Acute Psychological and Neurophysiological Effects of MDMA in Humans†

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Abstract—Since the mid 1990s, MDMA has been increasingly used as a recreational drug called "Ecstasy" by young people in Europe and the United States. However, despite the widespread recreational use of Ecstasy, systematic data on the psychological and neurobiological effects of MDMA have been scant. To further our understanding of the mechanism of action of MDMA, the authors conducted several studies in healthy human volunteers in an effort to characterize the psychological, cognitive and behavioral effects of MDMA in healthy human volunteers. Prospective placebo-controlled within-subject study designs and standardized psychometric ratings and neuropsychological tests were used to assess the acute, short-term and prolonged effects of the drug. To elucidate the role of various neurotransmitter and receptor systems involved in the action of MDMA in humans, the blocking effects of specific receptor antagonists on MDMA-induced psychological alterations and measures of sensory information processing were studied. To identify the functional neuroanatomy involved in the action of MDMA, Positron Emission Tomography (PET) was used. The present contribution summarizes the acute effect of MDMA on psychological and cognitive measures, information processing, and regional brain activity in healthy human volunteers.

Keywords—human, 3,4-Methylenedioxymethamphetamine (MDMA), psychological effects, PET, prepulse inhibition (PPI) of the startle reflex, receptor interactions

3,4-methylenedioxymethamphetamine (MDMA) is a phenylethylamine 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 (Nichols 1986; Shulgin

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1986). Indeed, limited clinical trials supported 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 (Gasser 1996; Downing 1986; Greer & Tolbert 1986; Greer 1985). 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: "touching within"), differentiating it from classical stimulants and hallucinogens (Gouzoulis-Mayfrank et al. 1998; Hermle et al. 1993; Nichols 1986).

Moreover, during the 1990s, MDMA was 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 (Curran 2000; Sondermann & Kovar 1999; Giroud et al. 1997; Milroy et al. 1986). Despite the widespread recreational use of Ecstasy, 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 (Parrott & Lasky 1998; Davidson & Parrott 1997; Solowij, Hall & Lee 1992; Peroutka, Newman & Harris 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 are likely to be biased by the extensive previous drug experiences of the subjects. 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 in healthy MDE-naïve subjects (Gouzoulis-Mayfrank et al. 1999; Gouzoulis et al. 1993; Hermle et al. 1993), but there was no placebo-controlled study into the effects of MDMA in MDMA-naïve healthy human volunteers.

NEUROTRANSMITTER EFFECTS OF MDMA

MDMA affects a variety of neuroreceptor systems (as shown in Figure 1). In animals, MDMA mainly releases presynaptic serotonin (5-HT) and, to a lesser extent, norepinephrine (NE) and dopamine (DA) (Rothman et al. 2001; Schmidt, Levin & Lovenberg 1987). The MDMA-induced release of 5-HT is thought to be due to reversal of the 5-HT uptake transporter (Rudnick & Wall 1992). In animals, selective serotonin reuptake inhibitors (SSRIs) blocked the MDMA-induced 5-HT and DA release (Gudelsky & Nash 1996), reduced the behavioral effects of MDMA (Geyer & Callaway1994; Callaway, Wing & Geyer 1990), and provided some protection against neurotoxicity (Schmidt 1987). These findings suggest that interaction of MDMA with the 5-HT uptake site is a primary and important mode of action of MDMA.

Serotonin Release and Mood Effects

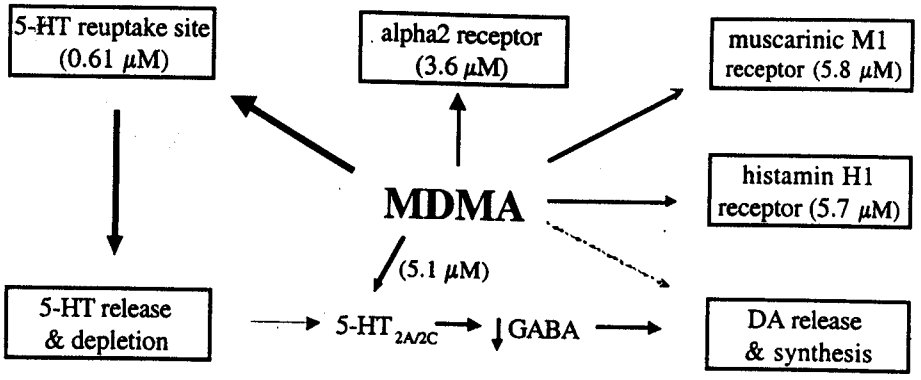
In humans, MDMA is also thought to mediate a large proportion of its effects via the serotonin system, and functional correlates of presumed short- and long-term 5-HT deficits or 5-HT selective neurotoxicity following Ecstasy (MDMA) use are increasingly reported (Boot, McGregor & Hall 2000; Morgan 2000; Schifano 1998). For example, there is a transient depression of mood in the days following MDMA use, consistent with short-term depletion of 5-HT (Parrott & Lasky 1998; Curran & Travill 1997). Long-term Ecstasy users in particular exhibit symptoms of depression (Hando, Topp & Hall 1997), anxiety, and sleep disorder (Parrott, Sisk & Turner 2000; Topp et al. 1999; Windhaber, Maierhofer & Dantendorfer 1998; McGuire, Cope & Fahy 1994). A variety of cognitive dysfunctions have also been described in Ecstasy users including deficits in working memory, short-term and longer term memory, and attention (Boot, McGregor & Hall 2000; Gouzoulis-Mayfrank et al. 2000; Morgan 1998). Recreational Ecstasy use was also associated with increased impulsiveness and hostility (Parrott, Sisk & Turner 2000; Morgan 1998).

Until the studies described below, it was unknown to what extent the release of 5-HT contributes to the acute psychoactive effects of MDMA in humans and whether SSRI treatment would reduce the acute mood effects in humans, as expected from animal studies. There are a few anecdotal reports that SSRIs, when used together with Ecstasy, dampened subjective and adverse responses to Ecstasy (Stein & Rink 1999; McCann & Ricaurte 1993). SSRIs have also successfully been used to treat panic disorders induced by Ecstasy (Windhaber, Maierhofer & Dantendorfer 1998). In contrast, a psychotic reaction to Ecstasy has also been reported in a patient who was treated with an SSRI for years (Lauerma, Wuorela & Halme 1998). Thus, the role of the 5-HT uptake site in mediating the acute effects of MDMA remained to be clarified.

5-HT2 Receptor Stimulation and Hallucinogen-like Effects

In addition to its interaction with the 5-HT transporter site, MDMA has also been shown to have moderate direct affinity for postsynaptic serotonergic 5-HT2 receptors. Stimulation of 5-HT2 receptors has been implicated in the psychological, particularly in the visual effects, of indole hallucinogens (Vollenweider et al. 1998b; Glennon, Titeler & McKenney 1984). For example, it has been shown that the binding affinity of a drug for the 5-HT2 receptor site predicts its potency for evoking hallucinations in humans (Glennon, Titeler & McKenney 1984). Although the

FIGURE 1
Main Receptor Systems Affected by MDMA



MDMA has highest affinity for the 5-HT transporter (Ki=0.61 (M) and lesser for the adrenergic (2 (Ki=3.6 (M), serotonergic 5-HT2 (Ki=5.1(M), muscarinic M1 (Ki=5.8(M), and histaminic H1 (Ki=5.7(M) receptor in rat brain. Present data suggest that the primary effect of MDMA is to release 5-HT in the brain via a direct interaction with the 5-HT transporter. Moreover, there is evidence that although MDMA has only negligible affinity for the dopamine transporter, it secondarily increases dopamine (DA) concentration in the brain via a disinhibition of the GABAergic tone by a direct and indirect stimulation of 5-HT2 receptors located on GABAergic interneurons.

hallucinogenic potency of MDMA is generally considered to be weak, Ecstasy users have reported hallucinogenic effects of MDMA at higher doses (Solowij, Hall & Lee 1992). Lasting psychotic syndromes including visual illusions, hallucinations, and visual "flashbacks" have also been noted after Ecstasy consumption (McGuire, Cope & Fahy 1994). Taken together, these data suggest an involvement of 5-HT2 receptors in the generation of the perceptual effects of MDMA.

