Appendix A: Structured Abstracts of Reports on Clinical MDMA Research

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Contains: summaries of all available studies (34 published and unpublished as of June 1, 2001) in the English-language literature in which MDMA was administered to humans.

Anderson et al. (1978). Absolute configuration and psychotomimetic activity.

Anderson, G. M., Braun, G., Braun, U., Nichols, D. E. & Shulgin, A. T. (1978). Absolute configuration and psychotomimetic activity. NIDA Research Monograph, 22, 8-15. http://www.maps.org/publications/1978_anderson_1.pdf

Purpose: Pharmacological, psychological; Comparison of effects of the R and S isomers of MDMA, and argument for placing MDMA in a classification separate from the classic hallucinogens on the basis of the profile of these isomers.
Design: Non-experimental uncontrolled within-subjects design, wherein all volunteers received at least one dose of each form of MDMA; racemate, R-MDMA and S-MDMA, at doses including those of 40-200 mg. (Also performed comparative studies on rabbits wherein hyperthermic response to racemate and each isomer of MDMA was compared with response to the phenethylamine classic hallucinogen, DOM).
Subjects: Unspecified number (perhaps 6 (6 x 5)?) of human volunteers, probably including the authors, gender and ages of volunteers not provided. Information on subject recruitment not provided. Criteria for Inclusion – Prior experience with psychedelic drugs. (An unspecified number of rabbits were used in studies of drug-induced hyperthermia).
Measures: An author-constructed five-point rating scale for overall drug effects, with rating dependent upon degree and intensity / intrusiveness (described as "disruptiveness") of subjective drug effects, and open-ended narratives wherein volunteers described drug effects. (Rectal hyperthermia in rabbits).
Analyses: No formal analyses were performed. Comparative drug effects of racemic MDMA, R-MDMA and S-MDMA are presented in descriptive form.
Results: Volunteers reported that racemic MDMA was active at 5 mg – 150 mg. S-MDMA was reported to be effective at doses of 80 mg – 120 mg. The effective doses for R-MDMA were far higher, and even 200 mg. R-MDMA did not produce the full intoxication obtained with racemic MDMA. Most of the emotional and sensory effects reported with the racemate are present with S-MDMA, but volunteers reported that they preferred the racemate to S-MDMA alone. The physiological effects of the racemate were also present with S-MDMA, including dilated pupils (mydriasis) and jaw clenching. R-MDMA did not produce these physiological effects. However, 2 / 6 or 2 / 35 reported "color enhancement" with R-MDMA but not with S-MDMA. (These volunteers reported experiencing color enhancement with racemic MDMA). The authors conclude that the effects found with each isomer, alone or summed, did not account for the effects of racemic MDMA. (In rabbits, S-MDMA produced greater elevation in body temperature (rectal hyperthermia) than either R-MDMA or racemic MDMA).
Overall Effects: S-MDMA was far more active than the R-enantiomer and moderately more active than the racemate. S-MDMA had a lower effective dose than the R-enantiomer and it seemed to produce most or all of the effects associated with racemic MDMA, including psychological effects and side effects. R-MDMA was found to have a much higher effective dose range, and it did not produce an intoxication comparable to racemic MDMA even after 200 mg R-MDMA. With the possible exception of altered perception of color, S-MDMA appeared to possess most of the effects of the racemate. Nevertheless, volunteers preferred the effects of the racemate to either R-MDMA or S-MDMA, and the authors conclude that racemic MDMA produces effects that are not simply the sum of the effects produced by each enantiomer alone. The authors argue that because the R-enantiomers of hallucinogens are typically

more potent than S-enantiomers and MDMA was more active as the S-enantiomer, MDMA should not be classed as a hallucinogen. (As with humans, studies with rabbits indicated that the S-enantiomer of MDMA was more active than the R-enantiomer, when hyperthermia is used as a test of activity).
Adverse Effects: See above; an unspecified number of volunteers reported sweating and jaw clenching with racemic MDMA and with S-MDMA.
Comments: This paper is the second published report of the effects of MDMA in humans, and the only report at present that describes the individual effects of the MDMA enantiomers in humans. It is unclear how many volunteers were involved in these trials or how many doses were sampled for each compound. However, this paper does offer some preliminary information about the effects of racemic MDMA and the effects R-MDMA and S-MDMA. On the basis of their findings, the authors propose that MDMA should not be classified as a hallucinogen.

Boone et al. (In Preparation). Neuropsychological Effects of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy).

Boone, K. B., Chang, L., Grob, C. S., & Poland, R. E. (In Preparation). Neuropsychological Effects of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy). Manuscript obtained from C. S. Grob, August, 2000.

Purpose: Neuropsychological, assessment of cognitive performance; "This current study evaluates…possible chronic and subacute effects of MDMA on brain function as measured by neuropsychological tests." (p. 2 in manuscript).
Design: Randomized, double-blind, placebo-controlled within-subjects design used to compare performance on neuropsychological test battery before receiving 2 separate doses of up to 2.5 mg / kg. MDMA (combined dose =0.75-4.75 mg/kg) with performance after receiving 2 doses of MDMA from 0.75 up to 2.5 mg/kg., with all volunteers assessed pre-drug and approximately 2 wks post-drug. (Study also compares MDMA-experienced subjects' performance on a (baseline) neuropsychological test battery with published norms matched for subject sample age or education, with comparison conducted on 14 volunteers + an additional 10 volunteers who did not take part in the pre-drug / post-drug study.)
Subjects: 24 MDMA-experienced subjects, 16 men, 8 women, average age 38, underwent baseline assessment only. 14 / 24 subjects, gender and age not provided, underwent baseline and post-drug assessment 2 wks after 2 doses of MDMA. (Volunteers in pre-test / post-test study belong to same sample reported on in Grob et al., 1996, Grob, 2000). All volunteers recruited via local advertisements. Criteria for Inclusion – Good health as assessed through medical examination, psychiatric interview and neurological examination. Lack of personal or family history of major medical or psychiatric illness. No history of substance abuse (except for MDMA or nicotine) and no history of head trauma with loss of consciousness over 30 min. At least 1 mo free of psychoactive medications or illicit drugs, and pre-session urine screen free of marijuana, barbiturates, cocaine, benzodiazepines or amphetamines. Not pregnant.
Measures: MRI – Performed via clinical 1.5 Tesla scanner.
Neuropsychological Assessment – Test battery administered at baseline for 24 / 24 subjects, conducted 193 + / - 225.3 days after last use of MDMA / ecstasy (range 7.5-780 days). Baseline assessment contained measures of intelligence (WAIS-R), attention (digit span), information processing (Stroop, Digit Symbol), language (Boston Naming Test), constructional ability (Rey-Osterrieth Complex Figure), Memory, Verbal (Logical Memory sub-test of WMS-R, Warrington Recognition Memory Test, Words, RAVLT), Memory, nonverbal (Visual Reproduction sub-test of WMS-R, Warrington Recognition Memory Test-Faces, Rey-Osterrieth Figure, 3 minute delayed, Continuous Visual Memory Test), and executive function (Stroop, Auditory Consonant Trigrams, WCST, Controlled Oral Word Association Test - Fluency. 14 / 24 volunteers assessed again with a less extensive test battery. Post-drug assessment included Digit Span, (Attention), Auditory Consonant Trigrams (Executive function), alternate forms of

RAVLT (verbal memory), Controlled Oral Word Association – Fluency (executive function) and Continuous Visual Memory (visual memory). Post-drug assessment conducted approximately 2 wk after receiving the second of 2 doses of MDMA as part of a controlled, laboratory study.
Analysis: Performance on each test scored for 24 volunteers at baseline and for 14 / 24 volunteers post-drug. Pre-drug performance compared with post-drug performance on each test via paired t-test. (24 / 24 performance scores on baseline test battery compared with published norms for each test, matched for sample age group, except for Copy and Recall scores for Rey-Osterrieth figure, matched for sample education. Spearman correlation coefficient used to assess relationship between MDMA user parameters (duration, frequency and recency of use) and performance on each assessment employed in baseline test battery.)
Results: MRI – MRI scans normal for all subjects.
Neuropsychological Assessment – Post-drug performance did not differ from baseline. MDMA did not reduce performance scores on measures of digit span, RAVLT, continuous visual memory, auditory trigrams, or verbal fluency when post-drug assessment was compared with baseline. (When baseline test performance matched with age-appropriate norms, MDMA users (24 / 24 subjects) found to score within normal range (25^{th} – 74^{th} percentile or higher) for all tests except WCST. Volunteers scored <25^{th} percentile on several WCST scores, including trials to identifying category, failure to maintain set (FTM and number of categories. Frequency of MDMA use negatively correlated with scores on tests of visual memory and verbal recognition memory, and frequency of use positively correlated with speed in test of mental speed and cognitive inhibition. Length of abstinence prior to assessment positively correlated with performance on measures of divided attention / working memory and visual memory).
Overall Effects: Recent administration of MDMA in controlled setting did not reduce performance on tasks involving attention, memory and executive function. Test battery scores attained at least 2 weeks after receiving the second of 2 doses of MDMA were no lower than scores attained at baseline. However, frequent use of MDMA was associated with poorer performance at baseline on tasks involving memory, with visual memory being particularly affected, and more recent use of MDMA was associated with poorer performance at baseline on a test of divided attention and working memory. At baseline, MDMA users also performed below norm on the WCST, a test of executive function. On the other hand, frequency of use is associated with faster performance on a test of mental speed.
Adverse Effects: Not reported in this paper; see Grob, 2000 dose-response study).
Comments: This is the first investigation into MDMA's effects on cognitive performance that uses a prospective design. Previous comparisons between MDMA users and MDMA-naïve controls have used retrospective designs. Their findings are subject to confounding factors that may arise when two self-selected groups are compared. While Boone and Grob's research probably will not settle the debate concerning MDMA's effects on cognitive function, this prospective study suggests that reductions in cognitive function will not arise after a small number of doses of MDMA. Instead, it may be chronic, frequent use of illicit ecstasy that is associated with cognitive deficits. These findings suggest that a few doses of MDMA can be administered in controlled settings without producing a decline in cognitive function.

Cami et al. (2000). Human pharmacology of 3,4-methylenedioxymethamphetamine ("Ecstasy"); psychomotor performance and subjective effects.

Cami, J., Farre, M., Mas, M., Roset, P. N., Poudevida, S., Mas, A., San, L. et al. (2000). Human pharmacology of 3,4-methylenedioxymethamphetamine ("Ecstasy"); psychomotor performance and subjective effects. Journal of Clinical Psychopharmacology, 20, 455-466.
http://www.maps.org/publications/2000_cami_1.pdf

Purpose: Neuropsychological, psychopharmacological; "…to assess the abuse liability of MDMA as compared with amphetamine and placebo." (p. 88). Study examined MDMA's effects on psychomotor performance and subjective effects, compared with amphetamine and placebo.

Design: Randomized, double-blind placebo controlled crossover (i.e. within subjects) design, with drug (placebo, 40 mg amphetamine, 75 mg MDMA or 125 mg MDMA) as a factor. all volunteers took part in all 4 conditions (placebo, amphetamine, 75 mg MDMA and 125 mg MDMA, with each session scheduled at least 1 wk after previous session.
Subjects: 14 MDMA-experienced men, with data presented for 8 / 14 men, aged 21-30, mean = 26.5. (same sample used in Mas et al., 1999).
Criteria for Inclusion - Lack of major psychiatric or medical illness as assessed through interview and physical examination, routine laboratory tests, urinalysis and ECG. Lack of substance abuse (except for nicotine dependence). Past use of MDMA (or ecstasy) at least five times in the past. Urinary drug screens for opioids, cocaine, amphetamines conducted before and after study; all were negative. Identified as extensive metabolizers (measure of CYP2D6) via dextromethorphan / dextorphan assay.
Measures: Mood – Measured via POMS, with POMS administered at 0, 1, 2, 4, 6, 8, 10 and 24 h post-drug administration.
Drug Effects, Alterations in Consciousness – Measured with Spanish-language ARCI and author-constructed visual analog scales (VAS), with both measures administered at 0, 15, 30, 45, 60, 90 min and 2, 3, 4, 6, 8, 10, 12 and 24 h post-drug.
Psychomotor Performance – Psychomotor performance measured via Digit Symbol Substitution Test (DSST), simple RT task and Maddox-Wing device. DSST = a test of visual pattern recognition; volunteers respond to patterns presented on screen, scored as % of correct patterns keyed into computer in 90 sec. Simple RT task = measure of sensory-motor performance, scored as speed of response after stimulus and Maddox-Wing device = measure of extraocular muscular movement, scored as either exophoria (tendency of eyes to move apart from each other, divergent squint), normal activity or esophoria (tendency for eyes to move toward each other, convergent squint). Measures of psychomotor performance administered at 0, 30, 60, 90 min and 2, 3, 4, 6, 8, 10, 12 and 24 h post-drug.
Drug Class Identification – Questionnaire administered 10 h post-drug in each condition; volunteers indicated which drug they thought they had received from the following list; benzodiazepines, alcohol, stimulants (like amphetamine), designer drugs (ecstasy-like), cocaine, hallucinogen, cannabis or others.
Analysis: Psychomotor performance scores, ARCI, POMS and visual analog scale scores transformed into differences from baseline. Peak effect within 6 h (maximum change from baseline) and AUC calculated via trapezoidal rule.
Mood – POMS analyzed via 1-way repeated measures ANOVA, with drug (placebo, amphetamine, 75 mg MDMA, 125 mg MDMA) as factor.
Drug effects, Alterations in Consciousness – 1-way repeated measures ANOVA performed on ARCI and VAS, with drug condition as factor.
Psychomotor Performance – Scores on RT, DSST and Maddox-Wing tasks analyzed via 1-way repeated measures ANOVA (described above), with drug condition as factor,
All Data - Post-hoc comparisons made via Tukey's test. Significance, p. = .05.
Results: Mood – Maximum change in mood generally occurred 90 min – 2 h post-drug and returned to baseline 4 h post-drug. Only 125 mg MDMA increased POMS "elation," "positive mood" and "confusion" scales compared with placebo or amphetamine.
Drug Effects, Alterations in Consciousness – Maximal alterations in consciousness occurred 90 min – 2 h post-drug and declined to baseline at 4 h post-drug.
Drug Effects, ARCI – All drugs (amphetamine, 75 and 125 mg MDMA) increased A (d-amphetamine-sensitive) scores. MDMA (at both doses) increased MBG (euphoria) and LSD (dysphoria) scores compared with placebo. Only amphetamine increased BG (energy, intellectual efficiency) score and only 125 mg. MDMA increased PGAG (sedation) score compared with placebo.
Drug Effects, VAS – Amphetamine and MDMA (75 mg, 125 mg) increased scores for "liking," "any effect," "stimulated" and "good effects" compared with placebo. 75 mg. And 125 mg. MDMA increased "drunken" rating compared with placebo, amphetamine. 125 mg. MDMA increased ratings of "high," "drunken" and "confusion" compared with placebo or amphetamine, and 125 mg MDMA increased "high" and "confusion" more than 75 mg MDMA. 125 mg. MDMA increased ratings of "changes in

shapes," "changes in lights," "changes in hearing," "different, changed unreal body feelings" and "different or unreal surroundings." Colors rated brighter, sounds sharper. 75 mg. MDMA only increased ratings of "different, changed unreal body feelings." No hallucinations reported. Amphetamine did not increase ratings of changed perception.
Psychomotor Performance – Maximal effects on performance seen 1 – 2 h post-drug. DSST – During peak effects, amphetamine and 75 mg. MDMA did not affect DSST performance, but 125 mg. MDMA slightly increased errors and reduced number of correct responses. Amphetamine slightly increased performance on DSST; improvement not statistically significant. RT Task – No changes in simple reaction time with any drug (amphetamine, 75 mg. MDMA or 125 mg. MDMA); amphetamine slightly decreased RT, effect not significant. Maddox-Wing Device – 125 mg. MDMA (and no other treatment) produced esophoria (convergent squint).
Drug Class Identification – 6 / 8 identified both doses (75 mg., 125 mg.) of MDMA as designer drug ("ecstasy-like.") 1 / 8 identified 125 mg. MDMA as a stimulant and 1 / 8 identified 125 mg. MDMA as a benzodiazepine. 1 / 8 identified 75 mg. MDMA as placebo, and 1 / 8 identified 75 mg. MDMA as a benzodiazepine. 6 / 8 correctly identified amphetamine as stimulant (other identifications not reported). 7 / 8 correctly identified placebo; 1 / 8 identified placebo as benzodiazepine.
Overall Effects: While MDMA appeared to share some effects with the stimulant amphetamine, as reflected in similar values for "stimulated," "good effects" and ARCI A (d-amphetamine sensitive) scale, MDMA produced a unique psychological profile. Both 75 and 125 mg MDMA increased positive mood, "drunken" feeling, "euphoria (ARCI MBG) and "dysphoria" (ARCI LSD). The higher (125 mg) dose of MDMA significantly altered perception in several modalities (without causing hallucinations) and increased ratings of "sedation" (ARCI PGAG) and "confusion." 125 mg MDMA also slightly impaired performance on the DSST, a test of visual pattern recognition. 125 mg. MDMA, but not 75 mg. MDMA or 40 mg amphetamine, produced a convergent squint (esophoria). Most volunteers correctly identified MDMA and successfully differentiated it from amphetamine. As noted below, both doses of MDMA were safely administered without producing severe psychological or physiological distress.
Adverse Effects: None reported in paper; authors indicate that none of the volunteers experienced severe adverse effects, and there was no need for clinical intervention for any subject in any of the drug conditions.
Comments: This is a companion paper to Mas et al's (1999) study of the cardiovascular effects and pharmacokinetics of MDMA in humans. This study is notable in identifying peak drug effects through multiple administration of psychometric and performance measures rather than administering measures at a pre-determined time when peak effects are expected to occur. By employing different measures of psychomotor performance, the authors are also able to draw more specific conclusions about MDMA's effects on attention; simple attending was less affected by MDMA than complex attending. Cami et al. interpret high ratings on the ARCI MBG scale as indicative of high abuse potential. However, both doses of MDMA also received high ratings (compared to placebo) on the ARCI LSD scale, said to measure "dysphoria." The findings in this paper seem to support placing MDMA in a separate class of drugs, entactogens, on the basis of its differential effects on psychological measures.

Chang et al. (2000). Effect of ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow; A co-registered SPECT and MRI study.

