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Review

Cannabis and Ecstasy/MDMA (3,4-methylenedioxymethamphetamine): an analysis of their neuropsychobiological interactions in recreational users

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Summary The majority of recreational Ecstasy/MDMA users (90–98%) also take cannabis. This co-drug usage is often viewed as a methodological confound, which needs to be removed statistically. Here we take a rather different approach, and debate the potential complexities of their psychobiological interactions. The ring-substituted amphetamine derivate MDMA (3,4-methylendioxymethamphetmaine, or 'Ecstasy') is a powerful CNS stimulant, whereas cannabis is a relaxant. Their co-usage may reflect opposing effects in three psychobiological areas: arousal, body temperature, and oxidative stress. Firstly MDMA is alerting whereas cannabis is sedating. Secondly MDMA is hyperthermic whereas cannabis is hypothermic. Thirdly MDMA increases oxidative stress whereas cannabinoids are antioxidant. Hence cannabis may modulate the acute and sub-acute reactions to MDMA, reduce the acute hyperthermia induced by MDMA, and ameliorate the oxidative stress caused by MDMA. The limited empirical evidence on each topic will be critically examined. In terms of chronic effects each drug is functionally damaging, so that polydrug users generally display cumulative neurobiological impairments. However in certain aspects their neuropsychobiological effects may interactive rather than additive. In particular, the combined use of cannabis and MDMA may have rather different neuropsychobiological implications, than their separate usage. In order to investigate these potential complexities, future research will need better empirical data on the exact patterns of co-drug usage.

Keywords: Cannabis; MDMA; Ecstasy; serotonin; cannabinoid; oxidative stress; antioxidant; hyperthermia; temperature; cognition

Cannabis incidence rates in recreational Ecstasy/MDMA users

Cannabis is the most widely used of all illicit drugs. It has been taken as a herbal relaxant in different societies for millennia, and is currently used as a recreational drug worldwide (Hall and Solowij, 1998; Gouzoulis-Mayfrank and Daumann, 2006; Parrott et al., 2004a, b; Pope et al., 2001a, b; Solowij et al., 2002). In contrast MDMA is a relative newcomer, having been first used as a recreational drug in the late 1970s (Renfroe, 1986; Parrott, 2001, 2006). Since then its use has increased dramatically, with surveys at the start of the millennium showing that MDMA had overtaken the parent compound amphetamine, in becoming the second most widely taken illicit drug after cannabis (Pope et al., 2001a), although cocaine has also become very popular as a club drug (Kelly et al., 2006; Martins et al., 2006). The common street name for MDMA is Ecstasy. Throughout the 1980s there were few problems with the purity of recreational Ecstasy tablets (Renfroe, 1986), but during the mid-1990s a relatively proportion of Ecstasy tablets contained substances other than MDMA. In recent years the purity problem has largely been resolved, so that since the late-1990s, the overwhelming majority of Ecstasy tablets have contained MDMA (Parrott, 2004a).

Most recreational Ecstasy users are polydrug users, since they report taking a range of other psychoactive compounds. These include other illicit stimulants such as cocaine or amphetamine, and hallucinogens such as LSD, while the use of legal drugs such as alcohol and nicotine is also higher than amongst similar aged controls (Fox et al., 2001, 2002; Kelly et al., 2006; Martins et al., 2006; Parrott et al., 2001; Scholey et al., 2004; Schifano, 2000; Winstock et al., 2001). Many surveys have also revealed that cannabis is one of the

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most widely taken co-drugs for recreational Ecstasy/MDMA users. Strote et al. (2002) surveyed 14,000 USA college students, and found that 5% had used Ecstasy/MDMA, while 92% of these Ecstasy users also took cannabis. Wish et al. (2006) found that 9% of a sample of east coast American college students had taken ecstasy/MDMA, with 98% of this sample also reporting cannabis use. Schuster et al. (1998) surveyed over 3,000 young Germans in the age range 14–24 years; 4% reported that they had taken MDMA at least once, and 97% of this group stated that they had also used cannabis. Males were more likely than females to have taken Ecstasy, but amongst the Ecstasy/MDMA users, cannabis was taken almost universally by both genders (Schuster et al., 1998). In a neurocognitive comparison of cannabis users, Ecstasy users, and non-users, Rodgers (2000, p. 20) noted that everyone in their ecstasy/MDMA group 'were also habitual cannabis users'.

