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A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers

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Abstract

This review of the literature aims to identify the acute effects of MDMA (ecstasy) in healthy volunteers. The wide range of relevant but methodologically diverse tests was first grouped into clusters to allow an evaluation of tests that would otherwise have been excluded due to their low frequency of utilization. The following three types of tests were evaluated: (1) functional tests quantifying executive, attention, visual, motor, visuomotor and auditory functions, (2) phenomenological tests assessing personal, subjective experiences, and (3) physiological measures reflecting neurophysiological, endocrine and physiological parameters.

MDMA showed robust effects on most of the phenomenological and physiological tests. Functional tests were scarce, preventing any meaningful conclusions to be drawn from their evaluation other than that these tests should be incorporated into future acute-effect studies.

A striking dose–response relationship appeared for cardiovascular effects. At doses below 1.0 mg/kg MDMA no change was observed relative to placebo while above this dose all studies reported significant increases. Furthermore, pupil size, plasma cortisol and plasma prolactin levels proved responsive to MDMA administration. The reported subjective effects of MDMA matched the entactogenic profile.

Although interest in the action of MDMA is considerable, the existing knowledge about the cognitive effects of MDMA in humans is still rather limited and further research into the drug's effects is recommended, also in view of potential therapeutic uses of the drug.

Keywords

3,4-methylenedioxymethamphetamine, MDMA, acute effects, healthy volunteers, review

Introduction

In Western societies a considerable percentage of young people expose themselves to 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) under less then ideal circumstances (Schifano *et al.* 1998; Parrott 2001; Gross *et al.* 2002). The potential hazards associated with this prevalent recreational use of the drug make in-depth knowledge about the acute effects of MDMA indispensable. Since trials to assess the therapeutic potential of MDMA are underway (Baggott *et al.*, 2005), a thorough understanding of the acute actions of MDMA has also become essential to ensure drug safety.

MDMA is rapidly absorbed following oral administration, is detectable in the blood within 30 minutes, reaches its T-max in 1–2 hours and has a half life of about 6–8 hours (Green *et al.*, 2003). The psychoactive effects last for approximately 2–4 hours in spite of persisting blood levels and, in concordance with the persisting MDMA levels objective impairment of mental functioning lasts longer than the subjective effects (Lamers *et al.*, 2003). The pharmacokinetics and metabolism of MDMA are described in more detail elsewhere (de la Torre *et al.*, 2000; Green *et al.*, 2003).

MDMA enters presynaptic serotonin nerve cells mainly by means of the presynaptic serotonin transporter (SERT), and releases the intra-cellular 5-HT storage into the synapse by reversal of the SERT. Depletion of 5-HT from its intracellular vesicles due to interference with the vesicular transporter (VMAT-2) has also been reported (Mlinar and Corradetti, 2003). Vesicular depletion leads to high cytoplasmic 5-HT levels, which can be transported into the synapse by the SERT or even 'leak' out of the cell, thus increasing synaptic 5-HT levels. The characteristic psychological effects of MDMA (augmented social interaction, friendliness and empathy towards others) are thought to be caused by the enhanced serotonin neurotransmission. In concordance with this, pretreatment with the 5-HT reuptake inhibitor citalopram, which

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effectively blocks SERT, was found markedly but not completely to attenuate the psychological effects of MDMA in healthy volunteers (Liechti and Vollenweider, 2000b).

As the characteristic effects of the drug are not observed in strict hallucinogens nor in stimulants, MDMA is referred to as an 'entactogen' (Nichols and Oberlender, 1990; Parrott, 2001; Vollenweider *et al.*, 2002). It also has arousing effects presumably induced by dopamine and/or noradrenaline release (Liechti and Vollenweider, 2000b; Liechti and Vollenweider, 2001; Colado *et al.*, 2004; Mills *et al.*, 2004).

Several studies have shown MDMA to be neurotoxic in rats and primates (Ricaurte *et al.*, 2000; Jones *et al.*, 2005). The process of neurodegeneration is exacerbated by high ambient temperatures and mainly occurs in fine serotonergic axons (Sanchez *et al.*, 2004). This effect was explained in a report in which increased temperature was found to raise the ratio of dopamine/serotonin uptake by SERT *in vitro* (Saldana and Barker, 2004). Dopamine degradation in the 5-HT terminal and the subsequent formation of radical oxygen species (ROS) thus might play a causal role in the drug's neurotoxicity (Colado *et al.*, 2004; Escobedo *et al.*, 2005), in addition to its own metabolism that also leads to ROS formation (Colado *et al.*, 2004; Johnson *et al.*, 2004; Jones *et al.*, 2005). Although neurotoxicity has clearly been demonstrated in animals, and some studies have suggested neurodegeneration in humans (Reneman *et al.*, 2001a; Reneman *et al.*, 2001b), functional impairment has not been convincingly linked to the actions of MDMA (Curran, 2000).

Many retrospective studies have been performed to identify functional impairment associated with the recreational use of ecstasy or 'XTC'. Although the results are inconsistent or even contradictory, memory is most frequently reported to be affected by MDMA (Verkes *et al.*, 2001; Verbaten, 2003; Daumann *et al.*, 2004). The most consistent predictor of cognitive impairment appears to be the number of tablets per occasion, i.e. the stacking of XTC pills to prolong the drug's effects (McCann *et al.*, 2005). This complies with the data on acute effects, where systemic metabolization leading to the formation of ROS is necessary for neurotoxicity to develop (Colado *et al.*, 2004). The stacking of pills is likely to exhaust antioxidant resources, thereby increasing toxicity, causing subsequent axonal degeneration. This hypothesis is strengthened by the finding that co-administration of drugs that lower the hyperthermic response and/or provide radical trapping with MDMA tend to decrease this nerve damage while the entactogenic MDMA effects remain unaltered (Escobedo *et al.*, 2005).

