Acute Psychological and Neurophysiological Effects of MDMA In Humans

Franz X. Vollenweider MD*
Mark Geyer PhD **
George Greer MD***

3,4-methylenedioxymethamphetamine (MDMA) is a phenethylamine with structural similarities to both classic hallucinogens such as mescaline and stimulants such as amphetamine. Initial scientific investigations reported that MDMA produces an "easily controlled altered state of consciousness with emotional and sensual overtones" and suggested that MDMA might be useful as an adjunct in insight-oriented psychotherapy (Shulgin, 1986; Nichols, 1986).

Indeed, limited clinical trials support the view that MDMA is a relatively mild, short-acting drug capable of facilitating heightened states of introspection and intimacy along with temporary freedom from anxiety and depression, almost without distracting alterations in perception, body image, or sense of self (Greer, 1985; Greer, Tolbert, 1986; Downing, 1986; Gasser, 1996). Based on these unique psychological findings, MDMA and related drugs (e.g. MDE, MDBD) have therefore been tentatively classified into a novel pharmacological class termed entactogens (from Greek and Latin roots: "touching within") differentiating them from classical stimulants and hallucinogens (Nichols, 1986; Hermle et al. 1993; Gouzoulis-Mayfrank et al. 1998).

Moreover, during the 1990s, MDMA has been increasingly used as a recreational drug called "Ecstasy" by young people in Europe and the United States. However, pills sold under this name show a large variability in composition and often contain other psychoactive substances such as N-ethyl-3,4-methylenedioxyamphetamine (MDE), N-methyl-1,3-benzodioxolbutanamine (MBDB), and d-amphetamine (Giroud et al. 1997; Milroy et al. 1996; Sondermann and Kovar, 1999; Curran, 2000). Despite the widespread recreational use of Ecstasy (MDMA), systematic data on the psychological and neurobiological effects of MDMA are scant. Although there are several studies describing the effects of Ecstasy in recreational drug users (Davison, Parrott, 1997; Parrott, Lasky, 1998; Solowij et al. 1992; Peroutka et al. 1988), these reports are of only limited value since most of them are retrospective and lack drug identification.

Furthermore, reports of recreational Ecstasy users and prospective placebo-controlled studies using MDMA in subjects with regular Ecstasy consumption (Vollenweider et al. 1998) are likely to be biased by extensive previous drug experience. Finally, until recently there existed only non placebo-controlled prospective studies assessing the effects of MDMA in normals (Downing, 1986; Greer, Tolbert, 1986) and a placebo-controlled study assessing the effects of its congener MDE (Gouzoulis-Mayfrank et al. 1999;

*Psychiatric University Hospital Zurich, Heffter Research Center, P.O. Box 68, CH-8029 Zurich, Switzerland
**University of California San Diego, Department of Psychiatry, La Jolla, California, 92093-0804
*** Heffter Research Institute, Santa Fe, New Mexico

Correspondence address:
Dr. F. X. Vollenweider, MD
Associate Professor of Psychiatry
Psychiatric University Hospital Zurich, P.O. Box 68, CH-8029 Zurich, Switzerland
Phone: -41-1-384 26 04
Fax: -41-1-384 33 96
e-mail: vollen@bli.unizh.ch