Chang, L., Grob, C. S., Ernst, T., Itti, L., Mishkin, F. S., Jose-Melchor, R., & Poland, R. E. (2000). Effect of ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow; A co-registered SPECT and MRI study. Psychiatry Research; Neuroimaging Section, 98, 15-28. http://www.maps.org/publications/2000_chang_1.pdf

Purpose: Neurophysiological, brain imaging: "This study evaluates the chronic and sub-acute effects of MDMA on brain function as measured by regional cerebral blood flow." (p. 16). Study compared pre-

MDMA scans with post-MDMA scans and also compared scans of MDMA users with scans from controls with no history of MDMA use.
Design: Randomized, double-blind, placebo-controlled within-subjects design for comparing SPECT scans made before receiving 2 separate doses of MDMA, (combined dose range = 2.25 to 4.75 mg / kg, mean 3.5 + / - .8 mg / kg) with SPECT scans made after volunteers received MDMA. All volunteers received pre-drug and post-drug scans. (Study also used between-subjects design to compare scans of MDMA-experienced volunteers (drug-free for at least 1 mo.) with MDMA-naïve controls.)
Subjects: 10 MDMA-experienced subjects, 6 men, 4 women, average age 38.4 + / - 12.5 (from a sample of 21 MDMA users, 17 men, 4 women, aged 43.4 + / - 12.5). MDMA-experienced is defined here as having used MDMA at least 6 times for at least one year. Volunteers recruited through local advertisements (in California area).
Criteria for Inclusion – Reported using low doses of MDMA, with low doses defined as (< 3 mg / kg per session), at least 6 times a year for at least one year, as assessed through screening questionnaire. Good health as assessed through medical examination, psychiatric interview and neurological examination. Lack of personal or family history of major medical or psychiatric illness. No history of substance abuse (except for MDMA or nicotine) and no history of head trauma with loss of consciousness for more than 30 min. At least 1 month free of psychoactive medications or illicit drugs, and pre-session urine screen free of marijuana, barbiturates, cocaine, benzodiazepines or amphetamines (MDMA would register if used within 48 h.) Not pregnant, and without metallic objects in body.
Measures: Imaging – 2 [99mTc]-HMPAO SPECT scans co-registered with MRI scans, with MRI and SPECT scan occurring before MDMA administration and another pair of scans (1 MRI, 1 SPECT) approximately 21 days after two separate doses of MDMA. 8 / 10 received scans approximately 2 weeks post-drug and 2 / 10 received scans approximately 2 months post-drug.
Analysis: Regions of interest (ROIs) selected by investigator blinded to drug use condition. 8 / 10 subjects' data analyzed via 3-way repeated measures ANOVA, with scan time (baseline, post-drug), brain hemisphere and brain region as within-subjects variables. Post-drug scans also compared with scans of 8 matched (non-MDMA user) controls via 3-way mixed measures ANOVA, with drug use as a between-subjects variable, and brain hemisphere and brain region as within-subjects variables. Effects of time since MDMA administration and combined dose of MDMA on measures of rCBF assessed through linear regression. Overall p. values corrected for multiple comparisons with Huynh-Feldt test. Post-hoc comparisons conducted with Fisher's PLSD with Bonferroni correction. (Scans of 21 MDMA users and 21 controls also compared).
Results: Global and, in most regions, regional CBF decreased post-MDMA when compared to pre-MDMA scans or when compared with scans 0f 8 MDMA-naïve controls who never received MDMA in study. There was a trend toward overall drug effect ($p < .07$) and a significant MDMA x region effect when comparing pre-drug with post-drug scans. Post-hoc comparisons between pre-drug and post-drug scans found significantly decreased CBF post-drug in the following regions; L, R visual cortex, L, R caudate, L, R superior parietal region and L, R dorsolateral frontal region. When compared with matched controls, post-drug scans show decreased rCBF in most regions examined, with greatest decreases in caudate (L, R), superior parietal region (L, R) and right dorsolateral frontal cortex (R only). Higher doses of MDMA were positively correlated with greater decrease in rCBF post-drug (compared to pre-drug), and recency of MDMA administration also correlated with decreased rCBF post-MDMA. Increased CBF found in post-drug scans of 2 / 20 volunteers who received scans 2 mo. after MDMA. (Overall study found no significant differences between 21 MDMA-using volunteers and 21 non-using controls in scans taken at baseline.
Overall Effects: There appeared to be no differences in rCBF (either increase or decrease) associated with low to moderate MDMA use, as SPECT scans from 21 MDMA-experienced volunteers did not differ from scans of 21 age and gender-matched MDMA-naïve controls. However, MDMA sub-acutely reduced rCBF in several brain regions, with reductions seen when baseline scans were compared with post-drug scans made 2 wks after MDMA administration and when post-drug scans were compared with scans of matched controls (who never received MDMA during course of study). CBF reduced in the

following regions bilaterally in post-drug scans; caudate, superior parietal region and dorsolateral frontal regions. CBF also appeared to be reduced in these and other areas when comparing post-drug scans to those of matched controls.
Adverse Effects: None reported in this study,
Comments: This is the first prospective study of MDMA's effects on rCBF, with measures taken both before and volunteers received MDMA. Unlike the majority of retrospective comparisons between MDMA users and non-users, the authors of this study can also be certain that the compound producing the differences in CBF is MDMA rather than a contaminant of illicit ecstasy or another compound entirely sold as ecstasy. Authors relate their study findings to a postulated enhancement of 5HT-induced vasoconstriction produced by MDMA or by one of its metabolites. These findings could support other hypotheses, such as neurotoxicity, transient changes in receptor activity after alteration by serotonin release, or sub-acute serotonin depletion. The paper is part of an ongoing examination of the psychological, physiological and neuroendocrine responses to different doses of MDMA in a placebo-controlled study, wherein a range of doses of MDMA were administered to MDMA-experienced subjects.

De la Torre et al. (2000). Non-linear pharmacokinetics of MDMA ("Ecstasy") in humans.

De la Torre, R., Farre, M., Ortuno, J., Mas, M., Brenneisen, R., Roset, P. N., Seguro, J. et al. (2000). Non-linear pharmacokinetics of MDMA ("ecstasy") in humans. Journal of Clinical Pharmacology, 49, 104-109. http://www.maps.org/publications/2000_delatorre_1.pdf

Purpose: Pharmacokinetic; A further investigation into an "unexpected observation" suggesting "nonlinear pharmacokinetics of MDMA." (p. 105).
Design: Pilot: Between-subjects single-dose study (no placebo control), wherein volunteers evenly divided into groups receiving 50, 100 and 150 mg MDMA (2 per cell). Final study; Randomized, placebo-controlled within-subjects design; with all volunteers taking part in all 4 conditions (placebo, 40 mg. amphetamine, 75 mg. MDMA, 125 mg MDMA).
Subjects: 14 MDMA-experienced men, aged 21-31, weight 66-83 kg), 6 in pilot study and 8 in final study. Volunteers recruited by word of mouth.
Criteria for Inclusion – Healthy as assessed through psychiatric interview, medical examination, ECG, and routine blood, urine analysis. Used MDMA / ecstasy at least 5 times, but no history of substance abuse (save nicotine dependence). Identified as extensive metabolizers (measure of CYP2D6) via dextromethorphan / dextorphan assay. (Same sample used in Mas et al., 1999, Cami et al., 2000).
Measures: Concentration of the following measured in plasma and urine; MDMA, MDA, HMMA, HMA, using solid-liquid extraction and gas chromatography with nitrogen specific detection. Measures of substances either made directly or after hydrolysis of glucuronide conjugates. AUC, Cmax, Tmax renal and non-renal clearance calculated for MDMA and MDA. "Blank" urine samples collected pre-drug to verify absence of MDMA metabolites.
Plasma – MDMA and metabolites measured in blood, with measures taken at baseline, .25, .5, .75, 1, 1.5, 2, 3, 4, 6, 8, 10, 24 h post-drug.
Urine – MDMA and metabolites measured in urine sampled at 0-8 h and 8-24 h post—drug in pilot study and in final study at 0-4 h, 4-8 h and 8-24 h post-drug.
Other Measures – Cardiovascular and psychological measures taken; relationship of plasma MDMA to diastolic BP reported here.
Analysis: Pharmacological statistics (Tmax, Cmax, AUC) calculated with pharmacokinetics software. Within-subjects comparisons at final study performed with student's t test. A 1-way between subjects ANOVA used to compare across all doses, including pilot study and final study. Plasma MDMA plotted against measures of diastolic BP.
Results: AUC for 125 mg MDMA significantly different from AUC for 75 mg MDMA (paired t test). When combined with pilot studies, authors found that while doses used in study (50 mg, 75 mg, 100 mg, 125 mg & 150 mg) varied by factor of 3, differences in AUC varied by factor of 10. A non-parametric

test comparing 100 mg MDMA to other doses found marginally significant differences between doses (50, 75, 125 and 150 mg, all versus 100 mg). 125 mg MDMA is not bioequivalent to 75 mg. MDMA.
Plasma – (Non-renal) clearance dose-dependent. Comparing 8 final study subjects, found 125 mg MDMA non-renal clearance reduced by .5 compared with 75 mg MDMA. Plasma samples compared across 5 subjects, 1 subject per dose, specifically examining HMMA and MDMA. While HMMA is major plasma product at doses of 50, 75 and 100 mg, this ratio reversed at 125 and 150 mg doses, with MDMA superceding HMMA as major plasma product. When plasma MDMA concentrations increase (with higher dose), so does measure of diastolic BP.
Urine – MDA and HMA only minor metabolites in urinary recovery study; HMMA and MDMA major metabolites. 50% recovery for MDMA in urine occurred, independent of MDMA dose administered. (Renal) clearance constant. Urine concetration of MDMA increased nonproportionally over doses. Doses increased by factor of 3 but MDMA concentrations increase by factor of 20.
Overall Effects: Increasing the dose of MDMA by a factor of 3 increased AUC by a factor of 10 and increased urine MDMA by a factor of 20. When MDMA and metabolites are compared with each other in plasma and urine, and when plasma and urine MDMA and metabolite concentrations are compared across dose, it appeared that while MDMA clearance in urine did not vary greatly with dose, it did vary dose-dependently in plasma. MDA and HMA were only minor metabolites, and unchanged MDMA and HMMA were major constituents in plasma and urine. HMMA was more common than MDMA in plasma at lower doses of MDMA, whereas MDMA was more common in plasma at higher doses. Higher doses of MDMA appeared to be metabolized differently than lower doses of MDMA, with metabolism possibly inhibited by MDMA itself at higher doses. The supralinear increase in plasma MDMA concentration was accompanied by similarly elevated diastolic BP.
Adverse Effects: None specifically reported in this paper; however, authors note that at 150 mg MDMA, volunteers experienced psychological and physiological (cardiovascular) effects that precluded using this dose in final study. For more details, see Cami et al., 2000 and Mas et al., 1999.
Comments: This paper presents direct evidence for a non-linear relationship between MDMA dose and its clearance in humans. The paper uses the same sample of MDMA-experienced males utilized in other papers by the Spanish team (e.g. Cami et al., 2000 and Mas et al., 1999). The authors believe that their data indicates that MDMA inhibits demethylenation, both by acting as a substrate for CYP2D6 and by possibly inhibiting CYP2D6 activity (as suggested by *in vitro* studies). The findings in this paper, particularly those from the final study suggests that care should be taken when using larger doses of MDMA, as the magnitude of drug effects may not be predictable from those of smaller doses. Specifically, larger doses may produce a non-proportionately higher elevation in diastolic BP. De la Torre's sample size is small enough to warrant further replication before their conclusions can be treated as representing the general population. However, the nonlinear pharmacokinetics found both across doses and in a smaller within-subjects comparison offer good support for these apparently nonlinear pharmacodynamics.

De la Torre et al. (2000). Pharmacology of MDMA in humans.

De la Torre, R., Farre, M., Roset, P. N., Hernandez Lopez, C., Mas, M., Ortuno, J., Menoyo, E., Pizarro, N., Segura, J. & Cami, J. (2000). Pharmacology of MDMA in humans. In Ali, S.F. (Ed). Neurobiological Mechanisms of Drugs of Abuse; Cocaine, Ibogaine and Substituted Amphetamines. New York; New York Academy of Sciences., pp. 225-237. Annals of the New York Academy of Sciences, vol. 914. http://www.maps.org/publications/2000_delatorre_2.pdf

Purpose: Neuroendocrine, pharmacological, physiological; Examines and summarizes the effects of various doses of MDMA in humans, including physiological, cardiovascular, psychomotor performance and neuroendocrine responses. Also analyzes metabolism and pharmacokinetics of MDMA. Most of the data presented in this paper has appeared in previous publications, except for a complete chart of

physiological responses for all doses of MDMA investigated and measurements of responses after 100 mg MDMA.
Design: All subjects – A randomized, double-blind placebo controlled design was used, wherein each subject received either placebo or a specific dose of MDMA. Doses used were 50 mg (2 / 27), 75 mg (10 / 27), 100 mg (13 / 27), 125 mg (8 / 27) or 150 mg (2 / 27). Dose Comparison - 8 / 27 participated in a study with a within-subjects design, with each subject taking part in three sessions; placebo, 75 mg MDMA and 125 mg MDMA.
Subjects: 27 MDMA-experienced men, ages not provided here. Recruitment information not provided here, but all previous studies conducted by this team recruited subjects via "word of mouth."
Criteria for Inclusion – Healthy, presumably assessed via medical and psychiatric examination, no history of substance abuse other than nicotine dependence, having used MDMA at least 5 times, and absence of any past medical or psychiatric adverse reactions to MDMA. Previous publications indicated that subjects were typed for CYP2D6 activity and found to be extensive metabolizers.
Measures: Vital signs, physiological measures – HR, systolic and diastolic BP and oral temperature were measured via vital signs monitor. Pupillary diameter was assessed with a pupil gauge. Schedule of measures not reported. In previous studies, physiological responses to MDMA were assessed at 15, 30, 45, 60 and 90 minutes after drug administration, and after 2, 3, 4, 6, 8, 10, and 24 hours after drug administration. All subjects also underwent continuous ECG throughout the study.
Psychomotor Performance – Attention and reaction time assessed via a simple reaction time task. Decision making and attention assessed with the Digit-Symbol task (DSST), a test of visual pattern recognition. Extra-ocular muscle movement was measured via the Maddox-Wing device. Schedule of assessments not reported here, but Cami et al, 2000 indicates measures of psychomotor performance administered at 0, 30, 60, 90 min and 2, 3, 4, 6, 8, 10, 12 and 24 h post-drug.
Neuroendocrine Response – Hormone analyses were conducted on blood drawn at the time of drug administration and at 30, 60 and 90 minutes after drug administration and at 3, 4, and 6 hours after drug administration. Hormone analysis was apparently only measured in subjects who received 75 mg, 100 mg and 125 mg MDMA. Serum cortisol concentration was measured with fluorescence polarization immunoassay, and serum prolactin concentration was determined via microparticle enzyme immunoassay (MEIA).
Pharmacokinetics – Detection of MDMA and its metabolites (MDA, HMMA and HMA) were measured in blood drawn at 0, 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 10 and 24 hours after drug administration. Samples were analyzed for MDMA and metabolites with gas chromatography coupled to a nitrogen phosphorus detector.
Analyses: MDMA and Metabolites – Cmax (peak concentration), time taken to reach peak conentration (Tmax) and area under the concentration-time curve (AUC) were calculated for MDMA and its metabolites in plasma.
All Variables - Measures of all variables were transformed into differences from baseline. Repeated measures ANOVAs were performed in all cases where sample size permitted this test, with drug condition (placebo vs. MDMA) and time of assessment serving as within-subjects variables. Differences in effects produced across MDMA dose were not formally analyzed. (Publications presenting the study with 75 mg and 125 mg MDMA did perform such comparisons).
Results: Vital signs, physiological measures – All doses above the 50 mg dose increased systolic and diastolic BP, pulse rate and pupillary diameter. Some individuals met criteria for hypertension or sinus tachycardia at doses at or above 75 mg MDMA (Reported in Mas et al, 1999). While all doses where statistical comparisons employed (75, 100 and 125 mg) increased systolic and diastolic BP at 1and 2 h post-drug, only doses above 75 mg increased systolic BP at 4 h post-drug, and only the 100 mg dose continued to increase diastolic BP at 4 h post-drug. Pulse rate remained significantly elevated (compared with placebo) up to 4 h after drug administration, but only 100 mg and 125 mg MDMA maintained significantly elevated pulse at 8 h after drug administration. Pupillary diameter remained increased for 75 mg, 100 mg and 125 mg MDMA up to 8 h post-drug. Changes in BT were biphasic, with a slight

decrease at 1 h post-drug and a slight increase at 2 and 4 h post-drug. BT was no longer significantly elevated at 8 h post-drug, when compared with placebo.
Psychomotor Performance – MDMA did not significantly affect reaction time at any dose measured, though there was a slight increase in reaction time with doses above 50 mg. MDMA impaired performance on the DSST in a dose-dependent manner. MDMA induced esophoria (convergent squint) as measured via Maddox-Wing device. Impairment on the DSST was significantly different from placebo for 125 mg MDMA at 1 h post-drug. MDMA produced longest decision reaction times and most errors at 1 h and 2 h post-drug.
Neuroendocrine Response – Serum cortisol and prolactin concentrations were elevated after all doses of MDMA measured (75 mg, 100 mg, 125 mg), with peak concentration of both hormones appearing at 2 h after drug administration.
Pharmacokinetics – Plasma MDMA in subjects receiving 100 mg MDMA reached Tmax at 2 h post-drug. Elimination half-life for MDMA was measured at 8 – 9 h. MDA appeared in plasma slowly after MDMA administration, reaching Cmax (13.1 ng / ml) at 5 – 7 h after drug administration, and elimination half-life for MDA estimated at 25 h. Plasma HMMA concentration followed similar pattern as plasma MDMA, and plasma HMA concentration pattern similar to that of MDA.
Overall Effects: MDMA increased systolic and diastolic blood pressure and produced elevated pulse rate, particularly at doses above 50 mg. Pupillary diameter was also enlarged after MDMA. The authors found a slight decrease in BT at 1 h after MDMA administration, with BT elevated at 2 and 4 h after MDMA administration, a finding that indicates that the effects of MDMA on body temperature may be complex. The decrease in body temperature occurring 1 h after drug administration is explained as the result of mucocutaneous vasoconstriction. While MDMA produced little or no impairment on a reaction time task, performance on a more complex task requiring decisions about visual patterns was impaired. MDMA produced convergent squint (esophoria), an effect compared with the divergent squint (exophoria) produced by sedatives. MDMA at 75, 100 and 125 mg. increased plasma concentrations of cortisol and prolactin. HMMA (reported as main metabolite in previous papers) in plasma paralleled MDMA concentration, and HMA paralleled that of MDA. As previously noted, the elimination half life of MDMA was measured at 8 – 9 hours while the half-life of MDA was 25 h.
Adverse Effects: None specifically measured or reported in this paper beyond individuals who met criteria for hypertension or sinus tachycardia during study and impairment on the DSST.
Comments: A large portion of this paper is devoted to summarizing findings already presented in other papers. However, the authors also present information for all measures taken at the 50 mg and the 150 mg doses of MDMA, and the paper describes the effects of MDMA in a larger sample given 100 mg MDMA. This paper is notable in finding that fluctuation in body temperature changes across time after MDMA administration, with an apparent dip in temperature preceding the more familiar rise in body temperature. The authors explain this as the result of altered peripheral vasoconstriction experienced 1 h after drug administration. Otherwise, the data presented in this paper are comparable to findings presented in other papers concerning the physiological and neuroendocrine effects of MDMA in humans.