Prospective studies investigating the effects of an illegal and potentially neurotoxic drug may be rejected or amended on the grounds of ethical issues, but the interpretation of retrospective studies into MDMA-induced functional impairments is hampered by methodological difficulties making conclusions questionable. The main confounding factor is that MDMA users are generally multidrug users, either consciously or due to the impurity of the XTC pills. As a result, any functional impairment cannot be strictly attributed to MDMA use since it might partly be associated with the concurrent substance or even to the multidrug use itself. A second confounder is that due to their design, retrospective studies rely on self-reported drug use. As discussed above, as the drug use might affect memory and may not be restricted to MDMA alone, and because the contents of the XTC tablets used is variable, the data and conclusions drawn are inherently controversial. And finally, pre-existing group differences are possible and remain unknown. For an in-depth discussion of this latter topic we refer to Curran *et al.* (2000).

With the present study we aimed to create a profile of the acute effects of MDMA in humans by verifying or dismissing current assumptions about these effects by means of a comprehensive review of the available literature. For inclusion in this review studies needed to meet stringent criteria and the effects reported were compared to the results of the other studies to substantiate the validity of the conclusions.

Method

Structured evaluation of the literature

We performed a literature search via PubMed using the following keywords: MDMA OR ecstasy OR XTC OR 3,4-methylenedioxymethamphetamine, and human OR volunteer. This yielded a total of 1446 articles, which were subsequently manually scanned for:

1. administration of MDMA in healthy volunteers,
2. a placebo-controlled design,
3. measurement of acute-effect parameters,
4. administration of a known and verified dose,
5. being an original investigation.

Only articles that met all the above-mentioned criteria were included and their references were also scanned for relevant articles. The test results mentioned in the selected articles were all recorded onto a datasheet, together with dose information and number of participants.

Grouping of individual test results

A structured procedure (de Visser *et al.*, 2001; de Visser *et al.*, 2003; Dumont *et al.*, 2005) was adopted to obtain an overview of the responses of tests or test variants to MDMA involving a progressive evaluation of all selected tests. The results from tests that were used only once or by one research group could not be generalized, and were therefore not analysed individually. Tests that could be regarded as variants from a basic form were grouped. Subsequently, clusters of tests were grouped further based on their predominant domain (see Table 1). The effects on these domains were also reviewed whenever relevant. The three categories we identified were:

1. 'Functional' tests; tests of neuropsychological function, i.e. executive function, attention, visual/visuomotor and auditory function and motor function.
2. 'Phenomenological' tests; tests that attempt to quantify personal experiences, i.e. subjective measurements.

3. Physiological measures; tests that measure physiological parameters, i.e. neurophysiological, endocrine and other physiological measures.

Because even for comparable methods a large diversity of test parameters was found, we were unable to quantitatively record the individual test results. Instead, if a test yielded a statistically significant difference from placebo or baseline this was scored as (+) when the effect indicated an improvement or increase; if the effect was not significant it was classified as (=) or as (−) when it significantly demonstrated an impairment or decrease. Whether a difference from placebo was scored as improvement (+) or impairment (−) depended on the psychosocial desirability of the response (i.e. an increase in reaction-time scores was interpreted as an impairment). Although, of course, statistical significance is not only determined by the variance and the size of the effect but also by factors like group size, these factors could not be taken into account as the results were too variable for a formal meta-analysis. Nonetheless, our semi-quantitative review did allow an evaluation of the applicability of a test as an effect measure in typical acute-drug-effects studies with limited numbers of participants. No efforts were made to further quantify the level of statistical significance.

Test criteria

Not all tests are equally valuable. Ideally, a test should meet the following criteria to be considered to be representing the effect of the drug of interest:

1. be sensitive to a specific effect of the drug of interest,
2. show a clear and consistent response across studies,
3. reflect a clear dose–response relationship,
4. demonstrate a plausible association between the effect and the pharmacology of the drug of interest.

However, only the first criterion is a prerequisite, with the other criteria strengthening the justification for the choice of a particular test.

Consistency of responses

As mentioned above, the response of a test to a drug can be either positive (increased compared to placebo) or negative (decreased compared to placebo), or it can show no change. A useful test is expected to show a consistent response to a drug within a certain dose range. A test is not considered useful if the outcome is as often positive as it is negative, i.e. showing large variations around baseline outcomes, or if a large proportion of studies fails to show significant effects. Tests were therefore arbitrarily considered to produce a consistent response when results were significant and reflecting a similar outcome (either positive or negative) in at least 20% of the reviewed studies. Accordingly, test results were judged as inconsistent when fewer than 20% of the tests showed statistically significant results, or when the directions of the responses were variable (i.e. when more than 20% decreased and more than 20% increased). This arbitrary cut-off value only eliminated tests that hardly ever responded to the drug and could therefore not be considered to be useful tests for this drug.

Results

Of the total, 29 articles were found to meet all criteria, yielding 150 separate tests that were subdivided into 39 clusters and eight domains (see Table 1). On average, each study included ten subjects (range: 2–16). The average age was 24.7 years, with ages ranging from 18 to 40 years. One of every four participants was female and all participants had completed some form of secondary education. Reported demographics were relatively uniform across studies, with a notable exception of the group of Vollenweider who included MDMA-naive participants whereas most studies had required previous MDMA use.

Results are presented as overall domain scores whenever appropriate, subdivided into cluster scores. Separate (i.e. non-grouped) tests that were performed more than four times and by more than one research group are reported per cluster. All the tests that were evaluated are listed in Table 2 together with their corresponding domains and clusters. The effects reflect significant MDMA-induced increases (+) or decreases (−) compared to placebo. The most striking result was the finding that, relative to the other groups, the group of neuropsychological tests yielded very few results. In the next paragraphs the various test results are discussed per domain and cluster.