The main venues for using Ecstasy/MDMA are at dance clubs, techno parties, and all night raves (Parrott, 2004b, 2006). Here again a high proportion of MDMA users also report taking cannabis. Winstock et al. (2001) undertook a questionnaire survey of over a thousand dance clubbers, and found that 96% had taken Ecstasy at least once, while 91% had used cannabis. Topp et al. (1999) interviewed over three hundred Australian Ecstasy users who took MDMA as a 'dance drug', and noted that 98% also used cannabis. These figures relate to lifetime usage. When usage over the last month is assessed, the incidence figures decrease slightly. For instance, Winstock et al. (2001) noted that 74% of lifetime Ecstasy users had taken cannabis in the last month. Scholey et al. (2004) found that in an internet survey of 282 lifetime Ecstasy users, 70% had taken cannabis in the last month.

Psychosocial and functional reasons for cannabis-MDMA co-usage

There are several possible reasons for this particular form of polydrug usage. In terms of psychosocial aspects, gateway theory suggests that once an individual had decided to use one illicit drug, they are more likely to take another proscribed substance. This may reflect an increase in 'drug exposure opportunity'. This model was supported by Wagner and Anthony (2002), in an epidemiological study of young tobacco and alcohol users. They were more likely than non-users to experience opportunities to use marijuana, and were more likely to accept the drug when an opportunity occurred. Similarly, marijuana users were more likely than non-users to find themselves exposed to cocaine and hallucinogens, and again they were more prone to try these other drugs once offered (Wilcox et al., 2002). Interestingly, this mechanism also applied to those individuals who were not actively seeking out an opportunity to use drugs. Hence, according to this model, the co-use of cannabis and Ecstasy fits a natural hierarchical progression from legal to illegal drugs (Parrott et al., 2004b).

However in a genetic study by Agrawal et al. (2004), the 'common risk factor' model best explained the co-use cannabis and other drugs, rather than the gateway theory. Although this model was supported only in males, in females it was not possible to distinguish the two models, possibly due to their lower overall prevalence of drug use. The risk factors included a range of genetic and environmental variables. Hence according to this theory, the same risk factors that lead people to become Ecstasy users, will also increase the risk for taking other psychoactive drugs including cannabis. In line with common risk theory, a survey of 1076 northern Italian high school students found that illicit polydrug use and alcohol abuse, were each associated with specific temperamental traits (high sensation seeking, social coping impairment, and direct aggressiveness), poor school achievement, and poor perceived parental care (Gerra et al., 2004). These findings concur with previous studies that showed a strong link between the trait of sensation seeking, and polydrug use (Pedersen et al., 1989). With regard to Ecstasy/MDMA use, Dughiero et al. (2001) found that Ecstasy users showed higher novelty seeking scores than non-user controls, while Ecstasy experimenters showed lower harm avoidance scores than Ecstasy abusers. Finally, a Norwegian school based study supported elements from all the above models. Pedersen and Skrondal (1999) found that ecstasy generally fitted the following sequence: alcohol, cigarettes, cannabis, amphetamines, ecstasy, than heroin. The use of these illicit drugs was highly associated with alcohol use, alcohol problems and conduct problems. However cannabis was more strongly associated with conduct problems than was Ecstasy, whereas Ecstasy showed a stronger association with the preference for House/Techno music.

