investigation into the effects of continuing drug usage, Vonmoos *et al.* (2014) found that more intensive cocaine usage led to further cognitive decline, whereas complete cessation led to a restoration of cognitive functioning. Laws and Kokkalis (2007) undertook a meta-analysis of retrospective memory functions in abstinent Ecstasy/MDMA users and found moderate to large effect sizes. Many other cognitive functions are also impaired in abstinent Ecstasy/MDMA users, including prospective memory, executive planning, information updating, complex visual display information processing, evoked response potentials, and problem solving (Heffernan *et al.*, 2001; Fox *et al.*, 2002; Fisk *et al.*, 2005; Mejias *et al.*, 2005; Murphy *et al.*, 2009; Montgomery *et al.*, 2010; Burgess *et al.*, 2011; Parrott,



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2013a, 2013b). Currently, there is insufficient empirical evidence to ascertain the long-term effects of the novel drug mephedrone, although early studies suggest similar types of psychobiological deficit (Schifano *et al.*, 2011; Freeman *et al.*, 2012). This is therefore an important area for future research.

*Hypothalamic–pituitary–adrenal axis and cortisol*

The HPA axis is important for maintaining the psychophysiological balance of the organism (Selye, 1956; Lovallo, 1997). Cortisol is the key neurohormone involved in the maintenance of homeostasis and shows a regular circadian rhythm in the well-balanced organism. However, when the HPA axis is over-stimulated by high levels of external demand, the organism can become chronically stressed, with disrupted patterns of cortisol secretion (Selye, 1956). CNS stimulant drugs are sympathomimetic and stimulate the HPA axis. Hence, the acute administration of any stimulant drug generates an acute increase in cortisol. Mello (2010) noted that 'nicotine and cocaine each stimulate HPA and hypothalamic–pituitary–gonadal axis hormones', while Mello also outlined the role of these hormonal changes for their mood effects and high addiction potential. In one study, they demonstrated a pronounced cortisol release after smoking a high-dose nicotine cigarette and that this did not occur after a cigarette with minimal nicotine; hence, it was an effect of nicotine rather than smoking. Mello (2010) demonstrated a similar increase in cortisol after an acute dose of cocaine, noting the similar rapid time profile for both drugs.

Cortisol release is also heightened by acute MDMA administration. Dumont and Verkes (2006) reviewed 12 laboratory studies of neurohormonal reactions to acute MDMA in humans and noted that 11 of these studies reported a significant increase in cortisol. For instance, Harris *et al.* (2002) found that 0.5 mg/kg MDMA led to a cortisol increase of 100%, while 1.5 mg/kg oral MDMA led to a larger increase of 150%. These neurohormonal changes are even more pronounced in recreational Ecstasy/MDMA users. Parrott *et al.* (2008) monitored a group of 12 Ecstasy users on alternative weekends, once when dance clubbing on-MDMA and the other time clubbing when abstinent. Cortisol showed a peak increase of 800% on-MDMA, whereas cortisol levels were largely unchanged while clubbing off-MDMA (Table 1). An 800% acute increase in cortisol was confirmed in a follow-up study at a house party (Parrott *et al.*, 2007). Cortisol is incorporated into the growing hair, and this allows 3-month cortisol levels to be calculated (Stalder *et al.*, 2012). Using this novel hair sampling technique, light Ecstasy/MDMA users showed a slight non-significant elevation of hair cortisol, whereas regular Ecstasy/MDMA users demonstrated a highly significant 400% increase in 3-month cortisol levels (Parrott *et al.*, 2014a, 2014b). Gerra *et al.* (2003) noted that cortisol responses were altered in abstinent Ecstasy/MDMA users and suggested that this may indicate a neuroendocrine dysfunction induced by the repeated use of MDMA. Wetherell and Montgomery (2014) also found that the cortisol awakening response was altered in recreational users.

Another consequence of recreational stimulants is disturbed sleep. Getting to sleep is generally more difficult, and there may be changes in sleep architecture during the post-drug recovery period. Sleep problems have been empirically demonstrated with all recreational stimulants, including nicotine (Wetter and Young, 1994), cocaine, amphetamine and methamphetamine (Cruickshank and Dyer, 2009; Carvalho *et al.*, 2012; Panenka *et al.*, 2013), MDMA (McCann *et al.*, 2007, 2009), and mephedrone (Schifano *et al.*, 2011). These sleep problems may be illustrated with research involving MDMA (McCann and Ricaurte, 2007). In an electroencephalogram (EEG) study, Allen *et al.* (1993) found reduced total sleep time, due predominantly to reduced stage 2 non-REM sleep, in drug-free Ecstasy/MDMA users. In a prospective sleep questionnaire study, Jones *et al.* (2008) found changing sleep patterns after weekend Ecstasy use, with reduction in total sleep time and sleep quality during the first few days, returning to normal after around 5 days. McCann *et al.* (2009) reported an increased incidence of sleep apnoea in young recreational sues, with an incidence related to lifetime MDMA usage. The authors noted that serotonin was involved in the control of breathing and that this medical sleep disorder might reflect serotonergic neurotoxicity.