Cognitive effects

The domains Executive function and Visual, visuomotor and auditory function both yielded only two test results and were therefore not further evaluated. None of the 11 tests in the Attention domain had generated a significant response. No studies were found that had employed tests assessing Memory. Of the six tests measuring Motor function, two showed significant improvement.

Subjective effects

A large majority of the studies we reviewed included some type of subjective test. For the subjective assessments, individual scales were grouped into the following 13 scale clusters: social interaction, arousal, euphoria, mood, extroversion, depression, confusion, sedation, aggression, anxiety, hallucination, drug effect and drug liking. The overall subjective effects are depicted in Fig. 1.

In the scale cluster Social interaction, reflecting the entactogenic effects of MDMA, five of the 14 test results proved to be elevated.

- POMS Friendly *w*as evaluated separately; two out of seven scores showed increase.

In the cluster Arousal, comprising scales measuring arousing,

Table 1 Overview of all reported tests and measurements (with the source studies between brackets), clusters and domains

Test name	Cluster
Executive domain	
Tower of London[Lamers *et al.*, 2003]	Planning
Word fluency[Lamers *et al.*, 2003]	Language
Attention domain	
DSST[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002]	DSST
Stroop test – % errors[Vollenweider *et al.*, 1998], Stroop test – reaction time[Vollenweider *et al.*, 1998]	Selective attention
Continuous Perfomance Task[Gamma *et al.*, 2000]	Continuous performance
DAT – tracking error[Lamers *et al.*, 2003], DAT reaction time[Lamers *et al.*, 2003], MCRT – initiation time[Lamers *et al.*, 2003], OMEDA – divided attention error[Lamers *et al.*, 2003]	Divided attention
Visual, visuomotor and auditory domain	
OMEDA – time to contact error[Lamers *et al.*, 2003]	Movement estimation
Signal detection task[Lamers *et al.*, 2003]	Visual search
Motor domain	
MCRT – movement time[Lamers *et al.*, 2003], Critical tracking[Lamers *et al.*, 2003]	Motor control
Vienna apparatus – reaction time[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002]	Reaction time
Subjective domain	
VAS closeness to others[Harris *et al.*, 2002], EWL emotional excitability – sensitivity[Liechti *et al.*, 2000a], VAS social[Tancer and Johanson, 2003], POMS friendly[Cami *et al.*, 2000; Lamers *et al.*, 2003; Tancer and Johanson, 2003; Tancer 2001], VAS friendly[Harris *et al.*, 2002; Tancer and Johanson, 2003]	Social interaction
VAS alert[Tancer and Johanson, 2003], POMS arousal[Cami *et al.*, 2000; Tancer and Johanson, 2003; Tancer, 2001], EWL mood questionnaire – activity[Frei *et al.*, 2001; Gamma *et al.*, 2000; Liechti *et al.*, 2000a; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Vollenweider *et al.*, 1998], SDEQ autonomic arousal[Harris *et al.*, 2002], SDEQ cognitive improvement[Harris *et al.*, 2002], VAS stimulated[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002; Tancer and Johanson, 2003; Tancer, 2001], ARCI A[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002; Tancer and Johanson, 2003; Tancer, 2001], ARCI BG[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002; Tancer and Johanson, 2003; Tancer, 2001], VAS performance[Cami *et al.*, 2000], VAS concentration[Cami *et al.*, 2000], POMS vigour[Cami *et al.*, 2000; Lamers *et al.*, 2003; Tancer and Johanson, 2003; Tancer, 2001]	Arousal
EWL well-being – heightened mood[Frei *et al.*, 2001; Gamma *et al.*, 2000; Liechti *et al.*, 2000a; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Vollenweider *et al.*, 1998], SDEQ mood euphoria[Harris *et al.*, 2002], VAS active[Cami *et al.*, 2000], VAS passive[Cami *et al.*, 2000], ARCI MBG[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002; Tancer and Johanson, 2003; Tancer, 2001]	Euphoria
OAV Oceanic Boundlessness[Frei *et al.*, 2001; Gamma *et al.*, 2000; Liechti *et al.*, 2000a; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Vollenweider *et al.*, 1998], EWL well-being – self-confidence[Frei *et al.*, 2001; Gamma *et al.*, 2000; Liechti *et al.*, 2000a; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Vollenweider *et al.*, 1998], VAS confident[Harris *et al.*, 2002; Tancer and Johanson, 2003], VAS fear[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], VAS miserable[Tancer and Johanson, 2003], POMS elation[Cami *et al.*, 2000; Tancer, 2001], VAS calm[Cami *et al.*, 2000], VAS contentedness[Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], SDEQ relaxation[Harris *et al.*, 2002], EWL emotional excitability[Frei *et al.*, 2001; Gamma *et al.*, 2000; Liechti *et al.*, 2000a; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Vollenweider *et al.*, 1998], POMS positive mood[Cami *et al.*, 2000; Tancer and Johanson, 2003], PANSS (positive and negative syndrome scale)[Harris *et al.*, 2002]	Mood
VAS self conscience[Tancer and Johanson, 2003], EWL anxiety – thoughtfulness- contemplativeness[Liechti *et al.*, 2000a], VAS insightful[Harris *et al.*, 2002], EWL – extroversion[Frei *et al.*, 2001; Gamma *et al.*, 2000; Liechti *et al.*, 2000a; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Vollenweider *et al.*, 1998]	Extroversion
EWL anxiety – depressiveness[Liechti *et al.*, 2000a], POMS depression[Cami *et al.*, 2000; Lamers *et al.*, 2003; Tancer and Johanson, 2003], VAS down[Tancer and Johanson, 2003], VAS depression or sadness[Cami *et al.*, 2000], VAS sadness[Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002]	Depression
EWL – inactivation – dazed state[Liechti *et al.*, 2000a], POMS confusion[Cami *et al.*, 2000; Tancer, 2001], VAS confusion[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002; Tancer and Johanson, 2003]	Confusion
EWL – inactivation – tiredness[Liechti *et al.*, 2000a], POMS fatigue[Cami *et al.*, 2000; Lamers *et al.*, 2003; Tancer and Johanson, 2003], VAS tired[Tancer and Johanson, 2003], VAS sedated[Tancer and Johanson, 2003; Tancer, 2001], EWL – inactivation[Frei *et al.*, 2001; Gamma *et al.*, 2000; Liechti *et al.*, 2000a; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Vollenweider *et al.*, 1998], SDEQ cognitive impairment[Harris *et al.*, 2002], VAS drowsiness[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], ARCI PCAG[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002; Tancer and Johanson, 2003; Tancer, 2001]	Sedation
VAS irritable[Tancer and Johanson, 2003], VAS on edge[Tancer and Johanson, 2003], POMS anger[Cami *et al.*, 2000; Lamers *et al.*, 2003; Tancer & Johanson 2003], EWL emotional excitability – aggression – anger[Liechti *et al.*, 2000a]	Aggression
ARCI LSD[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002; Tancer and Johanson, 2003; Tancer, 2001], EWL anxiety – apprehension anxiety[Liechti *et al.*, 2000a], State-Trait Anxiety Inventory (STAI) [Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a], POMS anxiety[Cami *et al.*, 2000; Lamers *et al.*, 2003; Tancer and Johanson, 2003; Tancer, 2001], OAV Anxious Ego Dissolution[Frei *et al.*, 2001; Gamma *et al.*, 2000; Liechti *et al.*, 2000a; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Vollenweider *et al.*, 1998], EWL anxiety[Gamma *et al.*, 2000; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Vollenweider *et al.*, 1998], AS nervous[Cami *et al.*, 2000], VAS anxious[Tancer and Johanson, 2003; Tancer, 2001], SDEQ tension[Harris *et al.*, 2002]	Anxiety

