The Influence of MDMA on Cognition and Psychomotor Function, and the Importance for Driving Capacity

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Abstract
In this study the influence of single doses of MDMA 75 mg and alcohol 0.5 g/kg on cognitive and psychomotor performance was assessed in 12 healthy recreational MDMA users. A single recreational dose of MDMA improved tracking performance under single and double task conditions. Movement speed in the choice RT paradigm improved increased after MDMA, while the ability to estimate time to collision was impaired after MDMA. Alcohol impaired tracking performance 1 and 2 hrs after alcohol but returned to baseline levels 3 and 5 hrs after drinking. While MDMA produced both stimulating and impairing effects on skills related to driving, it is concluded that further research employing real driving paradigms and interaction studies with alcohol and possibly THC are needed.

Introduction
(±)-3,4-Methylenedioxymethamphetamine (MDMA; ecstasy), is a commonly used psychoactive recreational drug related to mescaline and stimulant drugs such as amphetamine (1,2). Surveys among young people visiting raves, indicate that as much as 64-96% of visitors of raves and big parties uses ecstasy (3,4). Up to 60% of the people that planned to drive a motorized vehicle after a rave were under the influence of ecstasy (3). Not much is known about the influence of MDMA on driving performance but case reports seem to justify concern about traffic safety behavior and involvement in traffic accidents after the use of MDMA (5). Driving performance consists of a complex combination of cognitive and psychomotor functions. MDMA is often associated with poor cognitive function. Cognitive impairment, such as memory impairment in abstinent users has been demonstrated in many studies (6,7) but only a few studies addressed the acute effects of MDMA on cognition and psychomotor function. When acute effects of ecstasy were studied under uncontrolled circumstances at a party, a significant reduction in verbal recall and visual scanning was observed (8). In studies conducted under controlled conditions a single dose of MDMA (range 0.9 – 1.9 mg/kg) did not affect immediate recall, digit repetition and selective attention. One prior placebo-controlled study addressed the acute effects of MDMA on psychomotor performance. No effect of a single dose of MDMA (75 or 125 mg) on simple reaction time was observed (9).
The current study investigated the acute effects of a recreational dose of MDMA (75mg) on psychomotor and cognitive performance, vital signs, mood and cortisol concentrations in recreational ecstasy users under experimentally controlled conditions. The tests described in this abstract comprise a variety of tasks measuring skills related to driving. They have been previously shown to be sensitive to a variety of psychoactive drugs (10). Furthermore an effort is made to investigate the relation between MDMA concentrations and task performance, physiology and mood. Alcohol treatment was implemented in the design as an active control.

**Methods**

**Design & procedure**

The study was conducted according to a placebo controlled, 3-way crossover, double blind, and double dummy design. Subjects underwent all 3 treatment conditions on three separate days, spaced at least two weeks apart, receiving placebo, alcohol or MDMA. Twelve healthy recreational MDMA and alcohol users, with no current or history of physical or psychiatric disease, completed the study. Drug use was prohibited throughout the study. Before entering a test day subjects were tested for recent drug use and females were also tested for pregnancy using a urine drugs screen and urine pregnancy test. Before treatment administration subjects consumed 2 sandwiches for lunch. Throughout the day subjects had free access to water, isotonic drinks, orange juice and sugar free chewing gum. At 1.15 p.m. subjects received study treatments. Placebo was administered as 400 ml orange juice and 25 ml bitter orange syrup. MDMA was administered by replacing part of the bitter orange syrup by MDMA 75 mg. During alcohol administration part of the orange juice was replaced by pure alcohol (.5mg/kg body weight).

**Driving-related task performance:**

The Critical Tracking Test (CTT) measures the ability to control an inherently unstable error signal in a 1st-order compensatory tracking task. Subjects attempt to keep a cursor centered in the middle of a display using a joystick while the cursor tends to move away from the center. The point where the subjects losses control is defined as the critical frequency or lambda-c (λ_c) expressed in radians per second (rad/sec). Theoretically, λ_c is the reciprocal of the operating delay lag in human closed-loop control. The CTT was conducted at 0, 1, 2, 3 and 5 h post treatment.

