Chapter 43

The Behavioral Effects of MDMA in Humans Under Controlled Laboratory Conditions

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Abbreviations

LSD Lysergic acid diethylamide
MDMA ±3,4-methylenedioxy-methamphetamine
PTSD Posttraumatic stress disorder
SERT Serotonin transporter

[With MDMA], I feel I can talk to anyone, and I do mean anyone, on their level. Making connections, even with people you would not normally make connections with, is not only easy, it is pleasant. Anyone I see…I have an overwhelming desire to communicate to. Most of the time I find that it has a positive effect on other people as well as they can sense a kind of comfort and warmth coming from me and they react positively. I've made more friends on ecstasy in one night than in one month without it.

Erowid Experience Report 60967.

INTRODUCTION

The above quote was taken from the Erowid Website forum, a compendium of anecdotal drug experiences from experienced users of a range of psychoactive drugs including hallucinogens such as lysergic acid diethylamide "LSD" and psilocybin, and amphetamine derivatives such as ±3,4-methylenedioxymethamphetamine (MDMA, "ecstasy," or "molly"). This quote is an excellent description of the reason many individuals reportedly use MDMA recreationally: namely, to experience a range of prosocial subjective and behavioral effects. Anecdotal reports suggest that MDMA increases feelings of empathy, sociability, friendliness, and interpersonal closeness. The drug also reportedly produces an increase in motivation to socialize and the perceived quality of social interactions. The above nicely illustrates many perceived effects of MDMA: the writer feels that she has made more friends specifically because of the acute psychoactive effects of the drug. Clearly, she thinks this is a good thing.

Undoubtedly, MDMA-related prosocial effects are motivating reasons for using the drug recreationally and/or therapeutically (Bravo, 2001; Sumnall, Cole, & Jerome, 2006). In the United States, prior to 1985, MDMA was used as an adjunct to psychotherapy because it decreased defensiveness and enhanced feelings of emotional closeness (Greer & Tolbert, 1986; Wolfson, 1986). More recently, growing evidence from controlled clinical trials suggests that the drug is an effective therapeutic adjunct in patients with posttraumatic stress disorder (Mithoefer et al. 2013; Oehen, Traber, Widmer, & Schnyder, 2013). This research is in the nascent stage and there remains a need for better and more complete information on MDMA-related therapeutic utility. Additionally, further research into the drug's acute effects might also provide a better understanding of why the drug is used recreationally.

The bulk of this chapter will focus on what is known about the acute effects of MDMA based on findings from controlled laboratory studies conducted using human research participants. Before describing these data, however, we will briefly review the chemical structure of MDMA, its mechanism of action, its recreational and clinical use, and its legal status as a controlled substance. This will put the drug into the context of other related drugs that are used recreationally and prescribed for a variety of disorders. Then, we will provide a brief discussion of MDMA-related concerns about possible detrimental effects of the drug, including neurotoxicity. We conclude the chapter with a discussion of the importance of continuous evaluation of the risk/benefit ratio when determining the utility of any drug regardless if it is used recreationally or therapeutically.

MDMA'S CHEMICAL STRUCTURE AND MECHANISM OF ACTION

The ring-substituted amphetamine analogue MDMA is closely related to other amphetamines, including D-amphetamine (the active ingredient in Adderall and Dexedrine) and methamphetamine (the active ingredient in Desoxyn). All three of these amphetamines are classified as phenethylamines, a broad chemical class

that contains dozens of other compounds considered to have some therapeutic value (e.g., bupropion: Hill & Thomas, 2011). Similar to other amphetamines, MDMA enhances monoamine neurotransmission. The monoamine neurotransmitters, dopamine, serotonin, and norepinephrine are thought to play an important role in mood regulation, reward, and arousal. One unique neurochemical action of MDMA is that it enhances the activity of brain oxytocin (Thompson, Callaghan, Hunt, Cornish, & McGregor, 2007), a hormone associated with social bonding and other social behaviors (Bos, Panksepp, Bluthe, & Honk, 2011). It is possible that this effect mediates or modulates MDMA-related prosocial effects.

A BRIEF HISTORY OF MDMA USE AND LEGAL CONTROL

MDMA was first synthesized in 1912 by the German pharmaceutical company Merck, who were searching for antihemorrhagic agents (Benzenhöfer & Passie, 2010). After going mostly unnoticed for half a century, MDMA began to be used recreationally in the late 1960s and early 1970s in the Western and Midwestern United States (Benzenhöfer & Passie, 2010; Siegel, 1986). Then, in the late 1970s in California, MDMA gained notice as a potential adjunct to psychotherapy largely because of its ability to reduce psychological avoidance and improve the therapeutic relationship, and by the early to mid-1980s, a growing number of clinicians and patients had been introduced to the drug (Benzenhöfer & Passie, 2010; Grob, 2000; Sessa, 2007). At the same time, nonmedical use of the drug became more prevalent in the United States, which contributed to the Drug Enforcement Administration placing MDMA onto Schedule I of the Controlled Substances Act in 1985 (Grob, 2000; Sessa, 2007; Siegel, 1986). This schedule is the most restrictive and means that the drug is deemed to be among the most dangerous drugs and has no approved medical use.