Table 1 continued

Test name	Cluster
SDEQ ambivalence[Harris *et al.*, 2002], HRS somaestasia[Tancer and Johanson, 2003; Tancer, 2001], HRS affect[Tancer and Johanson, 2003; Tancer, 2001], HRS perception[Tancer and Johanson, 2003; Tancer, 2001], HRS cognition[Tancer and Johanson, 2003; Tancer, 2001], HRS intensity[Tancer and Johanson, 2003; Tancer, 2001], OAV Visionary restructuralisation[Frei *et al.*, 2001; Gamma *et al.*, 2000; Liechti *et al.*, 2000a; Liechti *et al.*, 2000b; Liechti and Vollenweider 2000a; Vollenweider *et al.*, 1998], VAS different surrounding[Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], VAS changes in colours[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], VAS changes in shapes[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], VAS changes in lights[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], VAS changes in hearing[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], SDEQ LSD[Harris *et al.*, 2002], VAS hallucinations – auditory[Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], VAS hallucinations – visual[Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], VAS hallucinations – seeing lights or spots[Cami *et al.*, 2000], VAS hallucinations – hearing sound or voices[Cami *et al.*, 2000], VAS hallucinations – seeing animals, things, insects, or people[Cami *et al.*, 2000], VAS different, changed, or unreal body feeling[Cami *et al.*, 2000], VAS different or unreal surroundings[Cami *et al.*, 2000], VAS changes in distances[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002)	Hallucination
VAS high[Cami *et al.*, 2000; Farre *et al.*, 2004; Harris *et al.*, 2002; Hernandez-Lopez *et al.*, 2002; Tancer and Johanson, 2003; Tancer, 2001], VAS hungry[Tancer and Johanson, 2003; Tancer, 2001], VAS drunken[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], VAS dizziness[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], VAS any effect[Cami *et al.*, 2000; Farre *et al.*, 2004; Harris *et al.*, 2002; Hernandez-Lopez *et al.*, 2002)	Drug effect
VAS bad drug effect[Tancer and Johanson, 2003], VAS good drug effect[Cami *et al.*, 2000; Tancer and Johanson, 2003], Drug liking questionaire[Tancer and Johanson, 2003], VAS drug liking[Harris *et al.*, 2002], VAS good effects[Farre *et al.*, 2004; Harris *et al.*, 2002; Hernandez-Lopez *et al.*, 2002], VAS liking[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002], VAS bad effects[Cami *et al.*, 2000; Farre *et al.*, 2004; Harris *et al.*, 2002; Hernandez-Lopez *et al.*, 2002]	Drug liking
Neurophysiological domain	
EEG[Frei *et al.*, 2001], LORETA[Frei *et al.*, 2001]	EEG
Prepulse inhibition – acoustic startle[Liechti *et al.*, 2001b; Vollenweider *et al.*, 1999]	Inhibition
rCBF change[Gamma *et al.*, 2000]	Cerebral blood flow
Maddox wing[Cami *et al.*, 2000; Farre *et al.*, 2004; Hernandez-Lopez *et al.*, 2002]	Extraocular muscle tension
Endocrine domain	
ACTH[Grob *et al.*, 1995]	ACTH
DHEA[Harris *et al.*, 2002]	DHEA
GH[Mas *et al.*, 1999]	GH
LH[Harris *et al.*, 2002]	LH
Progesterone[Harris *et al.*, 2002]	Progesterone
FSH[Harris *et al.*, 2002]	FSH
Estradiol[Harris *et al.*, 2002]	Estradiol
Prolactin[Grob *et al.*, 1995; Harris *et al.*, 2002; Mas *et al.*, 1999; Pacifici *et al.*, 2004]	Prolactin
ADH[Forsling *et al.*, 2001]	ADH
Cortisol[Farre *et al.*, 2004; Forsling *et al.*, 2001; Harris *et al.*, 2002; Lamers *et al.*, 2003; Mas *et al.*, 1999; Pacifici *et al.*, 1999; Pacifici *et al.*, 2001; Pacifici *et al.*, 2004; Tancer and Johanson 2003)	Cortisol
Physiological domain	
IL-1β[Pacifici *et al.*, 2001], IL-4[Pacifici *et al.*, 2001], IL-6[Pacifici *et al.*, 2001], TNFα[Pacifici *et al.*, 2001], IFNγ[Pacifici *et al.*, 2001] IL-2[Pacifici *et al.*, 2001; Pacifici *et al.*, 2004], IL-10[Pacifici *et al.*, 2001; Pacifici *et al.*, 2004], TGF-β1[Pacifici *et al.*, 2001; Pacifici *et al.*, 2004], CD3[Pacifici *et al.*, 1999], CD19[Pacifici *et al.*, 1999; Pacifici *et al.*, 2001; Pacifici *et al.*, 2004], NK cells[Pacifici *et al.*, 1999; Pacifici *et al.*, 2001; Pacifici *et al.*, 2004], CD8[Pacifici *et al.*, 1999; Pacifici *et al.*, 2001; Pacifici *et al.*, 2004], CD4/CD8 ratio[Pacifici *et al.*, 1999; Pacifici *et al.*, 2001; Pacifici *et al.*, 2004], CD4[Pacifici *et al.*, 1999; Pacifici *et al.*, 2001; Pacifici *et al.*, 2004]	Immune function
[Na^+][Forsling *et al.*, 2001]	Ions
Respiratory Rate[Harris *et al.*, 2002]	Respiratory rate
Osmolality[Forsling *et al.*, 2001]	Osmolality
Temperature[Farre *et al.*, 2004; Grob *et al.*, 1995; Harris *et al.*, 2002; Lamers *et al.*, 2003; Liechti *et al.*, 2000a; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Liechti and Vollenweider, 2000b; Mas *et al.*, 1999; Tancer and Johanson, 2003; Vollenweider *et al.*, 1998)	Temperature
Pupil-diameter[Farre *et al.*, 2004; Harris *et al.*, 2002; Lamers *et al.*, 2003; Mas *et al.*, 1999)	Pupil-diameter
Systolic Blood Pressure[Farre *et al.*, 2004; Gamma *et al.*, 2000; Grob *et al.*, 1995; Harris *et al.*, 2002; Lamers *et al.*, 2003; Lester *et al.*, 2000; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Liechti and Vollenweider, 2000b; Mas *et al.*, 1999; Tancer and Johanson, 2003; Tancer, 2001; Vollenweider *et al.*, 1998], Diastolic Blood Pressure[Farre *et al.*, 2004; Gamma *et al.*, 2000; Grob *et al.*, 1995; Harris *et al.*, 2002; Lamers *et al.*, 2003; Lester *et al.*, 2000; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Liechti and Vollenweider, 2000b; Mas *et al.*, 1999; Tancer and Johanson, 2003; Tancer, 2001; Vollenweider *et al.*, 1998], Heart Rate[Farre *et al.*, 2004; Harris *et al.*, 2002; Lamers *et al.*, 2003; Lester *et al.*, 2000; Liechti *et al.*, 2000b; Liechti and Vollenweider, 2000a; Liechti and Vollenweider, 2000b; Mas *et al.*, 1999; Tancer and Johanson, 2003; Tancer, 2001)	Cardiovascular