Downing (1986). The psychological and physiological effects of MDMA on normal volunteers.

Downing, J. (1986). The psychological and physiological effects of MDMA on normal volunteers. Journal of Psychoactive Drugs, 18, 335-340.
http://www.maps.org/publications/1986_downing_1.pdf

Purpose: Exploratory; pilot study of the acute and sub-acute psychological, neuropsychological and physiological effects of MDMA in humans. "…a pilot study of the effects of a single exposure to MDMA in 21 healthy volunteers…" (p. 336).
Design: Uncontrolled single dose one-session design, with drug dosage self-selected by each subject; range .8 mg /lb – 1.9 mg / lb, mean = 1.14 mg / lb. Baseline-after MDMA comparisons made for some

physiological and neuropsychological measures. Additional data gathered via retrospective self-report survey.
Subjects: 21 MDMA-experienced volunteers (13 men, 8 women) aged 20-58. No information on subject recruitment provided; author states volunteers were "well known" to clinic staff, so perhaps recruited via "word of mouth."
Criteria for Inclusion – At least 1 previous experience with MDMA, and good mental and physical health as assessed through self-report and by clinic staff. "…subjects personally known to a member of the research staff, stated that they were in good health (with two exceptions), and were considered mentally stable, both by their own account and by the staff." (p. 336). Health exceptions; glaucoma (1 woman), legal blindness (1 man).
Measures: Alterations in Consciousness – Alertness, lucidity of thought, as assessed by clinicians, who assayed subject's orientation in time, evidence for perceptual alterations, quality of thinking. Observers requested self-reports from patients during or after peak effects of MDMA.
Neuropsychological function – Digit repetition, unspecified memory task, multiplication task (possibly mental multiplication), hypothetical decision making task and finger to nose task, with at least memory task and finger to nose task conducted at baseline and again during peak effects of MDMA.
Physiological Effects / Vital Signs – BP and pulse measured in all 21 subjects, with measures taken during baseline, 30 minutes, 1, 2, 3, 4, 5, 6, and 24 h post-drug. Pupillary diameter measured in 10 / 21 subjects. ECGs were performed on 5 of 21 subjects.
Adverse Effects – Measured during session for 10 / 21 subjects, probably via observation of volunteers and requests for information about subjective effects by staff.
Blood Chemistry - A 25-item standard panel, including total protein, albumin, globulin, albumin / globulin ratio, bilirubin, total, direct and indirect serum glutamic oxalotransminase, alkaline phosphatase, gamma-glutamyl peptidase, serum glutamic-pyruvic transminase, lactic dehydrogenase, blood urea nitrogen, creatinine, blood urea nitrogen / creatinine ratio, uric acid, calcium, phosphorous, cholesterol, triglycerides, glucose, sodium, potassium and chloride. 11/ 21 volunteers provided blood samples at preingestion, 6 h post drug and 24 h post drug, 16 / 21 provided preingestion and 6 h post drug samples.
MDMA Experience Survey – 14 / 21 completed a survey containing items on subject demographics, features of past MDMA experience, general health, use of other psychoactive drugs, adverse effects of MDMA, possible effects of MDMA on social adjustment, preferred frequency of MDMA use and recommendations for legal status.
Analyses: No formal analysis performed. Baseline measures were compared with on-drug and post-drug measures without using tests of significance or effect size. Blood chemistry panels assessed via comparison with published norms. Number of responses counted on survey.
Results: Alterations in Consciousness – Volunteers reported experiencing euphoria, physical and emotional energy. No evidence of confused thinking or hallucinations (visual or auditory) and subjects' attention focused on present rather than past or future. Euphoria, time focus diminished at 3 h post-drug. No depression / crash observed 24 h after dose (in 12 / 21 returning 24 h post-drug). 2/ 12 reported more sleep than usual; no insomnia. Several (unspecified) reported slight enhancement of mood at 24 h.
Neuropsychological Function – 10 / 21 volunteers examined during peak drug effects. Digit repetition and short term memory test scores did not differ between baseline and peak drug effects. 3 / 10 volunteers had difficulty with multiplication during peak drug effects; volunteers stated they had "difficulty focusing on" task. 4 / 10 volunteers gave idiosyncratic responses to decision-making task (implying impaired judgment), and 2 / 10 volunteers had trouble with finger to nose task.
Physiological Effects – BP and pulse increased in all 21 subjects. Mean peak increase in BP occurs within an hour of ingestion. One case (at 1 mg / lb) of diastolic BP at 200 / 120 in woman, aged 58. Subject on highest dose (1.9 mg / lb) had strongest cardiovascular responses (increase in pulse and BP) but no physical discomfort during session. 14 / 21 volunteers remained after 6 h post-drug, and BP fell below pre-drug levels in 9 / 14 subjects. 12 volunteers measured at 24 h, 5 / 12 still below pre-drug levels. Pupil dilation measured in 10 / 21 subjects; pupillary dilation increased from baseline to peak

drug effects for 9 / 10 volunteers (no change in blind subject). 5 / 21 volunteers given ECGs; all ECGs normal.
Blood Chemistry Panel – No positive findings in the blood chemistry panel. Glucose elevated in 6 subjects, and potassium and sodium in 5 subjects, but difficult to interpret these differences due to study's lack of controls for pre-session food or drink consumption.
MDMA Experience Survey – 14 / 21 volunteers responded; responses to selected items listed here.
General Health – All volunteers considered themselves healthy. Woman with glaucoma had used MDMA 13 times previous to study with no ill effects. 70% (10 / 14) reported that MDMA had no effects on health and 4 did not respond. MDMA bad for health in own opinion? 5 / 14 reported "good," 1 / 14 "bad" and 6 did not respond. Negative Effects – 80% reported jaw clenching, 60% reported headaches and 20% eyelid twitches. No one objected to these effects. Reported mental deficits "during or after MDMA" not described, reported as "minimal and hard to describe." Possible Effect on Social Adjustment – 6 / 14 reported major life change after MDMA experience(s); two marriages, two divorces, also reported finding better jobs. All (14) wished to continue using MDMA and 90% stated relationships improved after MDMA use. 10% either didn't answer or reported no change in relationships after MDMA and none reported relationships worse after MDMA. Preferred Use, Legal Status. – Preferred frequency of use: range monthly – every 4 months, mean 2.2 mo. Preferred dose; range, 75-200 mg, mean 158 mg,- (near mean dose, 165 mg, chosen for study). Legal status: 11/ 14 answered, answers open-ended. Either "MDMA used with therapists and spiritual leaders only," "prescription only" and "over the counter," with 8 / 11 supporting legal controls and 3 / 11 supporting over the counter use. 3 / 11 supported "prescription," 1 / 11 "therapist only" and 4 / 11 both "prescription" and "therapist."
Overall Effects: MDMA reliably increased mood, emotional and physical energy, blood pressure and pulse. MDMA did not produce abnormal cardiac activity, as assessed through ECG. While volunteers did not become confused, did not hallucinate and retained short term memory, observers reported that people had some difficulty concentrating during peak drug effects and judgment was impaired in some subjects. People experienced some adverse effects but were not troubled by them. MDMA did not affect blood chemistry. Most volunteers personally felt MDMA good for them, with only one dissenter. People reported that MDMA had little or no effects on their social adjustment, and reported some apparent life benefits to MDMA use. While all preferred legal MDMA, most also preferred legal controls on use of MDMA.
Adverse Effects: During Session – 3 / 10 volunteers experienced nystagmus in all directions, 6 / 10 reported jaw clench, increase in jaw reflex, deep tendon reflexes enhanced in 8 / 10 subjects, finger-to-nose test impaired in 2 / 10 subjects, gait affected in 7 / 10 subjects, difficulty concentrating (as assessed through multiplication task) in 3 / 10 subjects, judgment impaired (as assessed through decision making in hypothetical situations) in 4 / 10 subjects, 1 / 10 reported nausea and vomiting. Appetite suppressed in 10 / 10 individuals (or perhaps all 21 individuals). Apparent hypertension in one subject. No evidence of insomnia (but author notes that study began in the morning, so not good for assessing distortions in sleep function).
Self-report – Data gathered from 14 / 21 subjects. 80 % of sub-sample reported jaw clenching, 60 % headaches and 20 % eyelid twitches.
Comments: This is one of the first studies attempting to record the acute and sub-acute effects of MDMA, and it does contain one of the most extensive arrays of measures (from subjective experience to blood chemistry). It may be the first paper attempting to assess MDMA's effects on organ function in humans with a prospective design and using blood chemistry panels. While impressive for its breadth, the study can only be viewed as exploratory due to a number of methodological flaws. No formal analysis is used for comparing baseline with on-drug scores, observation is used rather than objective measures in some cases and in other cases, the objective measures used are not specified (as with the measure of short-term memory or judgment). Different assessments are performed on different sub-samples of volunteers without any means for associating responses on one measure with responses on another measure, since composition of each sub-sample is unknown. Furthermore, it is an uncontrolled, single-dose study with no placebo condition. Nevertheless, the paper does indicate that even when

minimal inclusionary criteria are used, MDMA can be administered without serious psychological or physical distress.

Fallon et al. (1999). Stereospecific analysis and enantiomeric disposition of 3,4-methylenedioxymethamphetamine (Ecstasy) in humans.

Fallon, J. K., Kicman, A. T., Henry, J. A., Milligan, P. J., Cowan, D. A. & Hutt, A. J. (1999). Stereospecific analysis and enantiomeric disposition of 3,4-methylenedioxymethamphetamine (Ecstasy) in humans. Clinical Chemistry, 45, 1058-1059.

Purpose: Pharmacokinetic. To investigate "the pharmacokinetic properties of the enantiomers of MDMA in humans" (p. 1059.
Design: Single dose, non-blind within-subjects design. All volunteers took part in treatment condition, receiving 47.5 mg. MDMA hydrochloride (equivalent to 40 mg. MDMA base), with pharmacokinetic parameters calculated from blood sampled over a 24 h period and urine collected over a 72 h period.
Subjects: 8 MDMA-naïve males, ages 22-32, 7 Caucasian, 1 Asian. No information on subject recruitment provided.
Criteria for Inclusion – Healthy, as assessed through physical examination. Normal HR, BP and liver function as assessed through laboratory tests. Not currently receiving any drugs for medical condition and not recently involved in "any other study of a similar nature." (p. 1060).
Measures: Plasma – Plasma levels of MDMA (both R and S isomers) and metabolites performed through capillary gas chromatography (CG). Plasma concentrations measured from blood collected at .5, 1, 2, 4, 6, 8, and 24 h post-drug (MDMA).
Urine - Urine levels of MDMA (R and S forms) and metabolites measured through CG. Metabolites measured in urine sampled at 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 and 24-48 and 48-72 h post-drug. (Authors also sought to validate method and assess its sensitivity through measuring accuracy across volunteers and over time, optical purity and limits of quantification).
Analysis: Cmax, Tmax and half-life calculated, with at least three data points used for each calculation. AUCs (estimated with trapezoidal method), apparent oral clearance and renal clearance all calculated. Values for each enantiomer or its metabolite compared with paired t tests. (Utility of using drug or metabolite enantiomeric composition for forensic applications also assessed via regression).
Results: Plasma – Maximal plasma concentration reached for both S and R MDMA at 4 h post-drug, mean R(-)MDMA versus mean S(+)MDMA (33.7 + / - 14.9 Ug / L vs. 21.2 + / - 10.8 Ug / L.); plasma concentrations of R and S isomers of MDMA significantly different, with more R than S isomer found. Tmax was between 4 and 8 h post-drug for MDMA. Fewer analyses conducted for MDA because later Tmax produced fewer data points. The enantiomeric ratio between R and S MDA (R: S) initially decreases, with low at 2 h post-drug (0.02 + / - .03), and then it steadily increases 1.29 + / - .15 at 24 h.
Urine – Most material recovered at 24 h post drug, <2% recovered in 24-72 h period. Mean R(-)MDMA recovered = 21.4%, mean S(+)MDMA = 9.3%, with significant differences in recovery of R versus S MDMA, with greater recovery for R isomer. Quantification of both enantiomers at 24 h only possible for 1 subject, and only the R enantiomers in 4 subjects, with only in one case could R(-)MDMA be detected in 48-72 h period. MDA also excreted within 24 h, recovering being < 1% for both enantiomers. Ratio of R to S MDMA (R: S) increased from 1:4 in 0-2 h period to 4.2 in 12 h sample. Mean ratio of R to S MDA (R:S) = .48 at the 2-4 h period to 1.2 at the 12-24 h post-drug sample.
Pharmacokinetic Variables - Authors provide evidence for enantioselective disposition of MDMA in humans, with shorter half-life, reduced AUC and increased clearance for S-isomer (the more active form), and more extensive distribution for S-isomer than for R-isomer.
Overall Effects: Human metabolism of S(+)MDMA (the more active form) was more rapid than that of the R isomer. S(+)MDMA was cleared more extensively in the bloodstream, as indicated by comparisons between levels of S(+)MDMA and R(-)MDMA in plasma, and the less-active R isomer was predominant in urine. In contrast, there was less difference between R and S isomers of MDA in urine.

Adverse Effects: None reported in this paper.
Comments: This paper is one of a few that examines the pharmacokinetics of two enantiomers of MDMA separately. Apparently, the S isomer seems to be more rapidly cleared from the body than the R isomer. More R(-)MDMA was excreted in urine unchanged, compared with S(+)MDMA. The S isomer seems to be more extensively transformed into MDA or HMMA, another metabolite not measured in this study. While sample size is still small in this paper, it is notably larger than the sample used in the Lanz paper, and this increases the chance that the findings in this paper accurately represent metabolic processes in the general population.

Gamma et al. (2000). 3,4-methylenedioxymethamphetamine (MDMA) modulates central and limbic brain activity as measured by [H215O]-PET in healthy humans.

Gamma, A., Buck, A., Berthold, T., Hell, D. (Liechti, M. E.), & Vollenweider, F. X. (2000). 3,4-methylenedioxymethamphetamine (MDMA) modulates central and limbic brain activity as measured by [H215O]-PET in healthy humans. Neuropsychopharmacology, 23, 388-395.

Purpose: Neuropsychological, brain imaging; "…to elucidate changes in regional cerebral blood flow (rCBF) produced by a single oral dose of MDMA in MDMA-naïve human subjects." (p. 389). Specific hypothesis tested – that MDMA-induced changes in CBF would be correlated with MDMA-induced changes in mood and state of consciousness as assessed through psychometric measures.
Design: Randomized double-blind placebo-controlled within-subjects study, with all volunteers taking part in 1 placebo session and 1 MDMA session, receiving 1.7 mg / kg MDMA. Volunteers received 4 PET scans per session (2 during control task / resting state, 2 during performance task).
Subjects: 16 MDMA-naïve volunteers (6 women, 10 men, mean age 26 + / - 2.5 years) recruited from university students and hospital staff.
Criteria for inclusion – Lack of major medical or psychiatric illness as assessed through medical history, psychiatric interview, physical exam, ECG and blood analysis. Lack of history of psychiatric illness for self and 1st-degree relatives, lack of any psychiatric, psychopharmacological or psychotherapeutic treatment, and no history of substance abuse.
Measures: PET – 4 60-second H2[15-O]-PET scans with PET set in 3D-acquisition mode. PET sessions conducted 75 min after drug administration (placebo or MDMA), at predicted time of peak drug effects.
Mood – Measured via AM, administered 4 h post-drug, after most drug effects have subsided, but with responses referring to subject's experience during PET scan.
Alterations in Consciousness – Assessed via ASC, measured 4 h post-drug, after most drug effects have subsided, but with responses referring to subject's experience during PET scan.
Adverse Effects – Measured via modified LC ("jaw clenching" added to scale), administered during session.
Task – Continuous Performance Task (CPT) used to standardize cognitive activity across volunteers and conditions. In this task, volunteers click a mouse button with right index finger whenever they view target sequence ("A" followed by "X") on screen, with stimuli presented for 120 ms in center of screen. Control task = Volunteers directed to relax and watch screen, and target sequence removed from display. Control task replaced with simple "resting state" in 5 / 16 subjects.
Physiological (Cardiovascular) Effects – BP and HR measured throughout session.
Analysis: PET – Comparisons between drug (placebo or MDMA) and task (CPT or control) conditions made on a voxel by voxel basis using t-statistic and linear contrasts with opposite weights used for contrasting, when contrasting between conditions. Resulting maps transformed to unit normal distribution. Significance set at $p. = .05$ and corrected for multiple comparisons.
Mood and Alterations of Consciousness – AM (mood) and ASC (alterations in consciousness) scores analyzed through a MANOVA, within-subjects design, with drug (placebo or MDMA) as within-subjects factor. Post-hoc comparisons made with Tukey's test.

