

Ecstasy/MDMA and cannabis: the complexities of their interactive neuropsychobiological effects

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Cannabis and Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) are two of the most widely used recreational drugs. This symposium considered their neuropsychobiological effects, both when taken singly and in combination. In neurocognitive terms, cannabis and Ecstasy/MDMA have detrimental effects on different, although sometimes overlapping, aspects of memory and cognition. Those who take both drugs can therefore display neurocognitive deficits in several areas. In neuropsychiatric terms, each drug is again linked with various problems, especially in those who have taken them regularly. However, their acute effects are opposite in terms of oxidative stress. In laboratory animals, MDMA increases oxidative stress, whereas cannabinoids decrease it. This leads to the prediction that, in humans, cannabis may be providing some degree of protection against the neurotoxic effects of MDMA.

This symposium was held at the International Congress of Biological Psychiatry, Sydney Australia on 9–13 February 2004. The symposium was entitled 'Neuropsychiatric and psychobiological consequences of cannabis and Ecstasy/MDMA use'. These are two of the most widely used recreational drugs, with polydrug use now the norm amongst illicit drug users. This meeting covered both acute and chronic aspects of their use, when taken singly or in combination. The four oral presentations were supplemented by several related poster presentations.

Nadia Solowij (2004) focused on the neuropsychiatric and psychobiological aspects of taking cannabis. During acute intoxication, cannabis can induce mild hallucinations, perceptual distortions and delusions in healthy users. Evidence was presented to suggest a causal relationship between cannabis use during adolescence, and the development of depression, anxiety and schizophrenia in vulnerable individuals. Age is also an important modulating factor, with younger adolescents being particularly vulnerable, probably due to the adverse effects of cannabis on neuronal maturation. The long-term neurobiological changes induced by cannabis may lead to an increased susceptibility to psychosis, or may interact with a pre-existing vulnerability to precipitate

psychosis. Cannabis is also used extensively by people with schizophrenia, despite exacerbating many of their symptoms. The mechanisms by which cannabis increases some symptoms, while apparently alleviating others, are thought to reflect complex interactions between dopaminergic, serotonergic, glutamatergic, GABAergic, cholinergic, opioid and endogenous cannabinoid systems (Solowij, 2003). An increased density of cannabinoid receptors has been found in the anterior cingulate and prefrontal cortex of people with schizophrenia, and cannabinoid antagonists are currently being assessed as potential antipsychotic agents. Elevated levels of the endogenous cannabinoid anandamide have been found in the cerebrospinal fluid of medication-naïve first episode acute schizophrenia patients, and in those in prodromal states, but the level of CSF anandamide was negatively correlated with psychotic symptoms (Leweke *et al.*, 2004a,b). This suggests that anandamide elevation may reflect a protective mechanism or a compensatory homeostatic adaptation to neurotransmitter imbalances associated with psychosis. These findings may lead to a greater understanding of the prevalence of cannabis use in schizophrenia and self-medication hypotheses. However, the less selective targeting by exogenous cannabinoids, as well as the differing pharmacodynamics of acute versus chronic cannabinoid administration, may explain the apparently contradictory current theories regarding cannabinoid involvement in psychosis (Solowij, 2003). Chronic cannabis use can result in elevated cannabinoid tone, generating schizophrenia-like neurotransmitter conditions in the prefrontal cortex, with desynchronized cortical and subcortical neural networks, with resultant psychotic symptomatology and cognitive deficits. Long-term users of cannabis thus show impairments of attention, memory and executive processing. The progressive deterioration of cognitive functions with increasing years of cannabis use suggests a gradual developing, and possibly enduring, alteration of brain functioning (Bolla *et al.*, 2002; Solowij *et al.*, 2002). Finally some ongoing (unpublished) functional imaging studies were presented. The findings provided further illumination on memory functioning in long-term cannabis

users, and neurobiological models of schizophrenia and comorbid substance use.