Table 2 Domain, cluster and dose-related test responses (in percentages) for all tests analysed

Domain	Cluster	Test	Response (%)	Dose range effect (mg/kg)	Dose range no effect (mg/kg)	*n*
Executive						2
Attention			=		1.0–1.7	11
Memory						0
Visual, visuomotor and auditory						2
Motor			33	1.1	1.1–1.7	6
Subjective						
	Social interaction		36	1.1–2.0	0.5–2.1	14
		POMS friendly	29	1.0–1.1	1.1–2.1	7
	Arousal		38	1.1–2.1	0.5–2.1	58
		POMS arousal	=		1.1–2.1	5
		POMS vigour	=		1.0–2.1	7
		ARCI A	88	1.1–2.1	1.6	8
		ARCI BG	38	1.3–2.0	1.1–2.1	8
		VAS stimulated	100	1.1–2.1		8
	Euphoria		88	0.5–2.1	1.1–1.6	16
		ARCI MBG	75	1.3–2.1	1.1–1.6	8
	Mood		62	0.5–2.0	0.5–2.1	42
		POMS elation	60	1.1–1.7	1.6–2.1	5
	Extroversion		70	1.5–1.7	0.5–2.0	10
	Depression		=		1.0–2.0	10
	Confusion		58	1.0–2.1	1.1–2.0	12
		POMS confusion	40	1.7–2.1	1.1–2.1	5
		VAS confusion	40	1.3–1.7	1.0–2.0	5
	Sedation		=	1.5–2.0	0.5–2.1	32
		ARCI PCAG	=		1.1–2.1	8
	Aggression		=		1.0–2.0	7
	Anxiety		67	0.5–2.1	1.1–2.0	36
		ARCI LSD	100	1.1–2.1		8
		POMS anxiety	57	1.0–2.1	1.1	7
	Hallucination		46	1.1–2.1	0.5–1.6	57
	Drug effect		53	1.1–2.1	0.5–2.1	30
		VAS any effect	84	1.1–1.7	0.5	6
		VAS high	90	1.1–2.1	0.5	10
	Drug liking		57	1.1–2.0	0.5–2.0	21
		VAS good effect	84	1.1–1.7	0.5	6
		VAS bad effect	16	1.5	0.5–1.7	6
Neurophysiological			89	1.3–1.7	1.1	9
Endocrine						
	Cortisol	Cortisol	92	0.5–2.0	0.5	12
	Prolactin	Prolactin	56	0.75–1.5	0.25–1.0	9
Physiological						
	Temperature	Temperature	21	1.0–1.5	0.25–1.7	14
	Pupil diameter	Pupil diameter	83	1.0–1.5	0.5	6
	Cardiovascular		69	1.0–2.1	0.25–1.0	61
		Heart rate	68	1.0–2.1	0.25–1.0	19
		Systolic blood pressure	71	1.0–2.1	0.25–1.0	21
		Diastolic blood pressure	71	1.0–2.1	0.25–1.0	21

Response (%) = percentage of results that showed an increase relative to placebo; Dose range effect (mg/kg) = dose range for responsive results; Dose range no effect (mg/kg) = dose range for non-responsive results; *n* = total number of reported test results.