Despite this tight restriction, illicit MDMA use has continued in the United States and many other countries. However, recreational MDMA use is relatively low compared with other recreational drugs, with the annual prevalence of MDMA use in the general population at an estimated for different global regions as follows: Africa 0.2% (1.08 million), the Americas 0.5% (3.21 million), Asia 0.4% (10.75 million), Europe 0.5% (3 million), and Oceania 2.9% (0.72 million), which combines into an estimated annual global prevalence of 0.4% (18.8 million) for ecstasy use (United Nations Office on Drugs and Crime, 2014). Data from the United States indicate that an estimated 4.1% of Americans aged 18–25 years used ecstasy in the past year, compared with 4.6% for cocaine, 13.7% for nonmedical use of psychotherapeutics, 31.5% for marijuana, and 77.4% for alcohol (Substance Abuse and Mental Health Services Administration, 2013).

CONCERNS ABOUT MDMA USE

One of the most persistent concerns associated with MDMA use is neurotoxicity, i.e., damage to or destruction of brain cells. There is large database collected using laboratory animals suggesting that MDMA produces neurotoxicity, especially to monoamine-containing neurons (Green, Mechan, Elliott, O'Shea, & Colado, 2003). In these experiments, researchers typically inject large bolus doses of MDMA repeatedly for one or more consecutive days to drug-naïve animals. In some cases, the animal is given as much as 10 times the amount of drug that a human would take. The animals are then killed and their brains are examined for markers of neurotoxicity. It is not surprising that MDMA, given in these large doses, can cause damage to brain cells. What is perhaps more interesting, however, is that MDMA-related (or amphetamine-related) neurotoxicity can be prevented with previous exposure to several days of escalating doses or by training the animal to self-administer the drug (Figure 1; Fantegrossi et al., 2004). It is also important to bear in mind that human recreational drug users usually increase their doses gradually over time as their drug use progresses. These observations make it difficult to extrapolate to humans the neurotoxic effects of MDMA demonstrated in laboratory animals. This situation highlights the importance of employing more ecologically relevant models in future animal studies when investigating the impact of amphetamine use in general.

There have been only a few published studies conducted in humans that indirectly address the issue of MDMA-related neurotoxicity. In these studies, abstinent MDMA users are compared

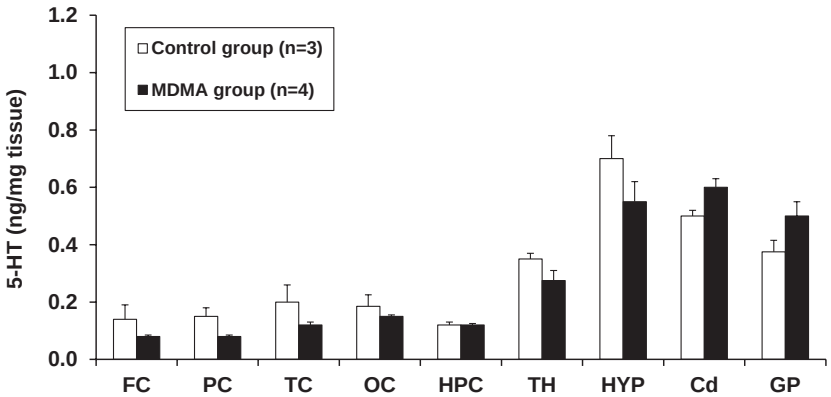

FIGURE 1 Concentrations of serotonin in rhesus monkey brains following long-term intravenous MDMA self-administration. Aggregated tissue concentrations of serotonin (5-HT) in several brain regions, showing no differences between the MDMA and control groups. Open bars represent group mean ± SEM for all control animals, filled bars represent group mean ± SEM for all MDMA monkeys. FC, frontal cortex; PC, parietal cortex; TC, temporal cortex; OC, occipital cortex; HPC, hippocampus; TH, thalamus; HYP, hypothalamus; Cd, caudate nucleus; GP, globus pallidus. *Figure and legend are adapted from Fantegrossi et al. (2004), with permission from the publishers.*

with nonMDMA users on measures of cognitive functioning, brain structure integrity and/or activity. For example, some neuroimaging studies have revealed less serotonin transporter (SERT) binding in current ecstasy users compared to nonusers (see Parrott, 2012 for review). However, for the most part there is a great deal of overlap in SERT binding between MDMA users and controls, suggesting that the differences are within the normal range of human variability (Kish et al., 2010). Additionally, a systematic review of cross-sectional studies found statistically significant increases in measures of anxiety, depression, and impulsivity, and decrements in measures of cognitive functioning among ecstasy users compared with polydrug controls (Rogers et al., 2009). However, across this meta-analysis these differences were consistently small and the effects feel within a normal range, suggesting that these statistically significant differences are unlikely to be clinically significant for the average user (Rogers et al., 2009). Ultimately, these human studies—like the animal studies described above—have at least two critical limitations that could substantially affect the results and should be taken into account when interpreting the findings. First, many of these studies do not control for other drug use, and the MDMA users often use other drugs at a greater frequency and magnitude than the controls. Second, any differences between the MDMA and control groups in brain structure or function, or differences in cognition or mood, could simply be the result of differences that predated MDMA use. Interestingly, when several potential confounds are controlled for (e.g., drug use, sex, gender, race/ethnicity, education, and lifestyle), researchers have failed to demonstrate long-lasting cognitive effects in ecstasy users compared with controls (Halpern et al., 2011). Thus, it remains unclear what the effects and consequences of MDMA use are if we only rely on human studies using cross-sectional designs.

