

MDMA affects both error-rate dependent and independent aspects of decision-making in a two-choice prediction task

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Abstract

Decision-making, i.e. selecting an action from a number of alternatives when the outcome is uncertain, is a complex process that is important for everyday life. 3,4-Methylenedioxymethamphetamine (MDMA), also known as 'Ecstasy', is a widely used recreational drug that is known to increase serotonin (5-HT) and, to a lesser extent, dopamine (DA) in animals. This study examined whether MDMA alters decision-making in a way that depends on the *degree of success* and outcome.

Forty-two normal, healthy volunteers were given placebo or 1.5 mg/kg p.o. MDMA in a randomized crossover design. Subjects completed the two-choice prediction task 120 min after administration of the drug. Decision-making characteristics were obtained at 20% error rate, 50% error rate or 80% error rate.

MDMA affected decision-making via a process that is dependent on success or failure. Administration of MDMA increased the degree to which the previous response predicted the current response (mutual

information) and the average response sequence predictability (average dynamical entropy) at low error rates. MDMA increased the degree to which the previous stimulus influenced the selection of the current response at 20%, 50% or 80% error rate. MDMA did not significantly alter basic response characteristics such as response latency or switching. Self-assessment of the psychological state induced by MDMA did not predict the MDMA induced decision-making patterns.

These results support the hypothesis that acute administration of MDMA affects success-related response selection during decision-making.

Keywords

3,4-Methylenedioxy-N-methylamphetamine, MDMA, Ecstasy, serotonin, decision-making, two-choice prediction task, sequential behaviour, human

Introduction

3,4-Methylenedioxymethamphetamine (MDMA), also known as 'Ecstasy', is a widely used recreational drug that is known to increase serotonin (5-HT) and, to a lesser extent, dopamine (DA) in animals. Animal studies have shown that both serotonin and dopamine are critical in modulating key cognitive processes such as attention and working memory (Roberts *et al.*, 1994; Robbins, 1997). In humans, there is some evidence that both dopaminergic and serotonergic modulation affects impulsivity (Rogers *et al.*, 1999a) and working memory (Mehta *et al.*, 2001). In controlled studies, MDMA produces feelings of well-being and euphoria, moderate derealization, depersonalization as well as heightened sensory awareness in healthy human subjects (Vollenweider *et al.*,

1998, 1999b; De la Torre *et al.*, 2000). MDMA produced no hallucinations and only moderately increased psychomotor drive (Vollenweider *et al.*, 1998; Liechti *et al.*, 2001a). Previous pretreatment studies using 5-HT re-uptake inhibitors and 5-HT₂ antagonist support the hypothesis that the psychological effects of MDMA are mediated primarily via the serotonergic system (Liechti *et al.*, 2000a, b; Liechti and Vollenweider, 2000). MDMA's effects on cognition, however, and information processing are less well understood.

MDMA not only has profound experiential effects but also affects information processing in both humans (Liechti *et al.*, 2001b) and animals (Martinez and Geyer, 1997). Specifically, a typical recreational dose of MDMA (1.7 mg/kg, orally) increased prepulse inhibition of the acoustic startle reflex, an operational

measure of sensorimotor gating, in subjects experiencing robust psychological effects (Vollenweider *et al.*, 1999b). In comparison, habituation was not altered by MDMA, although MDMA-induced individual differences on habituation and experiential symptoms were inversely correlated (Liechti *et al.*, 2001b). Moreover, MDMA did not significantly alter inhibition as measured by the Stroop task (Vollenweider *et al.*, 1998). These results support the hypothesis that MDMA may affect some but not all aspects of cognition and information processing.

Decision-making is a complex process and involves many functions. In general, decision-making occurs whenever a person has an option to select among several available alternatives that can be associated with positive or negative outcomes, which may be uncertain. One way to probe decision-making behaviour is to use a simple experimental paradigm such as the two-choice prediction task. This task examines how subjects make predictions, i.e. select an action based on an anticipated outcome that has been derived from a history of prior experiences, in the presence of 'random' feedback. Under these circumstances, subjects will generally select the response according to the anticipated reinforcement, i.e. how frequent a response resulted in a successful prediction, which is consistent with previous studies (Calfee and Atkinson, 1966; Ludvigson, 1966; Goulet and Barclay, 1967). This behaviour corresponds to the well-known matching law that has been observed in a large number of animal studies (Herrnstein *et al.*, 1997). Decision-making in this task is comprehensively quantified by the degree to which a response sequence is predictable, the frequency of high and low predictable response sequences, and the degree to which the previous response and the previous stimuli influence the current response (Paulus *et al.*, 1999). Using these measures, the response sequences of normal volunteers are characterized by a non-random complex sequential structure even in the presence of random reinforcement (Paulus, 1997).