Dopamine Release and Stimulant-like Effects

Finally, MDMA releases DA by reversal of the DA uptake carrier and secondarily via 5-HT2A receptor stimulation (Bankson & Cunningham 2001; Gudelsky, Yamamoto & Nash 1994). DA is known to play an important role in the mediation of euphoria and of the rewarding effects produced by classical stimulants such as d-amphetamine and cocaine (Volkow et al. 1997; Laruelle et al. 1995). Drug discrimination studies in animals that are believed to model the subjective effects of drugs in humans showed that both D1 and D2 dopamine agonists mimic the discriminative stimulus effects of amphetamine and D1 and D2 antagonists block these effects (Brauer, Goudie & de Wit 1997). Drug discrimination studies using MDMA, however, showed only a weak dopaminergic component as compared to its serotonergic effects (Schechter 1989; Oberlender & Nichols 1988). Human studies using D2 antagonists prior to amphetamine or cocaine revealed mixed results. In cocaine abusers, administration of the dopaminergic D2 antagonist haloperidol (8 mg intramuscularly) significantly attenuated the self-rated "high" but not the "rush" induced by 40 mg intravenous cocaine (Sherer, Kumor & Jaffe 1989). Similarly, Nurnberger and colleagues (1984) found that 0.014mg/kg intramuscular haloperidol attenuated observer-rated "excitation" and "elation" responses to 0.3 mg/kg intravenous amphetamine. In contrast, Brauer and de Wit (1997) found that the D2 antagonist pimozide had only little effect on amphetamine-induced elation, euphoria or vigor despite its reducing these ratings compared to placebo when given alone. Despite these disparities, these studies provide some evidence that dopaminergic D2 receptor stimulation might contribute to the euphoric effects of classical stimulants.

Hyperactivity: The role of 5-HT1B and 5-HT2 Receptors

Indirect 5-HT1B receptor stimulation is known to play a role in the mediation of MDMA-induced hyperactivity in animals. 5HT1B agonists elicit behavioral responses in animals similar to those caused by low doses of MDMA (Rempel, Callaway & Geyer 1993). 5-HT1B but not 5-HT1A antagonists completely reversed hyperactivity caused by low doses of MDMA (McCreary, Bankson & Cunningham 1999). In contrast, 5-HT2A antagonists blocked the hypermotility induced by high doses of MDMA (20mg/kg), but hyperactivity elicited by a low dose of MDMA (3mg/kg) was unaffected (Bankson & Cunningham 2001). 5-HT2A receptors are thought to play a permissive role in the MDMA-induced activation of the DA system. In particular, DA release and hyperactivity evoked by high

doses of MDMA can be blocked by 5-HT2A antagonists (Gudelsky, Yamamoto & Nash 1994; Kehne et al. 1996). These data indicate that MDMA-induced locomotor hyperactivity partially results from 5-HT1B receptor stimulation at low doses and from 5-HT2A receptor mediated DA stimulation at higher doses of MDMA. In the authors' human studies, MDMA produced some stimulant-like effects including increased emotional excitation, inner tension, restlessness, and tremor that could be regarded as a correlate of MDMA-induced hyperactivity in animals. These effects of MDMA in humans were reduced by the 5-HT2 antagonist ketanserin, but not by the SSRI citalopram (Liechti et al. 2000a, b). Thus, it appears that the activating, stimulant-like properties of MDMA in humans might, at least to some extent, be directly related to 5-HT2A receptor activation.

Norepinephrine Release and Cardiovascular Effects

Rothman and colleagues (2001) determined the neurochemical mechanism of action of various stimulants (including d-amphetamine, ephedrine, and racemic MDMA) using in vitro methods. They found that the most potent effect of these stimulants was to release NE. In addition, the reported oral dose of these stimulants which produced stimulant-like subjective effects in humans correlated with their potency in releasing NE, not DA. For MDMA, IC_{50} values for release of 5-HT, NE, and DA was 56.6nM, 77.4nM, and 376nM, respectively. Thus, in this assay, MDMA released 5-HT and NE with about the same potency. In animals, the blood pressure response to MDMA has recently been shown to involve alpha 1- and possibly alpha 2-adrenoceptors and 5-HT2 receptors (McDaid & Dochery 2001). In humans, activation of the NE system produces sympathomimetic effects including elevated blood pressure.

Acetylcholine Release and Histamine Receptors

MDMA has recently been shown to release acetylcholine (ACh) from rat striatal slices (Fischer et al. 2001) or in vivo as measured by microdialysis (Acquas et al. 2001). Given that MDMA itself has considerable affinity for histamine (H) H1 receptors (Battaglia et al. 1988) and only a H1 antagonist reduced the MDMA-induced ACh release (Fischer et al. 2001), direct MDMA-H1 receptor interaction is likely to be responsible for the MDMA-induced ACh release. Furthermore, MDMA itself has moderate affinity for muscarinic M1 receptors (Battaglia et al. 1988). Yet, the significance of ACh and H in the mechanism of action of MDMA in humans is unknown. ACh and H are involved in the regulation of arousal, motor activity, and memory, and various interactions with the monoamine systems are known. With regard to their human studies, the authors observed a significant interaction of MDMA and ketanserin (5-HT2 but also H1 antagonist) on scales measuring inactivation ("dazed state" and "tiredness") and vigilance reduction (Liechti et al. 2000b) that might be due to the common affinity for H1 receptors.

RECENT RESEARCH AT THE UNIVERSITY OF ZURICH

Since 1996 several studies have been conducted at the University of Zurich in healthy human volunteers, aimed at a broad characterization of the psychological and behavioral effects of MDMA and the concomitant neurochemical and neurophysiological changes underlying them. All studies were 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 semistructured 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 on 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 to 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 the authors began 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 also because 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, the authors 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 which measures alterations in mood, thought processes, perception, and experience of the self/ego and of the environment (Dittrich, von Arx & Staub 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, it was found that a typical recreational and nontoxic 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. 1998a). Affective changes, both measured and subjectively reported, were of a generally positive nature. Consistent with previous and more recent studies with MDMA (Lester et al. 2000; Liechti et al. 2000a, b; Mas et al. 1999; Downing 1986; Greer & Tolbert 1986;) and MDE in healthy volunteers (Gouzoulis-Mayfrank et al. 1999, 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 depersonalisation phenomena and perceptual disturbances as measured by the OAV rating scale (Vollenweider et al. 1998a; 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 anxiety 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 (Figure 2). 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, these findings provide further support for the view that MDMA and related drugs may constitute a new class of psychoactive substances (Nichols 1986).