HUMAN BEHAVIORAL PHARMACOLOGY STUDIES OF ACUTE MDMA EFFECTS

One way to further our understanding of the effects of MDMA in humans is to study the relevant effects of known doses under placebo-controlled laboratory conditions. These studies can provide crucial complementary information because they assess MDMA-related effects immediately before and after administration of the drug, while controlling for other extraneous variables. This methodology also allows researchers to obtain information about MDMA-related dose response and time course of action. Ultimately, this methodology provides information that is useful for at least two important reasons. First, it gives us reliable information about the drug's risk/benefit ratio, providing critical data about the conditions under which the drug may produce beneficial or adverse effects. Another useful outcome of this research is that it can provide critical information about the cognitive, social, and behavioral mechanism(s) underlying a broad range of effects produced by MDMA. Overall, data obtained from this experimental approach could be used in a therapeutic setting for disorders and patients that are resistant to other types of treatments (e.g., posttraumatic stress disorder (PTSD); Mithoefer et al., 2013), and/or to enhance safety among recreational users.

Here, we focus our discussion on relatively recent studies that have been conducted to investigate a wide range of MDMA effects, including physiological, subjective, cognitive, and behavioral effects. These studies are all double-blind, placebo-controlled and examine the effects of MDMA dose levels within the relevant recreational and therapeutic dose ranges (i.e., 50–150 mg) on a wide range of dependent variables of interest, from heart rate, blood pressure, and temperature, to the drug's effects on cognition and social behavior.

PHYSIOLOGICAL EFFECTS

A range of physiological effects produced by MDMA has been studied in the human laboratory. For the purposes of this chapter, we will focus on heart rate, blood pressure, and body temperature because these have been the most frequently studied measures and because this information has direct clinical relevance. Similar to other amphetamines, MDMA produces dose-related increases on measures of heart rate and blood pressure (Figure 2; Kirkpatrick, Lee, et al., 2014). These results are consistent with

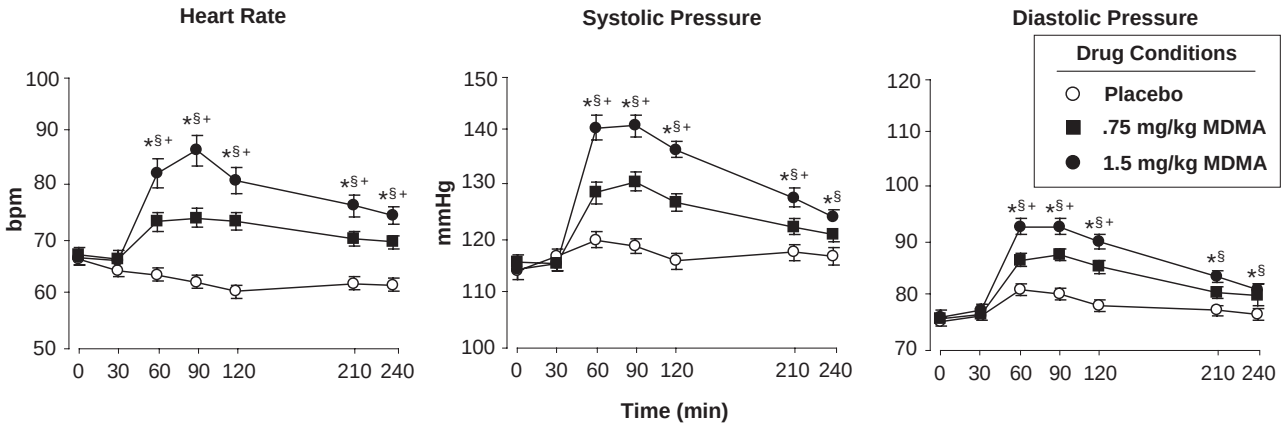

FIGURE 2 Cardiovascular effects of MDMA over a 4-h session. Mean (SEM) heart rate and blood pressure following administration of MDMA or placebo as a function of dose and time. * indicates 1.5 mg/kg MDMA significantly different from placebo ($p < 0.05$). § indicates 0.75 mg/kg MDMA significantly different from placebo ($p < 0.05$). + indicates 1.5 mg/kg significantly different from 0.75 mg/kg MDMA ($p < 0.05$). *Figure and legend are adapted from Kirkpatrick, Lee, et al. (2014), with permission from the publishers.*