Behavioural characteristics during decision-making may be critically affected by ascending dopaminergic and serotonergic systems (Robbins *et al.*, 1998; Rahman *et al.*, 2001). Therefore, acute administration of MDMA may result in changes of strategies underlying decision-making in a simple two-choice prediction task. Specifically, an increased serotonergic tone and associated feeling of well-being that is observed with MDMA may lead to an altered response to success or failure in the immediate environment. If this were true, one would expect that decision-making is particularly affected when predictions are frequently incorrect. Accordingly, if MDMA were to lower the effects of prediction failures during decision-making, one would expect to observe an increased effect at high error rates. Conversely, if MDMA were to increase the effect of prediction success, one would predict the strongest effect of MDMA when predictions are frequently correct. Alternatively, if MDMA affects decision-making via a process that is independent of success or failure, one would predict that MDMA changes the behavioural characteristics independent of error rates. To examine these hypotheses, MDMA was administered in a randomized crossover design, while subjects completed the two-choice prediction task that contained three blocks with different error rates, i.e. 20% errors, 50% errors or 80% errors.

Materials and methods

Subjects

The Ethics Committee of the University Hospital of Psychiatry, Zurich, approved the study and the Swiss Federal Health Office, Department of Pharmacology and Narcotics, Berne authorized the use of MDMA. Forty-four healthy volunteers were recruited from University Hospital staff and at the Medical School of the University of Zurich. Some subjects had minimal prior drug experiences (once or twice, all more than 6 months prior to the study); all other subjects were drug-naïve. Specifically, 20 of the 42 subjects had tried cannabis, five MDMA, nine a hallucinogen, three were light smokers. None of the subjects had used d-amphetamine or cocaine. All volunteers gave their written consent after being informed through a written and oral description of the aim of the study, the procedures involved, and the effects and possible risks of MDMA administration. Subjects were healthy according to medical history, clinical examination, electrocardiography and blood analysis, and were screened by psychiatric interview to exclude those with personal or family (first-degree relatives) histories of major psychiatric disorders. Subjects with regular alcohol or substance abuse were excluded.

Drug

Racemic MDMA was obtained through the Swiss Federal Health Office, Department of Pharmacology and Narcotics, Berne, and prepared as capsules of 10 and 50 mg. Subjects received MDMA at a moderate dose of 1.5 mg/kg PO. This dose of MDMA is known to have robust psychological effects (Vollenweider *et al.*, 1998). The dose was also carefully evaluated to minimize possible risks and is unlikely to produce lasting harmful effects (Lieberman and Aghajanian, 1999; Vollenweider *et al.*, 1999a, 2001).

Experimental protocol

This study was part of a larger series of experiments examining the effects of dopaminergic and serotonergic blockers on the acute administration of MDMA. For this investigation, only subject data from the placebo and acute MDMA condition of these experiments were used. Details of these experiments have been published elsewhere (Liechti *et al.*, 2001b). Specifically, of the 44 subjects, 16 received the selective serotonin uptake inhibitor citalopram as pretreatment (12 male, four female; mean age 27 years, range 21–39); 14 received the D₂ dopamine antagonist haloperidol as pretreatment (nine male, five female; mean age 26 years, range 21–38); 14 subjects received the 5-HT_{2A/C} antagonist ketanserin as pretreatment (13 male, one female; mean age 26 years, range 21–41). Subjects received each treatment condition (placebo, MDMA, dopaminergic or serotonergic blocker, and combination) in randomized and counterbalanced order separated by a 2–4 week interval to avoid carry-over effects. A between-subjects ANOVA (factor: experiment) was used to determine whether participation in a particular blocker experiment affected the behavioural results of the placebo or MDMA condition. This

analysis showed that placebo and MDMA effects did not differ significantly across experiments. Therefore, all subsequent analyses were based on the data from the placebo and MDMA condition only. Behavioural testing was conducted between 90–120 min after administration of the second placebo dose or MDMA. Psychometric data and decision-making measures were available from 42 subjects (32 male: mean age 27.0 years, ± 6.1 ; and ten female: mean age 25.4 years, ± 3.5). Data on the startle response findings have been reported elsewhere (Liechti *et al.*, 2001b).