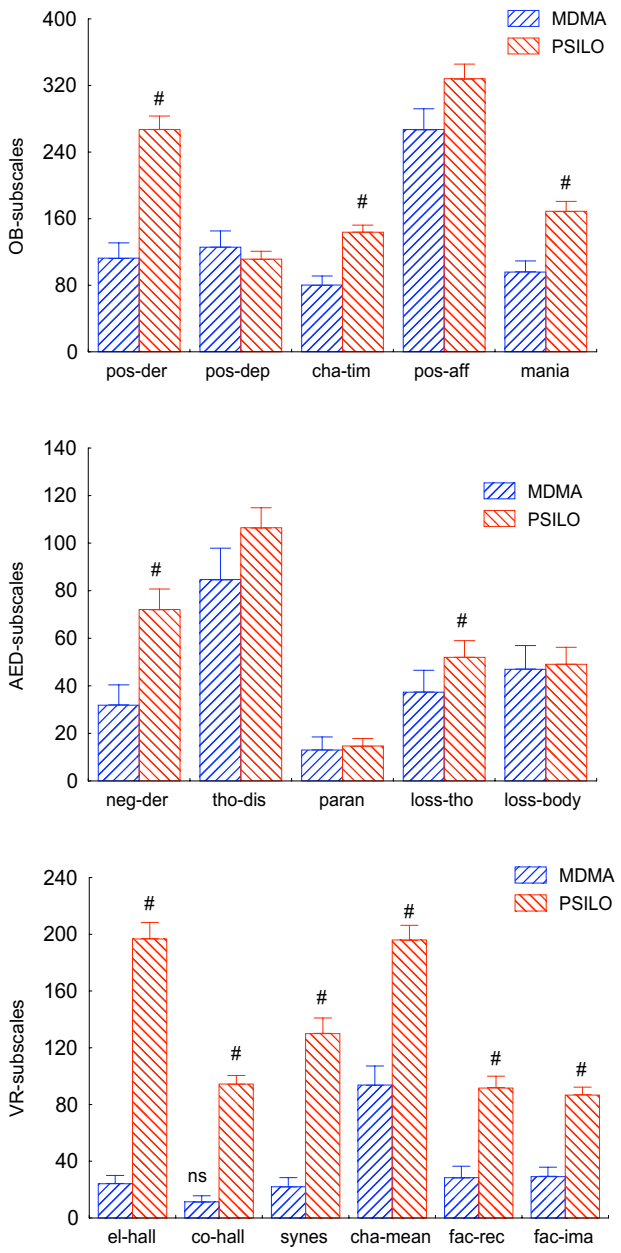

Figure 1 a-c compares the subscale scores of the OAV rating scale between MDMA (n=55; 1.5-1.7 mg/kg) and Psilocybin (n=99; 0.26 mg/kg) in healthy volunteers. With the exception of complex hallucinations, MDMA-induced scores are all significant compared to placebo (p<0.05 or less). Significant differences between Psilocybin (Psilo) and MDMA are indicated by # (p<.05).

a) The OB scale measures derealization and depersonalization associated with a positive basic mood ranging from heightened feelings to exaltation and alterations in the sense of time. The corresponding item clusters are "pos-der" = positive experienced derealization, "pos-dep" = pos. exp. depersonalization, "cha-tim" = changed sense of time, "pos-aff" = positive basic mood, "mania" = mania-like experience.

b) The AED scale measures ego-disintegration and loss of autonomy and self-control associated with arousal and anxiety. The item clusters are "neg-der" = negative experienced derealization, "tho-dis" = thought disorder, "paran" = paranoia, "loss-tho" = loss of thought control, loss-body = loss of body control.

c) The VR scale measures alterations in perception and meaning. The item clusters are "el-hall"= elementary hallucinations and illusions, "co-hall"= scenery hallucinations, "synes"= synesthesias, "cha-mean"= changed meaning of percepts, "fac-rec"= facilitated recollection, "fac- ima"= facilitated imagination.

Gouzoulis et al. 1993; Hermle et al. 1993) in healthy MDE-naïve subjects, but there was no placebo-controlled study of the effects of MDMA in MDMA-naïve healthy human volunteers.

Animal studies have suggested that MDMA might mediate its behavioural effects through its potent ability to release serotonin (5-HT), and to a lesser extent dopamine (DA) (Geyer, Callaway, 1994). Thus it appeared that research into the mechanisms of action of MDMA in humans might further our understanding of the regulation of mood in health and affective disorders in which these neurotransmitters have been implicated. Furthermore, in view of its extensive recreational use, obtaining detailed information on the psychological, physical, and behavioural effects of MDMA is important to assess possible risks to which Ecstasy users might be exposed.

Based on this rationale, we have since conducted several studies in healthy human volunteers, aimed at a broad characterization of the psychological and behavioural effects of MDMA and the concomitant neurochemical and neurophysiological changes underlying them. All studies have been approved by the local Ethics Committee and the Swiss Federal Health Office. The studies involved the oral administration of a single dose of MDMA, 1.35-1.8 milligrams per kilogram of body weight (mg/kg) to healthy, mostly MDMA-naïve subjects in placebo controlled double-blind experimental designs.

Prior to admission to one of the studies, all subjects were screened by a semi-structured psychiatric interview and by thorough medical examination to minimize the risks of possible acute or long-term complications related to the mind-altering experience. After being informed of the procedures involved in the experiments and the possible risks and benefits of MDMA administration, all subjects gave their written consent. Participants were mostly university students aged 20-30. The present contribution summarizes the effects of MDMA on psychological measures, sensory information processing, and brain activity obtained in about 75 healthy subjects (for more detailed information the reader is referred to the original literature).

