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Acute psychomotor effects of MDMA and ethanol (co-) administration over time in healthy volunteers

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Abstract

In Western societies, a considerable percentage of young people use 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy'). The use of alcohol (ethanol) in combination with ecstasy is common. The aim of the present study was to assess the acute psychomotor and subjective effects of (co-) administration of MDMA and ethanol over time and in relation to the pharmacokinetics. We performed a four-way, double blind, randomized, crossover, placebo-controlled study in 16 healthy volunteers (nine men, seven women) between the ages of 18 and 29. MDMA (100 mg) was given orally while blood alcohol concentration was maintained at pseudo-steady state levels of approximately 0.6‰ for 3 h by a 10% intravenous ethanol clamp. MDMA significantly increased psychomotor speed but did not affect psychomotor accuracy and induced subjective arousal. Ethanol impaired both psychomotor speed and accuracy and induced sedation. Coadministration of ethanol and MDMA improved psychomotor speed but impaired psychomotor accuracy compared with placebo and reversed ethanol-induced sedation. Pharmacokinetics and pharmacodynamics showed maximal effects at 90–150 min after MDMA administration after which drug effects declined in spite of persisting MDMA plasma concentration, with the exception of ethanol-induced sedation, which manifested itself fully only after the infusion was stopped. In conclusion, results show that subjects were more aroused when intoxicated with both substances combined compared with placebo, but psychomotor accuracy was significantly impaired. These findings may have implications for general neuropsychological functioning as this may provide a sense of adequate performance that does not agree with a significant reduction in psychomotor accuracy.

Key words
dynamics; ethanol; human; kinetics; MDMA; psychomotor

Introduction

In Western societies, a significant proportion of young people expose themselves to 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') (Parrott, 2001). Ecstasy has gained widespread use in the 'club' scene, typically at all-night parties with loud, intense music and lights (Winstock, *et al.*, 2001). The average dose of ecstasy used recreationally is reported to contain around 80–90 mg of MDMA with considerable individual variation (Tanner-Smith, 2006). Ecstasy users are generally polydrug users, having experience with different psychoactive substances

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and combining them with ecstasy (Gouzoulis-Mayfrank and Daumann, 2006). Alcohol (ethanol) is frequently used with ecstasy (Barrett, *et al*., 2005; Izco, *et al*., 2007).

MDMA releases serotonin (5-HT) from presynaptic 5-HT terminals by reversal of the reuptake transporter and thus increases 5-HT levels at the postsynaptic receptors (Liechti and Vollenweider, 2000; Mlinar and Corradetti, 2003; Pifl, *et al*., 1995). MDMA is also a potent releaser of dopamine and (nor) adrenaline (Colado, *et al*., 2004; Liechti and Vollenweider, 2001; Sprague, *et al*., 2004).

MDMA is rapidly absorbed following oral administration. Within 30 min MDMA is detectable in the blood. Plasma levels peak 1–2 h after drug intake. Maximal behavioural and subjective effects also occur around 1–2 h and decline after 4 h (de la Torre, *et al*., 2004; Green, *et al*., 2003). A moderate increase of plasma MDMA levels when ethanol is coadministered with MDMA has been reported (Hernandez-Lopez, *et al*., 2002) but also disputed (Kuypers, *et al*., 2006).

Ethanol depresses both excitatory and inhibitory postsynaptic potentials by allosterically potentiating the action of Gamma Aminobutyric Acid (GABA) at its receptor-complex (Suzdak, *et al*., 1988). Consequently, alcohol has both arousing and sedating effects that are dose-dependent with high inter-individual variability (Gulick and Gould, 2007).

Reports on the effects of coadministration of MDMA and ethanol in humans are relatively sparse (Hernandez-Lopez, *et al*., 2002; Kuypers, *et al*., 2006; Pacifici, *et al*., 2001; Ramaekers and Kuypers, 2006). Of these, two studies reported on psychomotor performance. Kuypers, *et al.* (2006) assessed the effects of 75 and 100 mg MDMA in combination with orally administered ethanol (mean peak blood alcohol concentration [BAC] reached was 0.6‰). They reported that certain aspects of psychomotor performance, assessed by actual driving tests (mean BAC below the legal limit [0.5‰] during driving tests), were impaired by ethanol (standard deviation of lateral position [SDLP]) and improved by MDMA (SDLP and standard deviation of speed [SD speed]). Coadministration of 100 but not 75 mg MDMA reversed ethanol-induced impairment of SDLP. Ethanol also increased brake reaction time (RT). Psychomotor performance assessed using the Critical Tracking Task (CTT) was impaired by ethanol and unaffected by MDMA. Another study assessed the effects of 100 mg MDMA and 0.8 g/kg ethanol (peak BAC of 1.25‰) coadministration on psychomotor function over time (Hernandez-Lopez, *et al*., 2002). In this study, ethanol impaired psychomotor performance using the Digit Symbol Substitution Task (DSST), an effect which was counteracted by MDMA co-administration. MDMA alone did not affect psychomotor performance. MDMA showed stimulant effects assessed with the Maddox wing test, an effect which was counteracted by ethanol coadministration. Maximal effects occurred 90 min after MDMA administration and declined thereafter.

We recently reported on the peak effects of MDMA and ethanol coadministration on neuropsychological function (Dumont, *et al*., 2008). Only moderate effects were observed, although the timing of tests relative to drug administration remained an issue. Although the time when Cmax is reached (Tmax) provides a guideline to assume peak effects, the dynamic effects do not necessarily follow the kinetic time profile of a compound. This study aimed to assess the acute psychomotor and subjective effects of MDMA and ethanol (co-) administration over time controlling for the pharmacokinetics. This study extends previous studies by using an ethanol clamp, effectively eliminating the variations in BAC of orally administered alcohol. As previous studies showed a robust neuroendocrine response after MDMA administration (de la Torre, *et al*., 2000b; Harris, *et al*., 2002; Mas, *et al*., 1999), the current study also assessed neuroendocrine response to assess possible moderating effects of ethanol coadministration on MDMA-induced neuroendocrine response.