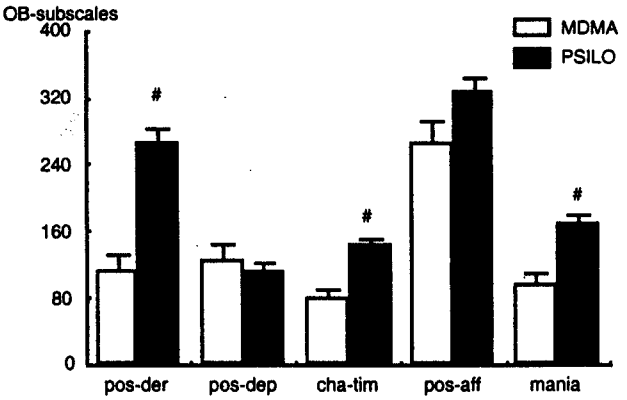
The unique subjective effects of MDMA have been confirmed in subsequent studies and turned out to be robust despite some differences in the experimental settings (Gamma et al. 2000; Liechti et al. 2000a, b; Liechti & Vollenweider 2000b). Statistical analysis of the pooled data of 74 subjects (20 women, 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 (Liechti, Gamma & Vollenweider 2001; see also 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 little 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 (Liechti, Gamma & Vollenweider 2001). 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, depersonalization and altered perception of time and space (Liechti, Gamma & Vollenweider 2001). 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 Liechti, Gamma & Vollenweider 2001; Liechti et al. 2000a, b; Liechti & Vollenweider 2000a, b).

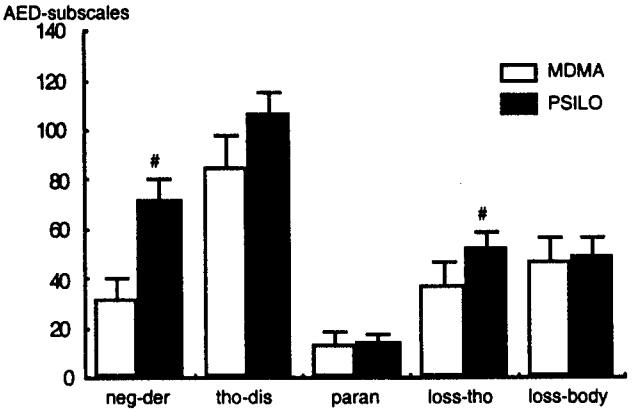
Neurobiological Correlates of MDMA

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 were 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

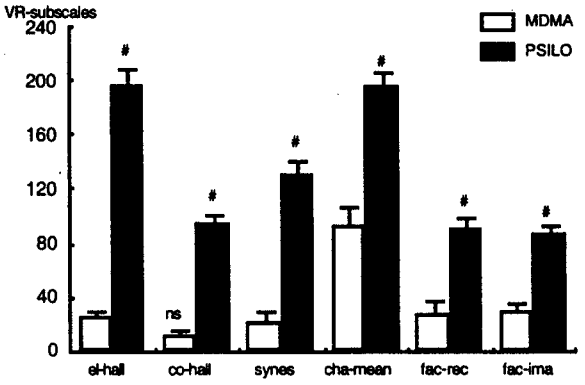
FIGURE 2
A Comparison of the OAV Rating Subscale Scores of MDMA and Psilocybin



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.

Note: Figure 2 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 # ($p<.05$).

on information processing as indexed by the prepulse inhibition paradigm.

Effects of MDMA on Neurotransmitter Systems

As outlined in detail above, in animals, MDMA mainly releases serotonin via interaction with the serotonin (5-HT) transporter, and, to a lesser extent, also dopamine and norepinephrine (Rudnick & Wall 1992; Fitzgerald & Reid 1990; Schmidt 1987; Nichols et al. 1982). In addition, MDMA has been shown to display moderate affinity for the serotonergic 5-HT2 and adrenergic alpha-2 receptors (Koch & Galloway 1997; Gudelsky & Nash 1996; Yamamoto, Nash & Gudelsky 1995; Schmidt, Sullivan & Fadayel 1994; Schmidt et al. 1992; Nash 1990; Battaglia et al. 1988). Based on these findings, the following hypotheses were made:

1. 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 behavioral effects of MDMA in animals (Gudelsky & Nash 1996; Geyer & Callaway 1994).
2. Given the fact that postsynaptic serotonergic 5-HT2 receptors have been implicated in the effects of classical hallucinogens (Vollenweider et al. 1998b), the authors speculated that 5-HT2 receptor stimulation might be responsible for the mild hallucinogen-like action of MDMA, such as the intensification of colors.
3. 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 may contribute to the mood enhancing effects of MDMA.

To test these hypotheses, the authors 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 reduces the psychophysiological effects of MDMA (1.5 mg/kg p.o.) in healthy human volunteers (for a summary see Liechti & Vollenweider 2001). 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 our 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. 1998a).

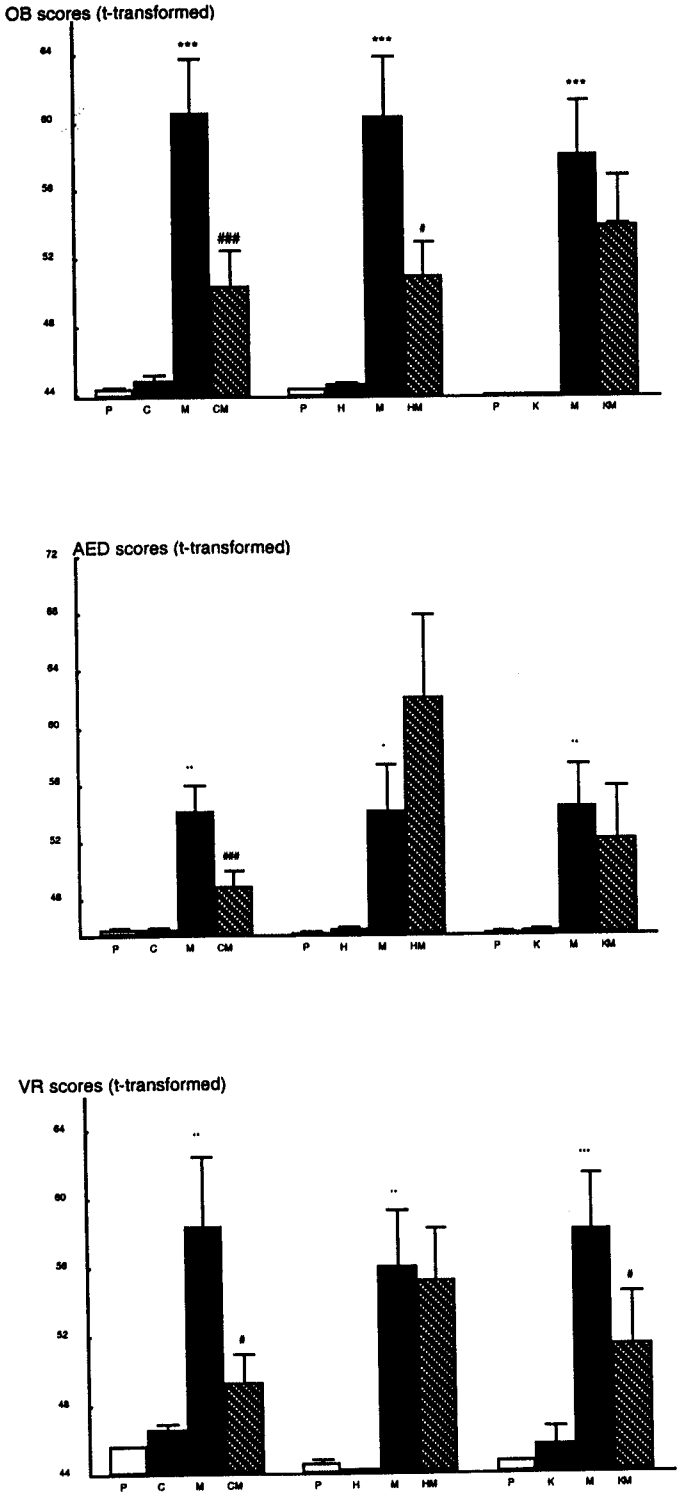
At the dose tested, citalopram markedly reduced most of the psychological effects of MDMA as evidenced by similar % reductions in all of the measured OAV scores (Liechti et al. 2000a; Figure 3). In addition, citalopram also reduced the acute cardiovascular response and side effects of MDMA (Liechti & Vollenweider 2000a, b). Thus it appears that citalopram prevented the interaction of MDMA with the serotonin transporter and thereby "buffered" 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. 2000b; see Figure 3). However, similar to studies with serotonergic hallucinogens such as psilocybin (Vollenweider et al. 1998b), 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 D2 antagonist haloperidol selectively reduced the euphoric (OB) effect of MDMA (Liechti & Vollenweider 2000b), but increased negative effects of MDMA such as anxious derealization (AED; see Figure 3). 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 2000b). Thus it appears that other neurotransmitters such as serotonin and/or norepinephrine or other receptor sites than dopamine D2 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 D2 receptor stimulation; while the mild hallucinogen-like perceptual alterations induced by MDMA depend on 5-HT2 receptor stimulation. However, further mechanistic studies using different doses of MDMA are needed 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 D1, and 5-HT1 receptor in the action of MDMA in humans.