In terms of functional aspects, one of the main reasons given by recreational users is that cannabis provides symptomatic relief against the feelings of anhedonia and depression which follow after Ecstasy. In a survey of over a thousand dance clubbers, 82% of the Ecstasy/MDMA users reported using cannabis to assist the post-MDMA comedown (Winstock et al., 2001). In an investigation of the functional aspects of single drugs and drug combinations, as described by 364 young polydrug users, 52% of the Ecstasy users reported using cannabis to relieve post-

MDMA come down effects (Boys et al., 2001; although this value may be an underestimate, since each user was restricted to listing just *three* main drugs from several possible polydrug combinations). The symptomatic relief model would explain why cannabis is often used in the immediate post-MDMA period. However it should be emphasized that there is no empirical data on the effectiveness of this apparent strategy (Parrott, 2001; Schifano, 2000). Many Ecstasy users also report taking cannabis during the initial acute stimulatory phase. Boys et al. (2001) noted that 36% of cannabis users reported taking it together with MDMA in order to 'improve its effects'. Further information on what this means subjectively was not presented, although informal conversations with users has revealed that cannabis is often used by those who want a more mellow experience on MDMA. Subjective aspects are however only one element of the drug response, and the wider psychobiological effects also need to be considered. The next section will therefore examine the acute psychobiological effects of each drug alone, before their combined effects are debated.

MDMA and cannabis: psychobiological effects of the individual drugs

The ring-substituted amphetamine derivative MDMA is a powerful CNS stimulant. It stimulates the release and inhibits the re-uptake of serotonin (5-HT), and it also affects dopamine and other neurotransmitter systems (Green et al., 1995, 2003; Hegadoren et al., 1998). The acute stimulation leads to a marked increase in metabolic activity, more free radicals, and hence greater oxidative stress (Zhou et al., 2003). This increase in cellular energy turnover overloads the normal metabolic processes of recovery and repair, and this is thought to generate the cellular damage and loss of distal axon terminals (Huether et al., 1997). The acute effects of MDMA are also heightened by concomitant stimulation, such as by ambient heat, overcrowding, social stimulation, or the parallel use of other stimulant drugs (Green et al., 2003; Huether et al., 1997). This may help to explain why Ecstasy/MDMA is typically taken in hot and crowded conditions, such as dance clubs and raves (Parrott, 2004b).

In laboratory rats, guinea pigs, monkeys, and primates, MDMA is a serotonergic neurotoxin (Ricaurte et al., 1985; Schmidt, 1987; Sprague et al., 1988). The extent of 5-HT distal axon terminal loss is influenced by several factors, including dosage, repetition of doses, ambient temperature, physical activity, and the co-administration of other CNS stimulants such as amphetamine (Green et al., 1995, 2003; Huether et al., 1997; Ricaurte et al., 2000). This axon terminal damage is caused by single or repeated periods of excessive neuronal stimulation, as outlined above (Huether et al., 1997). Oxidative stress is one of the core underlying mechanisms, while general cellular exhaustion, and MDMA metabolites, may contribute to the process of local cellular damage (Green et al., 2003; Huether et al., 1997; Schmidt, 1987; Sprague et al., 1988). Furthermore, stimulatory factors which further heighten acute neurotransmitter release (e.g. ambient heat, closely repeated doses, physical activity, other CNS stimulant drugs), can exacerbate this serotonin distal axon terminal loss. Whereas factors which counteract the acute neuronal stimulation induced by MDMA (e.g. cold, rest, quietness), are neuroprotective (Green et al., 2003; Huether et al., 1997). Various antioxidants have been found to provide a degree of protection against the neurotoxic effects of MDMA (see Green et al., 2003, for a detailed review). The neuropsychobiological effects of recreational Ecstasy/MDMA usage include memory problems, other cognitive deficits, reduced immuno-competence, and psychiatric distress (Parrott, 2001, 2007); they are described more fully later.

Turning to the neurobiological effects of cannabinoids, these are still being delineated, since cannabinoid/anandamide receptors were discovered fairly recently. In broad terms, the acute effects of cannabis contrast markedly with those of MDMA (Hall and Solowij, 1998; Parrott et al., 2004; Sala and Braida, 2005). Relaxant, anti-oxidant, excitotoxicity prevention, anti-inflammatory, and other potentially beneficial properties (Table 1), have each been documented (Croxford, 2003). Hampson et al. (2000) investigated the effects of cannabinoids on rat cortical neurone cultures exposed to neurotoxins. Cannabinol and 9-delta THC both demonstrated neuroprotective properties. This is thought to reflect their antioxidant properties, with the degree of protection they provided being much greater than that of other antioxidants such as ascorbate. In a longitudinal magnetic resonance imaging study, THC reduced neuronal damage in an animal model of neurodegeneration, via a CB_1 cannabinoid receptor-mediated mechanism (Van der Stelt et al., 2001). Grundy et al. (2001) concluded that the underlying mechanisms for cannabinoid neuroprotection comprised a variety of receptor-dependent and receptor independent mechanisms.