We hypothesise that the stimulating effects of MDMA will moderate ethanol's subjective as well as objective sedation. As MDMA also induces mild hallucinogenic effects that are expected to impair cognitive function, we hypothesize that tests not reliant on psychomotor speed would not benefit from MDMA coadministration compared with ethanol (Dumont, *et al*., 2008). Peak drug effects were hypothesized to coincide with MDMA Tmax, although effects were expected to decline in spite of persisting plasma levels as previously reported (Hernandez-Lopez, *et al*., 2002).

Materials and methods

Study design

This study used a four-way, double blind, randomized, cross-over, placebo-controlled design and was conducted according to the principles of the Declaration of Helsinki. Each volunteer received a capsule containing either MDMA 100 mg or placebo and an ethanol/placebo infusion (target BAC of 0.6‰) with a washout of 7 days between each treatment.

Study outline

Subjects were admitted to each study day after a urinary drug check (opiates, cocaïne, benzodiazepines, amphetamines, methamphetamines and delta-9-tetrahydrocannabinol, AccuSign®, Princeton BioMeditech, Princeton, USA) (drug use was not allowed 14 days prior to the first study day until study completion) and the recording of possible signs and symptoms of health problems. A light breakfast was offered 2 h before drug administration. Drug administration was scheduled at 10:30 h, and the ethanol infusion was started at 11:00 h. Subjects received a standardized lunch at 14:00 h and were sent home around 17:00 h.

Outcome measures were assessed repeatedly, that is, before MDMA administration and at 30, 90, 150, 240, 300 and 360 min after drug administration and consisted of pharmacokinetic samples of breath (for ethanol) or blood (for MDMA

and 3,4-methylenedioxyamphetamine [MDA]) and pharmacodynamic assessments as specified below. Parts of these data were presented at a meeting of the Dutch Society for Clinical Pharmacology, the abstract of which has been published (Dumont, *et al*., 2007).

Subjects

A total of 16 healthy volunteers (nine men, seven women), regular users of ecstasy (at least eight exposures in the last 2 years) and alcohol (at least one exposure per week), 22.1 ± 2.9 (mean ± SD) years of age (range 18–29) and within 80–130% of their ideal body weight were recruited through advertisement on the internet and at local drug testing services. Lifetime ecstasy exposure was on average 95 doses (SD = 138; range 14–431). More detailed demographic data have been reported elsewhere (Dumont, *et al*., 2008). Exclusion criteria included pregnancy, (history of) psychiatric illness assessed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition axis 1 disorders, nonpatient version (First, *et al*., 1994), Axis II disorders were excluded using the Temperament and Character Inventory (Svrakic, *et al*., 1993), use of over-the-counter medication within 2 months prior to the study start, (history of) treatment for addiction problems, excessive smoking (>10 cigarettes/day) and orthostatic dysregulation. Physical and mental health was determined by assessment of medical history, a physical and electrocardiogram examination as well as standard haematological and chemical blood examinations. The local Medical Ethics Committee approved the study. All subjects gave their written informed consent before participating in the study and were paid for their participation. Subjects were aware that the active drug conditions would be ethanol, MDMA and ethanol and MDMA coadministration, but that the order in which they received the treatments was randomized.

One subject had a mild adverse reaction (local vascular reaction) to the ethanol infusion and one subject did not refrain from drug use, both (one men, one women) were excluded from further participation, and results obtained from these subjects were not included in the final data analysis.

Ethanol clamping

Ethanol (or glucose 5% as its placebo) was administered continuously by i.v. infusion of 10% ethanol in 5% glucose solution, aimed to maintain a blood ethanol concentration of 0.6‰ for 3 h. The infusion rate was calculated using frequent breath alcohol concentration measurements, according to a previously designed algorithm (Amatsaleh, *et al*., 2006a). Breath alcohol concentration was assessed using a HONAC Alco Sensor IV® Intoximeter, Apeldoorn, the Netherlands. The process was semiautomated using a computer spreadsheet programme, which used measured breath alcohol concentrations to calculate the infusion rate needed to maintain the ethanol level at 0.6‰. The operator of the breath alcoholmeter and the ethanol infusion pump was unblinded for alcohol-treatment but did not communicate with the study team or the subjects about the results at any stage of the trial. A sham procedure was used during ethanol placebo occasions.

The alcohol clamp was targeted at 0.6‰ because in many European countries, driving is prohibited at BACs at or around this level. Consequently, the psychomotor effects of an ethanol concentration equal to or exceeding 0.6‰ are likely to affect an individual's ability to drive a car. Recent studies showed that a BAC of 0.6‰ induces significant effects on eye movements (Amatsaleh, *et al*., 2006b; Nyberg, *et al*., 2004). Moreover, despite significant CNS effects, this dose is considered to be a safe and relatively moderate dose. A BAC of 0.6‰ is equivalent to approximately 2–3 alcoholic beverages, reflecting normal social drinking.

MDMA

MDMA (or matched placebo) was given as a capsule in a single oral dose of 100 mg. MDMA 100 mg orally is a relevant dose in the range of normal single recreational dosages. Previous experiments in humans used doses up to 150 mg without serious adverse events. MDMA was obtained from Lipomed AG, Arlesheim, Switzerland and encapsulated according to Good Manufacturing Practice by the Department of Clinical Pharmacy of Radboud University Nijmegen Medical Centre.

Reagents

All reagents were of analytical grade.

Analytical methods

A high-performance liquid chromatography–diode array detection (HPLC-DAD) method was used to measure plasma MDMA and MDA concentrations. In brief, 100 μL internal standard solution (1.27 μg 3,4-methylenedioxy-*N*-ethylamphetamine [MDEA] in 1.0 mL water) was added to 1.0 mL plasma, 500 μL borate buffer (0.05 M, pH 9.3) was added, the solution was mixed, and 5 mL dichloromethane added. The tube was stoppered and shaken for 10 min. Thereafter, the tube was centrifuged for 5 min at 2500 g. The organic layer was separated from the water layer and transferred into a clean tube and 500 μL mobile phase (880 mL 0.015 M phosphate buffer, pH 3.3 plus 120 mL acetonitrile) was added. The tube was shaken for 10 min and centrifuged for 5 min. An aliquot of 60 μL from the upper layer was injected onto the HPLC-DAD system consisting of a model 1100 solvent delivery system (Agilent Technologies, Amstelveen, the Netherlands), column oven (Agilent Technologies) with a Symmetry C18 column (Waters, Middelburg, the Netherlands), model 1100 DAD (Agilent Technologies). Flow was 1 mL/min and separation took place at 50°C. Peaks were recorded from 199–400 nm. Recovery was >90% for MDMA, MDA and MDEA with a coefficient of variation (CV) of <2%. The lower limit of detection for both MDMA

and MDA was 3 μg/L with a CV of 20%. The upper limit of detection was 500 μg/L for MDMA and 165 μg/L for MDA. Peak purity was >0.995 for positive identification of MDMA, MDA and MDEA. MDMA, MDA and MDEA were kindly obtained from the Dutch Forensic laboratory. Dichloromethane was obtained from Biosolve (Valkenswaard, the Netherlands), and acetonitrile was obtained from Rathburn (Walkerburn, United Kingdom).