Cardiovascular Effects - A 2-way within-subjects ANOVA conducted on cardiovascular data, with drug (placebo or MDMA) as within-subjects factor. Post-hoc comparisons made with Tukey's test.
Adverse Effects – Not reported; probably a two-way ANOVA, within-subjects design with drug (placebo or MDMA) as within-subjects factor, and with post-hoc comparisons made with Tukey's test.
Task – Drug effects on CPT and control task measured through within-subjects MANOVA, with drug (placebo or MDMA) as within-subjects factor. Post-hoc comparisons made with Tukey's test.
Psychological Effects with PET – Correlations between mood (AM) and altered state of consciousness (ASC) scores and PET scan made for MDMA condition only. An ANCOVA model was performed with psychometric scores as covariates and mean scan over all tasks (CPT / control or resting), with p set at .05, corrected for multiple comparisons (procedure not described).
Results: PET – Analysis found main effects for drug (MDMA vs. placebo) and task (CPT vs. control task / resting) but no task x drug interactions, indicating that task did not affect MDMA's effects on rCBF (MDMA Effects – Compared with placebo, MDMA increased rCBF in ventromedial prefrontal area (L, R), inferior temporal region, also referred to as fusiform gyrus (L, R), occipital lobe (L, R) and cerebellum (widespread activation throughout cerebellum). Compared with placebo, MDMA decreased rCBF in dorsal posterior and anterior cingulate (L, R), precentral, paracentral cortex (hemispheres not listed), superior temporal gyrus (L, R), insula (L, R) and dorsomedial thalamus (L,R). Decreases also seen in R uncus and R parahippocampus and L amygdala.
Task Effects – When compared with control task, the CPT produced an increase in rCBF in; R medial occipital cortex, L precentral gyrus, L superior temporal gyrus, L superior frontal gyrus and L anterior cingulate. Compared with the control task, the CPT produced decreased rCBF in: R medial temporal gyrus, L superior temporal gyrus, R precuneus, with trend for difference in R medial frontal cortex.
Mood – When compared with placebo, MDMA produced increases in well-being, heightened mood, self-confidence, extroversion and emotional excitability (emotionality, sensitivity) as assessed by AM.
Alterations in Consciousness – When compared with placebo, MDMA increased all three item-clusters of the ASC; OB, VR and AED. Increase in OB scores after MDMA largely due to increase in positive mood, derealization and depersonalization. Increase in VR due to increased ratings of change in meaning of percepts, visual illusions, facilitated recall, facilitated imagination, but no hallucinations reported. Volunteers also reported intensification of tactile awareness. Increase in AED chiefly due to increases in thought disorder and loss of body control.
Correlations between Psychometric Scores and PET – None of the correlations between drug-induced changes in rCBF and AM (mood) scores or ASC (alterations in consciousness) scores reached statistical significance. Significance value lowered for exploratory purposes. Correlations reaching significance under the lower p value are as follows; Heightened mood positively correlated with CBF in the R parietal region and heightened mood negatively correlated with CBF in the R caudate nucleus; Extroversion (on AM) correlated positively with CBF in L precuneus.
OB score (on ASC) positively correlated with CBF in the R lateral prefrontal cortex, R supramarginal gyrus and R fusiform / lingual gyrus; AED score (on ASC) correlated positively with CBF in L amygdala, L superior temporal gyrus and AED negatively correlated with CBF in the R inferior temporal / fusiform gyrus;
Continuous Performance Task (CPT) Performance – No significant differences between task performance under MDMA and performance under placebo. Trend for greater number of errors under MDMA compared with placebo ($p. < .06$), with errors increasing from .15% errors to .3% errors, and trend for decrease in correct responses under MDMA compared with placebo ($p. <.09$), with 99% correct responses under placebo and 97.9% correct under MDMA.
Cardiovascular Effects – MDMA produced significant increase in systolic and diastolic BP, both compared with placebo and compared with pre-drug levels, with peak increase between 75 and 150 min post-drug. Changes in HR data not reported.
Adverse Effects – Jaw clenching, lack of appetite, thirst, sweating, difficulty concentrating all reported by volunteers after MDMA (see details in Adverse Effects). Volunteers did not report any great discomfort from any of the adverse effects.

Overall Effects: MDMA consistently produces changes in regional cerebral blood flow, as compared with placebo, and these changes were not moderated by performing a task demanding attentional resources (the CPT). Increases in rCBF were seen in some brain areas related to emotion, such as the cingulate (CBF increase in ventral anterior cingulate and CBF decreases in dorsal anterior and posterior cingulate), left amygdala, perhaps pre-frontal regions (increase in CBF in ventromedial prefrontal cortex) and even the cerebellum. Performance on a task that requires visual attention and response to specific stimuli was slightly impaired on MDMA (compared with placebo). The authors' hypothesis was not confirmed; a few relationships between CBF and psychometric scores were found, but correlations fell below the pre-set significance value. These include an association between the OB score (measuring positive mood and pleasant derealization) and CBF in the right lateral prefrontal cortex, the right supramarginal gyrus and the right lingual / fusiform gyrus, an association between AED (fear of ego dissolution and losing control) with CBF in the left amygdala, the left superior temporal lobe and a negative association between AED and CBF in the inferior temporal lobe / fusiform gyrus. MDMA was well tolerated in this sample of drug-naïve subjects, and they were not overly troubled by the minor discomforts of the experience (such as jaw clenching, lack of appetite).
Adverse Effects: Jaw clenching (64%), lack of appetite (63%), sweating (50%), sensitivity to cold (50%), dry mouth / thirst (50 %), palpitations (38%) and difficulty concentrating (50%), though difficulty concentrating also reported in 31% after placebo.
Comments: This was an ambitious paper packed with data. Not only did the authors attempt to compare rCBF under MDMA with rCBF under placebo, but they also attempted to find relationships between brain activity and scores on measures of mood and alterations in consciousness. They were not entirely successful in this ambitious goal, since the relationships they did report were only uncovered after using a more lenient test of significance (i.e. a higher probability value). Yet the authors report that some of their findings, such as an association between euphoria and decreased CBF in the left amygdala, have been replicated in investigations using other drugs (like amphetamine.) They also acknowledged that it is possible that MDMA-associated changes in CBF may not be related to psychological effects. Instead, it might be due to direct cerebrovascular effects that uncouple CBF from neuronal activity. Still, as an exploration of the connections between subjective experience and brain activity, this study stands out as a good preliminary effort. This paper also demonstrated that PET can be conducted on MDMA-naïve volunteers while they experience the peak effects of MDMA without severe psychological distress.

Greer & Tolbert (1986). Subjective reports of the effects of MDMA in a clinical setting.

Greer, G. & Tolbert, R. (1986). Subjective reports of the effects of MDMA in a clinical setting. Journal of Psychoactive Drugs, 18, 319-327.

Purpose: Summary of qualitative outcome data, preliminary psychotherapeutic outcome study; Authors present effects of MDMA-assisted psychotherapy immediately after 1 MDMA sessions and again 2 months to 2 years after sessions. "…summary report of data gathered from the first 29 people administered MDMA in a clinical setting."
Design: Non-randomized, without blinds or placebo controls; used in context of MDMA-assisted psychotherapy; number of sessions undefined, all patients took part in at least 1 MDMA-assisted psychotherapy session, receiving 75-150 mg MDMA (1 used 200 mg)., with booster dose of 50-75 mg. offered as effects of initial dose subsided and 20-40 mg propanolol or 5 mg diazepam offered to unspecified number of patients to reduce sympathomimetic effects. L-tryptophan offered to unspecified number of patients to reduce discomfort later in session.
Subjects: 29 individuals receiving MDMA-assisted psychotherapy conducted in California or New Mexico from 1980 to 1983. Information on subjects' age, gender or past experience with MDMA not provided, but examining paper indicates at least 2 women took part in study and eldest subject aged 78. Patients recruited through referrals from friends or therapists; none received therapy from author's practice.

Criteria for Inclusion – No history of hypertension, heart disease, hyperthyroidism, diabetes, hypoglycemia, seizure disorder, glaucoma, or liver dysfunction. Not currently pregnant. No history of "vocationally disabling" psychological conditions. Willingness to deal with any disturbing experience they might have while on drug. Health Exceptions - 1 subject with "essential hypertension" controlled with medication, 1 had macular edema and ocular implant.
Measures: Questionnaire - Verbally conducted interview after session(s), written follow-up questionnaire administered 2 months – 2 years later. Questionnaire contained items concerning benefits during session, undesirable effects, realization of the session's purpose, (following refer to post-session) change in psychiatric disorders, mood changes, attitudinal changes, belief changes, relationship changes, occupation changes, activity changes, spiritual and physical practice changes, substance use changes, changes in life goals, changes in experiences sought. Changes in experiences avoided, and changes in attitudes preventing self-actualization
Analysis: No formal analyses applied to data; descriptive information (number of patients experiencing a particular effect) presented. Data presented in narrative form.
Results: Session and Short-term Sequelae, Benefits during session – All patients in group or couple sessions (27 / 29) experienced increased closeness, intimacy. All patients (29 / 29) reported positive changes in their attitudes or feelings. 22 / 29 reported cognitive benefits during session. 5 / 29 reported "clear cognition." Undesirable Effects – All (29) reported some undesirable effects during session. All (29) reported some undesirable physical effects, 16 / 29 reported undesirable emotional effects and 4 / 29 reported undesirable cognitive effects during session [See details in "adverse effects"]. Realization of Session's Purpose – 28 / 29 had goal for session; 16 / 28 felt goal completely realized after session, 4 / 28 felt significant progress had been made toward goals post-session, 7 / 28 felt some goals realized while others were not realized post-session and 1 / 28 felt no goal beyond goal of satisfaction of curiosity realized after session.
Post-session Changes, Changes in Psychiatric Disorder - 9 / 29 had minor psychiatric disorders (5 with dysthymia / depression, 3 personality disorders, 1 anxiety disorder). 9 / 9 with disorders reported significant relief from problem. 2 / 9 reported "full and lasting remission" (follow-up after nine months), 7 / 9 reported improvement. 1 / 29 previously without diagnosis experienced anxiety attacks post-session and entered long-term therapy (but did not regret MDMA session). Mood Changes – 18 / 29 reported positive changes in mood post-session, mostly good feelings and mood elevation, duration, several hours – several weeks, average 1 week post-session. 2 / 29 reported increased alertness, and 1 / 29 more relaxation. Attitudinal Changes – 23 / 29 reported positive attitude changes and 7 / 29 reported negative attitude changes post-session. Belief Changes – 16 / 29 reported persisting belief changes post-session. Relationship Changes – 29 / 29 reported positive relationship changes post-session and 2 / 29 reported negative relationship changes post-session. Positive changes lasted a few days to two years (at follow up). 14 / 29 reported positive changes in relationships with people besides spouse. Occupation Change – 16 / 29 reported positive occupational changes and 2 / 29 reported negative occupational changes. 1 / 29 changed jobs post-session. Activity Changes – 6 / 29 reported changes in non-work activities (hobbies, spiritual activities) post-session, with all changes either positive or neutral. Spiritual and Physical Practice Changes – 14 / 29 reported positive changes in spiritual or physical practices (i.e. meditation, exercise). 2 / 29 experienced MDMA-like states during meditation. 3 / 29 started new exercise programs, 2 / 29 increased exercise, 1 / 29 changed diet (more "health food"). Substance Use Changes – 14 / 28 reported reduction in use of psychoactive substances and 3 / 28 reported increased use of psychoactive substances. 2 / 28 (the only cocaine users in sample) reported abstention from cocaine (1) or decrease in desire for it, but without indication of changed use (2). Changes in Life Goals – 15 / 29 changed life goals post-session, all patients implying positive changes. Changes in Experiences Sought Out – 9 / 29 reported positive changes in experiences sought in life (in relationships, life goals). Changes in Experiences Avoided – 9 / 29 reported positive changes in experiences avoided (avoiding negative goals or behaviors). Changes in Attitudes Preventing Self-Actualization – 13 / 29 reported positive changes in these attitudes (presumably a reduction in them), including increased insights into psychological problems

(7 / 29), reduced guilt (3 / 29), fewer beliefs about limited possibilities (2 / 29), less self-defeat and less defensiveness (1 / 29 each).
Overall Effects: MDMA-assisted psychotherapy did not produce any severe physical or psychological distress during the session. Most people experienced positive changes in emotion, self-awareness and (when applicable) increased closeness and intimacy with others during the session, and most also experienced some minor adverse effects as well. In all but one case, people experienced positive change or no change in psychiatric function after MDMA, and most reported improvements in previous psychiatric problems. One subject experienced anxiety attacks post-session, attributed them to the MDMA-assisted session, but did not regret having undertaken this session. Most patients reported positive changes in attitudes, beliefs and behaviors, with only a few negative changes (many related to state immediately post-session). Changes included greater commitment to goals, more open communication in relationships, improvement on the job (either feeling better on the job or actually improved conditions) and changed beliefs about the self, but with a few reports of post-session difficulty on the job and relationship break-up. Effects on substance use are mixed, with substance use sometimes increasing and sometimes decreasing post-session. Patients felt their changes in life goals were positive; often with reported changes toward more inner-directed or spiritual life goals. Follow-up questionnaires suggested that improvement may persist for months and up to 2 years. Overall, patients reported more gains than losses after MDMA-assisted therapy, but the treatment did cause some difficulties and problems.
Adverse Effects: <u>During session</u> – Lack of appetite (28 / 29) – none found it unpleasant, fatigue (4 / 29), jaw-clenching, teeth shaking (22 / 29), with jaw clenching relieved by diazepam for 2 / 22 and by propanolol in 2 / 22 cases (propanolol worsened jaw clenching for 1 subject), nausea (7 / 29), muscle tension / tightness (6 / 29), nervousness / anxiety (5 / 29), reported impaired gait (3 / 29), 2 sweating (2 / 29), feeling cold (2 / 29), brief sadness or fear (3 / 29). <u>Dose x Age</u> - Oldest subject, aged 78, received highest dose (200 mg, after no response at lower doses) and had highest number of undesirable effects; nausea, vomiting, jaw clenching, less taste for alcohol (immediately post session?), strong body odor, urinary urgency, blurred vision, brief short-term memory loss, brief impairment of depth perception and hallucination, with effects continuing for evening and day after (lack of appetite, insomnia, jaw clench through sleep, fatigue, impaired gait for 2 days. All other effects listed by 1 subject only.
<u>Post-session</u> – Fatigue (16 / 29), insomnia (11 / 29), jaw clenching (3 / 29), muscle tension (2 / 29), stomach upset (2 / 29), depression (2 / 29), All other effects listed by 1 subject only. Note: Post-session appearance or anxiety attacks for 1 subject.
Comments: This is the first published paper describing outcomes after MDMA-assisted psychotherapy, and the collected reports indicate that MDMA sessions did benefit most subjects, though it caused harm on one occasion. People had more positive attitudes about themselves and their life-goals post-session, and they reported strengthened relationships with others. However, it is difficult to draw conclusions about the utility of MDMA-assisted therapy on the basis of this paper. The study had no comparison group and neither patient nor therapists were blind to treatment. Furthermore, many of the patients were directly reporting responses to the therapists, and may have been motivated to suppress any report of lack of benefit or occurrence of harm after an MDMA session in order to please the therapist or to justify their own participation in MDMA-assisted therapy. However, despite these problems, the study suggests that, at least when conducted using Greer & Tolbert's methods, MDMA-assisted psychotherapy produces little or no detected harm to most participants and does some good in many cases.

Grob et al. (1996). Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations.

Grob, C. S., Poland, R. E., Chang, L. & Ernst, T. (1996). Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations. <u>Behavioral Brain Research</u>, 73, 103-107.

Purpose: Exploratory neuropsychological, neurophysiological and neuroendocrine study. "…inquiry into MDMA's effects into central nervous system function." (p. 104). Investigates elements of subjective experience and physiological effects in MDMA-experienced humans.
Design: Randomized double-blind mixed within-subjects / between-subjects design. All volunteers participated in all 3 conditions (placebo, MDMA-dose 1, MDMA-dose 2). 2 of 4 different dosages assigned to each subject, with doses ranging from .25 mg / kg to 1 mg / kg. 1 dose volunteers received always .25 mg / kg away from the other. No information on scheduling; on the basis of knowledge of studies, probably approximately 2 weeks between each session.
Subjects: 6 MDMA-experienced subjects, gender and age range not reported here. Recruited through local advertisements.
Criteria for Inclusion – Lack of history of major medical or psychiatric illness, no history of substance abuse or seizure disorder. Volunteers abstained from psychoactive medication or illicit drugs 1 month prior to sessions.
Measures: Mood – STAI (state anxiety scale only) and the POMS, with measures taken at baseline and immediately after session.
Alteration in Consciousness - The ASGP, administered at 15-minute intervals beginning 1 h pre-drug and continuing the duration of the session.
Physiological Effects – BP, HR and oral BT measured at 30-min intervals, with 4 samples pre-drug administration and 12 samples taken post-drug.
Neuroendocrine measures – ACTH and prolactin concentration in blood measured. Blood samples taken at 30-minute intervals beginning 2 h before drug administration (4 samples) and continuing for 6 h post-drug (12 samples drawn). ACTH was measured through a two-site IRMA procedure and prolactin was measured through a standard radioimmunassay.
Analyses: Tests of significance were not conducted in this paper. Change (delta) scores calculated by subtracting average pre-drug measures from each post-drug measure, with measures have been plotted out for each of the four dosages plus placebo.
Results: Mood and Alteration in Consciousness - Positive mood increases after MDMA, increasing in a dose-dependent manner in doses ranging from .25 mg / kg to 1 mg / kg.
Physiological Effects – .25 to 1 mg / kg MDMA modestly increase HR and BP, no clear increase in BT. HR and BP increase in a dose-dependent manner, whereas body temperature does not appear to increase in a dose-dependent manner with these dosages (.25 mg / kg to 1 mg / kg).
Neuroendocrine measures – Threshold dose for stimulating ACTH and prolactin is between .5 and .75 mg / kg of MDMA. Peak elevation of both hormones appears between three and four hours after drug administration, (examining time course plot).
Overall Effects: All volunteers tolerated MDMA at doses of .25 mg /kg to 1 mg / kg. They reported increases in arousal (alertness) and positive mood after MDMA. In doses of .25 mg / kg - 1 mg / kg, MDMA produces positive mood and a small increase in HR and blood pressure, without a great deal of state anxiety. Level of hormones thought to be related to serotonin function also increased with these low to moderate doses of MDMA.
Adverse Effects: Adverse effects are neither reported nor measured in this paper.
Comments: This paper describes the first double blind, placebo-controlled laboratory study of MDMA in humans. This paper represents preliminary findings, and the results are not subjected to formal analyses, though they are plotted out in time-course charts. However, it does offer information on the effects of a range of low to moderate doses of MDMA. Surprisingly, mood, physiological and neuroendocrine effects appear even at these relatively low doses. The sample size is small, making generalizations to general population difficult. The study this paper describes is part of a larger study that includes investigating the effects of the 4 doses of MDMA described and 6 doses above 1 mg / kg. This paper indicates that these doses of MDMA can be administered to MDMA-experienced volunteers without any severe psychological or physiological distress.

Grob et al. (In Preparation). Psychological, physiological and neuroendocrine effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") in healthy humans.

Grob, C. S., Poland, R. E., and others (In preparation). Psychological, physiological and neuroendocrine effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") in healthy humans. As of September-October 2000.