Grundy (2002) also reviewed the therapeutic potential of cannabinoids as possible neuroprotective agents: 'The ability of this diverse family of compounds to modulate neurotransmission and act as anti-inflammatory and antioxidative agents has prompted researchers to investigate their potential as therapeutic agents. Indeed various canna-

Table 1. *Psychobiological effects of MDMA/Ecstasy alone, cannabis alone, and MDMA-cannabis drug combinations*

Psychobiological function	Drug	General effect (reference citation)
Body temperature	MDMA	increased (Freedman et al., 2005)
	Cannabis	decreased (Hayakawa et al., 2004)
	Drug combination	attenuation in animals (Morley et al., 2004)
	Drug combination	attenuation in recreational users (Parrott and Young, 2005)
Oxidative stress	MDMA	increased (Zhou et al., 2003)
	Cannabis	decreased (Grundy et al., 2001)
	Drug combination	attenuation in animals* (Morley et al., 2004)
	Drug combination	attenuation predicted in humans (Parrott, 2006)
Alertness	MDMA	increased (Lock et al., 2006)
	Cannabis	decreased (Solowij et al., 2002)
	Drug combination	modulation of mood and alertness changes (Winstock et al., 2001)
Memory	MDMA	impaired (Zakzanis and Campbell, 2006)
	Cannabis	impaired (Ranganathan and D'Souza, 2005)
	Drug combination	additive-additional impairments (Gouzoulis-Mayfrank et al., 2000; Rodgers et al., 2001)
Other functional and structural aspects	MDMA	various impairments (Schifano, 2000; Parrott, 2001, 2003)
	Cannabis	various impairments (Gouzoulis-Mayfrank et al., 2000; Gouzoulis-Mayfrank and Daumann, 2006)
	Drug combination	complex: attenuated and/or exacerbated** (Milani et al., 2005; Daumann et al., 2003)

* Cannabis neuroprotection, hypothesized via a temperature modulated reduction in oxidative stress.
** Possible attenuation when taken together. Exacerbation when taken separately, since their deleterious psychobiological effects will be additive and cumulative.

binoids rescue dying neurones in experimental forms of acute neuronal injury'. Gilgun-Sherki et al. (2001) reviewed the practical utility of exogenous antioxidants, but concluded that their ability to reduce reactive oxygen species was often compromised by an inability to cross the blood brain barrier. However this does not affect the cannabinoids, since they readily pass the blood brain barrier. Another well documented property of cannabinoids such as delta(9)-tetrahydrocannabinol (THC), is their ability to reduce body temperature. Hayakawa et al. (2004) showed that the neuroprotective effects of THC were related to this induction of hypothermia, whereas the neuroprotective effects of cannabidiol were temperature-independent.

MDMA and cannabis in combination: acute effects

The above findings allow two predictions to be made about the effects of cannabis and MDMA when taken together. Firstly, cannabis should lessen the oxidative stress caused by acute MDMA. Secondly it should reduce any MDMA-induced hyperthermia. Both predictions may be rather speculative, being based on data about each drug when administered separately (Table 1). Yet despite the paucity of empirical data into the acute effects of cannabis-ecstasy combinations, there are some relevant findings (Parrott et al., 2004; Sala and Braida, 2005; Gouzoulis-Mayfrank and Daumann, 2006). Perhaps the most pertinent study is by Morley et al. (2004), who examined the interactions between cannabinoids and MDMA in male Wistar rats. The co-administration of MDMA with Delta 9-THC prevented MDMA-induced hyperthermia, and it also tended to decrease the MDMA-induced hyperactivity. In relation to the longer term effects, Delta 9-THC partially prevented the depletion of 5-HT and 5-HIAA, which was induced by MDMA-alone in some brain regions, but not others. In this same study, the co-administration of 9-THC prevented from MDMA induced increased anxiety 6 weeks later in the emergence test, although this was not found in the social interaction test (Morley et al., 2004). The partial neuroprotection provided by THC may be due to its hypothermic properties, since decreases in core body temperature have been shown to ameliorate MDMA-induced neurotoxic damage in laboratory animals (Colado et al., 2001; O'Shea et al., 2002). A number of further animal studies involving drug-discrimination, self-stimulation, and conditioned place preference tasks (Braida and Sala, 2002; Braida et al., 2005), are summarized in the review by Sala and Braida (2005). This review should be consulted for its detailed coverage of the behavioral data on cannabis and MDMA co-administration in laboratory animals. The empirical findings allowed them to conclude that in laboratory rats: 'the endocannabinoid system is involved in MDMA self-administration . . .the findings may help to explain the use of marijuana and MDMA together by poly-drug users' (Sala and Braida, 2005).

