

MDMA (3,4-Methylenedioxymethamphetamine) or Ecstasy: The Neuropsychobiological Implications of Taking It at Dances and Raves

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Key Words

3,4-Methylenedioxymethamphetamine · MDMA · Ecstasy · Amphetamine · Rave · Heat · Exercise · Cognition

Abstract

MDMA (3,4-methylenedioxymethamphetamine) or 'ecstasy' is a ring-substituted amphetamine derivative, which is widely used as a recreational drug, most particularly at dances and raves. Around 80–95% of dancers/ravers report using ecstasy/MDMA, compared to 5–15% of young people in general. This paper will consider the possible contribution of stimulatory environmental conditions to the neuropsychobiological effects of MDMA. Animal research shows that heat and crowding potentiate the acute effects of MDMA. Social interaction and intravenous drug self-administration in laboratory rats are significantly enhanced when MDMA is given under hot ambient temperatures. Loud noise and physical activity can also contribute to the general overarousal. Furthermore, MDMA impairs homeostatic thermal control in rats, leading them to overheat in hot environments. The human implications of these findings are that the hot, noisy and overcrowded conditions at raves may be providing the ideal environment to heighten the acute

drug response. In recreational users, the acute medical dangers of MDMA comprise a constellation of hyperthermia-related ab reactions, which generally only occur when it has been taken in hot and crowded environments. MDMA is well established as a serotonergic neurotoxin in laboratory animals, but heat and overcrowding increase the degree of distal axon terminal loss. If this also occurs in humans, then the stimulatory environments of clubs and raves may heighten the likelihood of adverse neuropsychological sequelae in recreational ecstasy users. Consistent with this prediction, the extent of self-reported dancing/exercise when on MDMA has recently been shown to be associated with significantly more psychobiological problems afterwards.

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Ecstasy: Its Recreational Use in Raves and Dance Clubs

Ecstasy or MDMA (3,4-methylenedioxymethamphetamine) is widely used as a recreational drug [1–4]. In general population surveys, around 5–15% of young people aged 18–30 years admit to having ever taken ecstasy/MDMA [3, 4]. However, when clubbers or ravers are sampled, far higher values of around 80–96% typically

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emerge. For instance in a Dutch survey of 1,121 rave/dance attendees, van de Wijngaart et al. [5] found that 81% reported having ever used ecstasy, while 64% stated that they had taken it the previous night. Winstock et al. [6] surveyed 1,151 dance music enthusiasts in the UK; 96% admitted to having ever used ecstasy, while 86% stated that they had taken it in the last month. Tossman et al. [7] interviewed over 3,000 techno music party attendees in Amsterdam, Berlin, Madrid, Prague, Rome, Vienna and Zurich, and found that a high proportion had used illicit drugs such as ecstasy. They also noted that 'visitors to techno parties have a considerably greater experience with ecstasy use than the general population of a corresponding age' [7]. In a review focusing on ecstasy/MDMA in Italy, Schifano [2] noted that its use was almost exclusively restricted to clubs, parties or raves. Indeed, the strong association between MDMA and the rave and clubbing scene has led many to label ecstasy/MDMA as a 'club or dance drug' [8, 9].

Rave and dance club venues are characterized by sensory and physical stimulation, with loud noise, bright lights and densely packed crowds of dancers [10]. The aim of this paper is to discuss the neuropsychobiological implications of the association between ecstasy/MDMA and the environmental stimulation of the dance/clubbing scene. Two aspects will be debated, acute or immediate effects and long-term or chronic consequences. In acute terms, it will be debated whether the hot, overcrowded and noisy conditions may contribute to the MDMA-induced activation. For instance, concomitant environmental stimulation may help to boost the drug-induced psychophysiological arousal and intensify the subjective drug experience, but also increase the likelihood of adverse medical reactions or fatalities. In terms of chronic or long-term effects, the animal literature suggests that taking MDMA under arousing environmental conditions can increase the probability of long-term serotonergic neurotoxicity.