Purpose: Neuropsychological, neurophysiological, neuroendocrine: A dose-response study performed to investigate the safety and tolerability of a range of doses of MDMA, with examination of psychological, neuroendocrine and physiological effects.
Design: Ascending-dose, randomized, placebo controlled, mixed-model design, with drug state (placebo versus MDMA) a within subject factor and drug dose (.25, .5, .75, 1, 1.25, 1.5, 1.75, 2, 2.25 or 2.5 mg / kg) as a between subjects factor. All subjects took part in 3 conditions (placebo, MDMA-dose 1, MDMA-dose 2), with second dose of MDMA .25 mg / kg higher than dose 1. Each session approximately 2 weeks after previous session. Subjects: 18 MDMA-experienced subjects, 13 men, 6 women aged 19-75. Subjects recruited through local advertisements. 10 / 18 subjects also represented in Chang et al, 2000, 6 / 18 represented in Grob et al, 1996 and 14 / 18 represented in Boone et al (unpublished) neuropsychological assessment study.
Criteria for Inclusion Good health as assessed through medical examination and psychiatric interview. Used MDMA at least 3 times, with duration of use lasting at least 1 year. No personal or family history of major psychiatric disorders (in 1st degree relatives). No history of substance abuse (except for MDMA, in the case of 2 / 18 subjects). Not on any psychoactive medication and not taking illicit drugs for approximately 1 month.
Measures: Mood Measured via POMS. Anxiety measured via STAI State anxiety scale. Both measures taken at baseline and immediately after session. Alteration in Consciousness ASGP, administered at 15 minute intervals beginning 1 h pre-drug and continuing until 6 h post-drug. Physiological Effects Oral BT, systolic and diastolic BP and HR measured, with measures taken at 30-minute intervals, with 4 pre-drug measures (2 h, 1.5 h, 1 h and .5 h pre-drug) and 12 taken after drug administration from 0 h to 6 h post-drug. Neuroendocrine measures - Blood samples drawn at 30-minute intervals beginning 2 h pre-drug up to 6 h post-drug. Serum concentration of cortisol measured; details on process unavailable at present. Serum ACTH concentration was measured via two-site IRMA procedure and serum prolactin concentration measured through standard radioimmunassay.
Analysis: Psychological Effects A 2-way mixed measures ANOVA performed on ASGP scores averaged over 0 to 6 h post-drug, with drug (placebo vs. MDMA) as a within-subjects factor and dosage (.25, .5, .75, 1, 1.25, 1.5, 1.75, 2, 2.25 or 2.5 mg / kg MDMA) as a between subjects factor. Peak change from baseline for all doses analyzed via one-way ANOVA with time of measure taken during MDMA, but not placebo, administration as within-subjects variable. Post-hoc comparisons made with Tukey's test.
Physiological Effects A 2-way mixed measure ANOVA conducted on measures of HR, BT, systolic and diastolic BP averaged from 0 to 6 h post-drug, with drug (placebo vs. MDMA) as a within-subjects factor and dosage (.25-2.5 mg / kg MDMA) as a between-subjects factor. A one-way repeated-measures ANOVA performed on measures over time taken during MDMA, but not placebo, administration, with time of sample as within-subjects factor. Post-hoc tests conducted with Tukey's test.
Neuroendocrine Measures A 2-way mixed measure ANOVA was conducted on serum prolactin, cortisol and ACTH across conditions (placebo and MDMA), using the average measure from ingestion to 6 h post-ingestion. Drug (placebo versus MDMA) was a within-subjects factor, with post-hoc comparisons made via Tukey's test. Effects over time for each hormone (ACTH, cortisol and prolactin) analyzed via one-way repeated measures ANOVA with time of sample as a within-subjects factor, and with post-hoc tests performed with Tukey's test.
Results: Psychological Effects When compared with placebo, MDMA increased arousal (wakefulness, alertness). MDMA induced greater arousal in a dose dependent manner in doses of .5 mg / kg to 1.5 mg / kg, and arousal level remains the same or drops when higher doses (2.25 mg / kg and 2.5 mg / kg)

compared with lower doses. Compared with placebo, MDMA induced elevated hedonic state (positive mood, euphoria). MDMA increased hedonic state in dose-dependent manner, with higher doses of MDMA producing a greater increase in hedonic state than lower doses. Both arousal and hedonic state peaked at 1.25 h post-drug and began to decline 2.5 h post-drug.
Physiological Effects Compared with placebo, MDMA increased systolic and diastolic BP, HR and BT. Systolic BP differentially increased by different doses, but only at a level that approached significance. A greater increase in systolic BP occurred with higher doses, with systolic BP at .5 mg / kg differing from effects at 1 mg / kg and 2.25 mg / kg. MDMA also significantly increased diastolic BP. In contrast with other physiological measures, MDMA's effects on diastolic BP and HR were not dose-dependent. Diastolic BP rose with each successive dose, with doses at 1 mg / kg 1.75 mg / kg, and with the 2.5 mg / kg producing a significantly lower rise in diastolic BP than the 1 mg / kg. HR increased with each successive dose, starting from .25 mg / kg MDMA to 1.25 mg / kg. HR then declined from levels reached at 1.25 mg / kg, with the decline more marked with each successive dose from 1.75 mg / kg to 2.5 mg / kg. MDMA (compared with placebo) induced a statistically significant rise in body temperature, with rise in body temperature higher with high doses than with low doses. However, MDMA did not increase BT in a dose-dependent manner; higher doses did not consistently produce higher BT. Systolic BP peaked at 2.5 h post-drug, and diastolic BP peaked at 2 h post-drug. Elevation in HR peaked at 1.5-2 h post-drug. Rise in BT peaked at 2 h post-drug.
Neuroendocrine Effects When compared with placebo, MDMA produced a significant increase in serum ACTH, cortisol and prolactin. MDMA induces a dose-dependent rise in serum ACTH and cortisol, with higher doses producing a greater increase in these hormones. Doses from .25 mg / kg to 1 mg / kg produce significantly less rise in ACTH compard with doses of 2.25 mg / kg, doses of .25-.75 mg /kg produce a significantly smaller rise in serum cortisol than doses of 2.25 or 2.5 mg / kg. While MDMA produced what seemed to be dose-dependent increases in serum prolactin, the dose-dependent relationship did not reach significance. ACTH peaked at 1 to 2 h post-drug after MDMA. Serum cortisol peaked 2.5 3.5 h post-MDMA, and when cortisol levels are plotted across time, decline in cortisol is slow and incomplete at 8 h post-drug. Serum prolactin rises rapidly from 5. H post-drug, peaks at 1.5 2 h post drug and rapidly declines thereafter.
Overall Effects: All doses of MDMA were well tolerated by this sample of MDMA-experienced subjects, with no severe psychological or physiological distress. MDMA reliably increases arousal, hedonic state, systolic and diastolic blood pressure and body temperature. This increase was dose-dependent for hedonic state, systolic BP and perhaps BT, but the relationship between dose and response for arousal, HR and diastolic BP may be more complex. Heart rate was increased with doses of MDMA up to 1.25 mg / kg, but then HR did not increase as much with higher doses of MDMA as might be expected (though heart rate remained elevated). While MDMA-induced euphoria increases in a dose-dependent manner, alertness increased with doses up to about 1.5 mg / kg and then increases no further, perhaps declining at highest doses. Psychological effects began to appear at doses of .5 mg / kg, with a significant increase in effects often produced between 1 mg / kg and 1.25 mg / kg. MDMA produced a rise in three hormones thought to be associated with serotonergic function; prolactin, cortisol and ACTH. MDMA's effects upon concentration of ACTH and cortisol were dose-dependent, but its effects upon prolactin were less clearly dose-dependent. Effects first appeared at doses between .5 mg / kg and .75 mg / kg.
Adverse Effects: Not reported in this study. While 2 / 18 met the criteria for hypertension, they did not require medical intervention; 1 case was possibly due to unreported use of medication to treat asthma prior to a session.
Comments: This paper compares the effects of MDMA in humans at a wide range of doses, from .25 mg / kg to 2.5 mg / kg. This paper's findings concerning neurohormone release are also comparable to findings in other papers indicating that MDMA induces release of two stress hormones (ACTH and cortisol) and prolactin. However, the sample is still small for making inter-dose comparisons, and there are two few people in the lowest and highest dose conditions (2/18 in the .25 mg / kg and 2 / 18 in the 2.5 mg / kg condition) to draw firm conclusions about the effects of MDMA at very low or moderately high

doses. However, this paper does allow for comparisons of MDMA effects at different doses, with the dosage range being fairly representative of typical recreational and therapeutic doses.

Helmlin & Brenneisen (1992). Determination of psychotropic phenylalkylamine derivatives in biological matrices in high-performance liquid chromatography with photodiode-array detection.

Helmlin, H.-J., & Brenneisen, R. (1992). Determination of psychotropic phenylalkylamine derivatives in biological matrices in high-performance liquid chromatography with photodiode-array detection. Journal of Chromatography, 593, 87-94.

Purpose: Pharmacokinetic; "…it was the aim of this work to develop a selective, specific and sensitive analytical procedure using…HPLC-DAD." (p.87). Study examines MDMA and MDA concentrations found in urine of humans given 1.7 mg / kg MDMA during psychotherapy. (Study also measures mescaline and other compounds found in cacti).
Design: Within-subjects study, comparing urine collected over time (pharmacological recovery study), with MDMA administered in course of psychotherapy (non-blind, uncontrolled design). Each subject received 1.7 mg / kg MDMA. Urine from volunteers also compared with prepared "blank" and "spiked" standards.
S**ubjects**: 4 patients (gender, age and information concerning previous experience with MDMA not reported) treated by psychiatrists of the Swiss Association for Psycholytic Therapy. No information on subject recruitment provided.
Criteria for Inclusion – None reported. Willingness to participate in MDMA-assisted psychotherapy.
Measures: Concentration of MDMA and MDA in urine measured through high performance liquid chromatography with photodiode array detection (HPLC-DAD). Quantitation was performed by measuring peak areas of MDMA and MDA, using external standards. Recovery of MDMA and MDA in urine measured, with spiked samples used to determine precision of measurement.
Analysis: Urine samples analyzed and compared with external standards, as described above. Tests of significance inapplicable in this case.
Results: After oral administration, most of 1.7 mg / kg dose of MDMA is recoverable in urine. MDMA concentration found in urine ranged from 1.48 to 5.05 Ug/ml. MDA also excreted in urine as main detected metabolite, in amounts ranging from .07 to .9 Ug / ml.
Overall Effects: MDMA is recoverable in urine samples from humans who took 1.7 mg / kg orally in clinical (psychotherapy) setting. Some MDMA is metabolized into MDA, as MDA is also recoverable in urine samples. There was a greater concentration of MDMA in urine than MDA.
Adverse Effects: None reported in this study;
Comments: This paper is one of several papers that examine MDMA metabolism by seeking to detect MDMA and MDA in human urine. At least at this dosage and in this sample, most MDMA apparently travels through the body unaltered, while some (but not all) is transformed into MDA. The sample sized used (2) is exceedingly small, so the results should be accepted with caution. In addition, metabolism appears to be partially dose dependent, and higher or lower doses may be metabolized differently.

Helmlin et al. (1996). Analysis of 3,4-methylenedioxymethamphetamine (MDMA) and its metabolites in plasma and urine by HPLC-DAD and GC-MS.

Helmlin, H.-J., Bracher, K., Bourquin, D., Vonlanthen, D., Brenneisen, R. & Styk, J. (1996). Analysis of 3,4-methylenedioxymethamphetamine (MDMA) and its metabolites in plasma and urine by HPLC-DAD and GC-MS. Journal of Analytical Toxicology, 20, 432-439.

Purpose: Pharmacokinetic, chemical detection: Using HPLC-DAD to detect MDMA metabolites in blood and urine and confirming results with gas chromatography. "It was the aim of this study to

establish the analytical methodology for monitoring MDMA and its metabolites in body fluids and to investigate the pharmacokinetic behavior of MDMA in man under controlled conditions." (p. 433).
Design: Within-subjects recovery study comparing metabolites in plasma and urine over time, using 2 detection methods; liquid chromatography and gas chromatography, with samples drawn from two people over 24 h after single dose of 1.5 mg / kg MDMA administered during psychotherapy.
Subjects: 2 subjects, 1 woman, aged 40 and 1 man, and aged 23. No information on subject recruitment provided. Presence or absence of previous experience with MDMA not indicated.
Criteria for Inclusion – None reported. Willingness to undertake MDMA-assisted psychotherapy.
Measures: HPLC-DAD and GC – Performed on plasma and urine, with blood samples collected at 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 170, 190, 220, 250, 310, 380 450 and 530 min (approximately 8.5 h) after MDMA administration and urine samples collected at 0, 1.5. 3.5, 5.5, 7.5, 10, 22 and 23.75 h for one subject and at 0, 1, 1.25, 1.5, 3.75, 4.2, 5, 5.5, 6.4, 8.4, 10.5, 12.5, 16 and 21.5 h after MDMA administration. Urine preparation included enzyme hydrolysis and acidic hydrolysis. Quantitation performed for MDMA, MDA, HMMA and HMA performed at 200 nm and measuring peak areas and using internal standard method.
Analysis: Sample size too small for tests of significance. Recovery assessed in plasma and urine through comparing to prepared spiked samples of each fluid. Results produced by HPLC-DAD compared with results with gas chromatography. Concentrations compared over course of time without reporting tests of significance.
Results: Method Comparison – HPLC-DAD is a good method for pharmacokinetic profiling of MDMA and its conjugated and unconjugated metabolites in plasma or urine. HPLC-DAD with gas chromatography recommended as confirmation method.
Recovery – 98% of 1.5 mg / kg MDMA p.o. recovered from plasma, and 99% recovered in urine. Extraction of metabolites considered good to excellent. Recoveries for metabolites in urine: MDA at 100%, HMMA at 90% and HMA at 68%
Pharmacokinetics – Plasma peak level of MDMA 331 ng / ml, at 2 h post-drug. Plasma peak level of MDA 15 ng / ml, at 6 h post-drug. Inter-individual differences found in time when peak urine level recorded, with early peak in MDMA and MDA for Subject A (5 h) and late peak MDMA and MDA for Subject B (21.5 h). Peak urine concentrations of MDMA 18.12 (A), 28.1(B) Ug / ml after 5 or 21.5 h post-drug. Peak urine MDA concentrations .11-2.3 Ug / ml at 16-21.5 h post-drug. Peak HMMA at 24.6-35.1 Ug / ml and HMA at 2.1 Ug / ml (B only), measured between 16-21.5 h post-drug. HMMA could be detected between 1.5 h and 16 h post-drug. Peak values for MDA appear to match those of MDMA. Highest concentrations of HMA appeared between 5 h and 21.5 h as well. HMMA found to be the major metabolite of MDMA found in urine, with concentrations exceeding MDA and (sometimes exceeding parent drug (MDMA).
Overall Effects: Both MDMA and MDA can be found in blood after MDMA administration. Assessing concentration of MDMA and three metabolites in urine after administering 1.5 mg / kg to 2 volunteers suggests that HMMA, and not MDA, is the major metabolite of MDMA. The authors conclude that the major metabolic pathways for orally administered MDMA in humans are cleavage of the methyelenedioxy bridge, through demethylenation and conjugation.
Adverse Effects: None reported in this paper.
Comments: This paper is one of several examining the metabolic pathways for orally administered MDMA by collecting samples from humans given known quantities of MDMA under clinical circumstances. As was also the case with the earlier Helmlin paper, it is difficult (and unwise) to generalize findings from two volunteers to the general population. This is particularly true given the great variability between the volunteers in peak concentration and time of peak concentration for all compounds studied. However, it appears that roughly the same ratio of metabolites arises in all volunteers (that is, the proportion of each compound in relation to the others). Helmlin et al's findings that HMMA, and not MDA, is the predominant metabolite match the findings of Lanz et al. and Fallon et al., and contrast with Helmlin et al's earlier report of MDA as the predominant metabolite.

Henry et al. (1998). Low-dose MDMA ("Ecstasy") induces vasopressin secretion.

Henry, J. A., Fallon, J. K., Kicman, A. T., Hutt, A. J., Cowan, D. A. & Forsling, M. (1998). Low-dose MDMA ("ecstasy") induces vasopressin secretion. Lancet, 351, 1784.

Purpose: Pharmacokinetic, neuroendocrine, exploratory: to investigate effects of MDMA on AVP secretion and "whether the hyponatraemic effect of MDMA is a direct effect of AVP secretion." (p. 1784). Specific hypothesis tested – that MDMA-induced release in AVP would reduce plasma sodium count.
Design: Non-randomized controlled mixed between subjects-within subjects study design, with all volunteers taking part in 1 treatment session and 3 / 8 volunteers taking part in no-placebo control session. Baseline plasma values for AVP (antidiuretic hormone), cortisol and MDMA measured in all sessions.
Subjects: 8 normally hydrated healthy males, aged 22-32 years. Information on presence or absence of MDMA use and recruitment not provided. If same sample as Fallon et al., 1999, then all MDMA-naïve. Criteria for Inclusion – Not reported beyond "healthy." Possibly used criteria described in Fallon et al., 1999. Criteria in Fallon et al. paper: good health as apparently assessed through physical examination. Normal HR, blood pressure and liver function as assessed through laboratory tests and not currently receiving any drugs for medical condition, also not participating in any study "similar in nature.").
Measures: AVP – Plasma concentration of AVP measured with RIA (radioimmunassay), with blood sampled pre-drug ingestion, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h and 1 day (24 h) post-drug.
MDMA – Plasma concentration of MDMA measured through GC-MS (capillary gas chromatography) with MDMA concentration measured from blood drawn at pre-ingestion, 30 min, 1, 2, 4, 6, 8 and 24 h post-drug.
Cortisol, Sodium – Procedure not described for measuring plasma concentration of cortisol or sodium, measures taken from blood drawn at pre-ingestion, 30 min, 1, 2, 4, 6, 8 and 24 h post-drug).
Analysis: All data either analyzed via repeated measures ANOVA comparing baseline values to post-drug values, or paired t-tests were used. AVP and MDMA concentration correlated using Spearman's correlation coefficient.
Results: AVP – Plasma AVP reached maximum at 1 to 2 h post-drug. AVP concentrations significantly increased at 2 h post-drug when compared with baseline values. Mean AVP concentration significantly higher after MDMA compared with control session.
Cortisol – Plasma concentration increased from baseline to post-drug, but the change in plasma cortisol concentration was not statistically significant.
Sodium – Plasma sodium concentration significantly changed from baseline to 2 h post-drug, with 7 / 8 showing a decrease in plasma sodium concentration and 1 / 8 showing an increase in plasma sodium.
MDMA – Plasma AVP values did not correlate with plasma MDMA values, author states probably due to differing half-lives (6 min for AVP and "hours" for MDMA.)
Overall Effects: A relatively small (40 mg) dose of MDMA increased AVP secretion and sodium decreases as AVP concentration increases. Authors concluded that AVP increase was not related to a "generalized stress response" because MDMA at this dose did not significantly increase cortisol. The authors' hypothesis is supported (with qualifier), in that MDMA appears to stimulate AVP release, with AVP reducing (or associated with reduction in) blood sodium content. However, MDMA concentration was not correlated with AVP concentration in plasma.
Adverse Effects: None described or measured in this report.
Comments: This study is reported as a brief communication in the form of a letter to the Lancet. It is clearly an exploratory study, as the authors do not randomize control versus MDMA sessions and do not use all volunteers when comparing effects after MDMA with effects without MDMA. It is unclear as to whether a placebo was administered in the control condition. The authors fear that larger doses of MDMA could stimulate secretion of even more AVP, further lowering sodium concentration, and causing hyponatremia. Hyponatremia in association with illicit ecstasy use has occurred when people drank large

quantities of water after ecstasy ingestion. However, it appears that MDMA-related hyponatremia is not reported under conditions of normal (as opposed to excess) hydration, suggesting that MDMA-induced AVP release is insufficient to cause hyponatremia on its own. (In fact, dehydration after MDMA due to insufficient water consumption is more commonly reported). However, Henry et al's findings suggest that AVP (or other hormones) could play a role in producing some of MDMA's physiological or psychological effects.