Neuroendocrine assays

Cortisol and prolactin were determined as measures of neuroendocrine activity, as previous research has shown that the serum concentrations of these neuropeptides increase after MDMA administration (de la Torre, *et al*., 2000b; Harris, *et al*., 2002; Mas, *et al*., 1999). Serum total cortisol was measured by fluorescence polarization immunoassay on a TDX batch analyzer (Abbott, Hoofddorp, the Netherlands). Serum prolactin was measured by fluorescence immunoenzymometric assay (FIEMA) on an AxSym automated immunoanalyzer (Abbott).

Saccadic and smooth pursuit eye movements

Saccadic eye movements are a measure for psychomotor speed and sedation. Eye movements were quantified by recordings of field potential changes due to eye rotations. Similar to EEG patterns and the architecture of evoked potentials in rats (Meeren, *et al*., 1998), saccadic motion is dependent on the state of alertness (van Steveninck, *et al*., 1999).

For the saccadic test, which lasted 1.5 min, the subject was presented with sudden changes of target position at random intervals. The target consisted of an array of light emitting diodes on a bar fixed at 50 cm in front of the head support. Each recording session consisted of 15 saccades of 15 degrees stimulus amplitudes. The outcome measures are peak saccadic velocity and RT.

For smooth pursuit eye movements, a measure for psychomotor accuracy, the target moved sinusoidal at frequencies ranging from 0.3 to 1.1 Hz, by steps of 0.1 Hz during 60 s. The amplitude of target displacement corresponded to 20 degrees eyeball rotation to both sides. The time in which the eyes were in smooth pursuit of the target was calculated for each frequency and expressed as a percentage.

Saccadic and smooth pursuit eye movements were recorded using Nihon-Kohden® and Cambridge Electronics Design (CED®) hardware and CED Spike2® software for sampling and analysis of eye movements. Effects on the saccadic eye movements, the Saccadic Eye Velocity (PV), were analysed according to published rules (Meeren, *et al*., 1998; Sundstrom and Backstrom, 1998). Head movements were restrained using a fixed head support. Eye movements are used to locate objects and predict the path of moving objects, and as such can be expected to be relevant for driving related abilities (Orban de Xivry and Lefevre, 2007). Moreover, they are sensitive to the effects of serotonergic challenges (Gijsman, *et al*., 2002), as well as to the effects of ethanol, at the currently used concentration (Amatsaleh, *et al*., 2006a).

Body sway

Subjects were asked to close their eyes while in upright position and were attached to the body sway apparatus that records cumulative horizontal body movement (in mm) for 2 min. The test is a measure for postural stability (Wright, 1971).

Subjective effects

Subjective effects were assessed using the short version of the Addiction Research Centre Inventory (ARCI). The ARCI is a 49 item self-report questionnaire that consists of five subscales, each representing the characteristics of a specific drug group, that is, pentobarbital-chlorpromazine-alcohol group (PCAG, a measure for sedation), morphine-benzedrine group (MBG, a measure for euphoria), amphetamine scale (A, an empirically derived scale sensitive to D-amphetamine effects), benzedrine group (BG, a measure for stimulant effects) and lysergic acid diethyl amide scale (LSD, a measure for dysphoria and psychomimetic changes) (Lamas, *et al*., 1994). The ARCI questionnaire was performed at baseline and 90 and 300 min after drug administration.

Statistical analyses

The pharmacodynamic parameters were analysed by mixed model analyses of variance (using SAS PROC MIXED) with treatment, time and treatment by time as fixed effects, with subject, subject by time and subject by treatment as random effects, and with the baseline value as covariate, where baseline was defined as the average of the available values obtained prior to dosing. Treatment effects are reported as the contrasts between the four treatments where the average of the measurements up to the last time point was calculated within the statistical model. Contrasts are reported along with 95% confidence intervals (95% CIs), and analyses are two-sided with a significance level of 0.05. Graphical representation shows mean and standard error of the mean of data.

Statistical evaluation of the differences in MDMA kinetics between MDMA only and MDMA and ethanol (co-) administration (using SPSS 11.5 for Windows, Chicago, Illinois, USA) was performed with general linear model repeated measures analysis of variance.

Results

Pharmacokinetics

MDMA and MDA kinetics did not differ between MDMA single and MDMA and ethanol conditions. The maximal

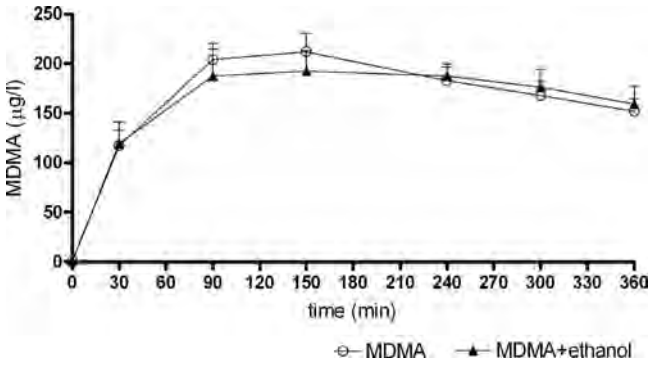

Figure 1 Plasma MDMA concentrations (mean, SEM) for the MDMA and the MDMA and ethanol condition. o, MDMA; ▲, MDMA + ethanol.

plasma MDMA concentration (Cmax) was on average 202.5 µg/L (SD = 74.1 µg/L) 150 min after drug administration (Figure 1). Plasma MDA concentration on average increased to 9.4 µg/L (SD = 3.6 µg/L) 360 min after drug administration.