Psychological Effects of MDMA

When we started our research with MDMA, most reports available on its psychological effects were retrospective, anecdotal, and lacked drug and dose identification. This situation was partly due to the fact that using MDMA for prospective, clinical studies was impossible or limited in most countries and that Ecstasy tablets sold for recreational use often contain other psychoactive compounds so that their effects cannot be reliably ascribed to MDMA alone. To avoid these limitations and to obtain robust data on the subjective effects of pure MDMA, we used prospective within-subject study designs with standardized psychometric ratings (measures of psychological effects) obtained during the peak effect of the drug.

The Altered State of Consciousness (OAV) rating scale is a visual-analog scale that measures alterations in mood, thought processes, perception, and experience of the self/ego and of the environment (Dittrich et al. 1985). The OAV questionnaire consists of three scales comprising several item clusters. The dimension OB ("Oceanic Boundlessness") measures derealization and depersonalization associated with a positive basic mood, and alterations in the sense of time. The second dimension, VR ("Visionary Restructuralization") refers to illusions, elementary and complex hallucinations, synaesthesias, changed meaning of percepts, facilitated recollection, and facilitated imagination. The third scale, AED ("Anxious Ego Dissolution") measures thought disorder, ego disintegration, and loss of body and thought control associated with arousal and anxiety (Dittrich, 1998). The Adjective Mood rating scale (AM) (Janke, Debus, 1978) consists of 14 scales measuring efficiency-activation, self-confidence, heightened mood, apprehension-anxiety, depressiveness, thoughtfulness-contemplativeness, extroversion, introversion, inactivation, dazed state, tiredness, sensitivity, aggression-anger, and emotional excitation.

In a first double-blind placebo-controlled study, we found that a typical recreational and non-toxic dose of MDMA (1.7 mg/kg p.o.) produced an affective state of enhanced mood, well-being, increased emotional sensitiveness, little anxiety, moderate thought disturbances, but no hallucinations or panic reactions (Vollenweider et al. 1998). Affective changes, both measured and subjectively reported, were of a generally positive nature. Consistent with previous and more recent studies with MDMA (Downing, 1986; Greer, Tolbert, 1986; Mas et al. 1999) and MDE in healthy volunteers (Gouzoulis-Mayfrank et al. 1999; Gouzoulis-Mayfrank et al. 1998; Hermle et al. 1993), subjects reported experiencing an increased responsiveness to emotions, a heightened openness and a sense of closeness to other people. Moreover, MDMA (1.5-1.7 mg/kg) also produced slight-to-moderate depersonalization phenomena and perceptual disturbances as measured by the OAV rating scale (Vollenweider et al. 1998; see also Figure 2). Depersonalisation phenomena and ego-impairment were mild and, in contrast to hallucinogens (e.g. psilocybin), not experienced as problematic or psychotic fusion, but as a pleasurable state of loosened ego boundaries (as indexed by the OB and AED scores). Although anxi-

ety was not explicitly reported, a certain degree of anxiety may have been associated in some subjects with first signs of loss of body control as measured by the low-to-moderate AED scores.

Unlike hallucinogens, MDMA did not produce hallucinations, but an intensification of all sensory percepts, and particularly visual illusions as indexed by the relatively low VR score. MDMA-induced thought disturbances included difficulty concentrating, accelerated thinking, thought blocking, and impaired decision making, but there was no evidence of confused or delusional thinking or paranoid ideations. Thus, the present findings provide further support for the view that MDMA and related drugs may constitute a new class of psychoactive substances (Nichols, 1986).

The unique subjective effects of MDMA have been confirmed in subsequent studies and turned out to be robust despite some differences in the experimental settings (Liechti et al. 2000a; Liechti et al. 2000d; Liechti, Vollenweider, 2000e; Gamma et al. 2000). Statistical analysis of the pooled data of 74 subjects (20 women, 54 men) demonstrate that most subjects under MDMA experienced a state of profound well-being, happiness, emotional warmth, increased extroversion and sociability, and slight derealization (Figure 2). They felt carefree, relaxed, and joyful. Physical sensations were more pleasurable than usual. The perception of space and time was altered and subjects felt dreamy or lost in thought. MDMA induced few perceptual changes. There was only a single report of scenic visual hallucinations, but elementary hallucinations such as distorted objects, flashes of light, and simple patterns were frequent. Colors appeared more lively and sounds seemed to be moved closer or farther away.