Before examining these topics, some caveats need to be raised. Firstly, there is a general paucity of empirical *human* data on these questions. The evidence largely comes from laboratory *animal* studies, where environmental factors such as heat and crowding have been systematically controlled. Thus, it is the findings from these laboratory animal studies which raise the implications for recreational users, which are being debated here. The limited human data on most of these topics are generally rather indirect and often lacking in methodological sophistication. Although recent empirical findings have confirmed that nondrug factors can contribute to the neu-

ropsychobiological problems reported by recreational users (see final section), in general the current article is largely exploratory. Its main aim is to draw attention to the relevance of environmental factors for our understanding about the effects of ecstasy/MDMA in humans.

Acute Effects of MDMA: Contributory Effects of Environmental Stimulation in Laboratory Animals

MDMA is a ring-substituted amphetamine derivative and CNS stimulant. In neurochemical terms, it is a potent indirect monoaminergic agonist and reuptake inhibitor. An acute dose leads to a marked increase in serotonin and dopamine, although other neurotransmitters are also affected, including noradrenaline, acetylcholine and histamine [11–15]. Laboratory animal research with amphetamines has shown that the environment has an important contributory role, with greater behavioral stimulation under arousing conditions. Temperature is a crucial factor with MDMA, since it impairs the hypothalamic thermal control mechanisms; laboratory rats therefore show impaired homeostasis following an acute dose of MDMA. In a cold environment, they cool down to a greater extent than control animals, whereas under high temperature conditions their body temperature rises to a significantly greater extent [16–18]. The two neurotransmitters implicated in these thermoregulatory changes are serotonin and dopamine, with dopamine possibly being more crucial [11, 13, 19, 20].

Cornish et al. [21] compared the effects of an acute dose of MDMA, under ambient temperature conditions of 21 and 30°C. Pairs of laboratory rats demonstrated significantly increased social interaction after MDMA under the lower room temperature. However, a significantly greater degree of social facilitation was evident after MDMA had been administered at 30°C. Cocaine and amphetamine were also assessed, but in contrast to MDMA, they led to less social interaction under both temperature conditions. This emphasizes that the pro-social effects of MDMA are not a typical characteristic of the CNS stimulants in general. Cornish et al. [21] further noted that intravenous self-administration was significantly greater under the high temperature condition, showing that the reinforcing properties of MDMA were enhanced by heat. Overcrowding can also heighten the stimulatory effects of amphetamine in laboratory animals, with 'aggregate toxicity' first being described over 60 years ago. Gunn and Gurd [22] reported that 'symp-

toms of excitement are much more pronounced if several injected animals are kept together'. The degree of hydration may also be important, since water deprivation increases the hyperthermic response of MDMA-treated rats, under conditions of high ambient temperature [23]. Another potentially important factor is noise, with the aggregate toxicity induced by methamphetamine in mice being significantly enhanced by loud music [24]. Presumably, loud noise contributes to a general increase in tonic arousal by stimulating the ascending reticular activation system [25]. This might explain why the mice were not too fussy about the composer, since the pop group Prodigy and classical Bach were similarly effective when played at 95 dB [24]. The authors noted that the effects of loud noise should also be investigated with other amphetamine derivatives, including MDMA.

Acute Effects of MDMA: Possible Contributory Effects of Environmental Stimulation in Humans

Clubs and raves provide a very stimulating environment, with bright lights, loud music, densely packed crowds and prolonged periods of dancing. Suy et al. [10] described the situation at a Dutch rave involving 14,000 dancers. They noted that disk jockeys used the powerful sensory stimulations at their disposal, both auditory and visual, to achieve heightened arousal amongst the dancers. In a personal recollection of the rave scene, Walsh [26] noted: 'The disk jockeys were canny in their deployment of music to augment the ecstasy experience. They would raise the mood, level us out, raise us, level us out again, then thwack us in the solar plexus with a surge of piano. There would be people literally passing out and falling off speakers.' The intense patterns of music are often enhanced by visual light shows which contribute to the overall sensory stimulation. When a group of American ravers were interviewed, they typically reported intense sensations, as the following testimony illustrates: 'I felt I had a stereo inside my body' [27].