Ethanol kinetics are shown in Figure 2, during the pseudo-steady state phase BAC was on average 0.56‰ (SD = 0.057‰).

Pharmacodynamics

Only significant results are mentioned in this section unless noted otherwise. Statistically significant main effects of treatment, time and treatment by time as well as drug condition comparisons are summarized in Table 1. For the drug condition comparisons, mean change, 95% CI and corresponding *P* values are reported.

Neuroendocrine measurements

Serum cortisol concentrations showed a pronounced increase after MDMA as well as after MDMA and ethanol (co-) administration compared with the placebo and ethanol condition (Figure 3A). The cortisol response did not differ between the MDMA and the MDMA and ethanol condition. Serum cortisol concentrations peaked 90 min after drug administration and decreased to baseline levels 360 min after drug administration in spite of persisting plasma MDMA levels.

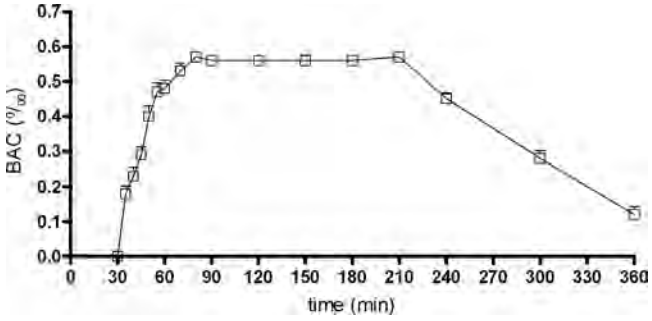

Figure 2 Blood alcohol concentrations (BAC, [mean, SEM]). □, ethanol.

Serum prolactin concentrations (Figure 3B) showed a profile similar to that of cortisol. Peak prolactin concentrations were observed 90 min after MDMA and MDMA and ethanol (co-) administration. Prolactin levels after MDMA and after MDMA and ethanol (co-) administration returned to baseline levels 300 min after administration of the drug(s). There was no significant difference between the MDMA and the MDMA and ethanol condition.

Body sway

There was no significant treatment or treatment by time effects for the body sway measurements.

Eye movements

Smooth pursuit eye movements (psychomotor accuracy) were significantly impaired after ethanol and after ethanol and MDMA (co-) administration compared with the placebo and MDMA condition (Figure 4).

Psychomotor speed and sedation/arousal were assessed by saccadic eye movements. Outcome measures are peak saccadic velocity (PV, see Figure 5A) and RT (see Figure 5B), respectively. Subjects showed increased PV after MDMA administration compared with the placebo, ethanol and MDMA-ethanol condition. Ethanol decreased PV compared with the placebo condition. Coadministration of MDMA with ethanol increased PV compared with the ethanol and placebo condition.

A trend for a significant treatment by time interaction for RT was observed ($P = 0.0571$). Drug comparisons showed that RT of saccadic eye movements was significantly increased after ethanol compared with placebo ($P = 0.023$), although the effect was moderate.

Subjective effects

All ARCI subgroups showed comparable time profiles. Maximal effects were observed 90 min after drug administration and effects had returned to baseline values 300 min after drug administration. The exception to this time profile was the ARCI PCAG and BG scores after ethanol administration, which showed a linear relation in time (positive for PCAG, negative for BG) with maximal effects 300 min after drug administration, that is, subjects felt increasingly sedated after ethanol compared with the placebo, MDMA and MDMA-ethanol conditions.

Drug-induced euphoria (ARCI MBG scores) was reported after MDMA and MDMA-ethanol (co-) administration compared with the placebo and ethanol condition.

Subjects reported amphetamine-like effects (ARCI amphetamine [A] group) in the MDMA and MDMA-ethanol condition compared with the placebo and ethanol condition.

Table 1 Results, main effects and drug comparisons (reported are mean difference, 95% confidence interval and *P* value)

Test	Treatment effect	Time effect	Treatment × time interaction	Ethanol versus placebo	MDMA versus placebo	MDMA + ethanol versus placebo	MDMA + ethanol versus MDMA	MDMA + ethanol versus ethanol	MDMA versus ethanol
Neuroendocrine									
Cortisol (μmol/L)	<0.0001	<0.0001	<0.0001	—	0.32(0.25,0.39) $P \leq 0.0001$	0.28(0.21,0.36) $P \leq 0.0001$	—	0.28(0.21,0.35) $P \leq 0.0001$	0.31 (0.24,0.39) $P \leq 0.0001$
Prolactin (mU/L)	<0.0001	<0.0001	<0.0001	—	213 (105, 322) $P = 0.0003$	196 (85, 307) $P = 0.0009$	—	223 (111, 335) $P = 0.0003$	240 (130, 351) $P \leq 0.0001$
Psychomotor									
Body sway (mm)	NS	<0.0001	NS	—	—	—	—	—	—
Smooth pursuit (%)	<0.0001	<0.0001	<0.0001	−7.6(−11.0,−4.1) $P \leq 0.0001$	—	−7.5(−10.8,−4.2) $P \leq 0.0001$	−9.2(−12.6,−5.9) $P \leq 0.0001$	—	9.3(5.9,12.7) $P \leq 0.0001$
Peak velocity (deg/s)	<0.0001	0.4030	<0.0001	−18.0(−33.8,−2.2) $P = 0.0269$	35.6(19.7,51.5) $P \leq 0.0001$	16.7(0.9,32.5) $P = 0.0393$	−18.9(−34.7,−3.1) $P = 0.0206$	34.7(19.0,50.5) $P = 0.0001$	53.7(37.9,69.4) $P \leq 0.0001$
Reaction time (ms)	NS	0.0001	NS	—	—	—	—	—	—
Subjective									
ARCI PCAG	0.0010	0.0075	NS	2.29(0.80,3.77) $P = 0.0035$	—	—	—	−2.90 (−4.37, −1.42) $P = 0.0003$	−2.64(−4.11,−1.16) $P = 0.0008$
ARCI MBG	<0.0001	<0.0001	<0.0001	—	2.93(1.49,4.37) $P = 0.0002$	3.72(2.28,5.16) $P \leq 0.0001$	—	3.19(1.75,4.63) $P \leq 0.0001$	2.40(0.96,3.84) $P = 0.0017$
ARCI A	<0.0001	0.0006	0.0009	—	1.64(0.84,2.44) $P = 0.0002$	2.15(1.36,2.94) $P \leq 0.0001$	—	1.69(0.89,2.48) $P = 0.0001$	1.18(0.36,2.00) $P = 0.0060$
ARCI BG	<0.0001	0.0018	0.0189	−1.00 (−1.93, −0.07) $P = 0.0351$	—	1.30(0.37,2.24) $P = 0.0073$	—	2.30(1.38,3.23) $P \leq 0.0001$	1.86(0.93,2.79) $P = 0.0002$
ARCI LSD	0.0007	0.0085	0.0023	1.32(0.30,2.34) $P = 0.0122$	2.00(1.00,3.00) $P = 0.0002$	1.93(0.92,2.94) $P = 0.0004$	—	—	—