The dose per body weight of MDMA (mg/kg) positively correlated with the intensity of perceptual alterations as measured by the VR scale, particularly in women. Thus, higher doses of MDMA in the range of 1.35 – 1.8 mg/kg produced more hallucinogen-like perceptual changes. MDMA also produced thought disturbances that included impaired decision making, accelerated thinking, and losing track of one's thoughts. Transient dysphoric reactions associated with anxiety occurred in a few subjects at drug onset, but passed with subjects getting acquainted with the drug effect and being reassured by the experimenter.

Interestingly, women generally showed stronger responses to MDMA than men, although baseline psychometric ratings were not different between the two genders. Women had significantly higher ratings for positive mood, depersonalisation, and altered perception of time and space (Liechti et al. 2000b). Women also reported stronger perceptual changes after MDMA, in particular a higher frequency of elementary hallucinations and optical illusions. Finally, women scored higher on anxiety-related measures. These increases were due to feeling helpless and defenseless and sensing an increased need for protection.

Thought disturbances, as described above, were also more pronounced in women, particularly including more fear of loss of body control. Women's increased sensitivity to MDMA even extended to its side effects: more women than men experienced jaw clenching, difficulty concentrating, dry mouth, thirst, impaired balance, and lack of appetite (for details see also Liechti et al. 2000d; Liechti, Vollenweider, 2000e; Liechti, Vollenweider, 2000f).

Neurobiological Correlates of MDMA

Different strategies to elucidate the neurobiological basis of the distinct psychological effects of MDMA in humans have been used by our group. The basic approaches are to examine the role of neurotransmitter and receptor systems involved in the action of MDMA by investigating the blocking effects of specific receptor antagonists on MDMA-induced psychological alterations, to identify the brain regions involved in the action of MDMA using functional brain imaging techniques such as Positron Emission Tomography (PET), and to investigate the effects of MDMA on information processing as indexed by the prepulse inhibition paradigm.

Effects of MDMA on Neurotransmitter Systems

In animals, MDMA mainly releases serotonin via interaction with the serotonin (5-HT) transporter, and, to a lesser extent, also dopamine and norepinephrine (Nichols et al., 1982; Schmidt, 1987; Rudnick, Wall, 1992; Fitzgerald and Reid, 1990). In addition, MDMA has been shown to display moderate affinity for the serotonergic 5-HT2 and adrenergic alpha-2 receptors (Gudelsky and Nash, 1996; Koch and Galloway, 1997; Nash, 1990; Schmidt et al., 1992; Schmidt et al., 1994; Yamamoto et al., 1995; Battaglia et al., 1988). Based on these findings, we have hypothesized, first, that the psychological effects of MDMA in humans might primarily be due to the principal neurochemical action of MDMA, which is 5-HT transporter mediated 5-HT release.

This view is supported by the finding that selective serotonin reuptake inhibitors (SSRI) block the ability of MDMA to increase 5-HT release and abolish the behavioural effects of MDMA in animals (Geyer, Callaway, 1994; Gudelsky and Nash, 1996). Second, given the fact that postsynaptic serotonergic 5-HT2 receptors have been implicated in the effects

of classical hallucinogens (Vollenweider et al. 1998), we have speculated that 5-HT2 receptor stimulation might be responsible for the mild hallucinogen-like action of MDMA, such as the intensification of colors. Third, since dopamine is thought to play an important role in the mediation of euphoria produced by classical stimulants such as d-amphetamine, it was conceivable that increased dopaminergic activity might contribute to the mood enhancing effects of MDMA.

To test these hypotheses, we investigated whether pretreatment with the specific 5-HT reuptake inhibitor citalopram (40 mg i.v., in 16 subjects), the serotonin 5-HT2 antagonist ketanserin (50 mg p.o., in 14 subjects), or the dopamine D2 antagonist haloperidol (1.4 mg/kg p.o., in 14 subjects) completely or partially reduced the psychophysiological effects of MDMA (1.5 mg/kg p.o.) in healthy human volunteers. Each of the three studies used a double-blind, placebo-controlled within-subject design. Thus all subjects participated in four experimental sessions involving administration of placebo, pretreatment alone, MDMA alone, and pretreatment plus MDMA. As in previous studies with MDMA, the Altered States of Consciousness Rating Scale (OAV) and the Adjective Mood (AM) rating scale were used to assess psychological effects during the peak effects of MDMA (Vollenweider et al., 1998).