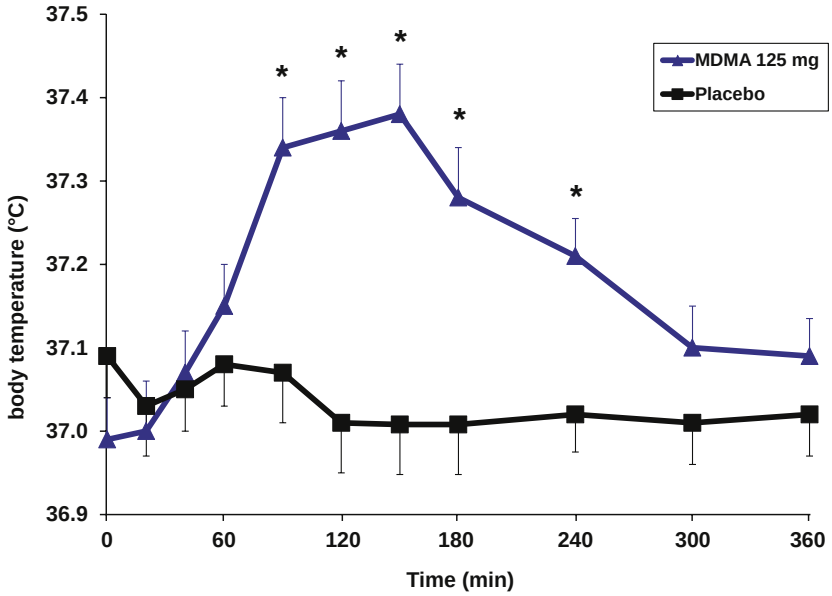

FIGURE 3 Body temperature over time following MDMA administration. Effects of MDMA (125 mg) and placebo on core body (tympanic) temperature in healthy subjects. Data values are mean ± SEM of absolute temperature values in 96 healthy subjects. *$p < 0.001$, significant differences compared with placebo for individual time points. *Figure and legend are adapted from Liechti (2014), with Open Access permission.*

data from similarly conducted studies, with MDMA-related increases in cardiovascular measures peaking between 60 and 90 min after drug administration and remaining elevated for the entire session (4 h post administration). Other studies have shown that these responses return to baseline within approximately 5–6 h (Tancer & Johanson, 2003). It is important to note that these cardiovascular increases following a single dose are well below tachycardic and hypertensive thresholds.

Some MDMA users report using multiple doses within a short period and this has raised concerns about potential dangerous additive cardiovascular effects. Two previous studies have investigated this issue and reported data consistent with this concern. In the first study, Farré et al. (2004) administered two 100 mg MDMA doses 24 h apart and assessed multiple measures, including cardiovascular effects. They found that the second MDMA administration produced significantly larger increases in heart rate and blood pressure than the first. In another study, Peiró et al. (2013) assessed MDMA repeated dose effects by administering a smaller dose (50 mg) followed 2 h later by a larger dose (100 mg) using a single 100-mg dose as a comparator. These researchers also reported significant cardiovascular elevations under the two active drug conditions. It is important to note that while the studies by Farre et al. (2004) and Peiró et al. (2013) found additive cardiovascular activity, these effects were small and unlikely to prompt clinical concerns. Nonetheless, this is an area that can benefit from further research.

The potential hyperpyrexia effects of MDMA have raised concerns because the drug is sometimes used recreationally in settings with high temperatures such as dance clubs. This coupled with the fact there are data collected in animals showing that dramatic increases in core temperature combined with high temperature environments is associated with neurotoxicity (Malberg & Seiden, 1998). Thus, understanding the thermoregulatory effects of MDMA using the human behavioral pharmacology methodology could have important public health implications.

Several studies have examined the effects of single doses of MDMA on body temperature (see Liechti, 2014 for review). A consistent finding is that MDMA produces relatively small increases in core body temperature in a dose-dependent fashion. Changes in core body temperature range between 0.2 and 0.8 °C and do not approach the level of hyperpyrexia (>40 °C; Figure 3). The effects of repeated doses of MDMA on core body temperature administered within short intervals are less well understood because of a dearth of studies investigating this issue. Even though MDMA-related hyperpyrexia is a rare occurrence, these data could be an important part of educating MDMA users on harm reduction practices.

SUBJECTIVE EFFECTS

The subjective effects of acute MDMA administration have been well studied. Several different instruments exist for this purpose and run the gamut from measures of general mood (for example, the Profile of Mood States), specific drug effects (such as feeling high and drug liking from the Drug Effects Questionnaire), perceived physiological effects and subjective experiences of sociability. In general, the subjective effects observed in the laboratory correspond quite well to anecdotal reports; they, like cardiovascular effects, are dose-dependent and follow a predictable time course, peaking between 60 and 120 min post drug administration and returning to baseline several hours later.

For the most part, MDMA produces an interesting pattern of subjective effects that appear to overlap a great deal with other amphetamines. For example, the drug produces dose-dependent increases in feelings of arousal (such as “I feel alert” and “I feel my heart beating fast”), positive mood (such as “I feel elated”), and drug euphoria (such as “I like the drug effect” and “I want