MDMA, 3,4-methylenedioxymethamphetamine; MDMA + ethanol, MDMA and ethanol co-administration; ARCI, Addiction Research Centre Inventory; PCAG, pentobarbital-chlorpromazine-alcohol group; MBG, morphine-benzedrine group; ARCI A, ARCI amphetamine; BG, benzedrine group; LSD, lysergic acid diethyl amide scale.

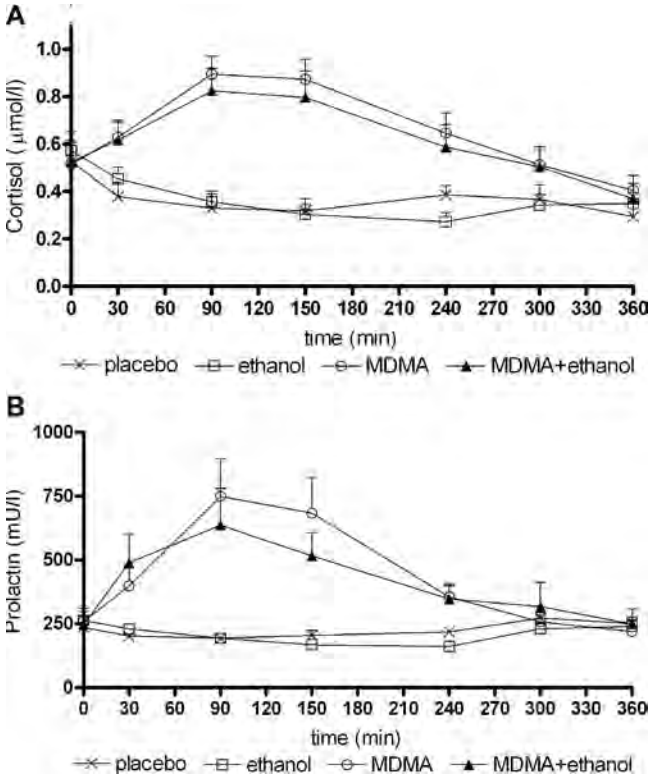

Figure 3 Neuroendocrine measures. (A) Serum cortisol concentration (mean, SEM). (B) Serum prolactin concentration (mean, SEM). x, placebo; □, ethanol; o, MDMA; ▲, MDMA + ethanol.

Arousal was assessed by the ARCI BG. MDMA administration showed a trend for increased arousal compared with the placebo condition ($P = 0.069$). MDMA and ethanol coadministration increased arousal significantly compared with the placebo condition. Ethanol decreased subjective arousal compared with the placebo, MDMA and MDMA-ethanol condition.

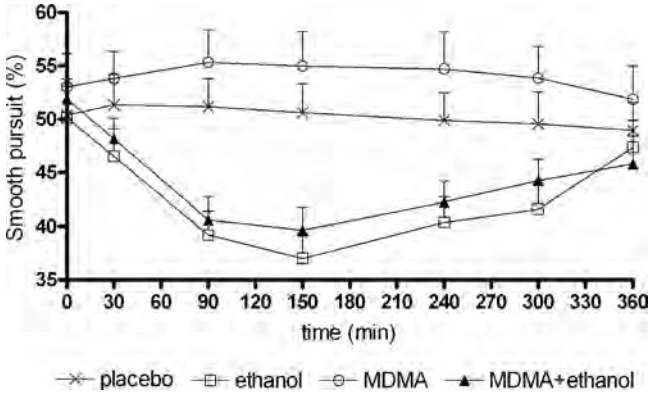

Figure 4 Psychomotor accuracy; smooth pursuit eye movements (mean, SEM). x, placebo; □, ethanol; o, MDMA; ▲, MDMA + ethanol.

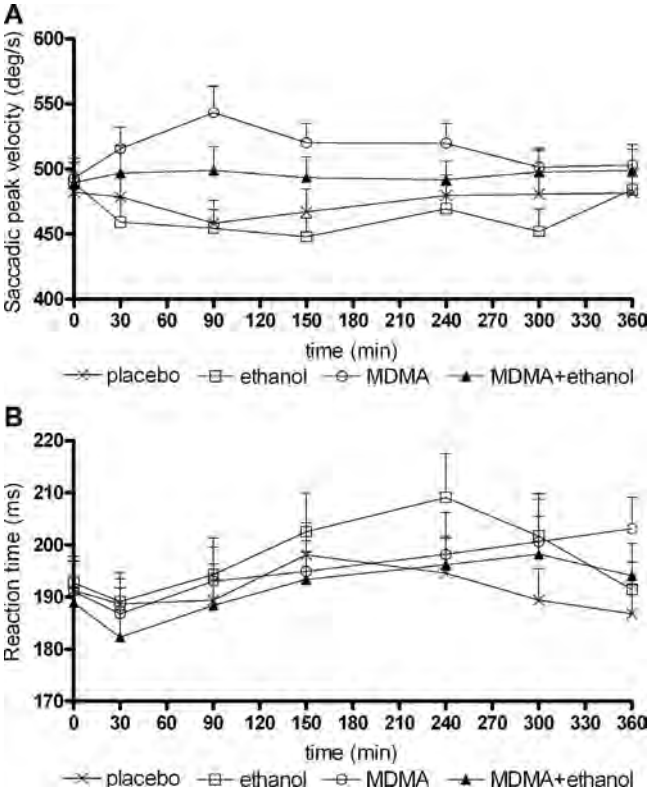

Figure 5 Psychomotor speed measures. (A) Saccadic peak velocity (mean, SEM). (B) Reaction time of saccadic eye movements (mean, SEM). x, placebo; □, ethanol; o, MDMA; ▲, MDMA + ethanol.