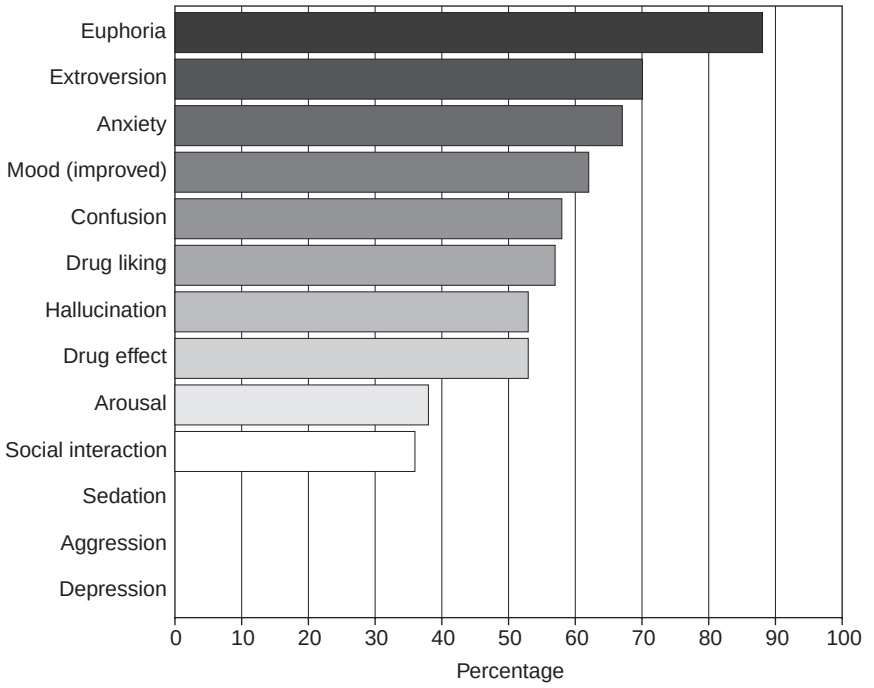

Figure 1 The subjective scales (clustered) with their reported increases (in percentages) after MDMA administration relative to placebo

% = percentage of studies showing increase.

activating effects, a total of 58 outcomes were analysed of which 22 were increased.

- POMS Vigour did not show a response.
- ARCI A was increased in seven of the eight test results.
- ARCI BG was reported eight times, of which three test results were increased.
- VAS Stimulated was increased in all eight test results.
- POMS Arousal did not show a response.

For the scale cluster Euphoria 16 test results were reported of which 14 showed an increase.

- ARCI MBG was increased in six out of eight test results.

The scale cluster Mood comprised a large group of subjective mood scales. MDMA induced robust effects here: 26 of the total of 42 test results were increased. Negative mood scales (fear, miserable) did not respond.

- POMS Elation was increased in two out of five test results.

Scores for the scale cluster Extroversion were increased in seven of ten test results.

The scale cluster Depression did not show a response.

Seven of the 12 test results in the cluster Confusion were increased.

- POMS Confusion was increased in two out of five test results.
- VAS Confusion was also increased in two out of five test results.

The scale cluster Sedation did not show show a response.

- One of seven ARCI PCAG scores was decreased.

The scale cluster Aggression did not show a response.

The scale cluster Anxiety showed increases in 24 of the 36 test results.

- ARCI LSD was reported eight times and all test results were increased.
- POMS Anxiety showed increase in four of seven test results.

The scale cluster Hallucination showed an effect profile similar to that of Anxiety scores with 35 of 66 test results being increased after MDMA. Note that the dose range inducing elevated values (1.1–2.1 mg/kg) was slightly higher than the range in the tests that failed to show an effect (0.5–1.6 mg/kg). In the scale cluster Drug effect, reflecting side effects attributed to the drug, 16 out of 30 test results were increased.

- VAS Any effect was increased in five out of six test results, the unresponsive dose being 0.5 mg/kg.
- VAS High showed no change in one test result (dose; 0.5 mg/kg) out of a total of ten, all other test results were increased.

The scale cluster Drug liking was increased in eight of the 15

test results. Most unresponsive test results were observed for negative drug-liking scales, most clearly illustrated by the two separately evaluated VAS scales:

- VAS Good effects was increased in five of six test results.
- VAS Bad effects was increased in only one of six test results.

Neurophysiological measurements

Neurophysiological measures were both few and diverse, although all but one test showed a significant response. No specific measure was reported often enough to justify a separate evaluation.

Endocrine measurements

The most frequently assessed hormones were cortisol and prolactin. Cortisol levels were increased in 11 of the 12 studies. The one study that failed to show a significant increase used the lower MDMA dose of 0.5 mg/kg. In five of the nine studies prolactin levels were elevated with the unresponsive results on average being associated with a lower dose.

Physiological effects

Temperature was increased in three of 14 test results and Pupil diameter was measured six times and increased in all studies using a dose range of 1.0–1.5 mg/kg; the one test using a dose of 0.5 mg/kg failed to demonstrate an effect.