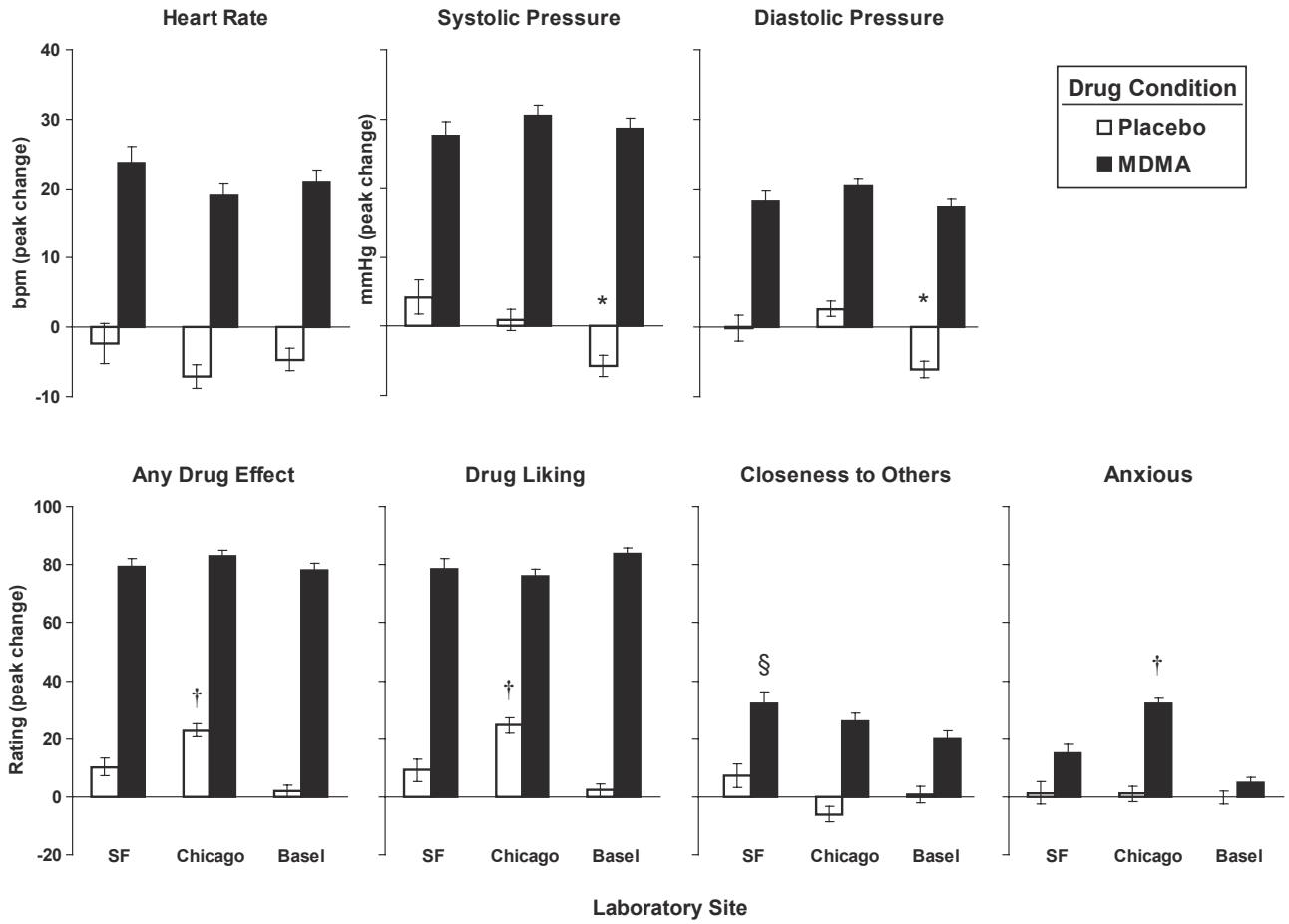

FIGURE 4 Cardiovascular and subjective effects of MDMA from three different laboratories in three different cities. Mean peak (change from baseline) cardiovascular measures and subjective-effect ratings as a function of laboratory site and drug (placebo, MDMA). Error bars represent 1 SEM. *$p < 0.05$, significant difference between Basel and the other two sites; †$p < 0.05$, significant difference between Chicago and the other two sites; §$p < 0.05$, significant difference between San Francisco (SF) and Basel. *Figure and legend are adapted from Kirkpatrick, Buggott, et al. (2014), with permission from the publishers.*

more of the drug"). MDMA also produces dose-dependent increases in feelings of sociability, including feelings of friendliness, desire to socialize, and gregariousness (Bedi, Hyman, & de Wit, 2010; Dumont et al., 2009; Hysek, Domes, & Liechti, 2012; Tancer & Johanson, 2003). Interestingly, in some studies—but not others—the drug also produces small but detectable increases in some negative subjective effects, such feelings of anxiety (Kirkpatrick, Lee, Wardle, Jacob, & de Wit, 2014). Overall, the subjective experience as measured in the laboratory is overwhelmingly a positive experience. Additionally, it shares a lot in common with other amphetamines. In a study from Carl Hart's laboratory at Columbia University, experienced users of both MDMA and methamphetamine received doses of both MDMA and methamphetamine on different days. Interestingly, when asked to identify the drug they received, the majority of participants were unable to distinguish between the two drugs (Kirkpatrick et al., 2012). This suggests that there is a great deal of overlap in subjective experience between these amphetamines.

Overall, there is a great deal of consistency in subjective effects across laboratories, suggesting that the drug produces reliable and predictable effects. There are, however, a few differences between studies and these differences suggest that the drug effects differ depending on the context or setting. Figure 4 shows data from several studies in three different laboratories that measured the same subjective effects using similar MDMA doses (Kirkpatrick, Baggott, et al., 2014). As you can see, in all three laboratories, the drug produced increases on several cardiovascular and subjective measures compared with placebo. However, only the Chicago laboratory reported greater increases in ratings of "anxious." An important methodological difference between these laboratories is that participants in the Chicago laboratory were in social isolation (i.e., in the experimental room alone) while those in San Francisco and Basel had a researcher present in the experimental room. It is possible that a drug that purportedly produces uniquely prosocial effects has different effects in the presence of people compared with when the individual is alone. Additionally, it is likely that setting influences the drug's subjective effects (as well as other behavioral effects) and this may increase or decrease the likelihood of continued MDMA use. Ultimately, to better understand MDMA's effects, future research should investigate the effects of the drug in the presence of others versus drug administration in social isolation.