Hensley & Cody (1999). Simultaneous determination of amphetamine, methamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA) and methylenedioxyethylamphetamine (MDEA) enantiomers by GC-MS.

Hensley D. & Cody, J. T., (1999). Simultaneous determination of amphetamine, methamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA) and methylenedioxyethylamphetamine (MDEA) enantiomers by GC-MS. Journal of Analytical Toxicology, 23, 518-523.

Purpose: Pharmacokinetic, describing and validating methods for detecting amphetamines and ring-substituted amphetamines in urine. "The methods were applied to control samples… and to a series of samples from a controlled study looking at the metabolism of MDMA." (p. 519).
Design: Methods of detection developed by comparing author-prepared concentrations of substances in urine. Measures in human volunteers used within-subjects design, with all volunteers receiving a single dose of 1.5 mg / kg MDMA and with urine sampled over time, with comparisons of MDMA and metabolites made over time. Authors state volunteers participated in "controlled" study but do not specify conditions.
Subjects: 8 subjects, gender and age unspecified, recruitment method unspecified.
Criteria for Inclusion – None reported. Willingness to ingest MDMA as part of a controlled study.
Measures: Urine samples taken "over 24 h" in 2 volunteers and "over 72 h" in 6 volunteers were analyzed with GC-MS after liquid-liquid extraction and derivitization with L-TPC. Specific times not provided but extrapolating from charts, appears samples taken at 0 h post-drug and at 2 h intervals afterwards up until 10 or 12 h post-drug; then samples at 24, 48 and 72 h post-drug. **Analysis:** No formal tests of significance applied. Human samples compared with internal standards prepared by authors. Ratios of R(-) to S(+) isomers of MDMA and MDA calculated for each sample. (Study also compares author-prepared samples of amphetamine, methamphetamine, R(-) and S(+)-enantiomers of MDMA, MDA and MDEA. Used selected ion monitoring (SIM) to compare these samples).
Results: Substance detection with both columns (DB-17 and HP-1) was found to be accurate and reliable for detecting amphetamines, including ring-substituted amphetamines. Using the HP-1 column provided higher resolution of analyte peaks. There was some difficulty in HP-1 column for measuring and differentiating enantiomers of ring-substituted amphetamines. More S(+)MDMA excreted in urine than R(-)MDMA, with excreted S(+)MDMA increasing over time whereas R(-)MDMA in urine decreased over time. This was true for all subjects, though charts suggest inter-subject differences in rate of clearance. More S(+)MDA is initially excreted than R(-)MDA, with amount of R(-)MDA gradually increasing until it exceeds amount of S(+)MDA in urine, with this reversal occurring within 36 h post-drug. All volunteers had the same pattern of S(+) to R(-)MDA excretion, but with apparent inter-subject differences in rapidity of excretions and percentage excreted for each isomer. Authors caution that accurately measuring enantiomers may be affected by purity of derivatizing agent, noting that their measurements were affected by different lots of L-TPC.
Overall Effects: The pattern of stereoselective excretion of MDMA and MDA as measured in urine was similar across a sample of 8 subjects. More S(+)MDMA was excreted as unchanged drug than R(-)MDMA, with difference in percentage of S(+)MDMA to R(-)MDMA growing over time (with S(+)MDMA always exceeding R(-)MDMA). At first volunteers excreted more S(+)MDA (metabolite of

MDMA), but the percentage of R(-)MDA gradually increased over 36 h post-drug, making R(-)MDA the predominant isomer in urine after 36 h post-drug.
Adverse Effects: None reported in this paper.
Comments: This is one of several papers investigating the pharmacokinetics of MDMA by examining samples drawn from studies performed in Switzerland. Hensley & Cody are notable for using the largest sample (comparable to those of Fallon et al). Hensley & Cody's findings appear to support others' findings of enantioselective metabolism of MDMA in humans, with one isomer metabolized more rapidly than the other. Though this paper employs a larger sample, it does not provide exact figures on recovery or clearance for each isomer of MDMA and MDA, and none of the other metabolites are measured.

Lanz et al. (1997). Enantioselective determination of 3,4-methylenedioxymethamphetamine and two of its metabolites in human urine by cyclodextrin-modified capillary zone electrophoresis.

Lanz, M., Brenneisen, R. & Thormann, W. (1997). Enantioselective determination of 3,4-methylenedioxymethamphetamine and two of its metabolites in human urine by cyclodextrin-modified capillary zone electrophoresis. Electrophoresis, 18, 1035-1043.

Purpose: Pharmacokinetic; To prepare, describe a method for separating the enantiomers of MDMA and its metabolites (specifically MDA and HMMA) and to describe stereoselectivity of metabolite excretion in human urine.
Design: Within-subjects study, with urine samples collected over time. Volunteers reportedly part of "controlled study" in Switzerland but details not provided. Urine samples drawn after administering a single dose of 1.5 mg / kg MDMA.
Subjects: 2 subjects, 1 man (PH), aged 45, weight 95 kg, 1 woman (UW), aged 24, weight 62 kg. Criteria for Inclusion – Not reported; willingness to ingest MDMA as part of "controlled study."
Measures: Enantiomers of MDMA and metabolites separated via capillary electrophoresis with a chiral selector (for detecting enantiomers). Samples compared with internal standards (blank urine and spiked samples.) Recovery studies performed on MDMA, MDA and HMMA (HMA not measured due to lack of material, as HMA too minor a metabolite). Urine samples collected at 0, 120, 240, 365, 480, 605, 720, 1445, 1800, 2190, 2880 and 4320 min post-drug. (Study also describes methods of validating detection method and comparing intraday and interday reproducability).
Analysis: No formal tests of significance conducted. Recovery calculated via comparing relative area ratios in spiked urine and standard samples containing same amount of each compound. Ratios of recovery for the R and S forms of MDMA and for detectable enantiomers of MDA and HMMA calculated for each sample. Data compared for intersubject differences.
Results: Electrophoresis able to detect R(-)MDMA and S(+)MDMA. Procedures detected 2 isomers of MDA and HMMA but unable to identify the 2 isomers. They are referred to as "1st" and "2nd" detectable forms. Most MDMA excreted unchanged (as MDMA) in both subjects; over 72 h post-drug. Over half 1.5 mg / kg MDMA excreted as MDMA; 52.4 % for PH and 37.98% for UW). R-(-)-MDMA predominant isomer in urine for both subjects. The S/R ratio after 2 h was close to 1 (.80 for PH, .86 for UW). 48 h post-drug, S/R ratios for MDMA were .032 for PH and .093 for UW. 72 h post-drug, only the R isomer of MDMA detectable in urine of PH, whereas S/R ratio in UW = .04. More MDMA excreted as (either isomer of) HMMA than (either isomer of) MDA (9.19 % HMMA vs. 4.25 % MDA for PH, and 12.88% HMMA vs. 1.53% MDA in UW). Enantoselective excretion of MDMA metabolites is time-dependent and varied across the 2 subjects. (PH showed higher excretion of "2nd detectable enantiomer" of MDA up to 30 h post-drug, then concentration of 2nd isomer in urine superceded by 1st enantiomer at 30-72 h post-drug. In UW, 2nd isomer of MDA was always greater than 1st form, but this difference decreased over time; at 72 h post-drug, nearly equal ratios of MDA enantiomers from UW samples. UW was slower in demethylating MDMA to MDA than PH. PH excreted more of 2nd isomer of HMMA whereas UW excreted more of 1st isomer of HMMA in urine. For both subjects, maximum peak of 2nd HMMA isomer to 1st HMMA isomer reached 4 h post-drug, 2.33 for PH and .933 for UW.

Overall Effects: MDMA is enantioselectively metabolized, with the S(+)form of MDMA more extensively metabolized than the R(-) isomer in both subjects, and with R isomer more likely to be excreted unchanged. The majority of 1.5 mg / kg MDMA is excreted as unmetabolized drug, followed by HMMA, then MDA. There are significant inter-subject differences in course of enantioselective metabolism of MDMA, as measured as ratios of 2 (unidentified) forms of MDA or as 2 (unidentified) forms of HMMA. It appears that one subject is slower at metabolizing MDMA into MDA.
Adverse Effects: None reported in this paper.
Comments: This investigation into the metabolism of the enantiomers of MDMA pre-dates that of Fallon et al. Unlike those researchers, Lanz et al. were unable to confirm the absolute enantiomeric identity of the MDA or HMMA they detected. Their sample size is also smaller than that of Fallon et al. (2 volunteers vs. 8 volunteers). Both papers support the existence of enantioselective metabolic pathways and preferential metabolism of S-MDMA vs. R-MDMA. The findings support the case for HMMA, but not MDA, as a major metabolite of MDMA. The findings also suggest that people may vary widely in how they metabolize MDMA over time, since both volunteers differ on several measures of metabolism.

Lester et al. (2000). The cardiovascular effects of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy).

Lester, S. J., Baggott, M., Welm, S., Schiller, N. B., Jones, R. T., Foster, E. & Mendelson, J. (2000). The cardiovascular effects of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy). Annals of Internal Medicine 133 (12), 969-973.

Purpose: Physiological, neurophysiological: To compare cardiovascular effects of .5 and 1.5 mg MDMA and three doses of the beta agonist dobutamine "…to evaluate the acute cardiovascular effects of MDMA using transthoracic two-dimensional (2D) and Doppler echocardiography." (p. 2).
Design: Placebo-controlled, ascending-dose double-blind within-subjects study, with 4 sessions; dobutamine (5, 20 and 40 Ug / kg /min in 1 session), placebo, .5 mg / kg MDMA and 1.5 mg / kg MDMA, with each session occurring at least 7 days after previous session.
Subjects: 8 MDMA-experienced volunteers (5 men, 3 women, aged 24-39, mean age = 29 + / - 5).
Criteria for Inclusion – Good health as measured through medical examination and laboratory screening. Lack of major medical or psychiatric illness, history of drug dependence (except caffeine and nicotine), no history of adverse reactions to study drugs or psychoactive drugs, and good P450 2D6 activity, as assessed through dextromethorphan phenotyping. No high risk of cardiovascular problems (cholesterol above 250 dL, smoking > 2.5 packs of cigarettes a day), and not pregnant.
Measures: Physiological (Cardiovascular) Measures – HR, systolic and diastolic BP measured at .25, .5, .75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 h after drug (placebo, dobutamine , .5 mg / kg MDMA or 1.5 mg / kg MDMA. Measures in dobutamine condition taken after ascending doses dobutamine i. v., (5 Ug/kg/min, 20 Ug/ kg / min and 40 Ug / kg / min, with doses increased every 5 min until final dose reached.
Echocardiography – Echocardiograms performed 1 h post-drug (MDMA or placebo) and during (5, 20 and 40 Ug / kg / min dobutamine), using Doppler echocardiography. End-systolic and end-diastolic volumes calculated and used for calculating average stroke volume, ejection fraction, and cardiac output. Meridional systolic wall stress calculated from cardiographic measures.
Mood Ratings – Not described here, but briefly summarized; rated strength of drug effect for each dose of MDMA and mood on-drug.
Analysis: A repeated measures ANOVA comparing cardiovascular response and echocardiogram after 5, 20 or 40 Ug / kg/ min), with drug condition (dobutamine, 5, 20, 40 Ug / kg / min), placebo, .5 mg / kg MDMA and 1.5 mg / kg MDMA) as 1 within subjects factor and time as 1 within-subjects factor. Post-hoc comparisons done via pairwise comparisons.
Results: Cardiovascular Effects (hemodynamic effects) – 1.5 mg / kg MDMA, 20 Ug / kg / min and 40 Ug / kg / min dobutamine significantly increased HR, diastolic BP and diastolic rate pressure product. .5 mg / kg MDMA and 5 Ug / kg / min did not significantly increase HR, diastolic BP, or diastolic rate

pressure product. 1.5 mg / kg MDMA produced greater increase in peak HR, systolic BP and systolic rate pressure product when compared to 20 Ug / kg / min dobutamine, but increases were not as high as with 40 Ug / kg / min dobutamine,
Echocardiography – Cardiac output increased by 1.5 mg / kg MDMA and with both the 20 and the 40 Ug / kg / min doses of dobutamine. 1.5 mg / kg MDMA produced increase in cardiac output similar to that produced by 20 Ug / kg / min dobutamine, but less than increase produced by 40 Ug / kg / min dobutamine. All doses of dobutamine decreased left ventricular end-systolic volume and increased ejection fraction. MDMA (.5 or 1.5 mg / kg) did not decrease left ventricular end-systolic volume or ejection fraction. None of the drugs produced significant increase in meridional wall stress. Meridional wall stress / ejection fraction ratio decreased with increase in dobutamine dose, with wall stress / ejection fraction ratio significantly reduced at 40 Ug / kg / min dobutamine. However, there was no differences between wall stress / ejection fraction ratio between the lower dose of MDMA (.5 mg / kg) and the higher dose (1.5 mg / kg).
Subjective effects: – Volunteers reported feelings of relaxation, increased well-being and elevated mood lasting 3 to 3.5 h. 6 / 8 rated .5 mg / kg dose of MDMA as "very weak," 2 / 8 rated it as "medium" in effect. Volunteers rated 1.5 mg / kg MDMA as "medium" to "somewhat strong" in effects.
Overall Effects: Cardiac abnormalities not recorded with either .5 mg / kg or 1.5 mg / kg MDMA in this study. Higher doses of MDMA and dobutamine produced comparable increases in cardiovascular responses and cardiac output when compared to lower doses of either drug. 1.5 mg / kg MDMA increased peak HR, systolic BP and systolic rate pressure product, with values falling between effects produced by 20 Ug / kg / min dobutamine and 40 Ug / kg / min dobutamine. While neither drug produced an increase in left ventricular wall end-diastolic volume, dobutamine, but not MDMA, decreased left ventricular wall end-systolic volume. Based on echocardiograms recorded for each drug, dobutamine, but not MDMA, has positive ionotropic effects. If MDMA is not iontropic, then it may produce more wall stress, a measure related to myocardial oxygen consumption.
Adverse Effects: None specifically reported in this study;
Comments: This is the first extensive investigation of cardiac activity after MDMA. Examining echocardiograms and comparing MDMA's effects with those of a beta agonist (dobutamine) provides more information on MDMA's cardiac effects than simple measures of heart rate and blood pressure. MDMA-induced increases in cardiac oxygen consumption may be greater than would be predicted on the basis of measured changes in heart rate and blood pressure alone. The findings in this paper suggest that recreational users of MDMA may be stressing their hearts more than might be expected when exercising vigorously (as when dancing at a rave), and this increase in cardiac stress might lead to increased risk for cardiac complications after MDMA.

Liechti et al. (2000). Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") are attenuated by the serotonin uptake inhibitor citalopram.

Liechti, M. E., Baumann, C., Gamma, A. & Vollenweider, F. X. (2000). Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. Neuropsychopharmacology, 22, 513-521.

Purpose: Neuropsychological, psychopharmacological; "…the present controlled study was undertaken to determine whether pretreatment with the highly specific 5HT uptake inhibitor citalopram would attenuate the psychoactive effects of MDMA, as measured by psychometric rating scales, in healthy human subjects." (p. 514). Specific hypothesis tested; that a 40 mg infusion of citalopram would reduce the psychological effects of 1.5 mg / kg MDMA.
Design: Randomized double blind, placebo controlled 2(Pretreatment: placebo/ citalopram) x 2 (Treatment: placebo/MDMA) within subjects design. All volunteers participated in all 4 conditions (placebo / placebo, 40 mg citalopram / placebo, placebo / 1.5 mg / kg MDMA and 40 mg citalopram / 1.5 mg / kg MDMA). Each session was conducted at least 2 weeks after the session preceding it.

Subjects: 16 mostly MDMA-naïve subjects, 12 men, 4 women, aged 21-39 years old, mean age 27.4 + / - 4.4 years, recruited at the university hospital and medical school; 15 / 16 either university students or physicians. Not all volunteers MDMA-naïve; 3 / 16 reported trying ecstasy once.
Criteria for inclusion – Healthy according to physical examination, psychiatric interview, and blood analysis. No history of major psychiatric disorders in subject or first-degree relatives, no history of head injury and no history of substance abuse. Normal "neuroticism" scores on FPI (no more than 2 standard deviations above norm).
Measures: Mood – Assessed via AM, with measures given 75 min post-treatment (at predicted peak of MDMA effects).
Alterations in Consciousness – ASC administered 75 min post-treatment.
Analyses: All data tested for normal distribution with Kolmogorov-Smirnov test. Scores on ASC scales were normally distributed, but scores for some AM scales were not normally distributed. Effects of MDMA on ASC assessed via MANOVA, with placebo and MDMA condition as within-subjects factors. A 2-way ANOVA was conducted on ASC scores, with pretreatment (placebo or citalopram) as one factor and treatment (placebo or MDMA) as another factor, with post-hoc comparisons made via Tukey's test. Due to non-normal distribution, Wilcoxon's matched pair test conducted on the AM scores. Significance set at $p. = .05$ for all tests.
Results: Duration, MDMA alone vs. Citalopram + MDMA – The effects of 1.5 mg / kg MDMA alone lasted approximately 3 h. After 40 mg citalopram pretreatment, the effects of MDMA were attenuated but lasted approximately 5 h.
Alterations in Consciousness, MDMA alone - MDMA alone increased scores on all 3 scales of the ASC, including OB, VR and AED. Greatest contributors to OB increase were "positive mood," "derealization," "alteration of sense of time," "mania-like state" and "depersonalization." Greatest contributors to increase in VR were "changed meaning of percepts," "facilitated recollection," and "facilitated imagination." Greatest contributors to increase in AED were "thought disorder," "loss of body control" and "loss of thought control
Alterations in Consciousness, Citalopram + MDMA – Significant pretreatment x treatment affects on all three item clusters of the ASC. Pretreatment with citalopram attenuated MDMA effects on OB, VR and AED scores. Specifically, citalopram pretreatment (when compared with MDMA alone) reduced ratings of "positive mood," "mania-like experience, " "derealization," "depersonalization," "alteration of sense of time," (in OB) "changed meaning of percepts," "facilitated imagination," (in VR) "thought disorder," "loss of thought control," and "loss of body control" (in AED). In all cases, citalopram pretreatment decreased the MDMA-associated increases in these scores.
Mood, MDMA Alone – MDMA increased self-ratings of "self-confidence," "heightened mood," "extroversion," "introversion," "emotional excitability," "sensitivity," and "thoughtfulness-contemplativeness." While MDMA (compared with placebo) reduced "tiredness," it increased "dazed state."
Mood, Citalopram + MDMA – Citalopram pre-treatment reduced MDMA-induced increase in ratings of: "self-confidence," "extroversion" and "efficiency-activation." Citalopram pre-treatment reduced ratings of "heightened mood," but effect only approached significance. Tendency for ratings increased by MDMA to be less increased with citalopram + MDMA. However, scores for "emotional excitability" and "sensitivity" remained high even after citalopram pre-treatment..
Overall Effects: Citalopram attenuated most of MDMA's effects; under citalopram pre-treatment, people did not experience the heightened or positive mood, extroversion, self-confidence, activation, alterations in perception, derealization or loss of body control and thought disorder usually induced by MDMA. This suggests that a large part of MDMA's effects are due to its capacity as a serotonin releaser and uptake inhibitor. However, citalopram did not reduce "emotional excitability," or "sensitivity." Also, 40 mg. citalopram only produced a 60% reduction in MDMA-induced effects rather than completely antagonizing all psychological and physiological effects. MDMA alone and with citalopram pre-treatment can be administered to a largely MDMA-naïve sample without causing severe psychological or physical distress.