Psychomimetic changes (ARCI lysergic acid [LSD] group) were experienced during all active drug conditions compared with placebo; these effects did not differ between drug conditions.

Discussion

Here, we report the acute pharmacokinetic and pharmacodynamic effects of MDMA and ethanol coadministration over time. The results suggest distinct effects of MDMA and ethanol on psychomotor function as well as on subjective experience. Coadministration effects were either averages of or comparable to single drug effects, but there was no reinforcement of the effects. We hypothesised that 1) the stimulating effects of MDMA would moderate ethanol's sedating effects, 2) tests not reliant on psychomotor speed would not benefit from MDMA coadministration compared with ethanol and 3) peak drug effects would coincide with MDMA Tmax, although effects were expected to decline in spite of persisting plasma levels.

Our results support these hypotheses as 1) coadministration of ethanol and MDMA reversed ethanol-induced subjective as well as objective sedation and 2) coadministration of ethanol

and MDMA improved psychomotor speed but impaired psychomotor accuracy compared with placebo. Third, MDMA's peak dynamic effects coincided with the time of maximal plasma MDMA concentrations (Cmax), although effects diminished thereafter in spite of persisting plasma MDMA levels. The time profile of MDMA-induced subjective and performance effects was congruent with neuroendocrine response, and MDMA and ethanol coadministration did not affect the neuroendocrine response compared with MDMA alone. The time course of ethanol-induced effects also correlated with its kinetic profile, with the exception of ethanol-induced sedation, which had peak effects that were delayed compared with the kinetic profile.

MDMA improved psychomotor speed but did not affect psychomotor accuracy. Lamers, *et al.* (2003) also reported increased psychomotor speed after 75 mg of MDMA in the Motor Choice Reaction Task. Although MDMA's most characteristic effect is the release of serotonin, it also releases dopamine (Colado, *et al.*, 2004; Liechti and Vollenweider, 2001). Psychomotor speed is likely to benefit from the increased dopamine availability and the resulting increase in arousal (Mehta and Riedel, 2006). However, tasks not solely depending on speed, like psychomotor accuracy, are less likely to benefit from the increase in arousal. Ethanol on the other hand generally impaired psychomotor function, in line with previous reports (Hernandez-Lopez, *et al.*, 2002; Kuypers, *et al.*, 2006; Dumont, *et al.*, 2008).

Coadministration of MDMA and ethanol caused a significant increase in psychomotor speed compared with placebo (although slightly less than MDMA alone). Hernandez-Lopez, *et al.* (2002) also reported that MDMA coadministration reduced ethanol-induced impairment of psychomotor function as measured with the DSST, although this did not reach the level of significance. This discrepancy may be due to the fact that the DSST is not a pure psychomotor speed task but also assesses other cognitive functions such as memory, which is impaired by MDMA (Dumont, *et al.*, 2008).

However, psychomotor accuracy decreased after the combination (compared with the effects of ethanol alone). These findings are similar to those of a previous study that reported that ethanol administration decreased performance on the CTT (a laboratory task) as well as measures of actual driving tests (increase of SD speed and SDLP) (Kuypers, *et al.*, 2006). In line with our hypothesis that MDMA may overcome ethanol-induced impairment of psychomotor speed but not accuracy, MDMA did not affect CTT scores, that is, MDMA coadministration could not overcome ethanol-induced impairment. Coadministration of 100 mg MDMA did however reverse ethanol-induced impairment of driving performance (ethanol increased SDLP, an effect which was counteracted by MDMA). Our finding of reversal of ethanol-induced sedation by MDMA coadministration (as measured by the RT of saccadic eye movements) is congruent with these results and supports our hypothesis that MDMA may overcome ethanol-induced sedation.

Subjective effects were as expected; MDMA was experienced as arousing and induced mild euphoria. Coadministration of ethanol with MDMA showed a profile similar to MDMA-induced subjective effects. Subjective effects returned to baseline values 5 h after drug administration, with the exception of ethanol-induced sedation, which increased with time and showed maximal effects 5 h after drug administration. Coadministration of MDMA with ethanol reversed ethanol-induced subjective sedation. This may have important implications, for instance when a subject who has used both MDMA and ethanol decides to drive. MDMA may cause him or her to feel fit enough to drive, while actual performance may be profoundly impaired by alcohol.

Remarkably, sedation as assessed by the RT of saccadic eye movements was also delayed relative to ethanol kinetics. Sedation was most pronounced 30 min after the ethanol infusion was stopped and declined thereafter, in line with reports which show that ethanol induces sedation mainly in the descending limb of the kinetic profile of ethanol (Pohorecky and Brick, 1988). As already mentioned, subjective assessments also reflected delayed increase in sedation compared with ethanol administration, whereas other subjective measures had a more direct relationship with BAC. The results reported here show that alcohol may increase sedation even after the intake has stopped. This is particularly relevant if an ethanol-intoxicated subject decides to drive home after a tiresome social event.

The Cmax after 100 mg orally administered MDMA (202.5 μg/L) was comparable to data reported elsewhere (de la Torre, *et al.*, 2000a). MDMA kinetics did not differ between MDMA single and MDMA-ethanol coadministration. Two studies investigated the effects of MDMA and ethanol coadministration on MDMA kinetics in humans, where ethanol coadministration increased plasma MDMA concentration significantly in one (Hernandez-Lopez, *et al.*, 2002) but not the other study (Kuypers, *et al.*, 2006). A possible explanation for this discrepancy might lie in the fact that the study by Hernandez Lopez, *et al.* (2002) achieved a peak BAC of 1.25‰, whereas Kuypers, *et al.* (2006) achieved a peak BAC of 0.59‰ comparable to our steady state BAC of 0.56‰. Future studies should address this issue by assessing the effects of coadministration of different doses of ethanol with MDMA.