The Divided Attention Task (DAT) assesses the subjects' ability to divide attention between tracking and monitoring tasks performed simultaneously. The tracking subtask is similar to the CTT, but the error signal velocity is fixed at 50% of individual’s optimal performance during training (λ_c/2). Tracking error is measured as the average absolute distance (mm) between the cursor's position and display center. The other subtask consists of monitoring 24 peripheral LED displays fixed to the corners of the screen, each presenting numerals, 0-9, which change asynchronously every 5 seconds. The subject removes his foot from a pedal as quickly as possible after detecting the target numeral, "2". Median correct reaction time (msec) to targets is the second response measure. The DAT was conducted at 1 and 3 h post treatment.

The Motor Choice Reaction Time (MCRT) is a test in which reaction time (RT) is studied as a function of task complexity. Reaction time is divided into initiation time (time between target and onset of response) and movement time (time of movement execution). The MCRT was conducted at 1 and 3 h post treatment.
The Object Movement Estimation under Divided Attention (OMEDA) task is in essence a task to estimate time to contact (TTC) of a moving object to a specific location. The subject is seated in front of a computer screen on which a yellow circle ocludes the center. The circle varies in size per trial (2, 100 or 200 pixels). From one of the corners, a red dot (target) travels towards the center of the screen and travels underneath the yellow circle and will no longer be visible. The subject estimates when exactly the target reaches the center of the screen by pressing a foot pedal. During the trial, 5 geometrical shapes appear; one on top of the occlusion circle and one in each of the corners. For the secondary task the subject has to press a button in case the geometric shape at the occlusion circle matches one of the others. Absolute TTC error and the number of correct responses to the geometric targets (divided attention) were combined using Z-scores.

The Signal Detection Task (SDT) is a visual search task. Small white squares are presented in a pseudo-random fashion on a computer screen. Twenty squares are randomly assigned being 2.5 cm apart. Squares move to a different location on the screen and subjects are required to respond to the target stimuli, defined as a set of four stimuli forming a square of 2.5 x 2.5 cm, by pressing a button as fast as possible. Sensitivity ($A'$) defined as the non-parametric proportion of correctly identified targets corrected for false positives is the dependent measure.

**Vital signs**
Starting from baseline, pulse rate, blood pressure and body temperature were assessed in a relaxed sitting position every 30 min. until 5.5 h after drug intake, using an automated vital signs monitor (Dinamap 1800 BP; Critikon Inc., Tampa FL and an in-ear thermometer, respectively).

**Pharmacokinetics**
MDMA was determined in plasma, saliva, sweat and urine, at baseline, and every hour until 5 hours after drug intake. All samples were frozen at -20°C until analyzed. Detailed information about the collection and analyses of samples are reported elsewhere (11).
Subject’s breath alcohol concentration (BAC) was assessed every 30 min., starting at baseline until 5.5 h after drug intake, by means of a Lion SD-4 Breath Alcohol Analyzer.

**Statistics**
Dependent variables representing task performance were tested for the main effect and interactions between Treatment and Time using a multivariate repeated measures analysis of variance (General Linear Model). Exceptions occurred for Initiation Time in the MCRT where Task Complexity was added as an extra within subjects Factor. Analyses of performance on the OMDA task were accomplished by entering both dependent variables (TTC error and divided attention error) in a bivariate 3 x 3 (treatment x occlusion diameter) repeated measures design. A polynomial contrast was used for Time and Complexity, while a simple contrast was used for Treatment for univariate comparisons of all drug-placebo differences. Correlations are analyzed using the intra-subject correlations. Pearson’s $r$ of all individual correlations between two factors are averaged and tested for significance using an independent one-sample t-test. The $\alpha$-probability criterion for determining the significance of mean differences and correlation was defined as ($p < .05$).