Turning to the temperature effects in humans, Tancer et al. (2003) investigated the effects of an acute dose of MDMA on temperature in a placebo controlled laboratory

study. A significant increase in core body temperature was demonstrated, under both normal and high ambient temperature conditions. Freedman et al. (2005) confirmed this finding in more comprehensive follow up study (Table 1). Some laboratory studies have generated a non-significant trend of an increase in body temperature; they are summarized in Parrott (2006). In a field study of dance clubbers, recreational Ecstasy users demonstrated significantly higher body temperature (tympanic-membrane) than non-Ecstasy users at the same venues (Parrott and Young, 2005). The correlation between MDMA and body temperature was positive and highly significant ($r = +0.45$, $p = 0.001$), whereas the correlation between cannabis and temperature was negative although non-significant ($r = -0.21$, $p = 0.089$). These acute findings provide support for the cannabis/MDMA interactions in laboratory animals (e.g. Morley et al., 2004), although more empirical data in humans is required (Table 1).

MDMA and cannabis in combination: chronic effects

The recreational use of MDMA alone is unusual, although there are two published reports of regular Ecstasy users who avoid other psychoactive substances for religious or socio-psychological reasons. Halpern et al. (2004), described the neurocognitive sequelae of MDMA in a group of young ravers from Salt Lake City, who mostly avoided all other psychoactive drugs, including alcohol, nicotine and cannabis. The light ecstasy users (less than 50 occasions lifetime) were similar to the non-user controls on all measures of cognition, whereas the heavier users (+50 lifetime occasions) demonstrated deficits of several of the neurocognitive tasks, especially those for working memory. Yip and Lee (2005) investigated cognitive functioning in young Ecstasy/MDMA users from Hong Kong, who reported comparatively light use of most other psychoactive drugs; again a pattern of significant neurocognitive deficits emerged. It should be noted that both studies involved young Ecstasy users who were also dancers/ravers (Halpern et al., 2004; Yip and Lee, 2005). This may be relevant, since the adverse psychobiological effects of MDMA are heightened by concomitant environmental stimulation (Parrott et al., 2004b, 2006). Hence the adverse cognitive effects of MDMA are exacerbated by prolonged periods of dancing when on-Ecstasy, and they are also related to feelings of being hot or overheated while on-Ecstasy (Parrott et al., 2006). Turning to the effects of cannabis, there is extensive data showing neurocognitive and other psychobiological deficits in regular users. These include deficits in aspects of working memory, executive processing, motivational problems, raised psychiatric symptom profiles, and full blown psychiatric disorders (Hall and Solowij, 1998; Parrott, 2003; Parrott et al., 2004b; Solowij et al., 2002). Ranganathan and D'Souza (2005) concluded that: 'Cannabinoids impair all stages of memory including encoding, consolidation, and retrieval. Several mechanisms, including effects on long-term potentiation and long-term depression and the inhibition of neurotransmitter (GABA, glutamate, acetylcholine, dopamine) release, have been implicated in the amnesic effects'.