In psychophysiological terms, many ecstasy-using clubbers are therefore in a state of hyperarousal. This is caused by the massive increase in neurotransmitter activity, since an acute dose of MDMA can indirectly release 80% of presynaptic serotonin into the synaptic cleft [12]. This results in a borderline state where many ecstasy-using clubbers display mild signs of the serotonin syndrome. Hyperactivity, mental confusion, hyperthermia and trismus (jaw clenching) are typical on-drug experi-

ences for most ecstasy users [28]. The overwhelming majority of ecstasy/MDMA-using clubbers report feeling hot, dehydrated and sweating excessively [29, 30], with one dancer noting: 'Feels like your blood is 115 degrees Fahrenheit' [27]. In a placebo-controlled laboratory study, Tancer et al. [31] investigated the effects of an acute dose of MDMA (2 mg/kg), in 4 experienced ecstasy users, under two temperature conditions: 18°C and 30°C. Core body temperature and skin temperature were significantly raised following MDMA, but unlike rats, this occurred under both the hot and cold ambient temperature conditions. Under placebo, the metabolic rate increased by 12% under both room temperatures, whereas under MDMA it increased by 57% at 18°C and by 75% at 30°C. Since MDMA is an amphetamine derivative, it also stimulates cardiac output and breathing rate [12–14, 32]. This can help to increase physical endurance so that 'ravers dance continuously... until the early morning' [10]. This prolonged exertion may also be helping to maintain a high body/brain temperature. Furthermore, some ravers demonstrate active behavioral thermoregulation strategies: wearing thick woolly hats while dancing or sitting on radiators when resting [Rodgers, pers. commun.].

These stimulatory conditions may help to intensify the subjective drug reaction, since personal experiences seem to be strongest at the clubs. When human volunteers were administered doses of 100–120 mg MDMA in a 'calm and comfortable laboratory environment' of medical setting, they described increased feelings across a wide range of positive and negative mood states. Significant group increases in pleasant moods were accompanied by parallel group increases in anxiety and depressiveness. In an equivalent fashion, the significant ANOVA increase in self-rated extraversion was accompanied by a significant group increase in introversion [32]. A similar range of contrasting mood changes occurred with the neurochemically similar MDE (3,4-methylenedioxyethylamphetamine) in the laboratory, when euphoria and sadness, talkativeness and withdrawal were all subjectively described [33]. Thus in a calm and neutral physical environment, MDMA and MDE display a general releasing function, when positive and negative moods can all be boosted. In contrast, the subjective experiences described by ecstasy-using clubbers tend to be far more euphoric: 'Pure energy, happy energy...being touched was so intense'; 'I don't think that anything could have brought me down. I loved it'; 'All I wanted to do was smile. I was so wide awake' [27]. It should be emphasized that there are no empirical data directly comparing the subjective effects of MDMA in different environments. Nevertheless, the mood

changes experienced at clubs and raves do seem to be far more intense than those occurring in less stimulating environments.

The use of stimulant drugs in hot and crowded environments can also have adverse medical consequences. Larger raves often provide medical facilities staffed by paramedics. Suy et al. [10] noted that ravers who required medical support were generally in a state of physical exhaustion, which was treated by rest and fluid replacement. Many drug users are aware of the dangers of becoming too hot so that they alternate periods of dancing with visits to the 'chill out' area, where the music is quieter and the light shows more relaxing [4]. Some clubs even spray water onto the crowded dancers to cool them down [28]. Despite this, a minority of users can become dangerously hyperthermic, when physical deterioration is rapid and may prove fatal. Henry et al. [34] described 7 MDMA fatalities in party-goers aged 16–21, whose resting temperatures at the intensive-care wards varied between 40 and 43°C. Fantegrossi et al. [35] also noted: 'An initial report on the lethal effects of MDMA in the human noted that in almost every case, a recreational dose of the drug had been taken at a dance club or party where crowds danced vigorously.' The causes of death can include: brain seizure, cardiac arrest, acute liver or kidney failure, rhabdomyolysis (destruction of skeletal muscle tissue) and disseminated intravascular coagulation (impaired blood clotting with bleeding through multiple sites [12, 27, 34]).