Sessions were conducted in a calm and comfortable laboratory environment. Participants were told to abstain from alcohol the day prior to each session and not to drink caffeine-containing beverages or to eat two hours prior to each session. The three light smokers were told to maintain their usual smoking habits, but did not smoke during sessions. After receiving placebo or the corresponding blocker pretreatments, subjects received placebo or MDMA in capsules (10 AM). Psychometric ratings and the two-choice prediction task were performed 120 min after MDMA/placebo intake, to coincide with the peak effect of MDMA. After the acute effects of MDMA had subsided completely, subjects remained in the hospital for another 2 h and were monitored clinically.

Two-choice prediction task

The two-choice prediction task has been used by several investigators to examine decision-making (Frith and Done, 1983; Lyon *et al.*, 1994; Paulus *et al.*, 1994) and has been described in detail elsewhere (Paulus, 1997). The basic goal in this task is to predict where a stimulus will be presented on a computer screen. The subject is given no predictive information and has to decide based on the history of preceding responses and outcomes. Briefly, a house flanked by a person to the left and right is shown on a computer screen. The goal for the subject is to respond in such a way that a person on the computer screen can meet up with a car that is presented on the far left or right side of the screen. The subject is told to decide on which side the car will be presented. After the subject has made a response, the car is presented for 300 msec on the far left or right side. If the selected response matches the side where the car is presented, the person on the selected side meets up with the car. Unbeknownst to the subject, the car is presented according to a pre-determined schedule. Specifically, a computer program, which takes the response of the subject into account, determines whether a response will be 'correct' or 'incorrect'. The two-choice prediction task was divided into three trial-blocks. During the first trial-block, which lasted 128 trials, the computer program assured that 50% of all responses were 'correct'. During the second trial-block, which consisted of 64 trials, 20% of all responses 'correctly predicted' the location of the car, and during the third trial-block, which comprised 64 trials, 80% of all responses were 'correct' predictions. Therefore, the trial-blocks correspond to 50%, 80% and 20% error rate, respectively.

Measures

The non-linear approach to analyse the sequences of responses during the two-choice prediction task are described in detail else-

where (Paulus, 1997). For the two-choice prediction task the following variables were recorded: (1) the choice selected by the subject (*left* or *right*), (2) the computer-selected response (*left* or *right*) and (3) the latency to select a response (time from the presentation of the current situation to the selection of the response). Based on these variables, the strategies of decision-making in the presence of uncertainty were assessed by three sets of measures: (1) General response biases: the number of *left* or *right* responses or *stay* (a *left* response followed by *left* response), versus *switch* (*left* followed by *right* response) responses. (2) The degree to which the current response is determined by the previous response (mutual information), the previous stimulus (cross-mutual information) or a combination of both (win-stay/lose-shift mutual information) is quantified by mutual information measures (Heizel and Grosse, 1995). (3) The predictability of the response sequence measured by the average entropy and the range of subsequent fluctuations between highly predictable and highly unpredictable response sequences, which operationally defines the degree of response dysregulation during the two-choice prediction task.

Psychological ratings

The Adjective Mood rating scale (AM) (Janke and Debus, 1978) and the Altered State of Consciousness (ASC) rating scale (Dittrich *et al.*, 1985; Dittrich, 1998) were used to assess psychological peak drug effects of MDMA. Both the AM and ASC scales had previously been shown to be sensitive to psychological effects of MDMA in humans (Vollenweider *et al.*, 1998). The AM questionnaire was used to access 'efficiency-activation', 'self-confidence', 'heightened mood', 'apprehension-anxiety', 'depressiveness', 'thoughtfulness-contemplativeness', 'extroversion', 'introversion' and 'emotional excitation'. The ASC rating scale is a visual-analogue scale that measures alterations in waking consciousness, including changes in mood, perception, experience of oneself and of the environment, as well as thought disorder. The ASC questionnaire consists of three scales comprising several item clusters. (1) OB ('oceanic boundlessness'), measures derealization and depersonalization accompanied by changes in effect ranging from heightened mood to euphoria and/or exaltation, and alterations in the sense of time. The corresponding item clusters are 'positive derealization', 'positive depersonalization', 'altered sense of time', 'positive mood' and 'mania-like experience'. (2) AED ('anxious ego dissolution') measures ego-disintegration associated with loss of self-control, thought disorder, arousal and anxiety. The item clusters are 'anxious derealization', 'thought disorder', 'delusion', 'fear of loss of thought control' and 'fear of loss of body control'. (3) VR ('visionary restructuration'), includes the item clusters 'elementary hallucinations', 'visual (pseudo-) hallucinations', 'synesthesia', 'changed meaning of percepts', 'facilitated recollection' and 'facilitated imagination'.