As noted earlier, the overwhelming majority of Ecstasy/MDMA users also take cannabis and other psychoactive substances. Amoungst these recreational Ecstasy polydrug users, there is extensive evidence for functional problems, and some evidence for structural changes in the serotonin system. Serotonergic markers (concentration of serotonin metabolite in the cerebrospinal fluid and serotonin transporter densities in the brain) have been found to be reduced in MDMA users compared to controls (McCann et al., 1998, 2000; Semple et al., 1999; Reneman et al., 2006); although there is also evidence for reversibility of these changes after prolonged periods of abstinence (Reneman et al., 2000, 2001, 2006; Thomasius et al., 2003). Functional problems which may be linked with 5-HT depletion have also been widely reported in Ecstasy polydrug users. These include heightened depression, phobic anxiety, impulsivity, impaired sleep, reduced immuno-competence, memory problems, and frontal-executive cognitive deficits (Fox et al., 2001, 2002; Gouzoulis-Mayfrank et al., 2000, 2003; Hegadoren et al., 1998; McCann et al., 2000; Morgan, 1999; Morgan et al., 2002; Parrott, 2001, 2002, 2006; Parrott et al., 1998, 2001, 2006; Parrott and Lasky, 1998; Rodgers, 2000; Rodgers et al., 2001, 2006; Schifano, 2000; Wareing et al., 2000; Zakzanis and Campbell, 2006). However, it is sometimes unclear whether they are direct sequelae of taking Ecstasy, or whether they represent preexisting characteristics of user populations, which might even predispose them to using of ecstasy and other recreational drugs. An important confounding factor is how these functional and structural deficits might be related to the use of other psychoactive drugs (Curran, 2000; Lieb et al., 2002).

In order to address this question, Daumann et al. (2003) compared cerebral activation patterns during working memory performance in three groups: pure MDMA users without other regular substance use, poly-drug Ecstasy users who took other dugs including cannabis, and matched controls. In this study, the pure ecstasy users presented somewhat different activation patterns from the controls and/or polyvalent users, whereas poly-drug users did not differ from controls (Daumann et al., 2003). These findings pro-

Table 2. *Brief Psychiatric Inventory scores, for five subgroups of ecstasy users differing in co-cannabis use, and alcohol/tobacco user controls (after: Milani et al., 2005)*

N	Controls (0) 121	No-cannabis (1) 44	Monthly use (2) 70	Weekly use (3) 31	Daily use (4) 103	Former heavy use (5) 32	p[a]	Pair comparisons[b]
Somatization	**0.56 ± 0.61**	**1.05 ± 0.80**	**0.62 ± 0.59**	0.69 ± 0.59	0.88 ± 0.69	0.75 ± 0.81	0.001	0, 2 < 1
Obsessive compulsive (OCD)	**1.04 ± 0.79**	**1.63 ± 0.84**	1.40 ± 0.86	1.25 ± 0.72	**1.58 ± 0.88**	1.50 ± 0.85	0.000	0 < 4, 1
Interpersonal Sensitiveness	1.02 ± 0.78	1.21 ± 0.77	1.17 ± 0.85	0.92 ± 0.88	1.16 ± 0.98	1.37 ± 1.05	NS	–
Depression	0.73 ± 0.77	1.07 ± 0.87	0.95 ± 0.92	0.79 ± 0.90	0.94 ± 0.85	1.01 ± 0.95	NS	–
Anxiety	0.69 ± 0.67	1.12 ± 0.84	0.82 ± 0.85	0.73 ± 0.60	0.93 ± 0.80	1.07 ± 0.86	0.013	–
Anger-Hostility	**0.74 ± 0.65**	**1.36 ± 0.82**	**0.76 ± 0.65**	**0.81 ± 0.62**	1.02 ± 0.79	1.10 ± 0.96	0.000	0, 2, 3 < 1
Phobic anxiety	0.33 ± 0.49	0.58 ± 0.56	0.34 ± 0.58	0.46 ± 0.77	0.55 ± 0.76	0.52 ± 0.79	NS	–
Paranoid ideation	**0.83 ± 0.76**	0.93 ± 0.54	0.95 ± 0.77	**0.79 ± 0.69**	**0.94 ± 0.72**	**1.32 ± 0.78**	0.047	0, 3, 4 < 5
Psychoticism	0.54 ± 0.60	0.88 ± 0.70	0.77 ± 0.72	0.55 ± 0.60	0.83 ± 0.73	0.70 ± 0.62	0.035	–
Global severity index	**0.75 ± 0.55**	**1.11 ± 0.55**	0.89 ± 0.64	0.80 ± 0.63	**1.03 ± 0.61**	**1.06 ± 0.64**	0.008	0 < 1, 4, 5
Positive symptoms total	23.11 ± 12.36	32.26 ± 12.26	26.43 ± 11.84	25.38 ± 12.64	28.65 ± 11.95	29.19 ± 10.92	0.001	0, 2 < 1
Positive symptoms distress index	1.59 ± 0.45	1.71 ± 0.44	1.64 ± 0.54	1.54 ± 0.46	1.78 ± 0.44	1.82 ± 0.51	0.026	–