In our human studies, MDMA produced cardiovascular stimulation including increases in diastolic and systolic blood pressure, as well as in heart rate (Liechti, Gamma & Vollenweider 2001; Vollenweider et al. 1998a). Of note, the SSRI citalopram significantly reduced these cardiovascular responses to MDMA, indicating that these physiological effects of MDMA are partially due to an interaction of MDMA with the 5-HT carrier and subsequent release of 5-HT (Liechti & Vollenweider 2000a). In addition, the 5-HT2 antagonist ketanserin, which also has

FIGURE 3
Effects of Different Neuroreceptor Blockers on MDMA-Induced Psychological Scores



Note: 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 $p<0.001$.

alpha1 adrenergic antagonistic properties, lowered diastolic blood pressure when given as a pretreatment to MDMA but also when given alone compared to placebo (Liechti et al. 2000b). It could be speculated that MDMA-induced 5-HT release might activate the NE system. In addition, MDMA has also direct affinity for alpha 2 adrenergic receptors (Battaglia et al. 1988). The role of NE in the mediation of the physiological and psychological effects of MDMA in humans remains to be elucidated. Studies using NE uptake inhibitors and postsynaptic NE receptor antagonists prior to MDMA could elucidate this issue.

Another source of pharmacological interaction between SSRIs and MDMA is at the level of metabolic P450 liver enzymes. The authors observed a prolongation of the subjective MDMA effect by about two hours after citalopram pretreatment as compared to MDMA alone (Liechti et al. 2000a). This finding could be explained by a pharmacokinetic interaction since citalopram is an inhibitor of the CYP2D6 enzyme, which is involved in the metabolisation of MDMA (Tucker et al. 1994). This inhibition of the breakdown of MDMA could prolong its central availability and thus its subjective effects. Given the high prevalence of depressive symptoms among Ecstasy users (Boot, McGregor & Hall 2000; Parrott & Lasky 1998), co-use and potential pharmacological interactions of SSRIs and MDMA might be frequent and should be more thoroughly investigated (Hegadoren, Baker & Bourin 1999).

The present data, in line with anecdotal reports from Ecstasy users who took MDMA while under therapy with an SSRI (Stein & Rink 1999; McCann & Ricaurte 1993), indicate that the use of MDMA after administration of the SSRI is unlikely to result in an adverse drug reaction. In contrast, adverse responses to pure MDMA were attenuated in the controlled study (Liechti & Vollenweider 2000a). Whether the use of MDMA prior to administration of the SSRI leads to an amplification of the MDMA effect or even to a serotonin-syndrome (Green, Cross & Goodwin 1995), cannot be inferred from this data.

Another similar pharmacological interaction has also recently been reported for MDMA and alcohol (Hernández-López et al. 2002). The combined administration of MDMA and ethanol produced longer-lasting subjective drug effects than MDMA or ethanol alone. In addition, plasma concentrations of MDMA showed a 13% increase after the use of alcohol. The mechanism of this interaction is unknown.

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 [H215O]-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 (Ketter et al. 1996; Schneider et al. 1995), orbitofrontal cortex (Ketter et al. 1996), ventral anterior cingulate cortex (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. (Ketter et al. 1996; Le Doux 1995; Schneider et al. 1995). Consistent with this, 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 (Ketter et al. 1996). These results raise the possibility that reduced activity in the amygdala as observed in our subjects during MDMA use 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 (Raleigh & Steklis 1981; Kling 1975; Franzen & Myers 1973; Butter & Snyder 1972). 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 (Swerdlow et al. 1995, 1993; Braff et al. 1992; Grillon et al. 1992; Braff & Geyer 1990; Geyer & Braff 1982; Braff et al. 1978). 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 (McGhie & Chapman 1961; Bleuler 1911).

Multiple neurotransmitter systems including dopamine, glutamate, GABA and serotonin have been shown to be involved in modulating PPI in animals (Swerdlow et al. 1992; Geyer et al. 1990). In 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 (Vollenweider et al. 1999; Martinez & Geyer 1997; Dulawa & Geyer 1996; Kehne et al. 1996; Mansbach et al.1989). 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-HT1A, 5-HT1B, and 5-HT2A receptor subtypes are involved in the mediation of the disruptive effects of MDMA in rats (Sipes & Geyer 1995, 1994; Rigdon & Weatherspoon 1992). For example, it has been demonstrated that the PPI-disruptive effects of MDMA and the hallucinogenic 5-HT2 agonist DOI (Sipes & Geyer 1994) can be blocked by the highly selective 5-HT2A receptor antagonist M 100907 (Sipes & Geyer 1997; Padich, McCloskey & Kehne 1996), indicating that MDMA may impair PPI in rats via postsynaptic 5-HT2A receptors. In addition, both 5-HT1A and 5-HT1B agonists reduce PPI in rats, and these effects are antagonized by the corresponding receptor antagonists (Sipes & Geyer 1995, 1994; Rigdon & Weatherspoon 1992). 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 (Sills 1999; Swerdlow et al. 1990; Mansbach , Geyer & Braff 1988). In sum, the present data obtained in animal studies suggest that MDMA may affect PPI in rats by acting at serotonin 5-HT1A, 5-HT1B and/or 5-HT2A and/or dopamine D2 receptor sites.