Statistics

Data were analysed using STATISTICA 5.5 (StatSoft%) for Windows (StatSoft, 1995). A two-way within-subjects analysis of

variance (ANOVA) with treatment (placebo versus MDMA) and error rate (20%, 50%, 80%) as repeated measures was used to assess whether MDMA affected decision-making in an error-rate related manner. The effect of MDMA on psychological measures (ASC and AM dimensions) was analysed by two-way ANOVAs with treatment (placebo versus MDMA) and psychological dimensions as repeated measure factors. Based on significant main effects or interactions, Tukey's post hoc comparisons were performed.

Furthermore, to control for potential order or carry-over effects of prior drug administration respectively, a two-way ANOVA with pretreatment condition (placebo or blocker) as between-subject factor and error rate as within-subject factor (20%, 50% and 80%) for the 'placebo-placebo' alone and for the 'placebo-MDMA' alone decision-making condition was conducted. This analysis revealed that there was no difference in the effects of MDMA on decision-making measures as well as on any psychological scores between those subjects receiving 'placebo plus MDMA' first and those receiving a 'blocker plus MDMA', 'blocker plus placebo' or 'placebo plus placebo' first (data not shown). And vice versa, the same analysis revealed that there was no difference in the 'placebo-placebo' decision-making values or psychological scores between those subjects receiving 'placebo plus placebo' first and those receiving 'blocker plus placebo', blocker plus MDMA or 'placebo plus MDMA' first (data not shown). Thus all of the 42 'placebo-placebo' and 'placebo-MDMA' condition were pooled for the current analysis. Multiple step-wise regression analysis was used to assess whether the psychological effects predicted changes in decision-making behaviour. The criterion for significance was set at $p < 0.05$.

Results

Choice task: MDMA compared to placebo

The first set of analyses evaluates simple behavioural characteristics on the two-choice prediction task of subjects after administration of MDMA or placebo. The results reveal similar effects of error-rate on response switching in both conditions. As shown in Fig. 1B, the degree of switching between alternative responses on successive trials was proportional to the error rate. Specifically, there was a main effect of error rate on the frequency of response switching (main effect [$F(2,78) = 35.5$; $p < 0.0001$], Tukey's post hoc tests $p < 0.001$) but there was no main effect of drug [$F(1,39) = 2.5$; $p < 0.12$]. There was no significant interaction between error rate and drug [$F(2,78) = 0.85$; $p < 0.4$]. Subjects took longer to select a response at 50% error-rates, i.e. when the outcome was most uncertain [$F(2,78) = 23.9$; $p < 0.0001$], however, there was no main effect of MDMA [$F(1,39) = 0.05$; $p < 0.8$] or a significant interaction between error rate and drug treatment (Fig. 1A).

The second set of analyses evaluates the effect of MDMA on rigidity of decision-making. First, response rigidity, as measured by the mutual information, quantifies the predictability of the current response by the previous response, and, second,

stimulus-response rigidity, as measured by the cross-mutual information, quantifies the degree to which the previous stimulus predicts the current response. Response rigidity was affected by MDMA in an error-rate related manner. The selection of an action during the two-choice prediction task was most predictable at low error-rates [$F(2,78) = 4.84$; $p < 0.01$], this effect was amplified by MDMA resulting in an interaction between error-rates and drug treatment [$F(2,78) = 3.5$; $p < 0.037$], Fig. 1C). In comparison, MDMA significantly affected stimulus-response rigidity in an error-rate independent manner. Specifically, the presentation of the previous stimulus was more likely to predict the selection of the current response after administration of MDMA relative to placebo [$F(1,39) = 12.5$; $p < 0.001$] (Fig. 1D).