PSYCHOMOTOR AND COGNITIVE PERFORMANCE ON STANDARDIZED COMPUTER TASKS

To date, the examination of MDMA-related effects on simple and complex cognitive performance has focused largely on standardized computer tasks that measure a range of cognitive functions, including visuospatial processing, learning and memory, reaction time, and divided attention. These tasks, and similar, have been examined extensively in human behavioral pharmacology studies of a range of drugs, including marijuana, alcohol, stimulants, sedatives, and opioids. This facilitates comparisons between these drug classes to examine the relative influence of a given drug on important cognitive functions.

Overall, under laboratory conditions it appears that MDMA produces few effects on measures of psychomotor and cognitive functioning on traditional laboratory batteries of tasks. Some researchers have reported data showing statistically significant slowing of reaction time on measures of visuospatial processing, suggesting that the drug may decrease functioning in this one domain (Cami et al., 2000). However, these findings are inconsistent even within the same laboratory (Farre et al., 2004). In other studies, during which researchers investigated a wider range of cognitive performance tasks, it appears that MDMA does not alter performance compared with placebo. Interestingly, the closely related compound methamphetamine improves performance on many of these tasks at dose levels that produce similar subjective intoxication, suggesting that the drugs minor differences in chemical structure may produce differential effects on cognitive performance, an effect that may be attributed to its differential effects on serotonin (Kirkpatrick et al., 2012). Finally, on more complex tasks, such as measures of real-world driving, it appears that MDMA may improve some measures of performance in experienced users of the drug (Kuypers, Samyn, & Ramaekers, 2006). Overall, this does not lend evidence to idea that MDMA causes cognitive dysfunction, at least in those with some experience with the drug.

EFFECTS ON SOCIAL AND EMOTIONAL PROCESSING AND SOCIAL BEHAVIOR

Another line of research focuses on the effects of MDMA on social and emotional processing and social behavior. The rationale for this work is that it is critical to understand the mechanisms underlying MDMA's prosocial effects. That is, what cognitive and behavioral mechanisms underlie the drug's purported effects of social motivation and behavior? This line of research has generated a growing amount of enthusiasm because increased knowledge of social cognition following MDMA administration might shed light on the reason why individuals use the drug recreationally. It may also illuminate the neurochemical and behavioral mechanisms by which it produces its social and therapeutic effects.

Studies examining MDMA-related effects on social and emotional processing have focused on a wide range of domains, including emotional reactivity, feelings of social acceptance and rejection, recognition of emotions in others, cognitive and emotional empathy, and generosity. For the most part, these have taken place in the absence of other individuals (a single participant in a room) and have involved computerized tasks. In general, MDMA affects performance in many of these domains. For example, MDMA has been shown to increase generosity and measures of cognitive and emotional empathy (Hysek et al., 2013). One of the most consistent findings across tasks and studies is that MDMA appears to increase attention to positive social stimuli and decrease attention to negative social stimuli. For example, MDMA at recreational dose levels (and those used in clinical trials for PTSD) increases the ability to identify masked positive expressions and decreases the ability to recognize masked negative facial expressions (Bedi et al., 2010; Hysek et al., 2012; Figure 5). Additionally, in a study, Frye, Wardle, Norman, and de Wit (2014) showed that MDMA blunted the emotional response to simulated social rejection in a computerized social ball-tossing game. Overall, these findings have interesting implications for therapeutic use. For example, increased empathy may aid in developing therapeutic rapport and trust with the therapist. Furthermore, it has

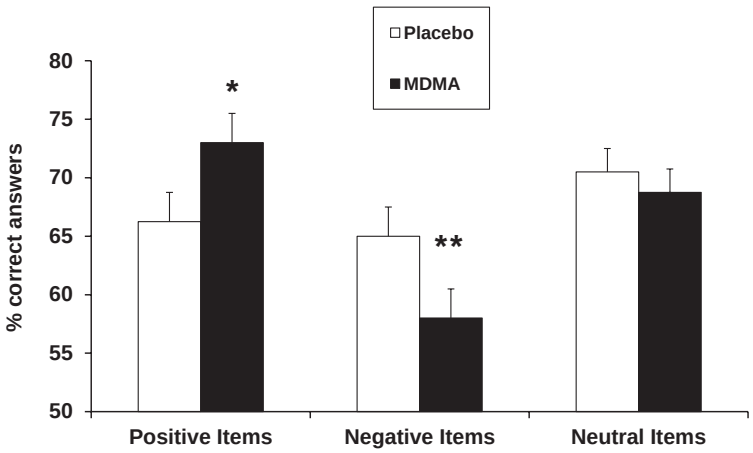

FIGURE 5 MDMA's effects on identification of facial expressions when presented with limited information. MDMA increases the ability in affective mind reading (in the Reading the Mind in the Eyes Test) for expressions with a positive emotional valence (positive items, *$p < 0.05$) and impaired mind reading for negative items (**$p < 0.01$) compared to placebo. Values are mean ± SEM accuracy (percentage of correct items). *Figure and legend are adapted from Hysek et al. (2012), with permission from the publishers.*

been suggested that a decreased attendance to negative stimuli may allow the patient to explore the traumatic situations without the exaggerated emotional and anxious response associated with PTSD (Mithoefer et al. 2013).