Adverse Effects: Adverse effects not reported in this paper. See Liechti et al., 2000.
Comments: This paper is part of a series of papers investigating the neurochemical correlates of the psychological and physiological effects of MDMA by attempting to block or antagonize a particular pharmacological action of MDMA through pre-treatment with other drugs. The physiological effects of MDMA with citalopram pre-treatment are explored in another paper (in press as of 10 / 2000). Other pre-treatments studied include a $5HT2_A$ receptor antagonist (ketanserin) and a D2 receptor antagonist (haloperidol). This study finds that serotonin release is a very important component in producing the effects that make MDMA "MDMA-like" or "entactogenic." However, the paper also notes that some aspects of the subjective experience, such as "emotional excitability" remain even after pre-treatment with an SSRI (citalopram) indicating that at least one important correlate of MDMA's psychological effects is not mediated by serotonin release. If replicated, these findings seem to indicate that serotonin release is responsible for most, but not all, of MDMA's "entactogenic" effects.

Liechti et al. (2000). Psychological and physiological effects of MDMA ("Ecstasy") after pretreatment with the $5HT_2$ antagonist ketanserin in healthy humans.

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

Purpose: Neuropsychological, neurophysiological, psychopharmacological; "…the present study examined the effects of the $5HT2_A/_C$ antagonist ketanserin on psychological and physiological responses to MDMA (1.5 mg / kg p. o.) in healthy volunteers." (p. 397). Specific Hypothesis Tested – that ketanserin would attenuate some of MDMA's moderately hallucinogen-like effects.
Design: Randomized double blind placebo-controlled within-subjects study with a 2(Drug 1; placebo / 50 mg ketanserin) x 2(Drug 2: placebo / 1.5 mg / kg MDMA) design, where all volunteers took part in all 4 conditions (placebo / placebo, ketanserin / placebo, placebo / MDMA and ketanserin / MDMA). Sessions were separated by at least 10 days.
Subjects: 14 mostly MDMA-naïve volunteers (13 men, 1 woman, ages 21-41) recruited from Medical School and the University Hospital at Zurich. 12 / 14 volunteers MDMA-naïve; 2 volunteers had tried ecstasy once. 7 / 14 had smoked cannabis a few times and 4 / 14 had tried a hallucinogen once.
Criteria for Inclusion – No current or past medical or psychiatric illness as assessed through medical history, psychiatric interview, physical exam, ECG and blood analysis. No personal or family (1^{st} degree relative) history of major psychiatric illness, and no history of substance abuse.
Measures: Mood – Measured via AM. Anxiety assessed through STAI. Measures administered 75 min pre-drug 2, 75 min post-drug (during predicted peak effects of MDMA) and 120 min post-drug 2.
Alterations in Consciousness – Measured with ASC-AV, a revised version of ASC with additional clusters for "auditory alterations" (AA) and "vigilance reduction" (VIR). Revised ASC administered 75 min pre-drug 2, and 75 min and 120 min post-drug 2.
Physiological Effects – BP (systolic and diastolic), HR and BT measured at 75 min pre-drug 2 and 0, 60, 90, 120 and 150 min post-drug 2.
Adverse Effects – Measured through the LC. Acute adverse effects measured during session, short term sequelae measured 1 and 3 days post-session.
Debriefing – Not described; probably subject's free-response (oral or written) to requests for description of all 4 sessions and comparisons between them, apparently with request as to whether subject could identify substances used in each session.
Analysis: After confirming normal distribution of data with Kolmogorov-Smirnov test, a repeated measures ANOVA was performed on all data, with ketanserin (drug 1: placebo or 50 mg. Ketanserin), MDMA (drug 2; placebo or MDMA) and time (75 min pre-drug 2, 75 min and 120 min post-drug 2) as within-subjects factors. ASC-AV and LC scores analyzed with a repeated measures ANOVA with ketanserin (placebo or ketanserin) and MDMA (placebo or MDMA) as within-subjects factors, with

separate analyses conducted for each time of administration (75 min pre-drug 2, 75 min, 120 post-drug 2). If there were no MDMA x ketanserin x time effects, but significant interactions between each drug and time, then additional post-hoc repeated measures ANOVAs performed with drug (MDMA versus ketanserin-MDMA) and time as within-subjects factors. Post-hoc comparisons made with Tukey's test. Significance was set at p = .05

Results: Duration: MDMA vs. Ketanserin + MDMA – Effects of MDMA alone lasted, on average, 3.5 h. Effects of MDMA with ketanserin pretreatment lasted, on average, 3 h.

Mood, MDMA Alone – MDMA did not induce significant changes in STAI score. On AM scale, 1.5 mg / kg MDMA alone increased scores on "well-being," "self-confidence," "extroversion," "thoughtfulness-contemplativeness," and "emotional excitability," (emotionality, sensitivity) also "inactivity" and "dazed state."

Mood, Ketanserin + MDMA – Pretreatment with 50 mg ketanserin did not effect MDMA-generated increases in scores on positive mood ("self-confidence," "heightened mood") or "extroversion." Ketanserin attenuated MDMA-induced "emotional excitability" and "thoughtfulness" (described by some volunteers as "dreamy state.") Ketanserin pretreatment did not change time course of MDMA's effects (no drug x time interaction). While ketanserin alone and MDMA alone both increased general inactivation and dazed state, ketanserin pre-treatment attenuated MDMA-induced scores on "inactivation" and "dazed state."

Alterations in Consciousness, MDMA Alone - 1.5 mg / kg MDMA significantly increased scores in all five ASC-AV scales, OB, VR, AED, AA and VIR. Increase in OB owed due to increase in "positive mood," "mania-like state," "derealization, " "depersonalization" and "alterations in perception of time." Increase in VR due to "changes in meaning of perception." (Volunteers reported an increased vividness of perception, including an intensification of colors and tactile awareness.) AED scores increased due to "thought disorder" and "fear of loss of body control." AA (auditory alteration) slightly but significantly increased, indicating alterations in auditory perception, but no auditory hallucinations. VIR increased, indicating reduced vigilance under MDMA.

Alterations in Consciousness, Ketanserin + MDMA – Ketanserin pretreatment significantly reduced VR scores and VIR (vigilance reduction) scores, but did not reduce MDMA-induced increases in OB or AED.

Physiological Effects, MDMA Alone – MDMA significantly increased BP, HR and BT.

Physiological Measures, Ketanserin + MDMA – Ketanserin alone reduces BP, HR and BT. When examining ketanserin + MDMA, initial analysis showed no ketanserin X MDMA effect. However, post-hoc ANOVA found that ketanserin also reduced MDMA-induced increases in BT and diastolic (but not systolic) BP. Ketanserin pre-treatment did not significantly reduce MDMA-induced increases in HR.

Adverse Effects, MDMA Alone – As listed in "adverse effects," MDMA alone produced difficulty in concentration (10 / 14), dry mouth / thirst (10 / 14), impaired gait (10 / 14), dizziness (8 / 14), jaw clenching (8 / 14), lack of appetite (7 / 14), restlessness (7 / 14) and other effects listed by less than 7 / 14 (or 50%) of the sample. (See "Adverse Effects" for more details).

Adverse Effects, Ketanserin + MDMA – Ketanserin pre-treatment attenuated most adverse effects (difficulty concentrating and dizziness only in 8 / 14 in ketanserin-MDMA instead of 10 / 14, jaw clenching in 4 / 14 rather than 8 / 14, and reduction in feeling cold (3 / 14 with ketanserin vs 6 / 14 MDMA alone). Some effects unchanged (lack of appetite, palpitation – actually increased from 6 / 14 to 7 /14), and weakness (also slight increase, 6 / 14 vs. 5 / 14 with MDMA alone). However, ketanserin had little effects on short term sequelae, measured 1 and 3 days post-MDMA, though jaw- clenching 24 h later eliminated with ketanserin + MDMA (3 / 14 with MDMA alone).

Debriefing Interview – Only 5 / 14 volunteers could distinguish ketanserin alone from placebo. 9 / 14 volunteers retrospectively reported that their MDMA experience less intense under ketanserin pretreatment, and 5 / 14 reported feeling little difference between MDMA alone and ketanserin pretreatment + MDMA.

Overall Effects: MDMA alone heightened mood, caused moderate alterations in perception and moderate thought disorder. It increased blood pressure, heart rate and body temperature, and produced some acute adverse effects, as listed above. Ketanserin antagonized perceptual alteration and emotional excitability,

and it reduced MDMA's effects on diastolic BP and BT. (Ketanserin did not significantly reduce MDMA-induced increase in HR.) While both ketanserin and MDMA alone increased scores for "inactivity" or "dazed state," and MDMA reduced "vigilance" combining the two produced a lesser increase in "inactivity" or "dazed state." MDMA alone was well tolerated when administered alone and with ketanserin pre-treatment. Most of the volunteers noticed that MDMA after ketanserin pretreatment was less intense, but a significant minority did not notice much of a difference between the 2 conditions. The authors' hypothesis is largely supported; ketanserin pretreatment specifically reduced MDMA-induced increases in diastolic BP, VR scores on the ASC, and some side effects common to hallucinogens (dizziness, difficulty concentrating). In addition, ketanserin pretreatment reduced MDMA-induced rise in BT, an effect not necessarily predicted from $5HT2_A$ receptor antagonism, and it acutely reduced some side effects more commonly associated with amphetamines (jaw clenching).
Adverse Effects: Acute - Difficulty concentrating (10 / 14), dry mouth / thirst (10 / 14), impaired gait (8 / 14), dizziness (8 / 14), jaw clenching-trismus (8 / 14), lack of appetite (7 / 14), restlessness (7 / 14), drowsiness (6 / 14), palpitations (6 / 14), being cold (6 / 14), inner tension (6 / 14); Mentioned by 5/ 14 or less (less than half of the subjects), nausea, transpiration, weakness, lack of energy, brooding, tremor, anxiety.
24 h later – Dry mouth / thirst (5 / 14), lack of appetite (4 / 14), drowsiness (4 / 14), jaw clenching (3 / 14), brooding (3 / 14), weakness (3 / 14), lack of energy (3 / 14) and in less than 3 / 14 subjects, difficulty concentrating, restlessness, transpiration, insomnia, hypersomnia
3 days later – Drowsiness (2 / 14). Only reported by one subject (1/ 14): dry mouth, jaw clenching, restlessness, inner tension, lack of energy, brooding, anxiety, hypersomnia.
Comments: This paper is one is a series investigating the neurotransmitter systems involved in producing MDMA's effects in humans. $5HT2_A$ and / or 5HT2c receptors play a role in the stimulus properties of MDMA (subjective experience associated with the drug), and ketanserin reduced some (but not all) physiological effects and unwanted effects. It is interesting to note that citalopram did not alter MDMA-induced changes in emotional excitability whereas ketanserin did attenuate this effect. This study demonstrates that MDMA can be administered to MDMA-naïve subjects, with or without ketanserin pre-treatment, without producing severe psychological or physiological distress.

Liechti & Vollenweider (2000). Acute psychological and physiological effects of MDMA ("Ecstasy") after treatment with haloperidol in normal healthy humans.

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

Purpose: Neuropsychological, neurophysiological, psychopharmacological: "…the present study examined the effects of the dopamine D2 antagonist haloperidol (1.4 mg i.v.) on the psychological and physiological responses to MDMA (1.5 mg / kg) in healthy human volunteers." (p. 290). Specific hypothesis tested – that haloperidol would attenuate some of MDMA's stimulant-like effects (not listed; assume referring to positive mood, activation, increase in BP and HR).
Design: Randomized double-blind placebo controlled 2(pretreatment: placebo or 1.4 mg haloperidol) x 2(treatment: placebo or 1.5 mg / kg MDMA) within-subjects design. All volunteers took part in all 4 conditions (placebo / placebo, haloperidol / placebo, placebo / MDMA and haloperidol / MDMA), with each session scheduled at least 10 days after a previous session.
Subjects: 14 mostly MDMA-naïve volunteers (9 men, 8 women, aged 21-38, average age 26, recruited from the University Hospital and the Medical School in Zurich; all but one were students or physicians. 13 / 14 volunteers were MDMA-naïve; 1 / 14 had tried ecstasy. 7 / 14 had smoked cannabis a few times, and 3 / 14 had tried a hallucinogen once. 2 / 14 current "light" smokers.
Criteria for Inclusion – Healthy as assessed through psychiatric interview, medical examination, ECG, blood analysis. No history of major medical illness and no history of personal or family (1^{st} degree

relative) major psychiatric illness, and no history of substance abuse. "Neuroticism" scores on the FPI within normal range (could not be 2 standard deviations above norm).
Alterations in Consciousness – Measured via ASC, with measures administered shortly after drug 2 (MDMA or placebo), 75 and 120 min after drug 2 administration.
Physiological Effects – BP and HR measured with subject in sitting position, and BT measured with an auxiliary clinical thermometer. Blood pressure, HR and body temperature measured at 0, 75, 120 after drug 2 administration.
Adverse Effects – Measured with LC, with adverse effects and short-term sequelae assessed during session, 1 and 2 days after session.
Debriefing Interview – Open-ended retrospective report of each session and subject's comparisons between sessions, and requests as to whether volunteers could identify substance administered in each condition.
Analysis: Mood and Alterations in Consciousness – AM and ASC scores analyzed in separate repeated measure ANOVAs, with haloperidol (placebo vs. haloperidol) as one factor and MDMA (placebo vs. MDMA) as another factor. STAI state anxiety scores analyzed via 3-way repeated-measures ANOVA, with haloperidol, MDMA and time (0, 75 and 120 min post-drug) as factors.
Physiological Effects – BP, HR and BT analyzed via 3-way ANOVA, with haloperidol, MDMA and time (0, 75 and 120 minutes post-drug) as factors.
Adverse Effects & Short Term Sequelae – LC scores for adverse effects compared at each time point (during session, 24 h post-drug, 3 days post-drug) with 2-way repeated measures ANOVAs with haloperidol and MDMA as 2 within-subjects factors.
All Data – Post-hoc comparisons were made using Tukey's test or simple effect tests. Significance value set at p. = .05.
Results: Duration, MDMA vs. Haloperidol + MDMA. 1.5 mg / kg MDMA alone produced effects lasting (average) 3.5 – 4 h. No differences in duration reported with haloperidol + MDMA.
Mood, MDMA Alone – MDMA increases ratings of well-being and emotional excitability (emotionality, sensitivity). MDMA had no effect on state anxiety scores at 75 min post-drug but (compared to placebo) significantly decreases state anxiety scores at 120 minutes post drug.
Mood, Haloperidol + MDMA – Haloperidol alone increased scores in "inactivation." No haloperidol x MDMA interaction, but haloperidol pretreatment decreased MDMA-induced increase in ratings of "well being." Haloperidol did not reduce MDMA-induced "emotional excitability." There was a significant MDMA x Haloperidol x Time interaction for STAI state anxiety score. While MDMA alone became anxiolytic over time and haloperidol alone increased state anxiety (compared with placebo) at both 75 min and 120 min post-drug, haloperidol + MDMA increased state anxiety at 75 min post-drug, with anxiety scores declining from 75 min post-drug at 120 min post drug. Haloperidol + MDMA produced anxiety scores that were higher than anxiety scores under haloperidol alone.
Alteration in Consciousness, MDMA Alone – MDMA increased all 3 ASC clusters; OB, AED and VR, compared with placebo. OB scores increased due to increase in "positive mood," "alteration in sense of time," "mania-like state," "derealization." AED scores increase due to increased ratings of "thought disorder," "loss of thought control," "loss of body control." VR scores increased due to increased ratings of "changes in meaning of percepts."
Alteration in Consciousness, Haloperidol + MDMA – Compared with MDMA alone, haloperidol + MDMA reduced OB, due to reduction in rated "positive mood" and "mania-like state," and increased AED, due to increase in ratings of "anxious derealization." No changes in VR reported.
Physiological Measures, MDMA Alone – MDMA increased systolic BP, diastolic BP, and HR, but not BT.
Physiological Measures, Haloperidol + MDMA – Haloperidol pretreatment did not reduce MDMA-induced increase in systolic or diastolic BP. Haloperidol alone decreased HR, but haloperidol pretreatment did not significantly reduce MDMA-induced increase in HR.
Adverse Effects, MDMA Alone – MDMA produced a number of adverse effects (see "Adverse Effects" for details) including jaw clenching, dry mouth / thirst, loss of appetite, difficulty concentrating and