Efi Gouzoulis-Meyfrank focused on Ecstasy, or MDMA, which is an established central serotonergic neurotoxin in experimental animals (Gouzoulis-Meyfrank and Daumann, 2004). There is evidence that humans may also be susceptible to the neurotoxic effects of MDMA. Recreational Ecstasy/MDMA users present with a range of diverse psychopathological symptoms, including depression, anxiety and psychotic episodes. Furthermore, they often display subtle neurocognitive impairments, particularly in the fields of learning and memory. These psychopathological and neurocognitive deficits may be related to the neurotoxic effects of MDMA on central serotonergic processing. However, because of the methodological problems in open field studies, particularly the concomitant use of other psychoactive drugs, it is often difficult to derive firm conclusions about causation. To provide more empirical data on this question, the findings from two recent studies were presented. The first cross-sectional study (Gouzoulis-Meyfrank *et al.*, 2000; Daumann *et al.*, 2001) examined the cognitive functions and psychopathology scores of 28 cannabis users, 28 combined Ecstasy/cannabis users and 28 non-user controls. The second prospective study (Gouzoulis-Meyfrank *et al.*, 2003; Daumann *et al.*, 2004) compared 30 heavy and 30 moderate club-drug and Ecstasy users with a parallel group of non-user control, over an 18-month period. The combined data from both studies indicted that it was cannabis, rather than Ecstasy, that played the major role in the psychopathological manifestations. In contrast, the neurocognitive symptoms, and particularly the memory impairments, were most closely related to the extent of previous Ecstasy/MDMA usage. The issues of progressive deterioration with continued usage, and their putative reversibility after prolonged abstinence, remained unresolved. Further prospective studies were recommended.

Jacqui Rodgers (2004) focused on the self-rated cognitive abilities of recreational Ecstasy/MDMA and cannabis users. An internet website had been established, and the findings from 753 respondents were described. There was a clear dissociation between the effects of these two drugs. Cannabis was associated with everyday memory problems, with moderate users (5–20 times/month) reporting 10% more errors, and heavy users (>20 times/month) reporting 18% more errors, than non-users of cannabis. MDMA was associated with prospective memory errors (e.g. missing an appointment) and mistakes when completing the questionnaire (Rodgers *et al.*, 2003). The rate of Prospective Memory Questionnaire long-term errors reported by a 'typical' ecstasy/MDMA user was 14% more than the non-Ecstasy drug users, and 23% greater than the non-drug users. The corresponding rates of completion error for the 'typical' ecstasy/MDMA user were 21% and 29% higher than the other two groups, respectively. These findings reported by Rodgers are in agreement with those presented by Gouzoulis-Meyfrank, and demonstrate that Ecstasy and cannabis affect rather different aspects of neurocognitive functioning. Furthermore, these cognitive problems are not just apparent in the laboratory, because recreational drug users are very aware of their own memory difficulties. This subjective awareness of drug-related problems was further illustrated by Rodgers (2004), who noted that the majority of heavy MDMA users reported a wide

range of problems that they attributed to Ecstasy. These included not only memory difficulties, but also poor concentration, depression, anxiety, mood fluctuation, tremors and twitches, weight loss and infections. Finally, the latest ongoing web study was outlined, which now includes online cognitive testing online. The website address is: www.drugsresearch.org.uk