There are also some empirical reports on the effects of MDMA on observable social behavior (that is, actual behavior instead of performance on computerized tasks). These are relatively fewer than those described above. To date, these studies have focused on production and quality of speech and video-recorded time spent in social interaction. Overall, this work is in its infancy and there is much to be done. The point of this work is to evaluate the social effects of MDMA in order to better understand why people take the drug. It is in no small part influenced by anecdotal reports as well as animal studies showing that rats spend more time engaging in social behavior following MDMA administration (Ramos et al., 2013; Thompson et al., 2007). A study was conducted in which groups of individuals received MDMA or placebo and were given time to socialize or not. It was shown that MDMA increased the time spent interacting and increased the time spent talking (Kirkpatrick & de Wit, 2014). The effect of MDMA on speech quality is mixed. In contrast to the study cited above, MDMA disrupted speech fluency in which participants had to describe a movie to a research assistant (Marrone, Pardo, Krauss, & Hart, 2010). This suggests that MDMA does not increase talking across the board and it is likely that its effects on speech are context-dependent. But MDMA does appear to alter the content of speech. Bedi et al. (2014) reported that MDMA increased the social content of speech using a machine learning analysis, in which the drug increased the use of words that were semantically close to "friend," "support," "rapport," and "empathy" (Figure 6). Overall, it is clear that MDMA has some effects on social behavior in the laboratory. However, it is not clear if this is unique to MDMA, as other drugs affect speech and other social behaviors (Higgins & Stitzer, 1988, 1989; Wardle, Garner, Munafo, & de Wit, 2012). Ultimately, a better understanding of MDMA's behavioral effects will require further study that contrasts the purported uniquely prosocial drug with the effects of other drugs that are used in social settings, including the related amphetamines and alcohol.

CONCLUSION

In this chapter, we have focused on findings from human laboratory studies investigating the acute effects of MDMA. MDMA has been used recreationally—and its potential therapeutic use has been discussed—for several decades. There has long been concern about the potential harmful effects of the drug, including possible neurotoxicity and mood and cognitive disruptions following long-term use. We argue that human behavioral pharmacology provides an additional important empirical approach to investigate the effects of known doses of the drug on a wide range of physiological, subjective, cognitive, and behavioral measures that are relevant to both the health and safety of its users. Using human behavioral pharmacology methods, researchers have observed several MDMA-related effects that could potentially benefit recreational users as well as patients with PTSD. For example, MDMA reliably increases core body temperature in the laboratory. Although these temperature increases do not reach hyperpyrexic levels in the human laboratory, increased core temperature following MDMA administration has been shown to be a causal factor in drug-related neurotoxicity in laboratory animals. Thus, recreational users of the drug should be educated about the potential thermoregulatory effects of MDMA, its implications for adverse outcomes, and how to mitigate the risks for these outcomes.

Additionally, researchers have consistently found that MDMA dose-dependently increases observable social behavior as well as positive mood and feelings of interpersonal closeness, and decreases reactivity to negative emotional stimuli. This pattern of effects may indicate some of the mechanisms by which MDMA might be a useful adjunctive psychotherapeutic for the treatment of PTSD, primarily by facilitating a social–therapeutic bond between the patient and the therapist while allowing the patient to focus on negative events without the accompanying heightened pathological stress response.

Human behavioral pharmacological studies of MDMA provide critical information about the acute effects of the drug in controlled laboratory conditions. Thus, this approach provides important information to further refine the assessment of the

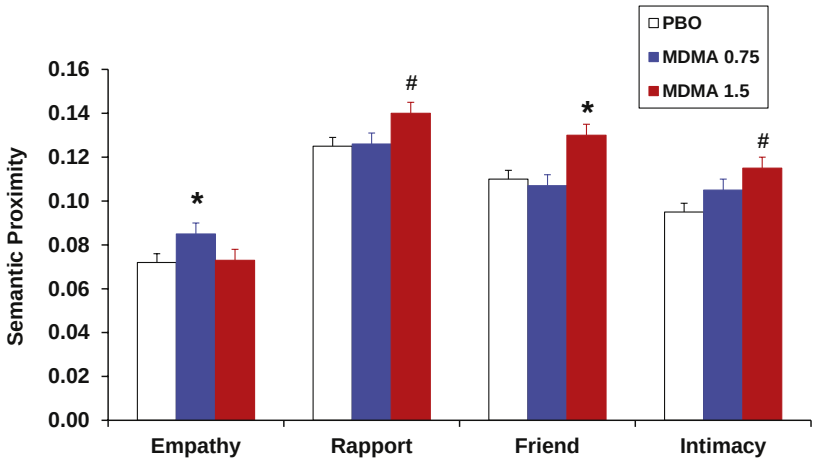

FIGURE 6 MDMA's effects on the content of speech. Effects of MDMA (0.75 and 1.5 mg/kg) on semantic proximity to selected concepts during a talking task (mean ± SD). PBO, placebo; MDMA 0.75, MDMA 0.75 mg/kg; MDMA 1.5, MDMA 1.5 mg/kg *significant differences from placebo ($p < 0.05$); #marginal differences from placebo ($p < 0.07$). *Figure and legend are adapted from Bedi et al. (2014), with permission from the publishers.*

risk/benefit ratio of the drug. It is important to continually review not only the risks of this drug, but also the benefits, in order to refine: (1) our assessment of the potential use of this drug as therapeutic under appropriate conditions, and (2) public health education outreach to recreational users in order to mitigate the risk of potential harm of MDMA use outside of the laboratory.