The third set of analyses examines whether MDMA changes the sequential structure of decision-making, i.e. how subjects generate and change strategies underlying the response selection during decision-making. A strategy refers to selecting a particular sequence of choices more often than would be expected by chance or avoiding a sequence such that it occurs less often than predicted by chance. The number of different strategies is estimated from average dynamical entropy. At low error rates, irrespective of pre-treatment, subjects utilized fewer different strategies, which resulted in an increased average predictability as measured by a decrease in dynamical entropy [$F(2,78) = 62.0$; $p < 0.01$]. MDMA affected the degree to which the sequence of response can be predicted in an error-rate related manner [$F(2,78) = 4.8$; $p < 0.01$]. At low error rates, subjects were more predictable after administration of MDMA relative to placebo (post hoc $p < 0.002$, Fig. 1E). Finally, the fluctuations between highly predictable and highly unpredictable response sequences quantifies how frequently subjects switch between different strategies. At low error rates, subjects were less likely to switch between strategies, which resulted in an increased spread between highly predictable and highly unpredictable choice sequences [$F(2,78) = 20.9$; $p < 0.01$]. As shown in Fig. 1F, MDMA did not affect the degree of switching between strategies in an error-rate related (main effect of drug: [$F(1,39) = 0.3$; $p < 0.6$]) or error-rate independent manner (error-rate by drug interaction: [$F(2,78) = 1.4$; $p < 0.3$]).

Psychological effects: MDMA compared to placebo

As previously reported in detail, MDMA (1.5 mg/kg) produced an affective state of positive mood, small-to-moderate derealization, heightened sensory awareness and a slight increase in psychomotor drive (Liechti *et al.*, 2001b). Subjective effects of MDMA began 45–60 min after drug intake, peaked at 90–120 min, and lasted for 1–2 h. Thus two-choice decision testing was done during the peak drug effect.

The subjective effects of MDMA and placebo are summarized in Table 1. MDMA significantly increased all ABZ scores (main effect of drug [$F(1,41) = 46.9$; $p < 0.001$], main effect of ABZ dimensions [$F(1,82) = 43.3$; $p < 0.001$], and interaction treatment $\times$ ABZ dimension [$F(1,82) = 43.8$; $p < 0.001$]. Tukey's post hoc test of the treatment $\times$ dimension interaction revealed that the increase in OB, AED and VR was significant. Subscale score analysis revealed that MDMA-induced elevation in OB scores was