At the dose tested, citalopram markedly reduced most of the psychological effects of MDMA as evidenced by similar percentage reductions in all of the measured OAV scores (Liechti et al. 2000a) (Figure 2). In addition, citalopram also reduced the acute cardiovascular response and side effects of MDMA (Liechti, Vollenweider, 2000f).

Thus, it appears that citalopram prevents the interaction of MDMA with the serotonin transporter and thereby "buffers" the overall MDMA experience. Interestingly, the subjective effects of MDMA were not only attenuated, but at the same time markedly prolonged after citalopram pretreatment. In contrast to citalopram, pretreatment with the 5-HT2 antagonist ketanserin resulted in only a moderate attenuation of the subjective MDMA experience (Liechti et al., 2000d)(Figure 2). However, similar to studies with serotonergic hallucinogens such as psilocybin, ketanserin significantly reduced the perceptual effects of MDMA as measured by the VR scores. Also euphoric responses (OB scores) were reduced in some, but not all, subjects. These results suggest that stimulation of 5-HT2 receptors mediates the hallucinogen-like action of MDMA in humans.

Finally, pretreatment with the dopaminergic D_2 antagonist haloperidol selectively reduced the euphoric (OB) effect of MDMA (Liechti and Vollenweider, 2000e), but increased negative effects of MDMA such as anxious derealization (AED)(Figure 2). These findings are consistent with the view that dopamine may contribute to the more euphoriant effects of MDMA. It is also of note that haloperidol did not reduce the cardiovascular responses to MDMA (Liechti, Vollenweider, 2000e). Thus it appears that other neurotransmitters such as serotonin and/or norepinephrine or receptor sites other than dopamine D_2 receptors may be involved in these effects of MDMA.

In sum, the present results suggest that the psychological effects of MDMA in humans are largely due to 5-HT transporter mediated enhanced serotonin release; the positive mood effects of MDMA relate, at least in part, to dopamine D_2 receptor stimulation, whereas the mild hallucinogen-like perceptual alterations induced by MDMA depend on 5-HT2 receptor stimulation.

Further mechanistic studies using different doses of MDMA are needed, however, to corroborate these findings and to elucidate the role of other neurotransmitter systems such as norepinephrine, and of other receptor sites such as the alpha-2, dopamine D_1, and 5-HT1 receptor in the action of MDMA in humans.

Effects of MDMA on Regional Brain Activity

To identify the functional neuroanatomy involved in the action of MDMA in humans, the effect of MDMA (1.7 mg/kg) or placebo on regional cerebral blood flow (CBF) was investigated in 16 healthy MDMA-naïve human subjects using Positron Emission Tomography and [$H_2{}^{15}O$]-PET (Gamma et al. 2000). MDMA produced distributed alteration of brain activity in cortical, limbic, and paralimbic structures.

Cerebral blood flow was increased bilaterally in the ventromedial prefrontal cortex, the anterior cingulate cortex, the inferior temporal lobe, the medial occipital cortex, and in the cerebellum. Decreases in CBF were found bilaterally in the motor and somatosensory cortices, the superior temporal lobe, the dorsal anterior and posterior cingulate cortex, the insula, and the thalamus. Unilateral decreases were found in the left amygdala, the right parahippocampal formation and the uncus. Concomitant with these changes, subjects experienced heightened mood, increased extroversion, slight derealization, and mild perceptual alterations. Activity in the left amygdala tended to correlate with scores for anxious ego-dissolution (AED).

These findings indicate that modulation of an extensive neural network including the left amygdala and related limbic/paralimbic structures may underlie the emotional effects of MDMA. These data are consistent with findings implicating the amygdala (Schneider et al. 1995; Ketter et al. 1996), orbitofrontal cortex (Ketter et al. 1996), ventral anterior cingulate cortex