Another issue is psychiatric well-being (Table 1; see also the earlier section on mood states). The HPA axis is important for psychiatric symptoms, and there are extensive empirical data showing an association between recreational stimulant use, heightened psychiatric distress, and altered HPA axis (Cruickshank and Dyer, 2009; Schifano *et al.*, 2011; Panenka *et al.*, 2012; Glasner-Edwards and Mooney, 2014). The diathesis–stress model has been outlined elsewhere, when it was noted that the adverse psychiatric consequences of recreational stimulants will reflect the complex interaction of two key factors: psychiatric vulnerability and drug-induced disruptions to the HPA axis. More specifically, problems are most likely to develop in those individuals with pre-existing vulnerability factors and following heavier drug usage



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(Parrott, 2006a, 2013b). Finally, the recreational use of stimulant drugs may have adverse effects on foetal development. Hence, it is important for pregnant women not to use stimulant drugs and for their male partners not to have a sperm that is overheated and potentially damaged. The foetal problems caused by recreational cocaine are well established, while the more recent drug MDMA has also been found to prospectively lead to impaired child development at 4 and 12 months post-partum (McElhatton *et al.*, 1999; Singer *et al.*, 2012a, 2012b); the neurohormonal aspects of this developmental damage were outlined in Parrott *et al.* (2013).

## OVERVIEW

There are a number of ways in which CNS stimulant drugs impair the neuropsychobiological integrity of the organism. They disrupt psychological equilibrium and impair homeostatic integrity. Moods are acutely stimulated but then impaired during the post-drug recovery period. Nicotine and crack cocaine generate the most rapid mood reversals, while other recreational stimulants lead to slower patterns of mood vacillation (Figures 1 and 2). Mood states are just one aspect of this vacillation in arousal. Hence, feelings of alertness, confidence, motivation, cognitive ability, and social interest may all show similar temporal patterns of vacillation. Every CNS stimulant has addiction potential, with this 'dependency' being a reflection of these vacillating psychological states. Stimulant drug users suffer a range of negative states when off-drug and feel better in numerous ways when on-drug, hence the strong addictiveness of every CNS stimulant. All drugs in this class also affect the HPA axis, impair homeostasis, and disrupt psychological integrity. Hence, sleep is often impaired, cognitive skills are reduced, psychosocial skills are also affected, and psychiatric problems worsened (Table 1).

In broad psychobiological terms, the human organism displays a natural balance between sympathetic and parasympathetic nervous system activities. The optimal resting state of arousal is just before the peak of the Yerkes–Dodson inverted U function (Yerkes-Dodson, 1908; Parrott and Hindmarch 1975). This allows it to increase its arousal and performance slightly, when it is required to react effectively and deal with an unexpected environmental event. Hence, the ideal resting state is *just below* the peak of the inverted U function. When humans use CNS stimulant drugs recreationally, they induce a state of repetitive sympathetic over-activation. They disrupt normal autonomic balance and reduce parasympathetic repair. This will be cumulatively damaging to the organism. In subjective terms, the recreational stimulants can be very seductive to potential users, because they can induce brief acute gains. Yet, their regular use is damaging, and the more these drugs are used, the greater the cumulative damage they cause. Furthermore, because of chronic tolerance, they become less effective over time, which leads to dosage escalation and yet more psychobiological problems (see Parrott, 2005, 2006, 2013b, for a description of this pattern with recreational Ecstasy/MDMA). Three broad conclusions can be offered. Firstly, it is not possible to repeatedly use any current recreational stimulant drug without causing neuropsychobiological problems. This is because any drug that causes repetitive sympathomimetic stimulation will be psychobiologically damaging to the organism. Secondly, the adverse neuropsychobiological effects of all recreational stimulants are broadly similar. Although nicotine, amphetamine, methamphetamine, cocaine, and MDMA display different profiles of action and have many unique or individual aspects, their core psychobiological effects are remarkably similar (Table 1). Finally, this suggests that any *novel* stimulant drug will cause a similar pattern of neuropsychological changes.

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