While the pharmacological effects of MDMA on PPI has been well studied in rodents, no similar studies were conducted in humans (for a review see Geyer & Callaway 1994). Therefore, the authors 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 behavioral 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. However, without mechanistic studies 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, the authors 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 (Martinez & Geyer 1997; Kehne et al. 1992). In support of this notion, we recently found that the selective 5-HT reuptake inhibitor citalopram not only markedly abolished the psychological effects of MDMA but also reduced the MDMA-induced increase in PPI in healthy volunteers (Liechti et al. 2001, 2000a). Moreover, pretreatment with the D2 antagonist haloperidol or the 5-HT2A/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. However, it is also obvious 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-HT1A agonists disrupt PPI in rats but increase PPI in mice (Dulawa et al. 1997; Sipes & Geyer 1995). Together with the finding that MDMA also increased PPI in mice lacking the 5-HT1B receptor (Dulawa et al. 2000), these results strongly suggest that 5-HT1A receptors may contribute to the increase seen in PPI in humans. Also marked neuroanatomical differences in the distribution of 5-HT1A 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-HT1A 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 animal 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-HT1 receptors, contribute to this discrepancy remains to be clarified. The present data also demonstrates the compelling need for parallel studies in animal and human to increase our understanding of the mechanism of action of MDMA in humans.

REFERENCES

Acquas, E.; Marrocu, P.; Pisanu, A.; Cadoni, C.; Zernig, G.; Saria, A. & Di Chiara, G. 2001. Intravenous administration of ecstasy (3,4-methylenedioxymethamphetamine) enhances cortical and striatal acetylcholine release in vivo. *European Journal of Pharmacology* 418: 207-11.

Adolphs, R.; Tranel, D. & Damasio, A.R. 1998. The human amygdala in social judgement. *Nature* 393: 470-74.

Bankson, M.G. & Cunningham, K.A. 2001. 3,4-Methylenedioxymethamphetamine (MDMA) as a unique model of serotonin receptor function and serotonin-dopamine interactions. *Journal of Pharmacology and Experimental Therapeutics* 297: 846-52.

Battaglia, G.; Brooks, B.P.; Kulsakdinum, C. & De Souza, E.B. 1988. Pharmacologic profile of MDMA (3,4-methyldenedioxymethamphetamine) at various brain recognition sites. *European Journal of Pharmacology* 149: 159-63.

Bleuler, E. 1911. *Dementia Praecox oder die Gruppe der Schizophrenien, I Edn.* Vienna: Deutike.

Boot, B.P.; McGregor, I.S. & Hall, W. 2000. MDMA (Ecstasy) neurotoxicity: Assessing and communicating the risks. *Lancet* 355: 1818-21.

Braff, D.L. & Geyer, M.A.1990. Sensorimotor gating and schizophrenia: Human and animal model studies. *Archives of* General *Psychiatry* 47: 181-88.

Braff, D.L.; Grillon, C. & Geyer, M.A. 1992. Gating and habituation of the startle reflex in schizophrenic patients. *Archives of General Psychiatry* 49: 206-15.

Braff, D.L.; Stone, C.; Callaway, E.; Geyer, M.A.; Glick, I. & Bali, L. 1978. Prestimulus effects on human startle reflex in normals and schizophrenics. *Psychophysiology* 15: 339-43.

Brauer, L.H. & de Wit, H. 1997. High dose pimozide does not block amphetamine-induced euphoria in normal volunteers. *Pharmacology, Biochemistry and Behavior* 56: 265-72.

Brauer, L.H.; Goudie, A.J. & de Wit, H. 1997. Dopamine ligands and the stimulus effects of amphetamine: Animal models versus human laboratory data. *Psychopharmacology* 130: 2-13.

Brothers, L. 1996. Brain mechanisms of social cognition. *Journal of Psychopharmacology* 10: 2-8.

Butter, C.M. & Snyder, D.R. 1972. Alterations in aversive and aggressive behaviors following orbital frontal lesions in rhesus monkeys. *Acta Neurobiologiae Experimentalis* 32: 525-65.

Callaway, C.W.; Wing, L.L. & Geyer, M.A. 1990. Serotonin release contributes to the locomotor stimulant effects of 3,4-methylenedioxymethamphetamine in rats. *Journal of Pharmacology and Experimental Therapeutics* 254: 456-64.

Curran, H.V. 2000. Is MDMA ("Ecstasy") neurotoxic in humans? An overview of evidence and of methodological problems in research. *Neuropsychobiology* 42:34-41.

Curran, H.V. & Travill, R.A. 1997. Mood and cognitive effects of +/-3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"): Week-end "high" followed by mid-week low. *Addiction* 92: 821-31.

Davison, D. & Parrott, A.C. 1997. Ecstasy (MDMA) in recreational users: Self-reported psychological and physiological effects. *Human Psychopharmacology* 12: 221-26.

Deakin, J.F.W. 1996. 5-HT, antidepressant drugs and the psychosocial origins of depression. *Journal of Psychopharmacology* 10: 31-38.

Dittrich, A. 1998. The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. *Pharmacopsychiatry* 31: 80-84.

Dittrich, A.; von Arx, S. & Staub, S. 1985. International study on altered states of consciousness (ISASC). Summary of the results. *German Journal of Psychology* 9: 319-39.

Downing, J. 1986. The psychological and physiological effects of MDMA on normal volunteers. *Journal of Psychoactive Drugs* 18: 335-40.

Dulawa, S.C. & Geyer, M.A. 1996. Psychopharmacology of prepulse inhibition in mice. *Chinese Journal of Physiology* 39: 139-46.

Dulawa, S.C.; Scearce-Levie, K.A.; Hen, R. & Geyer, M.A. 2000. Serotonin releasers increase prepulse inhibition in serotonin 1B knockout mice. *Psychopharmacology* 149:306-12.

Dulawa, S.C.; Hen, R.; Scearce-Levie, K. & Geyer, M.A. 1997. Serotonin 1B receptor modulation of startle reactivity, habituation, and prepulse inhibition in wild-type and serotonin 1B receptor knockout mice. *Psychopharmacology* 132: 125-134

Duncan, G.E.; Knapp, D.J.; Breese, C.R; Crews, F.T. & Little, K.Y. 1998. Species differences in regional patterns of 3H-8OH-DPAT and 3H-zolpidem binding in the rat and human brain. *Pharmacology, Biochemistry and Behavior* 60: 439-44.

Fischer, H.S.; Zernig, G.; Schatz, D.S.; Humpel, C. & Saria, A. 2001. MDMA ("ecstasy") enhances basal acetylcholine release in brain slices of the rat striatum. *European Journal of Neuroscience* 12: 1385-90.

Fitzgerald, J.L. & Reid, J.J. 1990. Effects of methylenedioxy-methamphetamine on the release of monoamines from rat brain slices. *European Journal of Psychology* 191:217-20.

Franzen, E.A. & Myers, R.E. 1973. Neural control of social behavior: Prefrontal and anterior temporal cortex. *Neuropsychologia* 11: 141-57.

Gamma, A.; Liechti, M.E. & Vollenweider, F.X. 2001. Giving MDMA to human volunteers in Switzerland. In: J. Holland (Ed.) *Ecstasy: The Complete Guide.* Rochester, Vermont: Park Street Press.

Gamma, A.; Buck, A.; Berthold, T.; Hell, D. & Vollenweider, F.X. 2000. 3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by (H215O)-PET in healthy humans. *Neuropsychopharmacology* 23: 388-95.

Gasser, P. 1996. Die psycholytische Therapie in der Schweiz von 1988 - 1993. Eine katamnestische Erhebung. *Schweizerische Archiv Fur Neurologie Und Psychiatrie* 2: 59-65.

George, M.S.; Ketter, T.A.; Parekh, P.I.; Horwitz, B.; Herscovitch, P. & Post, R.M. 1995. Brain activity during transient sadness and happiness in healthy women. *American Journal of Psychiatry* 152: 341-51.