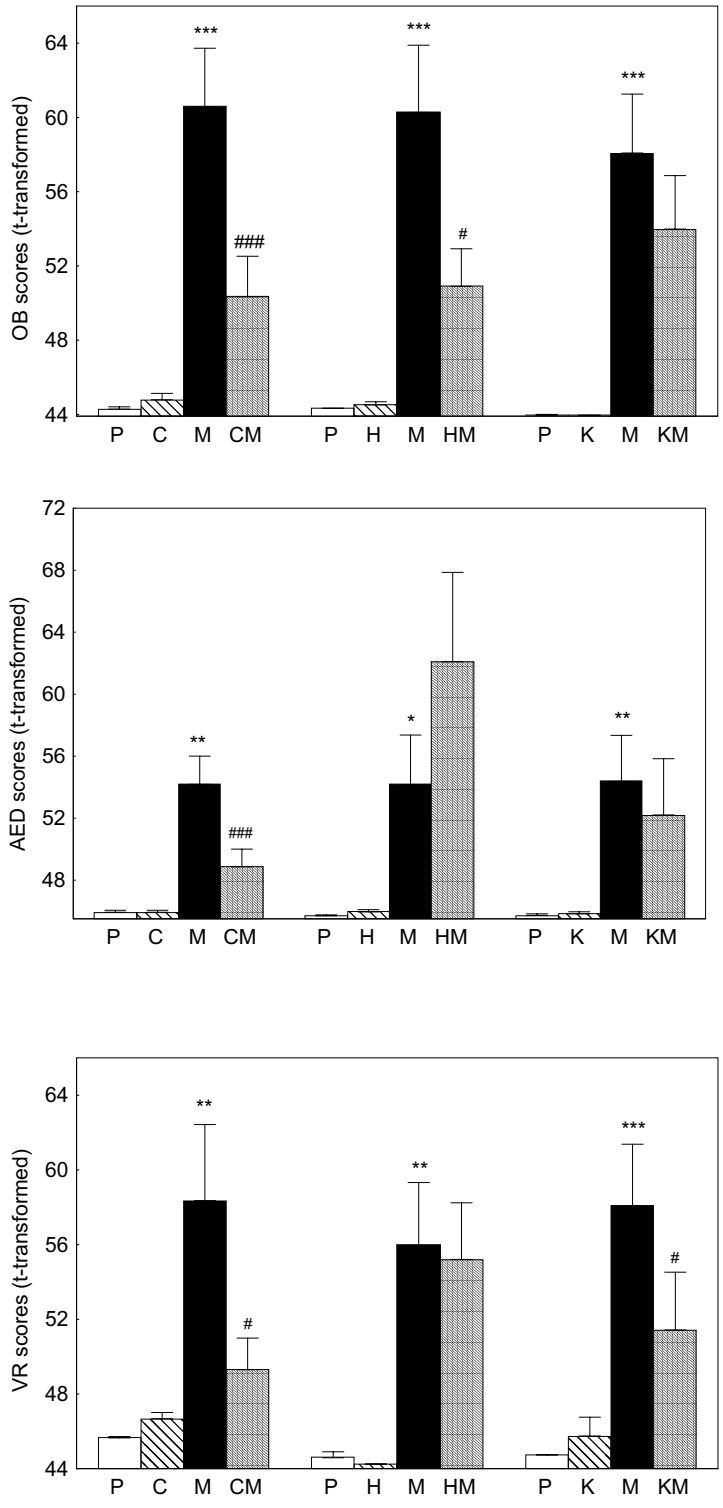

*Figure 2 shows the effects of different neuroreceptor blockers on MDMA-induced psychological scores (OB = oceanic boundlessness, AED = anxious ego-dissolution, VR = visionary restructuralization. P = placebo, C = citalopram, H = haloperidol, K = ketanserin, and M = MDMA. Significant MDMA-induced changes are indicated by * for p<0.05, ** for p<0.01, and *** for p<0.001 compared to placebo. Significant reductions of MDMA-induced scores by different blockers are indicated by # for p<0.05, and ### for p<0.001.*

(Ketter et al. 1996; George et al. 1995), prefrontal cortex, temporal lobe, and thalamus (George et al. 1995) in the regulation of mood and emotion. In this network, the amygdala appears to play a pivotal role in the mediation of both positive and negative emotions (Le Doux, 1995; Schneider et al. 1995; Ketter et al. 1996).

Consistent with this hypothesis, in our study as well as in many previous functional imaging studies, higher left amygdalar activity correlated with higher scores in anxiety-related psychometric measures. Other brain imaging studies had found that the reverse was also true: lower activity in the left amygdala correlated with pleasurable mood states including euphoria. These results raise the possibility that reduced activity in the amygdala as observed in our subjects during MDMA may be a correlate of MDMA-induced enhancement of mood and well-being.

Also of interest is the finding that the facilitation of social communication and interaction in MDMA subjects, reflected by a significant increase in the "Extroversion" subscale of the Adjective Mood Rating Scale (AM), correlated with CBF in the temporal cortex, amygdala, and orbitofrontal cortex. These brain regions are richly interconnected and together form the basolateral circuit, which, according to current theories, is involved in the mediation of social communication (Brothers, 1996; Deakin, 1996). Lesions or disturbances of this circuit can lead to decreased social interaction, inadequate social behavior or even the inability to decode social cues (Kling, 1975; Franzen, Myers, 1973; Butter, Snyder, 1972; Raleigh, Steklis, 1981).