[a] MANOVA significance levels.
[b] Tukey paired comparison tests (Bonferroni corrected), all at $p < 0.05$ significance levels.

vided support for the notion that cannabis may serve to protect Ecstasy users from neurotoxicity, both at the molecular and the neuro-functional level. They may also help to explain why the evidence for neurotoxicity in ecstasy polydrug users (i.e. in PET and SPECT studies), is often weaker than what might have been expected from animal studies involving pure MDMA treatment regimens (Reneman et al., 2000, 2001, 2006; Thomasius et al., 2003).

With reference to functional aspects, Milani et al. (2002) investigated the influence of several types of co-drug usage, on the psychobiological profiles of 278 Ecstasy/MDMA users. As expected the co-use of other CNS stimulants such as amphetamine, cocaine and nicotine, heightened some of the adverse psychobiological profiles. In marked contrast, cannabis was associated with significantly with higher positive moods, lower depression, better interpersonal sensitivity, and less total negative symptoms (see also: Milani et al., 2000). In a follow-up study, Milani et al. (2005) found that in sample of 280 Ecstasy polydrug users, those who reported heavy cannabis use in the past displayed higher paranoid symptoms compared with Ecstasy users who were smoking cannabis on a weekly or daily basis. In addition, former heavy cannabis users were the most likely to complain of a variety of Ecstasy related long-term problems. However, participants with no concomitant use of cannabis displayed more self-rated aggression and somatic symptoms compared with monthly or weekly cannabis users (Table 2). These findings indicate that heavy cannabis and Ecstasy use is associated with long term psychological problems, which may emerge after a period of abstinence from both drugs; while moderate cannabis use can ameliorate Ecstasy-related perceived aggression and somatophorm symptoms. In contrast, other recent studies including a longitudinal investigation, have suggested that the self-reported psychopathology of ecstasy users was predominantly attributable to regular cannabis use (Daumann et al., 2001, 2004; Morgan et al., 2002). In the longitudinal study (Daumann et al., 2004), abstinence from cannabis and not Ecstasy, seemed to be an appropriate predictor for remission of psychological complaints in ecstasy users, most notably, anxiety, depression, interpersonal sensitivity and obsessive-compulsive behaviour. Furthermore, there was evidence for significant relationships between the duration of regular cannabis exposure, and various psychopathological symptoms.

Studies into the effects of ecstasy and cannabis on cognitive performance have also generated a range of findings. Most studies employing objective measures of neurocognitive function, have reported dose-related impairments of learning and memory performance, also some deficits in short-term memory, working memory, and executive functions in the abstinent ecstasy users (Bhattachary and Powell, 2001; Bolla et al., 1998; Croft et al., 2001; Fox et al., 2001, 2002; Gouzoulis-Mayfrank et al., 2000, 2003; Hanson and Luciana, 2004; Krystal and Price, 1992; McCardle et al., 2004; Morgan, 1999; Parrott et al., 1998; Parrott and Lasky, 1998; Reneman et al., 2000; Rodgers, 2000; Wareing et al., 2000; Zakzanis and Young, 2001; Zakzanis and Campbell, 2006). Cannabis is also linked to a range of motivational, memory and other neurocognitive