Serum cortisol and prolactin concentrations increased significantly after MDMA administration, although both concentrations returned to baseline values before a decrease in MDMA levels was observed. In other words, the neuroendocrine response diminished in spite of persisting plasma MDMA concentrations, a pattern observed in most other outcome measures as well. As MDMA is a serotonin releaser, both by reversing the direction of the reuptake transporter and by releasing neurotransmitter from the vesicles (Mlinar and Corradetti, 2003), it is likely that the available neurotransmitter pool is rapidly depleted, and as a result, the neuroendocrine effects of MDMA diminish in spite of persisting plasma MDMA concentration (Green, *et al.*, 2003).

A short-term reduction of sensitivity to MDMA may also explain why users often take multiple doses of this drug during

the night, so-called 'drug-binging' (Gross, *et al*., 2002). Several anecdotal reports and personal communication with subjects indicate that the purpose of 'binging' is to prolong rather than to increase the effects (de la Torre, *et al*., 2000a; Parrott, 2006; Riley, *et al*., 2001).

Several limitations of our study should be mentioned. First, although eye movements play a significant role in everyday psychomotor performance (Orban de Xivry and Lefevre, 2007), and the results of this measure are in agreement with those of actual driving tests, the relevance of the effects measured using laboratory tests for actual driving performance remains arguable. Second, subjective effects were assessed only at baseline and 90 and 300 min after drug administration, which limits the conclusions regarding the time profile of subjective effects. However, Hernandez-Lopez, *et al*. (2002), who assessed subjective effects more frequently over time, also reported that peak effects occurred at 90 min after drug administration after which effects declined. Third, although the ARCI measures several aspects of subjective performance, we did not directly assess subjective driving performance. We would recommend such a measure in future studies as it would provide a simple yet effective method of relating objective driving abilities to subjective perception of driving performance (Kuypers, *et al*., 2006). Last, our conclusions are based on a BAC of 0.56‰. As suggested in the discussion of the effects of ethanol on MDMA kinetics, ethanol effects might be dose-dependent, an issue which warrants further research.

In conclusion, we have shown that MDMA significantly increased psychomotor speed but not accuracy and induced significant subjective arousal, effects which were maximal around MDMA Cmax and declined thereafter. In contrast, Ethanol impaired both psychomotor speed and accuracy and induced sedation. Only the latter effect did not correspond with ethanol kinetics, and sedation was observed during the descending limb of the BAC profile only. Coadministration of MDMA with ethanol reversed ethanol-induced sedation and improved psychomotor speed to above placebo levels, although psychomotor accuracy remained impaired. These findings may have implications for general functioning and when driving. Individuals will be more aroused when intoxicated with both substances, which may provide a false sense of better performance, although the accuracy of their performance is actually significantly impaired.

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References

Amatsaleh, AA, Dumont, GJ, Schoemaker, RC, van Gerven, JM (2006a) Optimisation of a novel method for alcohol infusion by clamping of breath alcohol concentration. Br J Clin Pharmacol *61*: 475.

Amatsaleh, AA, Schoemaker, RC, van Gerven, JM (2006b) Investigation of the effects of ethanol on central nervous system parameters in healthy volunteers. Br J Clin Pharmacol *61*: 626.

Barrett, SP, Gross, SR, Garand, I, Pihl, RO (2005) Patterns of simultaneous polysubstance use in Canadian rave attendees. Subst Use Misuse *40*: 1525–1537.

Colado, MI, OShea, E, Green, AR (2004) Acute and long-term effects of MDMA on cerebral dopamine biochemistry and function. Psychopharmacology (Berl) *173*: 249–263.

de la Torre, R, Farre, M, Ortuno, J, Mas, M, Brenneisen, R, Roset, PN, *et al*. (2000a) Non-linear pharmacokinetics of MDMA ('ecstasy') in humans. BrJ Clin Pharmacol *49*: 104–109.

de la Torre, R, Farre, M, Roset, PN, Lopez, CH, Mas, M, Ortuno, J, *et al*. (2000b) Pharmacology of MDMA in humans. Ann N Y Acad Sci *914*: 225–237.

de la Torre, R, Farre, M, Roset, PN, Pizarro, N, Abanades, S, Segura, M, *et al*. (2004) Human pharmacology of MDMA - pharmacokinetics, metabolism, and disposition. Ther Drug Monit *26*: 137–144.

Dumont, GJ, Valkenberg, MM, Schoemaker, R, Buitelaar, JK, van Gerven, JM, Verkes, RJ (2007) Acute MDMA and ethanol interaction effects on psychomotor performance. Br J Clin Pharmacol *63*: 503.

Dumont, GJ, Wezenberg, E, Valkenberg, MMGJ Jong de, CAJ, Buitelaar, JK, Gerven van, JMA, et al. (2008) Acute neuropsychological effects of MDMA and ethanol (co-) administration in healthy volunteers. Psychopharmacology (Berl) *197*: 465–474.

First, MB, Frances, AJ, Pincus, HA, Vettorello, N, Davis, WW (1994) DSM-IV in progress. Changes in substance-related, schizophrenic, and other primarily adult disorders. Hosp Community Psychiatry *45*: 18–20.

Gijsman, HJ, van Gerven, JM, Verkes, RJ, Schoemaker, RC, Pieters, MS, Pennings, EJ, *et al*. (2002) Saccadic peak velocity and EEG as end-points for a serotonergic challenge test. Hum Psychopharmacol *17*: 83–89.

Gouzoulis-Mayfrank, E, Daumann, J (2006) The confounding problem of polydrug use in recreational ecstasy/MDMA users: a brief overview. J Psychopharmacol *20*: 188–193.

Green, AR, Mechan, AO, Elliott, JM, OShea, E, Colado, MI (2003) The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Pharmacol Rev *55*: 463–508.

Gross, SR, Barrett, SP, Shestowsky, JS, Pihl, RO (2002) Ecstasy and drug consumption patterns: a Canadian rave population study. Can J Psychiatry *47*: 546–551.

Gulick, D, Gould, TJ (2007) Acute ethanol has biphasic effects on short- and long-term memory in both foreground and background contextual fear conditioning in C57BL/6 mice. Alcohol Clin Exp Res *31*: 1528–1537.