Chronic MDMA: Possible Role of Environmental Stimulation to Serotonergic Neurotoxicity in Animals

In laboratory animals, MDMA is a serotonergic neurotoxin, causing the loss of axon terminals in higher brain regions. The cell bodies in the midbrain regions are left intact, while the distal axon terminal projections in the cerebral cortex are lost. In rats, monkeys and primates, single high doses, or a series of lower doses, can cause this serotonergic axon terminal loss [15, 36–38]. The environmental conditions of the laboratory modulate these longer-term neuronal changes, with temperature again being a crucial factor. Cool environments are neuroprotective, whereas under hot conditions the extent of neuronal damage increases as a direct function of the prevailing temperature [16, 18]. Repeated dosing with MDMA also causes an enduring impairment in the thermoregulatory control of rats, and this has led Dafters and Lynch [16] to note

that 'long-term disturbances in thermoregulation ability' should be added to the list of potential hazards for human MDMA users. Another potentially important environmental factor is overcrowding, which increases the lethality of acute MDMA and may also increase the incidence of chronic longer-term problems [35]. Loud noise has also been found to increase the neurotoxic effects of aggregate toxicity induced by methamphetamine in mice, and similar effects may also occur with MDMA [24].

McGregor et al. [39] administered a neurotoxic regimen of MDMA to socially grouped rats at ambient temperatures of 16 and 28°C, then assessed them on a behavioral battery 2–4 months later. MDMA pretreatment was associated with poorer memory on an object recognition test, but only after MDMA had been given at 28°C. The other measures were also adversely affected, including behaviors modeling anxiety and depression, but these deficits were apparent after earlier dosing at both temperatures. Furthermore, against predictions, serotonin levels were significantly reduced under both temperature conditions. Intriguingly, given the possible importance of dopamine for these thermal control changes ([20], see earlier), there was a significant loss of dopamine in the striatum. However, there was no significant difference in the extent of this dopaminergic loss between the two temperature conditions, although the trend was for greater loss at the higher temperature (–606 ng/g tissue loss at 16°C, compared to –1,666 ng/g loss at 28°C; from their table 3). Finally, 5-HIAA levels were reduced by a significantly greater extent after 28°C compared to 16°C in 2 of the 4 brain regions assessed, the amygdala and hippocampus; these changes were thus similar to the pattern of memory deficits (see above).

Huether et al. [40] outlined an animal model for how stimulatory conditions can often increase the extent of MDMA-induced serotonergic neurotoxicity. The main effect of MDMA is to cause the release of massive amounts of serotonin from the presynapse over several hours. This overstresses the cellular processes of metabolic recovery and repair so that MDMA is inherently neurotoxic irrespective of the environmental conditions. This explains why McGregor et al. [39] found structural and functional deficits, even when MDMA was administered under comparatively low temperature conditions (see previous paragraph). Huether et al. [40] noted that any stimulatory factors which further stress the presynapse, can contribute to additional long-term neuronal damage. For instance the combined use of two stimulants, such as MDMA with amphetamine, induces more neurotransmitter release and thus heightens neurotoxicity [40]. In contrast, any

factors which retard this neuronal overstimulation are neuroprotective. Hence low temperatures can help to protect against MDMA-induced neurotoxicity, as do drugs which inhibit neurotransmitter release [19, 40].

Chronic MDMA: Possible Role of Environmental Stimulation to Structural and Functional Deficits in Humans

The above animal findings raise the question of whether MDMA also causes long-term neuropsychobiological problems in humans. Abstinent recreational users display a range of structural markers for serotonergic loss, including positron emission tomography, single photon emission computed tomography, magnetic resonance imaging and more indirect indices of serotonin activity [12–14, 41–45]. Many functional problems with serotonergic aspects have also been described in abstinent recreational ecstasy/MDMA users. These include heightened depression, impulsivity, anxiety, sleep disorder, memory difficulties, executive cognitive deficits and loss of sexual interest. The extent of these changes has been shown to be related to various factors, including the extent of past MDMA usage, age of first use, other psychoactive drug use, gender, premorbid characteristics and lifestyle aspects such as irregular sleep and eating [2–4, 42, 46–54]. There is also some limited evidence for the functional deficits being associated with structural changes [44, 55, 56].