The cluster Cardiovascular effects comprised 61 test results of which 18 did not show any change (dose range 0.25–1.0 mg/kg). Of the six trials that used 1.0 mg/kg, three reported increases. Studies administering a dose of 1.0–2.1 mg/kg MDMA all reported increased levels.

This remarkable dose–response association was also seen in the separately analysed tests within this group, whose outcomes are depicted in Fig. 2. Systolic blood pressure was reported on 21 times with a dose range of 0.25–1.0 mg/kg (n = 6) failing to induce a change whereas all tests using a dose range of 1.0 to 2.1 mg/kg ($n = 15$), were increased. The results reported for Diastolic blood pressure were identical to the values reported for systolic pressure. Finally, of the total of 19 heart-rate measurements six showed no change, all within the dose range 0.25–1.0 mg/kg. The remaining 13 tests using doses between 1.0–2.1 mg/kg yielded increases.

Discussion

To our knowledge this review comprises all placebo-controlled studies published to date that administered MDMA to healthy humans. The tests reported in the selected studies were reviewed, and the dose-related results were recorded in a database. Most studies that were discarded did not measure acute effects in humans, while a small percentage of the remaining studies per-

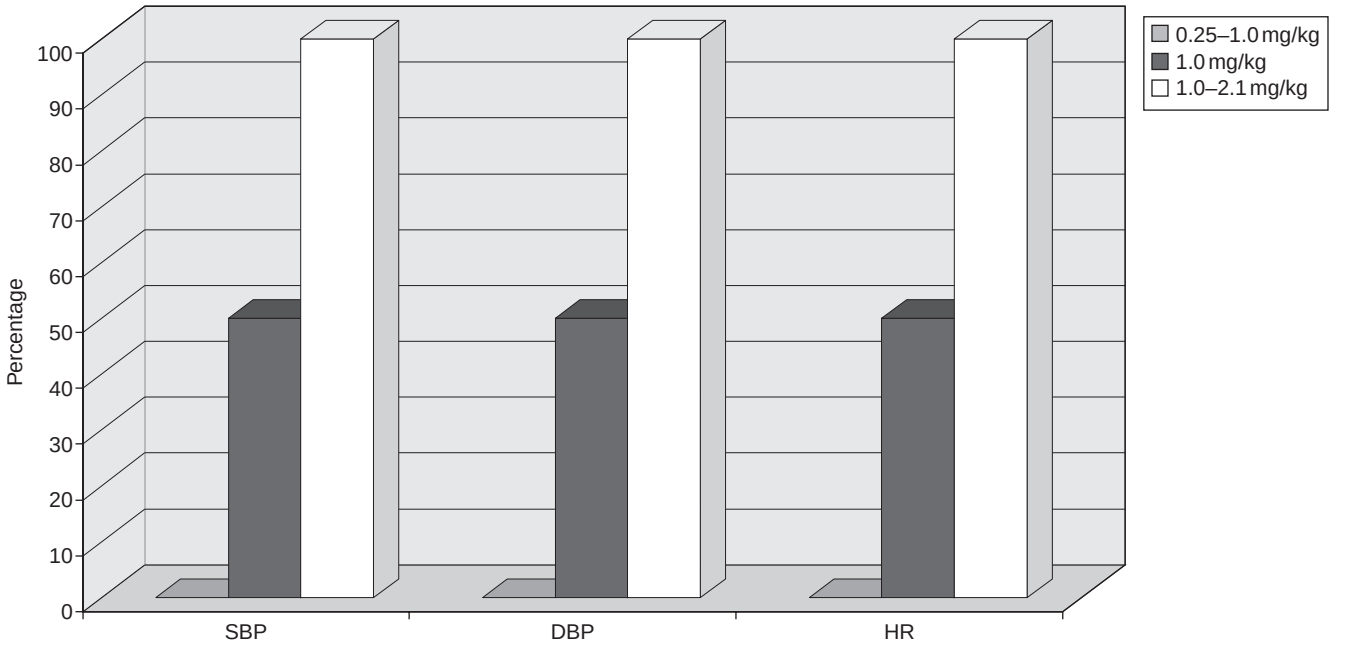

Figure 2 Dose–response (mg/kg) relationship for the MDMA-induced cardiovascular effects (in percentages) relative to placebo

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; % = percentage of studies reporting an increase.

formed the research in a 'naturalistic' setting thus not conforming to our selection criteria.

The majority of the tests were performed infrequently and, rather than rejecting tests on the basis of their limited application – by which we would have ignored possibly valuable information – we opted for an evaluation of tests grouped according to the effect or function they measured. Arguably, as a result of methodological or other differences, such group appraisals may compromise the comparative value of or even devaluate the effects reported. Any manipulation of data might obscure information: tests that in fact represent the 'ideal' measure (i.e. represent an MDMA effect) could be masked by other non-responsive tests in the same group. However, rejection of these tests on the basis of limited experience would have ignored possibly valuable information. Our evaluation effectively yielded three categories of tests measuring functional, phenomenological or physiological aspects. Next a summary and the implications of our findings will be discussed for the various domains of each category.

The studies that performed clinical research into the acute effects of MDMA in healthy volunteers almost without exception employed subjective and physiological tests, but assessments of neuropsychological functioning were not as frequent. Most surprising was the complete lack of studies reporting on memory even though retrospective studies into the long-term effects of MDMA most consistently indicate this area to be affected (Verkes *et al.*, 2001; Verbaten, 2003). The domains Executive and Visual, visuomotor and auditory also suffered from a low number of reported results, which prohibited their evaluation (see Table 2). The domain Attention comprised 11 results but showed no change, while the Motor domain, with a total of six results, showed modest increase. The limited number of tests in these domains clearly hinders any meaningful conclusion to be drawn from their evaluation, although this category is in potential most valuable.