problems (Hall and Solowij, 1998). These deficits can sometimes normalize after a period of abstinence (Pope et al., 2001b), although they may also endure over time (Solowij et al., 2002). In an internet study involving over two hundred ecstasy users and over three hundred cannabis users, both drugs were independently associated with different types of self-rated memory problems (Rodgers et al., 2001). The recreational use of cannabis was linked to everyday memory problems, short-term and internally cued prospective memory problems, whereas the use of MDMA was associated with higher rates of long-term prospective memory problem; this meant that users of both drugs suffered from both types of memory deficit. Some studies employing objective measures of neurocognitive function reported some additional impact of the extent of the co-use of cannabis with ecstasy use having still the strongest influence on cognitive, particularly memory performance (Gouzoulis-Mayfrank et al., 2000, 2003). However, a minority of studies even found that cognitive impairments in combined users closely mirrored the amount of cannabis consumed, rather than ecstasy (Croft et al., 2000; Simon and Mattick, 2002; Dafters et al., 2004). The empirical data on cognitive functioning in Ecstasy/MDMA users is extensively debated in Parrott (2006). The general pattern to emerge was that their relative contribution reflected their comparative usage. Hence those studies which showed a cannabis deficit, involved polydrug users where MDMA usage was comparatively light and the use of cannabis was relatively heavy; those studies which showed a primary MDMA-related deficit, typically involved heavier users of MDMA; the majority of studies showed that both drugs contributed to cognitive deficits. The numerous studies on which this conclusion is based, are described in Parrott (2006).

Conclusions

The recreational use of Ecstasy/MDMA and cannabis, are each associated with neurocognitive and psychobiological deficits. Yet although regular users of both substances often display high rates of problem (Gouzoulis-Mayfrank et al., 2000, 2003; Gouzoulis-Mayfrank, 2006; Milani et al., 2000; Parrott, 2003; Parrott et al., 2001, 2004a, b; Rodgers, 2000; Rodgers et al., 2001, 2006; Topp et al., 1999), their adverse effects do not always fit a simple additive factors model. Instead, the two drugs can often display a more interactive profile (Daumann et al., 2003; Milani et al., 2005). The notion that cannabis may provide some degree of neuroprotection against the damaging effects of Ecstasy, is currently only a working hypothesis. Nevertheless it has a clear theoretical rationale. For instance, in comparisons of different antioxidants as preventatives for glutamate toxicity, cannabidiol was found to be superior both to ascorbate and alpha tocopherol (Hampson et al., 1998, 2000). The effects of cannabinoids as antioxidants have been mostly studied on AMPA, NMDA and kainate receptor mediated neurotoxicity in rat cortical neurons. Hence the administration of MDMA to rat brain neurons, and assessing the neuroprotective effects of cannabinoids, needs to be undertaken to provide a direct experimental test. In a similar style to the elucidation of dopamine circuitry by the heroin analogue MPTP, a retrospective approach using the antioxidant effects of cannabinoids, could also lead to a more precise identification of the neural circuitry involved with MDMA. In terms of its human implications, this working model might help to explain why PET scans often fail to detect widespread neurotoxicity in ecstasy polydrug users. Furthermore, while cannabis may have some beneficial effects at the cellular level, its effects may be more damaging at the neurotransmitter level, and these would add to the problems caused by MDMA. This would explain why in broader neurocognitive terms, cannabis and MDMA are both linked to a wide range of motivational, psychiatric, amnesic, and other neurocognitive problems.

To summarize, the neurotoxic effects of MDMA are known to be modulated by various factors, in both animals (Green et al., 2003) and humans (Parrott, 2006). There are sound theoretical reasons for predicting that cannabinoids, with their hypothermic and antioxidant properties, are an important modulating factor (Table 1). In particular, cannabis may provide some degree of acute cellular protection, against the powerful stimulant effects of MDMA (Parrott et al., 2004; Gouzoulis-Mayfrank and Daumann, 2006). However the overall contribution of cannabis will still be predominantly negative, due to its numerous adverse effects as a monosubstance: impairing motivation, neurocognition, health, and general well-being. The overall effects of drug combinations will be complex, and related to both acute dosage, and cumulative or lifetime usage. Yet perhaps the most crucial factor is whether they are being taken separately or together, since different psychobiological effects would be predicted (Table 1). Future research will therefore need far better data on the exact patterns of cannabis and MDMA co-usage.

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