One potentially important factor which has been rarely investigated is 'usage at raves', with few empirical studies describing the drug-taking venues of their participants. One exception is the study by Hansen et al. [57], who assessed a group of ecstasy users, 'none of whom identified themselves as belonging to the rave/dance music scene'. They described comparatively light patterns of drug use and comparatively few drug-related problems, despite having taken MDMA for an average of 3.5 years. Their findings can be compared with another Australian study of 'dance drug users', who had been taking MDMA for a similar time period (3.6 years), but followed more intensive patterns of usage [30]. They reported an average of 8 and 4 physical side effects, which were attributed either to ecstasy use alone or to a combination of ecstasy with other factors. The overall profiles of these two groups differed markedly so that attending raves, intensive MDMA usage and the development of multiple drug-attributed problems were all closely associated together.

The effect of physical activity when on MDMA was assessed in a recent internet study involving 206 recreational users, who noted their usual patterns of dancing/exercise on ecstasy [58; Parrott et al., submitted]. Scores on the Prospective Memory Questionnaire long-term subscale were significantly higher in those who reported dancing/exercise 'all the time' when on MDMA. The extent of dancing/exercise on MDMA was also significantly associated with more memory problems in the days afterwards; post-MDMA memory 'come-down' problems were reported by 33% of those who stated that they never danced whilst on MDMA, by 57% of those who danced frequently when on ecstasy and by 73% of those who danced 'all the time' when on ecstasy. Self-reported depression, weight loss, concentration problems and organizational difficulties were also significantly associated with the extent of dancing/exercise when on ecstasy [58; Parrott et al., submitted]. Feelings of being hot/overheating on MDMA were also significantly associated with various psychobiological problems afterwards, including more reports of concentration difficulty, impulsivity and mood fluctuation.

Conclusion

Most psychobiological explanations of behavior emphasize the complex and dynamic interaction between internal biological processes and external environmental influences. The recreational use of MDMA provides a topical example of this relationship. The traditional explanation for the association between ecstasy/MDMA and raves is that stimulant drugs help to boost moods and facilitate prolonged periods of dancing [59]. While this may well be correct, it reflects only one side of the associative equation. Laboratory animal research shows that hot and stimulating conditions boost the acute drug response, and humans have discovered the practical utility of taking 'dance drugs' such as MDMA under stimulatory conditions. Loud music, bright lights and prolonged exercise, in hot and crowded conditions, can all combine to heighten sympathetic and cortical arousal [10]. It seems that recreational MDMA users may have learnt, either consciously or unconsciously, to seek out those conditions which maximize the acute drug response. The resulting state of hyperthermic overarousal may help to boost moods yet further and clearly heightens the dangers of heat exhaustion [26, 28, 34, 58].

The animal literature shows that these sympathomimetic conditions can exacerbate long-term serotonin neu-

rotoxicity, although it should be emphasized that MDMA is inherently neurotoxic even when administered under normal temperature conditions [39, 40]. Future animal studies should investigate the separate and combined effects of all these drug and nondrug factors, using traditional ANOVA designs, where dosage, ambient temperature, crowding, physical activity, noise and hydration could all be systematically manipulated. Preliminary findings with humans have confirmed that factors such as dancing/exercise when on MDMA and feeling hot/overheating when on drug are linked with more psychobiological problems afterwards [58, Parrott et al., submitted]. In terms of future human research topics, the thermoregulatory abilities of recreational ecstasy/MDMA certainly

need to be investigated. Those who regularly take MDMA at raves/dances could also be compared with more sedentary ecstasy users, using a range of structural and functional measures. Another topic is the contributory effects of other codrugs. Amphetamine and cocaine increase both hyperactivity and hyperthermia, and should lead to more acute and chronic problems in MDMA users [25]. In contrast, cannabis is a relaxant and induces hypothermia [60], so it may help to attenuate these problems (see also Parrott et al. [61], for the effects of cannabis on oxidative stress). However, the prime concern is that recreational ecstasy users may be putting themselves at greater risk of developing neuropsychobiological problems, by taking MDMA at hot and crowded raves or dances.

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