**Results**
8 Male and 4 female subjects completed the study (mean age 23.5, range 21-30; mean weight 65.9 kg, range 60-73 kg). All subjects used ecstasy (mean lifetime use: 39, range 5-125), marijuana (mean lifetime use: 760, range 3-3500) and alcohol (mean units/week: 17, range 4-50).
Mean plasma C\textsubscript{max} of MDMA was 178 ng/ml (range 85-295 ng/ml) at 3 hours after drug intake. Mean BAC peak concentration was reached 60 minutes after alcohol intake (.31 mg/ml) and during the second repetition of the test battery BAC had dropped to 0.01 g/ml. During last assessments the BAC’s had dropped to 0 in all subjects (12).

**Driving-related task performance:**

Tracking performance in the CTT improved after MDMA as compared to placebo, resulting in higher $\lambda_c$. Alcohol had no main effect on $\lambda_c$. There was an interaction of Treatment by Time between alcohol and placebo caused by the fact that $\lambda_c$ was lower at 1 and 2 h after alcohol relative to placebo, while $\lambda_c$ was higher than post placebo 3 and 5 h after alcohol ($p=.001$). In the DAT, MDMA improved sub-critical tracking performance, represented by tracking error, as compared to placebo. Alcohol did not affect tracking error in the DAT. Movement Time improved after MDMA as compared to placebo (100 and 108 msec respectively while movement time after alcohol (111 msec) did not differ from placebo. There was no effect of MDMA or alcohol on initiation time. In the Omeda task, there was a trend towards an impairing effect of MDMA on performance. MDMA also tended to impair TTC estimation more when occlusion diameter was larger ($p=.066$). Alcohol did not affect TTC error compared to placebo. Alcohol or MDMA did not affect visual search performance on the SDT.

**Table 1:** mean (sd) performance averaged over all assessments after treatment of the CTT, DAT, MCRT and Omeda and the outcome of the univariate analyses under the influence of placebo, alcohol and MDMA ($\uparrow$ = improvement, $\downarrow$ = impairment)

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Placebo</th>
<th>Alcohol</th>
<th>Mdma</th>
<th>Placebo</th>
<th>Alcohol</th>
<th>Placebo</th>
<th>Mdma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracking (CTT)</td>
<td>4.52 (.14)</td>
<td>4.54 (.15)</td>
<td>4.87 (.16)</td>
<td>p=ns</td>
<td>p=.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracking error (DAT)</td>
<td>17.32 (1.25)</td>
<td>18.35 (.94)</td>
<td>15.18 (1.14)</td>
<td>p=ns</td>
<td>p=.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Movement Time (MCRT)</td>
<td>107.6 (5.47)</td>
<td>110.4 (7.27)</td>
<td>99.40 (4.87)</td>
<td>p=ns</td>
<td>p=.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTC error (Z-transformated Units; Omeda)</td>
<td>-.076 (.08)</td>
<td>-.021 (.06)</td>
<td>.103 (.13)</td>
<td>p=ns</td>
<td>p=.055</td>
<td>↓</td>
<td></td>
</tr>
</tbody>
</table>

**Vital signs**

Vital signs, presented by pulse rate, body temperature and blood pressure all rose as a function of MDMA as compared to placebo. Alcohol had no effect of vital signs.

**Correlations**

Intra-subject correlations between the MDMA levels in blood plasma, urine, saliva, sweat and physiology, and performance are presented in table 2.

**Table 2:** the intra-subject correlations between blood plasma, urine, saliva, sweat and body temperature, pulse rate, blood pressure and task performance over all assessments after placebo and MDMA treatment. (Significance: * $p<.05$, ** $p<.001$).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Blood plasma</th>
<th>Urine</th>
<th>Saliva</th>
<th>Sweat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body temperature</td>
<td>.24*</td>
<td>.30**</td>
<td>.20</td>
<td>.20</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>.40**</td>
<td>.39**</td>
<td>.49**</td>
<td>.27*</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>.37**</td>
<td>.39**</td>
<td>.35**</td>
<td>.29**</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>.53**</td>
<td>.49**</td>
<td>.51**</td>
<td>.39**</td>
</tr>
<tr>
<td>Performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical tracking</td>
<td>.32*</td>
<td>.33**</td>
<td>.34*</td>
<td>.27*</td>
</tr>
<tr>
<td>Tracking error</td>
<td>-.37*</td>
<td>-.35*</td>
<td>-.48**</td>
<td>-.37*</td>
</tr>
<tr>
<td>Movement time</td>
<td>-.57**</td>
<td>-.31</td>
<td>-.63**</td>
<td>-.66**</td>
</tr>
<tr>
<td>Time to contact error</td>
<td>.25</td>
<td>.28</td>
<td>.28</td>
<td>.25</td>
</tr>
</tbody>
</table>
Discussion