Geyer, M.A. & Callaway, C.W. 1994. Behavioral pharmacology of ring-substituted amphetamine analogs. In: A.K. Cho & D.S. Segal (Eds.) *Amphetamine and its Analogs: Psychopharmacology, Toxicology, and Abuse.* San Diego: Academic Press.

Geyer, M.A. & Braff, D.L. 1982. Habituation of the blink reflex in normals and schizophrenic patients. *Psychophysiology* 19: 1-6.

Geyer, M.A.; Swerdlow, N.R.; Mansbach, R.S. & Braff, D.L. 1990. Startle response models of sensorimotor gating and habituation deficits in schizophrenia. *Brain Research Bulletin* 25: 485-98.

Giroud, C.; Augsburger, M.; Sadeghipour, F.; Varesio, E.; Veuthey, J-L. & Rivier, L. 1997. Ecstasy—la situation en Suisse romande. Composition des saisies, analyse des échantillons biologiques et brève revue de son action pharmacologique et de sa toxicité. *Schweizerische Rundschau Fur Medizin* 86: 510-23.

Glennon, R.A.; Titeler, M. & McKenney, J.D. 1984. Evidence for 5-HT2 involvement in the mechanism of action of hallucinogenic agents. *Life Sciences* 35: 2505-11.

Gouzoulis, E.; von Bardeleben, U.; Rupp, A.; Kovar, K.A. & Hermle, L. 1993. Neuroendocrine and cardiovascular effects of MDE in healthy volunteers. *Neuropsychopharmacology* 8: 187-93.

Gouzoulis-Mayfrank, E.; Daumann, J.; Tuchtenhagen, F.; Pelz, S.; Becker, S.; Kunert, H.J.; Fimm, B. & Sass, H. 2000. Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). *Journal of Neurology, Neurosurgery and Psychiatry* 68: 719-25.

Gouzoulis-Mayfrank, E.; Thelen, B.; Habermeyer, E.; Kunert, H.J.; Kovar. K-A.; Lindenblatt, H.; Hermle, L,; Spitzer, M. & Sass, H. 1999. Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and d-methamphetamine in healthy volunteers. *Psychopharmacology* 142: 41-50.

Gouzoulis-Mayfrank, E.; Thelen, B.; Maier, S.; Habermeyer, E.; Spitzer, M. & Sass, H. 1998. Modulation of semantic priming effects by psilocybin, MDE (Ecstasy), and d-methamphetamine. *Neurology, Psychiatry and Brain Research* 6: 19-28.

Green, A.R.; Cross, A.J. & Goodwin, G.M. 1995. Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxy-methamphetamine (MDMA or "Ecstasy"). *Psychopharmacology* 119: 247-60.

Greer, G. 1985. Using MDMA in psychotherapy. *Advances* 2: 57-62.

Greer, G. & Tolbert, R. 1986. Subjective reports on the effects of MDMA in a clinical setting. *Journal of Psychoactive Drugs* 18: 319-27.

Grillon, C.; Ameli, R.; Charney, D.S.; Krystal, J. & Braff, D.L. 1992. Startle gating deficits occur across prepulse intensities in schizophrenic patients. *Biological Psychiatry* 32: 939-43.

Gudelsky, G.A. & Nash, J.F. 1996. Carrier-mediated release of serotonin by 3,4-methylenedioxymethamphetamine: Implications for serotonin-dopamine interactions. *Journal of Neurochemistry* 66: 243-49.

Gudelsky, G.A.; Yamamoto, B.K. & Nash, J.F. 1994. Potentation of 3,4-methylenedioxymethamphetamine-induced dopamine release and serotonin neurotoxicity by 5-HT2 receptor agonists. *European Journal of Pharmacology* 264: 325-30.

Hando, J.; Topp, L. & Hall, W. 1997. Amphetamine-related harms and treatment preferences of regular amphetamine users in Sydney, Australia. *Drug and Alcohol Dependence* 46: 105-13.

Hegadoren, K.H.; Baker, G.M. & Bourin, M. 1999. 3,4-methylenedioxy analogues of amphetamine: Defining the risk to humans. *Neuroscience and Biobehavioural Reviews* 23: 539-52.

Hermle, L.; Spitzer, M.; Borchardt, D.; Kovar. K.A. & Gouzoulis, E. 1993. Psychological effects of MDE in normal subjects: Are entactogens a new class of psychoactive agents? *Neuropsychopharmacology* 8: 171-76.

Hernández-López, C.; Farré, M.; Roset,. P.; Menoyo, E.; Pizarro, N.; Ortuño, J.; Torrens, M.; Camí, J. & de la Torre, R. 2002. 3,4-Methylenedioxymethamphetamine (Ecstasy) and Alcohol interactions in humans: Psychomotor performance, subjective effects, and pharmacokinetics. *Journal Pharmacology and Experimental Therapeutics* 300: 236-44.

Janke, W. & Debus, G. 1978. *Die Eigenschaftswörterliste (EWL-K) - Ein Verfahren zur Erfassung der Befindlichkeit, 1 Edn.* Göttingen, Germany: Hogrefe.

Kehne, J.H.; Padich, R.A.; McCloskey, T.C.; Taylor, V.L. & Schmidt, C.J. 1996. 5-HT modulation of auditory and visual sensorimotor gating: I. Effects of 5-HT releasers on sound and light prepulse inhibition in Wistar rats. *Psychopharmacology* 124: 95-106.

Kehne, J.H.; Ketteler, H.J.; McCloskey, T.C.; Sullivan, C.K.; Dudley, M.W. & Schmidt, C.J. 1996. Effects of the selective 5-HT2A receptor antagonist MDL 100,907 on MDMA-induced locomotor stimulation in rats. *Neuropsychopharmacology* 15: 116-24.

Kehne, J.H.; Timothy, C.; McCloskey, T.C.; Taylor, V.L.; Black, C.K.; Fadayel, G.M. & Schmidt, C.J. 1992. Effects of the serotonin releasers 3,4-methylenedioxymethamphetamine (MDMA), 4-chloroamphetamine (PCA) and fenfluramine on acoustic and tactile startle reflexes in rats. *Journal of Pharmacology and Experimental Therapeutics* 260: 78-89.

Ketter, T.A. Andreason, P.J.; George, M.S.; Lee, C.; Gill, D.S.; Parekh, P.I.; Willis, M.W.; Herscovitch, P. & Post, R.M. 1996. Anterior paralimbic mediation of procaine-induced emotional and psychosensory experiences. *Archives of General Psychiatry* 53: 59-69.

Kling, A. 1975. Brain lesions and aggressive behaviour of monkeys in free living groups. In: W.S. Fields & W.H. Sweet (Eds.) *Neural Bases of Violence and Aggression.* St. Louis, Missouri: H. Green, Inc.

Koch, S. & Galloway, M.P. 1997. MDMA induced dopamine release in vivo: role of endogenous serotonin. *Journal of Neural Transmission* 104: 135-46.

Laruelle, M.; Abi-Dargham, A.; van Dyck, C.H.; Rosenblatt, W.; Zea-Ponce, Y.; Zoghbi, S.S.; Baldwin, R.M.; Charney, D.S.; Hoffer, P.B.; Kung, H.F. & Innis, R.B. 1995. SPECT imaging of striatal dopamine release after amphetamine challenge. *Journal of Nuclear Medicine* 36: 1182-90.

Lauerma, H.; Wuorela, M. & Halme, M. 1998. Interaction of serotonin reuptake inhibitor and 3,4-methylenedioxymethamphetamine? *Biological Psychology* 43: 929.