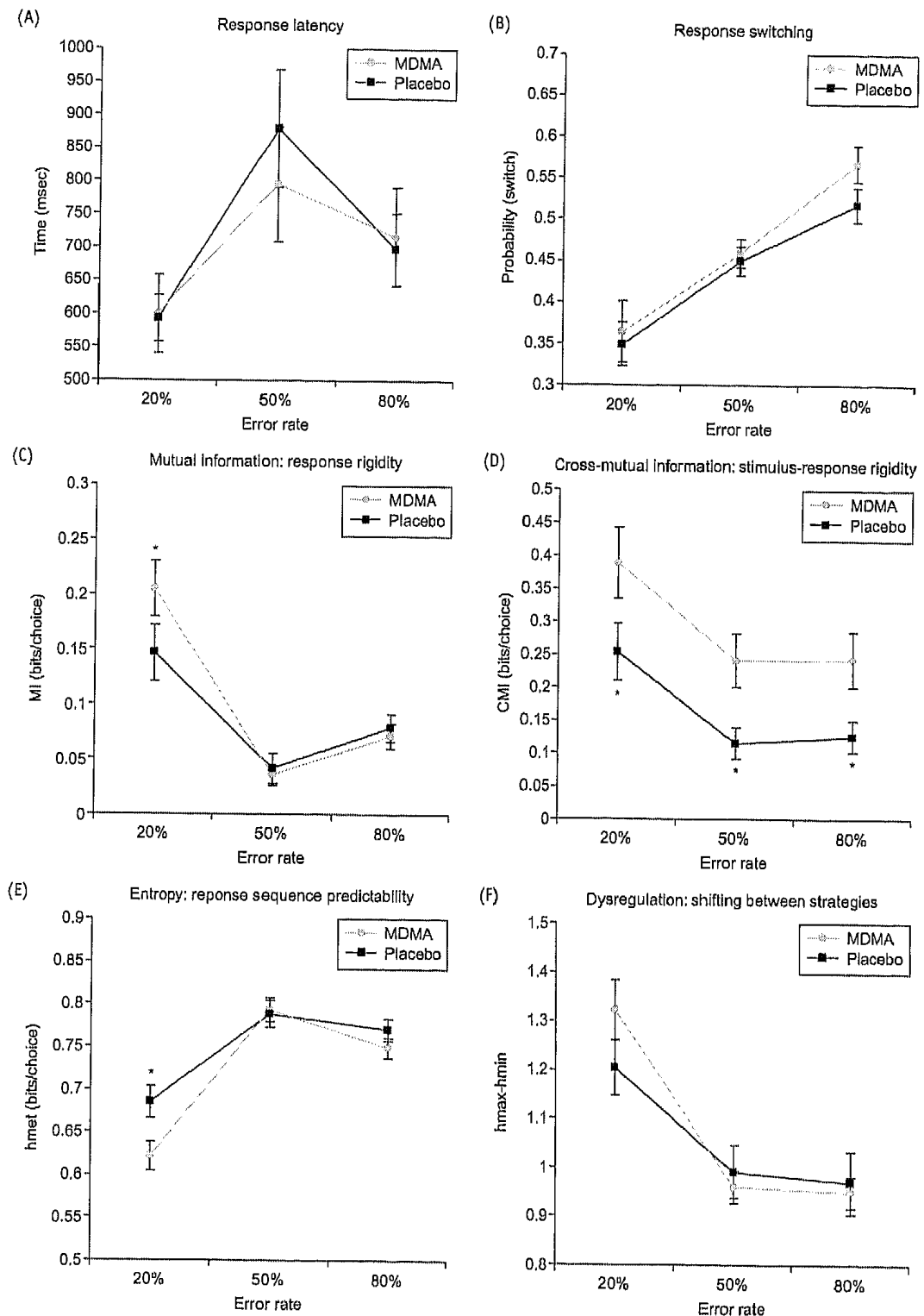


Figure 1 This figure summarizes the behavioural effects of MDMA on the two-choice prediction task. The average and standard error of mean (SEM) are shown for the response latency (A), probability of response switching (B), mutual information (C), cross-mutual information (D), average dynamical entropy (E), and the degree of response dysregulation (F) (* $p < 0.05$)

Table 1 Psychometric scores ($n = 42$)

	Placebo		MDMA	
	Mean	SD	Mean	SD
<i>ASC scale</i>				
OB (oceanic boundlessness; sumscore)	5.81	2.60	626.43***	83.84
positive derealization	0.31	0.21	83.52	16.42
positive depersonalization	1.38	0.78	131.36	24.05
altered time sense	0.88	0.57	70.19	12.11
positive mood	2.43	1.11	245.45	27.66
mania-like symptoms	0.81	0.46	95.90	15.08
AED (anxious ego-dissolution; sumscore)	4.60	1.90	226.36***	41.15
anxious derealization	1.86	1.45	30.31	9.82
thought disorder	0.60	0.37	79.52	14.83
paranoia	0.00	0.00	12.38	6.72
fear loss of thought control	0.40	0.27	33.98	10.01
fear of loss of body control	0.88	0.50	42.02	9.62
VR (visionary restructuring; sumscore)	1.69	0.88	161.12***	38.80
elementary hallucinations	0.07	0.07	18.36	5.74
visual (pseudo) hallucinations	0.10	0.07	9.55	5.19
synesthesias	0.00	0.00	19.55	6.20
changed meaning	1.71	0.87	85.52	14.97
facilitated recollection	0.10	0.10	26.17	8.26
facilitated imagination	0.57	0.46	30.12	7.82
<i>AM mood rating</i>				
Efficiency-activation	3.06	0.41	3.93	0.48
Self-confidence	4.33	0.39	6.33***	0.26
Heightened mood	5.40	0.50	8.14***	0.41
Apprehension-anxiety	0.13	0.06	0.64	0.20
Depressiveness	0.32	0.15	0.75	0.23
Thoughtfulness-contemplativeness	0.79	0.17	2.60***	0.32
Extroversion	3.62	0.32	5.30***	0.25
Introversion	0.40	0.20	1.10	0.32
Emotional excitation	0.70	0.25	4.22***	0.59

Significant changes from placebo are indicated by *** for $p < 0.001$ (Tukey's *post hoc* test).

due mainly to increases in 'positive mood', positively experienced 'depersonalization' and euphoria. The increase in AED scores was due mostly to 'thought disorder' and slight 'fear of loss of body control'. Thought disturbances were moderate and mostly included difficulty concentrating and accelerated thinking. Increases in VR scores were slight and mainly attributable to 'changes in the meaning of percepts', 'facilitated recollection' and 'facilitated imagination'. No hallucinations were reported, but subjects described an intensification of sensory perception.

MDMA also affected several dimensions of the AM rating scale (main effect of drug [$F(1,41) = 63.2$; $p < 0.001$], main effect of AM dimensions [$F(8,328) = 83.9$; $p < 0.001$] and interaction treatment $\times$ AM dimension [$F(8,328) = 8.3$; $p < 0.001$]). Tukey's *post hoc* test of the treatment $\times$ dimension interaction revealed that MDMA significantly increased the scores for 'self-confidence', 'heightened mood', 'extroversion', 'emotional excitation' and

'thoughtfulness-contemplativeness'. MDMA had no significant effect on 'apprehension-anxiety' or depressiveness (Table 1). Although female subjects tended to have higher scores on some psychological measures, there were no significant gender differences in subjective responses to MDMA in this study.