Although several research groups have performed detailed work on MDMA effects, with Vollenweider *et al.* (Vollenweider *et al.*, 2002) extensively researching acute MDMA effects, de la Torre *et al.* (Pacifici *et al.*, 2000) focusing on immune function and Lamers *et al.* (Lamers *et al.*, 2003) on driving-related behaviour, we feel that reproduction and extension of their work is warranted to allow the results obtained by these research groups to be generalized.

In contrast to the functional studies, our search yielded an abundance of phenomenological data (see Fig. 1). The entactogenic profile of MDMA was represented in that, relative to placebo, increases were reported for the pleasurable subjective effects, as reflected by the scale clusters Euphoria, Extroversion and Social interaction scores, whereas the scores for the negative clusters Aggression, Sedation and Depression failed to show change.

Most neurophysiological measurements that were evaluated responded to MDMA administration, but none of the tests was performed often enough to warrant separate evaluation. However, since neurophysiological assessments are designed to detect changes in physiological parameters of the CNS rather than to measure a specific cognitive function, these tests will respond to almost any psychoactive drug, not just MDMA.

Endocrine effects were limited to the evaluation of plasma cortisol and prolactin measurements. Results were as may be expected from a primary serotonin-releasing agent: the increase in cortisol levels was more robust than that of prolactin.

Of the physiological effects that were evaluated, only temperature showed a very weak effect. The implications of this divergent outcome will be discussed later in this section.

A remarkable dose–response association was observed in the cardiovascular measurements, where 1.0 mg/kg showed to be a clear cut-off dose for MDMA to have cardiovascular effects; below 1.0 mg/kg MDMA failed to induce any changes while all the studies that administered more then 1.0 mg/kg MDMA reported significant increases compared to placebo (Fig. 2).

Pupil diameter measurements all proved very sensitive to MDMA. All but one result, linked to a low dose (0.5 mg/kg), were increased after MDMA administration. This measure, although very sensitive, is not specific for MDMA, however, as many agents that interact with the autonomic nervous system cause pupil dilation (Dumont *et al.*, 2005). This limitation holds for all physiological measures which, as discussed in the methods section, devaluates the relevance of these tests. Nevertheless, physiological data are, of course, crucial when formulating safety guidelines.

Clinical research into the actions of psychoactive compounds has a drawback in that the outcomes may not reflect the effects the same drug would induce in 'normal' situations. Clearly, the drug's effects are dependent upon the user's surroundings and mood, factors that are nearly impossible to fully reconstruct in the laboratory. This holds for the current weak temperature-related findings, for example, where robust increases after MDMA administration have been reported: some reports even mentioned ecstasy-induced hyperthermia and fatal complications (Garcia-Repetto *et al.*, 2003; Ravina *et al.*, 2004). It should be noted that animal studies have shown that the effects of MDMA on body temperature are dependent on ambient temperature (Green *et al.*, 2004), where normal room temperature (20–22 °C) proved not to induce any changes in body temperature. As the temperature in clinical laboratories is most likely to be around the 20 °C mark, the studies conducted in this setting will inherently not show a significant effect of MDMA on body temperature.

On a related note, the scale cluster Anxiety showed an increase, which seems to conflict with the drug's overall subjective profile of pleasurable, desired effects. However, this unexpected effect may be associated with the unusual circumstances the participants found themselves in, which may have caused considerable psychological stress. Also, the cluster contains data of studies with MDMA-naive volunteers in whom the unfamiliar experience with the drug might have translated into anxiety. Yet, an analysis of the anxiety scores of the subgroup of MDMA-familiar volunteers still yielded a 58% increase. Similarly, the Social-interaction scores did not increase as much as as we had expected from this entactogenic drug. Again, for social interactions to increase, circumstances and surroundings are crucial, making it plausible that the laboratory conditions also depressed this characteristic property of MDMA.

Psychopharmacological research into the acute effects of drugs in humans is heavily dependent on the tests that are employed.

With this in mind it is important that validated test batteries are used that can detect alterations in the broad range of CNS functions. This would vastly improve the transparency of experimental findings and facilitate the comparison and generalization of results obtained in clinical trails with psychoactive compounds. Although advances have been made, to date no such generally approved compendium of tests that is both sensitive to stimulation and sedation of the CNS has been developed. MDMA research of course also suffers from this lack of standardization. On the other hand, in this review firm conclusions were even more hindered by the generally limited number of neuropsychological tests the selected studies employed. Future studies should avoid these shortcomings. Moreover, the authors welcome a broad debate to identify which tests are most sensitive or best suited for detecting improvement or impairment in the several specific areas of cognitive functioning featuring in this report.

The assembled data showed that typical MDMA effects are fully expressed at doses above 1.0 mg/kg, at which level the drug's adverse effects will also manifest themselves. These side effects are addressed in a comprehensive report in which Vollenweider and team review their own work into MDMA (Liechti *et al.*, 2001a). The most prevalent adverse drug reactions were difficulty in concentrating, jaw clenching, lack of appetite, dry mouth/thirst and impaired balance. The effects of MDMA on the body's hydration balance (induction of ADH release) are significant and it is a potent stimulant of the sympathetic nervous system, causing increases in blood pressure, heart rate and perspiration. Since these effects can potentially set off serious complications in susceptible participants, researchers intending to mount clinical trials should be aware of these hazards.

In conclusion, MDMA displays all its prominent features at doses of 1.0 mg/kg and above, which is in line with the desirable doses reported by recreational users (Croft *et al.*, 2001; Soar *et al.*, 2004). The potentially hazardous adverse effects are also fully expressed at this level. In the relevant studies generated by our search of the literature, findings reflecting the subjective (the entactogenic profile), physiological (cardiovascular, pupil diameter) and endocrine effects (cortisol, prolactin) were the most prominent and abundant. MDMA effects on neuropsychological functioning were reported infrequently, thus rendering firm conclusions impossible and supporting our recommendation for more intensive research into the acute cognitive effects of MDMA.

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