Le Doux, J.E. 1995. Emotion: Clues from the brain. *Annual Review of Psychology* 46: 209-35.

Lester, S.J.; Baggott, M.; Welm, S.; Schiller, N.B.; Jones, R.T.; Foster, E. & Mendelson, J. 2000. Cardiovascular effects of 3,4-methylenedioxymethamphetamine. A double-blind, placebo-controlled trial. *Annals of Internal Medicine* 133: 969-73.

Liechti, M.E. & Vollenweider, F.X. 2001. Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. *Human Psychopharmacology* 16: 589-98.

Liechti, M.E. & Vollenweider, F.X. 2000a. The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ("Ecstasy") in healthy volunteers. *Journal of Psychopharmacology* 14: 269-74.

Liechti, M.E. & Vollenweider, F.X. 2000b. Acute psychological and physiological effects of MDMA ("Ecstasy") after haloperidol pretreatment in healthy humans. *European Neuropsychopharmacology* 10: 289-295

Liechti, M.E.; Gamma, A. & Vollenweider, F.X. 2001. Gender differences in the subjective effects of MDMA. *Psychopharmacology* 154: 161-68.

Liechti, M.E.; Geyer, M.A.; Hell, D. & Vollenweider, F.X. 2001. Effects of MDMA (Ecstasy) on prepulse inhibition and habituation of startle in humans after pretreatment with citalopram, haloperidol, or ketanserin. *Neuropsychopharmacology* 24: 240-52.

Liechti, M.E.; Baumann, C.; Gamma, A. & Vollenweider, F.X. 2000a. Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. *Neuropsychopharmacology* 22: 513-21.

Liechti, M.E.; Saur, M.R.; Gamma, A.; Hell, D. & Vollenweider, F.X. 2000b. Psychological and physiological effects of MDMA ("Ecstasy") after pretreatment with the 5-HT2 antagonist ketanserin in healthy humans. *Neuropsychopharmacology* 23: 396-404.

Mansbach, R.S.; Braff, D.L. & Geyer, M.A. 1989. Prepulse inhibition of the acoustic startle response is disrupted by N-ethyl-3,4-methylenedioxyamphetamine (MDEA) in the rat. *European Journal of Pharmacology* 167: 49-55.

Mansbach, R.S.; Geyer, M.A. & Braff, D.L. 1988. Dopaminergic stimulation disrupts sensorimotor gating in the rat. *Psychopharmacology* 94: 507-14.

Martinez, D.L. & Geyer, M.A. 1997. Characterization of the disruptions of prepulse inhibition and habituation of startle induced by a-Ethyltryptamine. *Neuropsychopharmacology* 16: 246-55.

Mas, M.; Magi, F.; De la Torre, R.; Roset, P.N.; Ortuno, J.; Segura, J. & Cami, J. 1999. Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. *Journal of Pharmacology and Experimental Therapeutics* 290: 136-45.

McCann, U.D. & Ricaurte, G.A. 1993. Reinforcing subjective effects of (+/-) 3,4- methylenedioxymethamphetamine ("Ecstasy") may be separable from its neurotoxic actions: clinical evidence. *Journal of Clinical Psychopharmacology* 13: 214-17.

McCreary, A.C.; Bankson, M.G. & Cunningham, K.A. 1999. Pharmacological studies of the acute and chronic effects of (+)-3,4-methylenedioxymethamphetamine on locomotor activity: Role of 5-Hydroxytryptamine1A and 5-Hydroxytryptamine1B/1D receptors. *Journal of Pharmacology and Experimental Therapeutics* 290: 965-73.

McDaid, J. & Docherty, J.R. 2001. Vascular actions of MDMA involve a_1 and a_2-adrenoceptors in the anaesthetized rat. *British Journal of Pharmacology* 133: 429-37.

McGhie A. & Chapman J. 1961. Disorders of attention and perception in early schizophrenia. *British Journal of Medical Psychology* 34: 103-16.

McGuire, P.K.; Cope, H. & Fahy, T.A. 1994. Diversity of psychopathology associated with use of 3,4- methylenedioxymethamphetamine ("Ecstasy"). *British Journal of Psychology* 165: 391-95.

Milroy, C.M.; Clark, J.C. & Forrest, A.R.W. 1996. Pathology of deaths associated with Ecstasy and Eve misuse. *Journal of Clinical Pathology* 49: 149-53.

Morgan, M.J. 2000. Ecstasy (MDMA): A review of its possible persistent psychological effects. *Psychopharmacology* 152: 230-48.

Morgan, M.J. 1998. Recreational use of "Ecstasy" (MDMA) is associated with elevated impulsivity. *Neuropsychopharmacology* 19: 252-64.

Nash, J.F. 1990. Ketanserin pretreatment attenuates MDMA-induced dopamine release in the striatum as measured by in vivo microdialysis. *Life Sciences* 47: 2401-08.

Nichols, D.E. 1986. Differences between the mechanism of action of MDMA, MBDB, and the classical hallucinogens. Identification of a new therapeutic class: Entactogens. *Journal of Psychoactive Drugs* 18: 305-13.

Nichols, D.E.; Lloyd, D.H.; Hoffman, A.J.; Nichols, M.B. & Yim, G.K.W. 1982. Effects of certain hallucinogenic amphetamine analogues on the release of 3H-serotonin from rat whole brain synaptosomes. *Journal of Medical Chemistry* 25: 530-35.

Nurnberger, J. I.; Simmons-Alling, S.; Kessler, L.; Jimerson, S.; Schreiber, J.; Hollander, E.; Tamminga, C.A.; Suzan Nadi, N.; Goldstein, D.S. & Gershon, E.S. 1984. Separate mechanisms for behavioral, cardiovascular, and hormonal responses to dextroamphetamine in man. *Psychopharmacology* 84: 200-02.

Oberlender, R. & Nichols, D.E. 1988. Drug discrimination studies with MDMA and amphetamine. *Psychopharmacology* 95 (1): 71-6.

Padich, R.A.; McCloskey, T.C. & Kehne, J.H. 1996. 5-HT modulation of auditory and visual sensorimotor gating:II. Effects of the 5-HT2A antagonist MDL 100,907 on disruption of sound and light prepulse inhibition produced by 5-HT agonists in Wistar rats. *Psychopharmacology* 124: 107-16.

Parrott, A.C. & Lasky, J. 1998. Ecstasy (MDMA) effects upon mood and cognition: Before, during and after a Saturday night dance. *Psychopharmacology* 139: 261-8.

Parrott, A.C.; Sisk, E. & Turner, J.J.D. 2000. Psychobiological problems in heavy "Ecstasy" (MDMA) polydrug users. *Drug and Alcohol Dependence* 60: 105-15.

Peroutka, S.J.; Newman, H. & Harris, H. 1988. Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. *Neuropsychopharmacology* 1: 273-77.

Raleigh, M.J. & Steklis, H.D. 1981. Effects of orbital frontal and temporal neocortical lesions on affiliative behavior of vervet monkeys (Cercopithecus aethiops sabaeus). *Experimental Neurology* 73: 378-89.

Rempel, N.L.; Callaway, C.W. & Geyer, M.A. 1993. Serotonin 1B receptor activation mimics behavioral effects of presynaptic serotonin release. *Neuropsychopharmacology* 8: 201-11.

Rigdon, C. & Weatherspoon, J. 1992. 5-HT1A agonists block prepulse inhibition of the acoustic startle reflex. *Journal of Pharmacology and Experimental Therapeutics* 263: 486-93.