Multiple step-wise regression analyses were conducted to examine whether psychological changes induced by MDMA were associated with the effect of MDMA on decision-making. Specifically, overall changes in ASC scores (OB, VR and AED) as well as the AM scores were used to predict changes in cross-mutual information and mutual information induced by MDMA across the three reinforcement conditions. Neither ASC scores ($[F(3,38) = 2.6$, NS]) of the multiple regression analyses for 50, 20 and 80) nor AM scores ($[F(3,38) = 0.6$, NS]) of the multiple regression analyses for 50, 20 and 80) were able to predict changes in cross-mutual or mutual information.

Discussion

As expected and detailed elsewhere (Vollenweider *et al.*, 1998; Liechti *et al.*, 2001b), MDMA elicits an affective state of positive mood characterized by feelings of euphoria, increased self-confidence and extroversion combined with moderate derealization, heightened sensory awareness and a slight increase in psychomotor drive. During this state, subjects' decision-making characteristics were assessed using the two-choice prediction task. It was hypothesized that, if MDMA's effect were due to an increased effect of failure information on response selection during decision-making, one would expect to find an increased change in behaviour at high error-rates. Alternatively, if MDMA's effects were due to an increase of success information on response selection during decision-making, differences should be observed predominately at low error rates. The main results of this investigation provide support for the latter but not the former hypothesis. Specifically, MDMA increased response rigidity as measured by mutual information and reduced the number of different strategies as measured by dynamical entropy at low error-rates. In addition, MDMA also affected decision-making in an error-rate independent manner. Specifically, MDMA increased the degree to which the previous stimulus influenced the selection of the current response irrespective of error rate. MDMA did not significantly alter basic response characteristics such as response latency or switching. Finally, neither the error-rate dependent nor the error-rate independent changes induced by MDMA were associated with the self-assessed psychological changes.

This investigation provides the first evidence that acute administration of MDMA affects decision-making cognition. In particular, some effects of MDMA were dependent on the degree of success or failure, whereas others were not. Specifically, ongoing response strategies, response-response interactions and the association between sequences of responses, on decision-making were particularly affected when the error-rate was low. This is consistent with the hypothesis that MDMA enhances the success-related effects on response selection during decision-making. The current results support the general hypothesis that MDMA affects response rigidity only when there is a high propensity to select a response that generates a correct prediction but also increases the effect of external stimuli. These two effects are not mutually exclusive or contradictory. In fact, an increase in mutual information at low error rates may point towards the increased effect of positive reinforcement (correctly predicting the outcome) by MDMA. Similarly, the increase in cross-mutual information independent of error rate supports the idea that this increase in stimuli is not only due to correct versus incorrect performance. If the error-rate related change were due to a serotonergic mechanism, one would expect to see a reversal of the increased predictability at low error rates by serotonin-selective re-uptake inhibitors or by serotonin receptor antagonists.

Recent studies have shown that serotonin may be critical for stimulus-reward associations (Rogers *et al.*, 1999a) as well as learning and memory tasks (Park *et al.*, 1994). Thus, an increase of serotonin may result in an increased effect of success on subsequent behaviour, which could result in increased response rigid-

ity at low error rates and in an increase of stimulus-response rigidity independent of error rates. In comparison, the MDMA induced effects on decision-making during the two-choice prediction task are not consistent with an altered attention to the task. For example, if the subject were to disengage from the ongoing task and simply respond by 'randomly' pressing the LEFT or RIGHT response, one would expect to see a decrease in cross-mutual information, an increase in dynamical entropy, and a decrease in mutual information. Alternatively, if subjects were to simply repeat responses or alternate between responses, one would expect to find an alteration in response bias measures (response switching, probability of right response) and an increase in mutual information or a decrease in the dynamical entropy. The current pattern of results, however, is most consistent with the notion that acute administration of MDMA enhances the effect of stimuli in general and of success-related outcomes in particular on response selection during decision-making.