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

As stated in this chapter, human behavioral pharmacology methods provide important data about the acute effects of known doses of MDMA under a variety of controlled conditions. Overall, this gives us more information about the drug's safety profile, as well as greater insight into both risks and benefits of the drug. This approach is highly relevant to other drugs of abuse, and in fact is used to systematically study the effects of a range of recreational drugs from other amphetamines such as methamphetamine, marijuana, opioids (such as heroin), alcohol, and nicotine. For all of these drugs, scientists, clinicians, policy makers, and the public are concerned about the possible adverse effects of these drugs as well as the possibility that they will cause long-term harm to the recreational user.

Human behavioral pharmacology is an additional empirical tool to investigate the effects of multiple drugs in order to elucidate the specific potential negative effects of these drugs, in order to provide greater information for the safety of recreational users. Furthermore, a greater understanding of the acute effects of these drugs provides insight into why users might take these drugs recreationally, thus providing insight into the abuse potential of these drugs. Additionally, and importantly, these types of studies provide crucial information about the potential beneficial therapeutic effects of these drugs to further refine our assessment of their risk/benefit ratios. Given that are no risk-free psychotherapeutic interventions, it is important to balance the known risks with the known benefits of each of these drugs. Thus, further study of both of these sets of effects (negative and positive) is critical to further develop effective medications for a variety of psychiatric disorders and medical conditions.

DEFINITION OF TERMS

Human behavioral pharmacology It is an interdisciplinary empirical approach that combines theories and techniques from cognitive, affective, and behavioral sciences, as well as neuroscience and pharmacology in order to elucidate the biological, psychological, and behavioral effects of psychoactive drugs in humans under controlled laboratory conditions.

Hyperpyrexia It is an extremely high body temperature. This has been conservatively defined as greater than 40 °C for the purposes of this chapter.

Phenethylamines It is a large family of monoamine alkaloids that includes several drugs known for their recreational and/or therapeutic use (e.g., amphetamine, metamphetamine, MDMA, and bupropion).

Prosocial drug effects It is a pattern of acute drug effects that may include increased subjective feelings of sociability, increased desire to socialize, enhanced social behavior, and altered social/emotional cognitive processing.

Risk/benefit ratio It is a ratio of the relative risks of a drug compared to its benefits in order to assess the drug's potential safety and efficacy as a therapeutic.

Subjective drug effects It is a pattern of drug-related subjective experiences including feelings of drug reward, and changes in physiology and mood.

KEY FACTS ABOUT MDMA AND ITS RECREATIONAL USE

- MDMA is part of a large chemical family called phenethylamines, which includes several drugs considered to have therapeutic value for disorders such as attention deficit disorder, depression, and obesity (e.g., amphetamine, methamphetamine, bupropion).
- Similar to other amphetamines, MDMA is potent releaser of monoamine neurotransmitters (dopamine, norepinephrine, serotonin), which play an important role in mood regulation, reward, and arousal.
- Additionally, MDMA enhances oxytocin levels, a hormone associated with social behaviors. It has been suggested that this neurochemical effect is one mechanism underlying MDMA-related prosocial effects.
- Throughout the world, MDMA is tightly restricted. For example, in the United States the drug is Schedule 1, meaning that it has no recognized medical use. Despite this, it is currently under investigation as a psychotherapeutic adjunct for PTSD.
- Recreational use of MDMA is relatively low compared with other drugs of abuse. For example, in the United States approximately 4.1% of Americans aged 18–25 years used the drug in the past year, compared with 4.6% for cocaine, 13.7% for nonmedical use of psychotherapeutics, 31.5% for marijuana, and 77.4% for alcohol.

SUMMARY POINTS

- This chapter focused on what is known about the acute effects of MDMA based on findings from controlled laboratory studies using human research participants.
- Similar to other amphetamines, MDMA enhances monoamine neurotransmission as well as brain levels of oxytocin (a hormone associated with social behaviors), which may underlie the drug's prosocial effects.
- Recreational use MDMA use is relatively low compared with other recreational drugs.
- Preclinical studies and retrospective studies in humans suggest that MDMA may have some long-term adverse effects including possible neurotoxicity; however, these studies have major limitations that make it difficult to draw conclusions about the specific risks of the drug.
- Human behavioral pharmacology is a methodology used to study both the positive and negative effects of MDMA in order to better assess the risk/benefit ratio of the drug.
- Using this methodology, researchers have observed prototypical stimulant effects including increased heart rate, blood pressure, and body temperature.

- Although, recreational dose levels of MDMA do not increase body temperature to hyperpyrexic levels, this is an area of concern that should lead to harm reduction education efforts for users.
- In the laboratory, MDMA produces a complex pattern of subjective effects including increased euphoria, feelings of sociability, and feelings of arousal.
- In the laboratory, MDMA increases objective measures of social behavior and decreases reactivity to negative emotional stimuli, suggesting that this may be one mechanism underlying its therapeutic efficacy for PTSD treatment.
- Overall, human behavioral pharmacology studies of MDMA provide critical information about the risk/benefit ratio of the drug in order to refine: (1) our assessment of the potential use of MDMA as psychotherapeutic under appropriate conditions; and (2) public health education outreach to recreational users who may be at risk for drug-related harm.

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