Rothman, R.B.; Baumann, M.H.; Dersch, C.M.; Romero, D.V.; Rice, K.C.; Carroll, F I. & Partilla, J.S. 2001. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse* 39: 32-41.

Rudnick, G. & Wall, S.C. 1992. The molecular mechanism of "Ecstasy" [3,4-methylenedioxymethamphetamine (MDMA)]: Serotonin transporters are targets for MDMA-induced serotonin release. *Proceedings of the National Academy of Sciences of the United States of America* 89: 1817-21.

Schechter, M.D. 1989. Serotonergic-dopaminergic mediation of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). *Pharmacology, Biochemistry and Behavior* 31: 817-24.

Schifano, F., Di Furia, L., Forza, G., Minicuci, N., Bricolo, R. (1998). MDMA ("Ecstasy") consumption in the context of polydrug abuse: a report on 150 patients. *Drug and Alcohol Dependence* 52: 85-90.

Schmidt, C.J. 1987. Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine. *Journal of Pharmacology and Experimental Therapeutics* 240: 240-47.

Schmidt, C.J., Levin, J.A., Lovenberg, W. 1987. In vitro and in vivo neurochemical effects of methylenedioxymethamphetamine on striatal monoaminergic systems in the rat brain. Biochemical Pharmacology 36: 747-55.

Schmidt, C.J.; Sullivan, C.K. & Fadayel, G.M. 1994. Blockade of striatal 5-hydroxytryptamine2 receptors reduces the increase in extracellular concentrations of dopamine produced by the amphetamine analogue 3,4-methylenedioxymethamphetamine. *Journal of Neurochemistry* 62 (4): 1382-89.

Schmidt, C.J.; Fadayel, G.M.; Sullivan, C.K. & Taylor, V.L. 1992. 5-HT2 receptors exert a state-dependent regulation of dopaminergic

function: studies with MDL 100,907 and the amphetamine analogue, 3,4-methylenedioxymethamphetamine. *European Journal of Pharmacology* 223: 65-74.

Schneider, F.; Gur, R.E.; Mozley, L.H.; Smith, R.J.; Mozley, P.D.; Censits, D.M.; Alavi, A. & Gur, R.C. 1995. Mood effects on limbic blood flow correlate with emotional self-rating: A PET study with oxygen-15 labeled water. *Psychiatry Research: Neuroimaging* 61: 265-83.

Sherer, M.A.; Kumor, K.M. & Jaffe, J.H. 1989. Effects of intravenous cocaine are partially attenuated by haloperidol. *Psychiatry Research* 27: 117-25.

Shulgin, A.T. 1986. The background and chemistry of MDMA. *Journal of Psychoactive Drugs* 18: 291-304.

Sills, T.L. 1999. Amphetamine dose dependently disrupts prepulse inhibition of the acoustic startle response in rats within a narrow time window. *Brain Research Bulletin* 48: 445-48.

Sipes, T.E. & Geyer, M.A. 1997. DOI disrupts prepulse inhibition of startle in rats via 5-HT2A receptors in the ventral pallidum. *Brain Research* 761:97-104.

Sipes, T.A. & Geyer, M.A. 1995. 8-OH-DPAT disruption of prepulse inhibition in rats: Reversal with (+)WAY 100,135 and localization of site of action. *Psychopharmacology* 117: 41-48

Sipes, T.A. & Geyer, M.A. 1994. Multiple serotonin receptor subtypes modulate prepulse inhibition of the startle response in rats. *Neuropharmacology* 33: 441-48.

Solowij, N.; Hall, W. & Lee, N. 1992. Recreational MDMA use in Sydney: A profile of "Ecstasy" users and their experiences with the drug. *British Journal of Addiction* 87: 1161-72.

Sondermann, N. & Kovar, K.A. 1999. Screening experiments of ecstasy street samples using near infrared spectroscopy. *Forensic Science Iinternational* 106 (3): 147-56.

Stein, D.J. & Rink, J. 1999. Effects of ecstasy blocked by serotonin reuptake inhibitors. *Journal of Clinical Psychology* 60: 485.

Swerdlow, N.R.; Paulsen, J.; Braff, D.L.; Butters, N.; Geyer, M.A. & Swenson, M.R. 1995. Impaired prepulse inhibition of acoustic and tactile startle response in patients with Huntington's Disease. *Journal of Neurology, Neurosurgery and Psychiatry* 58: 192-200.

Swerdlow, N.R.; Benbow, C.H.; Zisook, S.; Geyer, M.A. & Braff, D.L, 1993. A preliminary assessment of sensorimotor gating in patients with obsessive compulsive disorder (OCD). *Biological Psychiatry* 33: 298-301.

Swerdlow, N.R.; Caine, S.B.; Braff, D.L. & Geyer, M.A. 1992. The neural substrates of sensorimotor gating of the startle reflex: a review of the recent findings and their implications. *Journal of Psychopharmacology* 1 6: 176-90.

Swerdlow, N.R.; Mansbach, R.S.; Geyer, M.A.; Pulvirenti, L.; Koob, G.F. & Braff, D.L. 1990. Amphetamine disruption of prepulse inhibition of acoustic astartle is reversed by depletion of mesolimbic dopamine. *Psychopharmacology* 100: 413-16.

Topp, L.; Hando, J.; Dillon, P.; Roche, A. & Solowij, N. 1999. Ecstasy use in Australia: Patterns of use and associated harm. *Drug and Alcohol Dependence* 55: 105-115.

Tucker, G.T.; Lennard, M.S.; Ellis, S.W.; Woods, H.F.; Cho, A.K. & Lin, L.Y. 1994. The demethylenation of methylenedioxymethamphetamine ("Ecstasy") by debrisoquine hydroxylase (CYP2D6). *Biochemical Pharmacology* 47: 1151-56.

Volkow, N.D.; Wang, G.J.; Fischman, M.W.; Foltin, R.W.; Fowler, J.S.; Abumrad, N.N.; Vitkun, S.; Logan, J.; Gatley, S.J.; Pappas, N.; Hitzemann, R. & Shea, C.E. 1997. Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* 386: 827-30.

Vollenweider, F.X.; Geyer, M.A. & Greer, G.R. 2001. Acute psychological and neurophysiological effects of MDMA in humans. *Heffter Review of Psychedelic Research* 2: 53-63.

Vollenweider, F.X.; Remensberger, S.; Hell, D. & Geyer, M.A. 1999. Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans. *Psychopharmacology* 143: 365-72.

Vollenweider, F.X.; Gamma, A.; Liechti, M.E. & Huber, T. 1998a. Psychological and cardiovascular effects and short-term sequelae of MDMA ("Ecstasy") on MDMA-naive healthy volunteers. *Neuropsychopharmacology* 19: 241-51.

Vollenweider, F.X.; Vollenweider-Scherpenhuyzen, M.F.I.; Bäbler, A.; Vogel, H.& Hell, D. 1998b. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport* 9: 3897-3902.

Windhaber, J.; Maierhofer, D. & Dantendorfer, K. 1998. Panic disorder induced by large doses of 3,4-methylenedioxymethamphetamine resolved by paroxetine. *Journal of Clinical Psychopharmacology* 18: 95-6.

Yamamoto, B.K.; Nash, J.F. & Gudelsky, G.A. 1995. Modulation of methylenedioxymethamphetamine-induced striatal dopamine release by the interaction between serotonin and gamma-aminobutyric acid in the substantia nigra. *Journal of Pharmacology and Experimental Therapeutics* 273: 1063-70.