The changes in psychological state induced by MDMA were not able to predict the patterns of responses during the decision-making tasks. Decision-making, the act of making up one's mind, refers to the process of forming preferences, selecting actions and evaluating outcomes. Decision-making is an iterative process, i.e. the current stage of decision-making is influenced by the history of preceding stages and directly influences the subsequent stages of processing. Sequential patterns of action selection emerge that follow two main principles. First, individuals organize their response patterns according to the previous history of their own actions, which results in non-random sequences of choices (Hodge and Riege, 1966; Restle, 1966; Paulus, 1997). Second, the history of positive versus negative action-outcome sequences predicts the probability of future action selection according to the generalized matching law (Prelec and Herrnstein, 1978; Herrnstein, 1990). Often, individuals are not aware of the strategies they employ in decision-making situations; therefore, the divergence of self-assessment and the behavioural changes during decision-making may be due to the fact that the decision-making changes are not consciously experienced by the subject. Alternatively, the psychological effects of MDMA may be dissociable from the effect on decision-making cognition. If this were true, one could speculate that these effects may be mediated by different neural systems and may be altered by a different set of receptor antagonists.

These effects of MDMA on the characteristics of human response sequences during a simple decision-making task are reminiscent of the effects of MDMA on the sequential structure of locomotor behaviour in rodents (Paulus and Geyer, 1992). Specifically, rats when treated with MDMA show a dose-dependent increase in repetitive straight and highly predictable movement patterns along the periphery of an enclosure. One possible explanation put forth for this thigmotaxis, or wall-hugging, behaviour has been the continued exposure of the animal's whiskers to the wall thereby providing continued sensory input to the animal. The increase in stimulus-contingent responding during the two-choice prediction task may represent an analogous behaviour in humans.

A distributed neural network mediates decision-making. For example, self-generated, as opposed to cue-generated, actions involve the activation of dorsolateral prefrontal cortex and anterior

cingulate (Frith *et al.*, 1991). Activity associated with anticipating a gaze response in a decision-making task was found in individual neurons in BA 9 and 46, i.e. the dorsolateral prefrontal cortex (DLPFC) (Kim and Shadlen, 1999). Activity of single neurons in the lateral parietal area was associated with selecting a response in a decision-making task in a reinforcement and reward-related manner (Platt and Glimcher, 1999). Explicit hypothesis testing in a two-choice decision-making task was associated with a significant activation of the left anterior cingulate, right precuneus, right thalamus, left inferior frontal gyrus and cerebellum (Elliott and Dolan, 1998). In a recent imaging study using functional Magnetic Resonance Imaging (fMRI) both right ventromedial and dorsolateral prefrontal cortex were activated in a two-choice guessing task relative to a choice reporting task (Elliott *et al.*, 1999). In a gamble task, Rogers *et al.* (1999b) found a discrete increase in blood flow in right inferior and orbital prefrontal cortex (BA 10, 11) and in the anterior portion of the inferior frontal gyrus (BA 47). Normal comparison subjects showed a task-dependent activation of the inferior prefrontal, parietal, and cingulate cortex during the two-choice prediction task (Paulus *et al.*, 2001). These cellular and neuroimaging studies support the hypothesis that decision-making involves prefrontal, parietal and cingulate cortex neural network. Moreover, the differences in task-related activation between methamphetamine dependent and normal comparison subjects in both dorsolateral prefrontal (BA 9) and orbitofrontal areas (BA 11) are consistent with previous studies, which show that these areas are critical for decision-making (Elliott *et al.*, 1997; Rogers *et al.*, 1999b, 2000), task-related reward contingencies (Elliott *et al.*, 1999), and violation of expectations (Nobre *et al.*, 1999). In summary, the two-choice prediction task involves a distributed neural system that is sensitively affected by chronic use of stimulants. Moreover, using water-labelled PET, MDMA has also been shown to affect the activity level of parts of this neural system. Specifically, MDMA administration in healthy volunteers increased neuronal activity in ventromedial prefrontal cortex, ventral anterior cingulate, inferior temporal cortex, and cerebellum and decreased activity in dorsal anterior cingulate, insula, left amygdale, and dorsomedial thalamus (Gamma *et al.*, 2000). Therefore, there is converging evidence from behavioural data and functional neuroimaging that supports the general hypothesis that the effect of stimulus-related information may be affected by modulating the fronto-parietal and cingulate decision-making network.

In summary, acute administration of MDMA significantly affects success-related response selection during decision-making by decreasing entropy and increasing mutual information during decision-making at low error rates and by increasing the stimulus-response rigidity independent of error rates. Future studies will determine whether this effect is related to MDMA's effect on increasing serotonin and whether it can be localized within a circumscribed part of the neural system underlying decision-making.

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