Andy Parrott (2004a) focused on the acute pharmacodynamic reasons for co-using MDMA and cannabis, and discussed the implications of their contrasting effects on oxidative stress. Many recreational Ecstasy users report using cannabis to relieve the unpleasant come-down effects that follow after MDMA. Furthermore, as chronic tolerance to MDMA develops, most regular users demonstrate dosage escalation (Parrott, 2004b), and report more neuropsychobiological problems (Peroutka, 1989; Parrott *et al.*, 2001). This may help to explain why so many heavy/regular users need to take relaxant drugs such as cannabis or opiates for symptomatic relief (Pedersen and Skrandal, 1999; Parrott, 2001). When taken acutely, MDMA and cannabis have opposing effects on oxidative stress. An acute dose of MDMA leads to increased oxidative stress, and this is thought to be a core mechanism for drug-induced serotonergic neurotoxicity (Green *et al.*, 2003). Antioxidants such as sodium ascorbate have been shown to attenuate the neurotoxic damage caused by MDMA in laboratory animals (for a summary, see Green *et al.*, 2003). Tetrahydrocannabinol and cannabidiol have also been shown to act as antioxidants in laboratory animals (Hampson *et al.*, 2000; Grundy, 2002). Furthermore, unlike many potential antioxidant agents, cannabinoids readily pass the blood–brain barrier (Gilgun-Sherki *et al.*, 2001). This leads to the prediction that cannabis may help to attenuate the neurotoxic effects of MDMA in recreational users. This hypothesis was first suggested to us by Daniele Selmi, and may help to explain some otherwise rather surprising empirical findings. In several studies, unexpectedly better psychobiological profiles have been found in Ecstasy users who take cannabis compared to those who do not. In a study of 278 Ecstasy users, Milani *et al.* (2002) found that monthly or weekly cannabis use was associated with significantly lower rates of anger and hostility compared to non-cannabis users (in addition to daily cannabis users being significantly more impaired on several psychopathology scales). Rodgers *et al.* (2003) found significantly greater procedural errors in Ecstasy/MDMA users compared to non-users (see above); however, amongst this group of Ecstasy users, the use of cannabis was significantly associated with less errors. In another study of 234 Ecstasy/MDMA users, Parrott *et al.* (2002) found that the use of cannabis was associated with significantly lower rates of depression, and fewer 'total negative symptoms'. Currently, the hypothesis that cannabinoids may provide some relief against the neurotoxic effects of MDMA, must be considered as only very tentative (Parrott *et al.*, in preparation). However, it might help to explain some of the variation in functional imaging findings. Indeed, in the subsequent discussion, Gouzoulis-Meyfrank noted that, in a recent imaging study, a small group of 'pure MDMA users' showed significantly lower functional magnetic resonance imaging (fMRI) BOLD responses in several brain regions, compared to a group of ecstasy polydrug users. These 'counter-intuitive' findings had previously been explained in terms of oxidative stress, particularly as

delta-THC may help to reduce the hyperthermia induced by MDMA (Daumann *et al.*, 2003).

Several poster presentations provided further data on the neuropsychobiological aspects of cannabis and Ecstasy use. In a Turkish psychiatric hospital study, Ozden *et al.* (2004) compared two groups of young people diagnosed with schizophrenia, who either smoked cannabis or were non-smokers. The use of cannabis was associated with more hospital readmissions, and higher symptom ratings. Respondek *et al.* (2004) won an Astra-Zeneca poster prize for their fMRI study of memory functioning in long-term cannabis users. Their preliminary findings indicted that long-term heavy cannabis users were most impaired on the neuropsychological test battery, and showed the smallest changes in blood oxygen level dependent activation in those brain regions relevant to memory. Milani and Parrott (2004) investigated WHO drug dependence criteria amongst young Ecstasy/MDMA users, and found that these dependence scores were more closely related to psychobiological distress than was lifetime Ecstasy dosage. Parrott *et al.* (2004) investigated the thermoregulatory abilities of abstinent Ecstasy/MDMA users in a hot thermal environment. Body temperature and thermal comfort ratings were very similar to the non-user controls. However, fluid intake over the entire session was 66% higher ($P = 0.06$, two-tailed) amongst the drug-free ecstasy users, while recognition memory for both groups was significantly poorer in the heat.

Throughout this symposium, it was repeatedly emphasized that cannabis and Ecstasy are just two of many psychoactive compounds used by polydrug users. The use of recreational drugs during pregnancy, both planned or unplanned, was noted as a topical research issue (email: daisy@uel.ac.uk for details of a prospective study seeking participants). Amphetamine, cocaine, ketamine and opiates can all modulate neuropsychobiological profiles, while legal drugs such as alcohol and nicotine may also have important contributory effects. Indeed, in one of the above studies where cannabis displayed beneficial associative effects, the use of amphetamine, cocaine and alcohol were each associated with poorer psychobiological profiles (Parrott *et al.*, 2002). The worst co-drug for Ecstasy/MDMA users was nicotine, with cigarette smokers showing significantly worse profiles on numerous dimensions. Although nicotine dependency is itself psychologically damaging (Parrott, 2003), the overwhelmingly negative profiles of those Ecstasy/MDMA users who also smoked tobacco was still very surprising. However, cigarette smoke contains hundreds of chemicals and is an important source of free radicals, and hence of oxidative stress (Halliwell and Gutteridge, 1999); it should be noted that the specific contribution of nicotine to oxidative stress is more mixed (Newman *et al.*, 2002). Thus, while one working hypothesis is that appropriately timed cannabinoids may help to attenuate the adverse neurobiological effects of MDMA, another is that regular tobacco smoke may be exacerbating the neurotoxic effects of MDMA.

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