In particular, a recent study has demonstrated impaired social judgment on the basis of facial appearance in patients with bilateral amygdala damage (Adolphs et al. 1998). The marked modulation of activity in the basolateral circuit produced by MDMA and its association with increased extroversion provide further support for a critical role of the basolateral circuit in the processing of socially relevant information.

In sum, the present findings suggest that an amygdalocentric network including ventral-frontal and temporal cortices underlies the co-occurrence of pleasurable emotion and enhanced social communication, providing a rationale for the inter-relatedness of emotional and social processes. Thus further research into the neurochemical mechanisms of MDMA could advance our understanding of the neuroanatomical regulation of mood and social interaction.

Effects of MDMA On Information Processing

The startle response is a constellation of reflex responses to a sudden intense stimulus (e.g. a loud noise) that has been used to study homologous forms of behavioral plasticity across species. In humans, the eyeblink reflex component of startle is measured using electromyography. In rodents, a stabilimeter is used to measure the whole-body flinch response. Prepulse inhibition (PPI) and habituation are two forms of behavioral plasticity that are studied using startle measures. PPI is the unlearned suppression of startle when the startling stimulus is preceded by a weaker prestimulus by 30 to 500 msec; it is not a form of conditioning and does not exhibit habituation or extinction over multiple trials. PPI is regarded as an operational measure of sensorimotor gating or filtering of cognitive and sensory information. Habituation refers to the decrement in responding when the same stimulus is presented repeatedly in the absence of any contingencies and has been considered to be the simplest form of learning.

PPI and startle habituation have been used as operational measures of sensorimotor gating and habituation functions, respectively, in both human and animal explorations of attentional deficits characteristic of patients with schizophrenia, Obsessive Compulsive Disorder (OCD), and Huntington's disease (Braff, Geyer, 1990; Braff et al. 1978; Braff et al. 1992; Geyer, Braff, 1982; Grillon et al. 1992; Swerdlow et al. 1995; Swerdlow et al. 1993). Gating deficits may cause these subjects to become overloaded with excessive exteroceptive and interoceptive stimuli which in turn could lead to a breakdown of cognitive integrity and difficulty in distinguishing self from non-self (Bleuler, 1911; McGhie, Chapman, 1961).

Multiple neurotransmitter systems including dopamine, glutamate, GABA, and serotonin have been shown to be involved in modulating PPI in animals (Geyer et al. 1990; Swerdlow et al. 1992). With respect to the serotonergic system, serotonin (5-HT) releasing compounds such as MDMA, MDE, AET (alpha-ethyltryptamine), and fenfluramine impair both PPI and habituation of the startle reflex in rodents (Kehne et al. 1996; Vollenweider et al. 1999; Mansbach et al. 1989; Martinez, Geyer, 1997; Dulawa, Geyer, 1996). The effects of MDMA-like drugs on PPI and startle habituation are reduced by pretreatment with selective serotonin uptake inhibitors (SSRIs), which prevent carrier-mediated release of presynaptic serotonin by MDMA (Martinez, Geyer, 1997; Kehne et al. 1992). These findings support the hypothesis that the effects of MDMA on PPI and habituation are mediated via release of endogenous serotonin. Furthermore, more recent data suggest that serotonin 5-HT_{1A}, 5-HT_{1B},

and 5-HT_{2A} receptor subtypes are involved in the mediation of the disruptive effects of MDMA in rats (Rigdon, Weatherspoon, 1992; Sipes, Geyer, 1994; Sipes, Geyer, 1995). For example it has been demonstrated that the PPI-disruptive effects of MDMA and the hallucinogenic 5-HT_2 agonist DOI (Sipes, Geyer, 1994) can be blocked by the highly selective 5-HT_{2A} receptor antagonist M 100907 (Sipes, Geyer, 1997; Padich et al. 1996) indicating that MDMA may impair PPI in rats via postsynaptic 5-HT_{2A} receptors. In addition, both 5-HT_{1A} and 5-HT_{1B} agonists reduce PPI in rats and these effects are antagonized by the corresponding receptor antagonists (Sipes, Geyer, 1995; Rigdon, Weatherspoon, 1992; Sipes, Geyer, 1994).