The purpose of the study was to investigate the effect of a single dose of MDMA 75 mg and a small dose of alcohol .5mg/kg on psychomotor performance, cognition, physiology and mood. An important part of the study was to investigate the influence of MDMA and alcohol on driving related behavior and to make a first attempt to analyze the correlations between MDMA levels and task performance and vital signs. Although there was no main effect of alcohol on $\lambda_c$ and tracking error, there seemed to be an effect of alcohol on tracking performance relative to placebo as indicated by a significant treatment x time interaction. In the CTT $\lambda_c$ was lower after alcohol as compared to placebo1 and 2 h post treatment, indicating impaired performance. When the test was repeated 3 and 5 h post treatment performance on the CTT returned to baseline after alcohol, while performance after placebo seemed slightly impaired. Alcohol had no effect on task performance of the MCRT.

A single dose of MDMA improved psychomotor performance. Critical tracking performance, i.e. $\lambda_c$, increased by 5.6-9.1% as compared to placebo. Tracking error in the Divided Attention Task decreased by 11.4% after MDMA as compared to placebo. In the MCRT, movement time increased after MDMA use, while initiation time –the time between presentation of the target and the onset of responds- was not affected by MDMA. A single dose of MDMA impaired performance on the primary OMDA task, the time to collision (TTC) task. The unique component of the OMDA task is the perception and correct estimation of object movement. After MDMA the error between estimated and actual TTC increased and subjects had more difficulty predicting the TTC as the occlusion of the center of the screen increased in size relative to placebo. The increment in TTC error after MDMA may reflect a disturbance in perception of time and space, also observed by other researchers (13,14). The decreased ability to estimate and predict movement can result in impaired estimation of other traffic movements at crossroads, leading to acceptance of smaller gap between vehicles, indicating increased risk taking behavior. Dangerous driving and accidents after MDMA use have already been reported in the past (5,15).

Furthermore, impaired co-ordination, difficulty concentrating and hallucinations have been observed in people while under the influence of MDMA (13-15). These factors, sometimes combined with exhaustion after a night of dancing, have already led to involvement in -even fatal- car accidents of MDMA users in the past (5,16). Furthermore, MDMA dosages may be higher than in the present study and are often used in combination with sedative psychoactive substances such as marijuana and alcohol. Often combining 2 or more psychoactive substances, e.g. marijuana and alcohol, often increases the impairment caused by a drug when taken alone (17). The current study was part of a larger experiment assessing aspects of driving and simulated driving under the influence of MDMA with and without other drugs and/or alcohol. The study assessing simulated driving confirms these findings. While MDMA alone only had minor effects on driving performance, MDMA combined with other drugs (mostly THC) and/or alcohol increased driving speed and smaller gap acceptance (18).

Alcohol had no effect on vital signs while MDMA increased body temperature, pulse rate and blood pressure.

The increased vital signs correlated with MDMA levels in most body fluids. MDMA levels also correlated with improved psychomotor function. MDMA levels did not significantly correlate with impaired task performance observed in this study. The analyses of correlations in this study were a first attempt to get more insight in the relation between MDMA levels and task performance. However, duplication of these findings in a larger study sample is necessary. Based
on current and future results, saliva may proof itself a good and easy collectable alternative for blood samples in off-road screening.

In sum we can conclude that certain aspects of vehicle control, e.g. tracking capacity improved after MDMA. Although tracking capacity is an important aspect of driving, improved tracking by no means automatically indicate increased driving safety. The increased risk taking and the users’ decreased ability to estimate and predict movement can result in impaired estimation of other traffic movements at crossroads, leading to acceptance of shorter gaps, especially when MDMA is used in combination with other drugs. This form of increased risk taking makes traffic safety under the influence of MDMA questionable.

References