Harris, DS, Baggott, M, Mendelson, JH, Mendelson, JE, Jones, RT (2002) Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. Psychopharmacology (Berl) *162*: 396–405.

Hernandez-Lopez, C, Farre, M, Roset, PN, Menoyo, E, Pizarro, N, Ortuno, J, *et al*. (2002) 3,4-methylenedioxymethamphetamine (ecstasy) and alcohol interactions in humans: psychomotor performance, subjective effects, and pharmacokinetics. J Pharmacol Exp Ther *300*: 236–244.

Izco, M, Orio, L, OShea, E, Colado, MI (2007) Binge ethanol administration enhances the MDMA-induced long-term 5-HT neurotoxicity in rat brain. Psychopharmacology (Berl) *189*: 459–470.

Kuypers, KP, Samyn, N, Ramaekers, JG (2006) MDMA and alcohol effects, combined and alone, on objective and subjective measures

of actual driving performance and psychomotor function. Psychopharmacology (Berl) *187*: 467–475.

Lamas, X, Farre, M, Llorente, M, Cami, J (1994) Spanish version of the 49-item short form of the Addiction Research Center Inventory (ARCI). Drug Alcohol Depend *35*: 203–209.

Lamers, CTJ, Ramaekers, JG, Muntjewerff, ND, Sikkema, KL, Samyn, N, Read, NL, *et al*. (2003) Dissociable effects of a single dose of ecstasy (MDMA) on psychomotor skills and attentional performance. J Psychopharmacol (Oxf) *17*: 379–387.

Liechti, ME, Vollenweider, FX (2000) The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers. J Psychopharmacol (Oxf) *14*: 269–274.

Liechti, ME, Vollenweider, FX (2001) Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. Hum Psychopharmacol *16*: 589–598.

Mas, M, Farre, M, de la Torre, R, Roset, PN, Ortuno, J, Segura, J, *et al*. (1999) Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans. J Pharmacol Exp Ther *290*: 136–145.

Meeren, HK, Van Luijtelaar, EL, Coenen, AM (1998) Cortical and thalamic visual evoked potentials during sleep-wake states and spike-wave discharges in the rat. Electroencephalogr Clin Neurophysiol *108*: 306–319.

Mehta, MA, Riedel, WJ (2006) Dopaminergic enhancement of cognitive function. Curr Pharm Des *12*: 2487–2500.

Mlinar, B, Corradetti, R (2003) Endogenous 5-HT, released by MDMA through serotonin transporter- and secretory vesicle-dependent mechanisms, reduces hippocampal excitatory synaptic transmission by preferential activation of 5-HT1B receptors located on CA1 pyramidal neurons. Eur J Neuroscience *18*: 1559–1571.

Nyberg, S, Wahlstrom, G, Backstrom, T, Poromaa, IS (2004) No difference in responsiveness to a low dose of alcohol between healthy women and men. Pharmacol Biochem Behav *78*: 603–610.

Orban de Xivry, JJ, Lefevre, P (2007) Saccades and pursuit: two outcomes of a single sensorimotor process. J Physiol *584*: 11–23.

Pacifici, R, Zuccaro, P, Lopez, CH, Pichini, S, Di Carlo, S, Farre, M, *et al*. (2001) Acute effects of 3,4-methylenedioxymethamphetamine alone and in combination with ethanol on the immune system in humans. J Pharmacol Exp Ther *296*: 207–215.

Parrott, AC (2001) Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. Hum Psychopharmacol *16*: 557–577.

Parrott, AC (2006) MDMA in humans: factors which affect the neuropsychobiological profiles of recreational ecstasy users, the integrative role of bioenergetic stress. J Psychopharmacol *20*: 147–163.

Pifl, C, Drobny, H, Reither, H, Hornykiewicz, O, Singer, EA (1995) Mechanism of the dopamine-releasing actions of amphetamine and cocaine – plasmalemmal dopamine transporter versus vesicular monoamine transporter. Mol Pharmacol *47*: 368–373.

Pohorecky, LA, Brick, J (1988) Pharmacology of ethanol. Pharmacol Ther *36*: 335–427.

Ramaekers, JG, Kuypers, KP (2006) Acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on behavioral measures of impulsivity: alone and in combination with alcohol. Neuropsychopharmacology *31*: 1048–1055.

Riley, SC, James, C, Gregory, D, Dingle, H, Cadger, M (2001) Patterns of recreational drug use at dance events in Edinburgh, Scotland. Addiction *96*: 1035–1047.

Sprague, JE, Brutcher, RE, Mills, EM, Caden, D, Rusyniak, DE (2004) Attenuation of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy)-induced rhabdomyolysis with alpha1- plus beta3-adrenoreceptor antagonists. Br J Pharmacol *142*: 667–670.

Sundstrom, I, Backstrom, T (1998) Citalopram increases pregnanolone sensitivity in patients with premenstrual syndrome: an open trial. Psychoneuroendo *23*: 73–88.

Suzdak, PD, Schwartz, RD, Skolnick, P, Paul, SM (1988) Alcohols stimulate gamma-aminobutyric acid receptor-mediated chloride uptake in brain vesicles: correlation with intoxication potency. Brain Res *444*: 340–345.

Svrakic, DM, Whitehead, C, Przybeck, TR, Cloninger, CR (1993) Differential diagnosis of personality disorders by the seven-factor model of temperament and character. Arch Gen Psychiatry *50*: 991–999.

Tanner-Smith, EE (2006) Pharmacological content of tablets sold as "ecstasy": results from an online testing service. Drug Alcohol Depend *83*: 247–254.

van Steveninck, AL, van Berckel, BN, Schoemaker, RC, Breimer, DD, van Gerven, JM, Cohen, AF (1999) The sensitivity of pharmacodynamic tests for the central nervous system effects of drugs on the effects of sleep deprivation. J Psychopharmacol *13*: 10–17.

Winstock, AR, Griffiths, P, Stewart, D (2001) Drugs and the dance music scene: a survey of current drug use patterns among a sample of dance music enthusiasts in the UK. Drug Alcohol Depend *64*: 9–17.

Wright, BM (1971) A simple mechanical ataxia-meter. J Physiol *218*: 27P–28P.