Finally, it is of note that MDMA also releases dopamine and that the dopamine releaser d-amphetamine as well as dopamine agonists disrupt PPI in animals and humans (Mansbach et al. 1988; Swerdlow et al. 1990; Sills, 1999). In sum, the present data obtained in animal studies suggest that MDMA may affect PPI in rats by acting at serotonin 5-HT_{1A}, 5-HT_{1B} and/or 5-HT_{2A} and/or dopamine D_2 receptor sites.

While the pharmacological effects of MDMA on PPI have been well studied in rodents, no similar studies had been conducted in humans (for a review see Geyer, Callaway, 1994). Therefore, we recently investigated in a comparison study the effects of MDMA on prepulse inhibition in healthy human volunteers and rats (Vollenweider et al. 1999). As expected from previous studies (Mansbach et al. 1989), MDMA decreased PPI in a dose-related fashion in rats. In contrast, a typical recreational dose of MDMA (1.7 mg/kg, orally) increased PPI under comparable conditions in subjects experiencing robust psychological effects (Vollenweider et al. 1999).

This surprising disparity between the effects of MDMA in rats and humans may reflect a species-specific difference in the mechanism of action of MDMA or in the behavioural expression of a similar pharmacological effect, or both. Based on the many mechanistic studies in animals (Geyer, Callaway, 1994), it has been so far widely assumed that the psychological effects of MDMA in humans are due to its actions as an indirect 5-HT agonist. Without mechanistic studies, however, no firm conclusion can be drawn as to why MDMA produces opposite effects on PPI in rats versus healthy human volunteers.

To further investigate the role of the serotonin and dopamine systems in mediating the subjective and behavioral responses to MDMA in humans we have therefore explored the effect of several neuroreceptor antagonists on MDMA-induced effects on PPI. Based on animal studies, we have hypothesized that pretreatment with selective 5-HT reuptake inhibitors given at doses that have no effects by themselves might prevent the disruptive effects of MDMA on PPI in humans (Kehne et al. 1992; Martinez, Geyer, 1997).

In support of this notion, we recently found that the selective 5-HT reuptake inhibitor citalopram markedly abolished the psychological effects of MDMA and reduced the MDMA-induced increase in PPI in healthy volunteers (Liechti et al. 2000c). Moreover, pretreatment with the D_2 antagonist haloperidol or the 5-$HT_{2A/C}$ antagonist ketanserin did not affect the PPI enhancing effects of MDMA in humans. Thus it appears that the effect of MDMA on PPI in humans is – similarly as in animals - also due to MDMA-induced release of serotonin. It is also obvious, however, that some of the functional consequences of the released serotonin differ between rats and humans since MDMA has opposite effects on PPI.

In fact, there is more recent evidence that species-specific differences may contribute to the opposite effects of MDMA on PPI in rats and humans. Specifically, it was found that 5-HT_{1A} agonists disrupt PPI in rats but increase PPI in mice (Sipes, Geyer, 1995; Dulawa et al. 1997). Together with the finding that MDMA also increased PPI in mice lacking the 5-HT_{1B} receptor (Dulawa et al. 2000), these results strongly suggest that 5-HT_{1A} receptors may contribute to the PPI increase seen in humans. Also, marked neuroanatomical differences in the distribution of 5-HT_{1A} binding sites between rats and humans suggest that different functional consequences may result after MDMA in rats and humans (Duncan et al. 1998). Thus the role of 5-HT_{1A} receptors in mediating effects of MDMA on PPI in humans remains to be elucidated. The present data also demonstrate the compelling need for comparison studies in animals and humans to increase our understanding of the role of the serotonergic systems involved in the regulation of information processing in health and disease.

Conclusion and Outlook

These findings suggest that the effects of MDMA in humans are mainly based on increased serotonergic activity involving an interaction with presynaptic 5-HT reuptake sites, although the dopamine system is also implicated. Consistent with previous PET studies on the effects of serotonin releasing agents, MDMA enhances mood and alters neuronal activity in cortical and limbic/paralimbic structures thought to be involved in the regulation of mood and emotion. Moreover, MDMA produces opposite effects on sensorimotor gating in humans versus rodents. Whether methodological differences or differences within the serotonergic system between humans and rodents, possibly involving 5-HT_1 receptors, contribute to this discrep-

ancy remains to be clarified. The present data also demonstrate the compelling need for parallel studies in animals and humans to increase our understanding of the mechanism of action of MDMA in humans.

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