impaired gait, when compared with placebo. Short-term sequelae at 1 day and 3 days post-MDMA (see below for more details) included fatigue, lack of appetite, thirst /dry mouth, insomnia, difficulty concentrating and weakness, and lack of energy.
Adverse Effects, Haloperidol + MDMA – Haloperidol alone produced fatigue (11 / 14), and occasionally restlessness (3 / 14) and difficulty concentrating (3 / 14). Haloperidol pretreatment decreased some of MDMA's adverse effects (jaw clenching, from 10 / 14 to 7 / 14), thirst / dry mouth (from 8 / 14 to 3 /14) and lack of appetite (from 7 / 14 to 4 / 14). However, haloperidol increased other MDMA-induced adverse effects, including difficulty concentrating (from 7 / 14 to 12 / 14), fatigue (from 4 / 14 to 8 / 14), restlessness (from 4 / 14 to 8 / 14) and inner tension (from 2 / 14 to 7 / 14). Haloperidol either did not alter or moderately increased other adverse effects (impaired gait, palpitations, vertigo, tremor). Haloperidol produced no significant changes in MDMA's short-term sequelae at 1 or 3 days post-drug.
Debriefing Interview – Discomfort and anxiety not reported under either haloperidol or MDMA alone, but were reported for the haloperidol + MDMA condition. Volunteers reported noticeable reduction in MDMA-induced rise in positive mood. Volunteers reported anxiety at drug onset in haloperidol + MDMA condition that disappeared after 1 h post-drug. 8 / 14 could not distinguish haloperidol from placebo. 13 / 14 rated study as positive experience. 7 / 14 expressed interest in taking MDMA in controlled setting, 13 / 14 did not express interest in recreational use of MDMA.
Overall Effects: 1.5 mg / kg MDMA alone increased positive mood, emotional excitability, and well-being, with a decrease in state anxiety during peak drug effects (120 min post-drug) and alterations in consciousness such as altered perception of time, thought disorders, loss of thought and body control and change in meaning of percepts. MDMA alone also increased systolic and diastolic blood pressure, heart rate, and the adverse effects listed below. When MDMA was preceded by an intravenous infusion of 1.5 mg haloperidol, well-being and positive mood were no longer increased by MDMA, and state anxiety at 75 was greater than with either drug alone. Haloperidol pre-treatment did not reduce MDMA-induced increase in systolic or diastolic BP, and it did not significantly reduce MDMA-induced increase in heart rate. Haloperidol decreased some adverse effects (jaw clenching, dry mouth) while increasing other adverse effects (especially difficulty concentrating, inner tension and fatigue.) The authors hypothesis was partially confirmed; haloperidol reduced positive mood and euphoria, both believed to be induced through dopaminergic pathways, and it reduced adverse effects believed to be "stimulant-like," such as jaw clenching, dry mouth, and lack of appetite. However, haloperidol did not reduce stimulant-like physiological effects, such as increased BP and HR.
Adverse Effects: During Session - Jaw clenching (10 / 14), dry mouth / thirst (8 / 14), lack of appetite 7 / 14), difficulty concentrating (7 / 14), impaired balance / gait (6 / 14), fatigue (5 / 14), restlessness (4 / 14). These experienced by less than 4 / 14; palpitations, vertigo, tremor, inner tension.
1 day post-drug – Fatigue (7 / 14), loss of appetite (7 / 14), thirst / dry mouth (5 / 14), insomnia (5 / 14), difficulty concentrating (4 / 14), weakness (4 / 14) and headache (4 / 14).
3 Days post-drug – Fatigue (4 / 14), lack of appetite (4 / 14), lack of energy (3 / 14).
Comments: This paper reports is one of several investigating the neurotransmitter systems involved in producing MDMA's effects in humans. As might be expected when considering other dopaminergic drugs, the findings in this paper suggest that dopamine plays a role in MDMA-induced positive mood and euphoria; D2 blockade with haloperidol reduced MDMA-induced positive mood and euphoria, and state anxiety is increased during drug onset. However, D2 receptors have far less influence over MDMA's effects on blood pressure, heart rate and body temperature. Changes in state anxiety over time evident under haloperidol pretreatment with MDMA suggest a possible avenue for further research into temporal changes in MDMA's effects. MDMA alone was well tolerated by volunteers, most of them MDMA-naïve, without any signs of psychological distress. Combining MDMA with haloperidol produces some discomfort, anxiety and minor distress. Despite the discomfort generated by haloperidol pre-treatment, nearly all volunteers still viewed the study as a positive experience. On the basis of the findings reported here, it would appear that haloperidol is not a good choice for coadministration with MDMA and is probably a poor intervention in cases of MDMA-produced distress.

Liechti & Vollenweider (2000). The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of MDMA ("Ecstasy") in healthy volunteers.

Liechti, M. E. & Vollenweider, F. X. (2000). The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of MDMA ("Ecstasy") in healthy volunteers. Journal of Psychopharmacology, 14 (3), 269-274.

Purpose: Neurophysiological, psychopharmacological: "…the current study was undertaken to determine whether pretreatment with the highly specific serotonin uptake inhibitor citalopram (40 mg i. v.) would attenuate cardiovascular, hyperthermic and vegetative effects of MDMA (1.5 mg/kg p.o.) in healthy human volunteers…" (p. 3 in manuscript). Specific hypothesis tested – that citalopram would attenuate physiological and adverse effects of MDMA.
Design: Randomized, placebo controlled double-blind 2(Pretreatment; placebo or 40 mg. Citalopram) x 2(treatment; placebo or 1.5 mg / kg MDMA) within subjects design. All volunteers took part in all 4 conditions; placebo/placebo, citalopram / placebo, placebo/ MDMA, citalopram / MDMA. Female volunteers tested during perimenstrual phase to reduce any variations due to menstrual cycle.
Subjects: 16 mostly MDMA-naïve subjects, 12 men, 4 women aged 21-39, recruited from the University Hospital or the Medical School. All but one were students or physicians. 13 / 16 MDMA-naïve; 6 / 16 had minor recreational drug experience; 2 / 16 had tried ecstasy, 3/16 had tried a hallucinogen and 1/16 had tried both ecstasy and a hallucinogen. (Same sample featured in Liechti et al., 2000; Psychological effects of citalopram).
Criteria for Inclusion – Healthy as assessed via medical history, medical examination and psychiatric interview, ECG and blood analysis. No history of substance abuse, no personal or family history (in 1st degree relatives) of major psychiatric illness, and no history of head injury. Normal "neuroticism" scores on FPI, with scores no more than 2 standard deviations above norm.
Measures: Physiological Measures – BP and HR measured by automated device with subject in sitting position. Measures taken at 0, 60 and 120 min after MDMA or placebo ingestion. BT measured, with measures taken at 0, 60 and 120 min after drug 2 (MDMA or placebo) ingestion.
Adverse Effects and Short-Term Sequelae – Measured with LC, with volunteers responding to LC during the session, 24 h (1 day), 72 h (3 days) and 2 weeks post-session.
Debriefing Interview – Conducted after all 4 sessions completed; volunteers provided retrospective reports of each session, compared each session with the others and answered requests for information about whether they could identify substances used in each session, and their future interest in controlled and recreational use of MDMA.
Analysis: Physiological Effects – HR, BT and BP analyzed via 2-way repeated measures ANOVA, with drug (MDMA vs. placebo) and time (0, 60 and 120 min post-drug) as within-subjects measures. Post-hoc comparisons made with Tukey's test. Specific inhibiting effect of citalopram on MDMA effects assessed with 2 separate 2-way repeated measures ANOVAs for 60 min and 120 min, with pretreatment (placebo or 40 mg. citalopram) and treatment (placebo or 1.5 mg / kg MDMA) as within-subjects factors.
Adverse Effects – Responses to LC analyzed with 1-way repeated measures ANOVAs, with all 4 conditions (placebo/placebo, citalopram/placebo, placebo/MDMA, citalopram/MDMA) as within-subjects factors. 4 separate analyses performed for LC at each time point (during session, 24 h later, 3 days later, 2 weeks later). Post-hoc comparisons performed via Tukey's test.
Results: Physiological measures, MDMA Alone – MDMA increased systolic and diastolic BP (60 and 120 min) compared with placebo and with baseline values. MDMA also elevated HR, compared with placebo or pre-drug values at both time points, and slightly but significantly elevated BT at both time points.
Physiological Effects, Citalopram + MDMA – Citalopram pretreatment reduced MDMA-induced increases in systolic and diastolic BP at 120 min, and systolic (but not diastolic) BP at 60 min. Citalopram reduced MDMA-induced increase in HR at 60 min but not at 120 min. Citalopram pretreatment did not reduce MDMA-induced increase in BT.

Adverse Effects, MDMA Alone, Acute – (See details in "Adverse Effects). MDMA alone produced difficulty concentrating, dizziness, lack of appetite, impaired gait, restlessness, restless legs, and jaw-clenching. 1 and 3 days post-drug – Short-term sequelae included lack of appetite, headache, difficulty concentrating, fatigue, exhaustability (after 1 day) with lack of appetite, difficulty concentrating sometimes lasting up to 3 days, 1/3 (3/16-4/16) reported irritability, gloomy thoughts and brooding at 3 days.
Adverse effects, Citalopram Alone – Citalopram alone produced tiredness (11/16), nausea without vomiting (6 / 16) and headache (5 / 16).
Adverse Effects, Citalopram + MDMA, Acute – Citalopram reduced most reported acute adverse effects, but increased inner tension (from 3 / 16 to 8 / 16). Citalopram did not significantly reduce short-term sequelae at either 1 or 3 days post-session (citalopram pretreatment reduced some short-term sequelae, but reduction not statistically significant).
Adverse Effects, 2 weeks post-session – No sign of any reported adverse effects after 2 weeks for all conditions.
Debriefing Interview – All volunteers reported MDMA-induced effects reduced in citalopram + MDMA condition. 8 / 16 unable to distinguish citalopram from placebo and 1 / 16 unable to distinguish MDMA from placebo. 14 / 16 volunteers had a pleasant experience overall, 2 / 16 reacted with moderate anxiety 1 to MDMA alone, one to citalopram alone). 7 / 16 reported they would consider taking MDMA again in a controlled setting, but none expressed interest in recreational use of MDMA.
Overall Effects: MDMA increased HR, BP and BT; it also produced acute and sub-acute side effects. Citalopram, an SSRI, reduced some, but not all, components of the physiological response to MDMA; heart rate, systolic and diastolic BP are reduced, but citalopram did not reduce MDMA-induced increase in BT or MDMA-induced increase in diastolic BP at 60 min post-drug. Citalopram also reduced many acute adverse effects, though it increased inner tension. It did not significantly reduce short-term sequelae measured 1 and 3 days later. The authors' hypothesis was partially confirmed; citalopram reduced MDMA-induced increase in BP and some adverse effects possibly related to serotonin release, (lack of appetite, dizziness / vertigo). However, citalopram did not reduce MDMA-induced increases in BT despite indications that BT is under serotonergic control, but citalopram did partially reduce MDMA-induced increase in HR, previously assumed to be largely controlled by dopaminergic or noradrenergic systems.
Adverse Effects: Acute – difficulty concentrating (10 / 16), dizziness / vertigo (8 / 16), impaired balance / gait (8 / 16), lack of appetite (8 / 16), thirst (7 / 16), jaw clenching (7 / 16)restlessness (7 / 16), restless legs (7 / 16) and inner tension (3 / 16).
Sub-Acute – I day post-drug: Headache (7 / 16), lack of appetite (6 / 16), fatigue (6 / 16), exhaustibility (5 / 16), difficulty concentrating (4 / 16), weakness (3 / 16), lack of energy (3 / 16). 3 days post-drug: Irritability (4 / 16), brooding (4 / 16), gloomy thoughts (3 / 16). No effects reported 2 weeks post-drug.
Comments: This paper is a companion to the Liechti, Baumann et al., 2000 paper investigating the effects of citalopram pretreatment upon MDMA's psychological effects in humans. The findings in this paper suggest that serotonin release plays an important role in generating "MDMA-like" or entactogenic effects. However, the findings also confirm a role for other neurotransmitters or receptors in producing MDMA's effects. Most (but not all) volunteers reported that participating in this study was pleasant, none of the volunteers experienced severe psychological or physical discomfort after MDMA, with or without citalopram pretreatment.

Liechti et al. (2001). Gender differences in the subjective effects of MDMA.

Liechti, M. E., Gamma, A. & Vollenweider, F. X. (2001). Gender differences in the subjective effects of MDMA. Psychopharmacology Online, DOI 10.1007/ s002130000648 published on-line January 19, 2001.

Purpose: Neuropsychological, physiological; Investigation performed to test the hypothesis that "women may show stronger psychological responses to the 5HT releaser MDMA."
Design: Randomized, double blind placebo controlled within-subjects design for all studies. Subjects in 2 studies participated in 1 placebo session and 1 MDMA session, receiving 1.7 mg / kg MDMA. Subjects in Study 3 participated in a 2(Pretreatment) x 2(1.5 mg / kg MDMA) within subjects study. Only the placebo / placebo and placebo / MDMA conditions were used for analysis in this paper. Actual doses in Studies 1 and 2 ranged from 1.64 mg / kg to 1.8 mg / kg, MDMA, and dosage ranges in Study 3 ranged from 1.35 – 1.77 mg / kg MDMA. Specific Hypothesis Tested – that women would have more a stronger psychological response to MDMA than men.
Subjects: 74 university students and hospital staff, (54 men, 20 women), ages 20-49, mean = 27, recruited from university hospital staff and medical school. 69 / 74 were MDMA-naïve, while 5 / 74 had tried ecstasy once or twice. In addition, 22 of the 45 individuals who took part in Study 3 had received MDMA plus pre-treatment before receiving MDMA without pretreatment. (Same samples featured in Vollenweider et al, 1998, Gamma et al, 2000, Liechti, Baumann et al, 2000, Liechti, Saur et al, 2000 and Liechti & Vollenweider, 2000).
Criteria for Inclusion - Healthy according to physical examination, psychiatric interview, and blood analysis. No history of major psychiatric disorders in subject or first-degree relatives, and no history of alcohol or substance abuse. Normal "neuroticism" scores on FPI (no more than 2 standard deviations above norm).
Measures: Mood – Mood was measured by the AM, administered at time of peak MDMA effects, at 105 and 120 min after drug administration (either placebo or MDMA).
Alterations in Consciousness – Alterations in consciousness were measured via the ASC at the time of peak MDMA effects, at 105 and 120 min after drug administration.
Physiological Measures – HR, systolic and diastolic BP, and BT measured at 0, 60, 90, 120 and 150 minutes after drug administration.
Adverse Effects – Self-reported side effects and short-term sequelae 24 h post-drug were measured via LC, administered while subjects experienced acute effects and 24 h after drug administration.
Analyses: All variables – Peak scores for mood, alterations in consciousness, HR, BP, BT, self-reported side effects and short term sequelae analyzed via a 2 x 2 ANOVA, with drug (placebo or MDMA) serving as a within-subjects factor and gender (male or female) serving as a between-subjects factor. Post-hoc comparisons were made via Tukey's test.
Dose Effects – Spearman's rank order correlations were used to test for a relationship between dose of MDMA and peak psychological and physiological effects of MDMA.
Results: Duration of Effects – The subjective effects of MDMA lasted for a mean of 3.5 h after drug administration. There were no gender effects.
Mood – Men reported being more activated or energetic after MDMA than did women. More women experienced increases in anxiety and depression after MDMA than did men, with increased anxiety and depression related to feelings of helplessness, defenselessness and an increased need for protection. A significant correlation was found between MDMA dosage and anxiety scores in women, but not in men. The only significant gender differences for AM scores in the placebo condition were for sensitivity and thoughtfulness, with women scoring higher on both of these scales than men.
Alterations in Consciousness – MDMA produced a greater increase in all three dimensions of the ASC in women when compared with men, including the OB, AED and VR dimensions. Gender differences in MDMA effects were most pronounced on the VR scale, with women experiencing much greater increases in perceptual changes compared to men. More women than men reported feeling "carefree," "free of

worries and obligations," "boundless joy" and "comprehensive love." Women also reported greater increases in "wonderful other world," "at one with surroundings," "dream-like state of the perception of space and time," "physical sensations more pleasurable" (OB). Women were more likely than men to report experiencing thought disorders (accelerated thinking, impaired decision-making, losing track of thoughts) and fear of loss of body control (AED). More women than men reported "objects had a new and unfamiliar meaning," "minor things carried a particular meaning," facilitated recall ("recalled long forgotten things") and facilitated imagination ("extraordinarily vivid imagination") (VR). Elementary hallucinations (flashes of light, simple patterns) reported in both genders, but women reported experiencing more of them, and more visual (pseudo)-hallucinations. No significant gender differences for the ASC were found in the placebo condition. As dosage increased, women, but not men, experienced an increase in VR scores. Neither OB nor AED scores increased with dosage.
Physiological Effects – While MDMA significantly increased systolic BP in both genders, the increase was significantly greater in men compared with women. While MDMA increased HR in both genders, the difference was only significantly different from placebo in men. MDMA also produced a significant increase in BT in men, while it did not produce a significant increase in BT in women. There were no correlations between MDMA dose and elevation of BP or BT.
Adverse Effects – A significantly greater percentage of women reported experiencing most of the acute adverse effects (side effects) measured, with the exception of nausea and sweating, more often experienced by men than by women. For example, gender differences exist for all the most commonly reported effects; difficulty concentrating (59% all, 75% women versus 54% men), jaw clenching (60% all; 65% women versus 56% men), loss of appetite (54% all; 75% women versus 46% men), dry mouth (53% all; 65% women versus 48% men). Compare sweating, sweaty palms (31% all; 20% women versus 35% men) and nausea (15% all; 10% women versus 17% men).
Short Term Sequelae – A greater percentage of women reported experiencing short-term sequelae 24 h after MDMA than did men. Gender differences were found in the frequency of commonly reported short term sequelae, such as fatigue (41% all; 55% women versus 35% men), lack of appetite (39% all, 50% women, 35% men), difficulty concentrating (28% all, 30% women, 28% men), dry mouth (34% all; 60% women versus 24% men), headache (27% all; 35% women versus 24% men), lack of energy (24% all; 40% women, 19% men), insomnia (24% all; 30% women, 22% men), and jaw clenching (20% all, 25% women, 19% men). Men reported more sweating (12% all; 5% women versus 15% men) and restless legs (11% all; 5% women versus 13% men).

Overall Effects: After pooling data from 3 separate studies, the authors detected gender differences in psychological and physiological effects of MDMA. The MDMA-induced increases in all three scales of the ASC were greater in women than in men, and this was particularly pronounced for the VR scale, a measure of changes in perception. Women were more likely to experience anxiety or dysphoric reactions acutely after MDMA, with anxiety related to feeling helpless. There was a relationship between MDMA dosage and increase in VR for women, but not for men (at a dose range of 1.35 – 1.8 mg / kg MDMA). The MDMA-induced increase in systolic blood pressure was greater for men than for women, and increases in heart rate and body temperature acutely after MDMA were only significantly higher in men. Acute side effects were more frequently reported by women than by men, with this being true for the most common side effects, such as loss of appetite, jaw clenching and difficulty concentrating. Sweating and nausea were the only acute side effects more frequently reported by men. More women than men also reported experiencing short term sequelae 24 hours after MDMA administration, such as fatigue, continued lack of appetite and continued jaw tension. Only sweating and restless legs were more frequently reported in men. The authors' hypothesis is largely confirmed, in that women experienced greater alterations in consciousness, more anxiety and more acute adverse effects and short-term sequelae than men. However, finding higher elevation in systolic blood pressure acutely after MDMA in men, and finding a trend for the physiological effects to be greater in men than in women suggests that men may be more sensitive to the sympathomimetic actions of MDMA. In addition, women's experience with

MDMA was qualitatively different from men's (rather than simply more intense) in that there were more "hallucinogen-like" alterations in perception and meaning, more thought disorder and less activation.
Adverse Effects: See above for most commonly listed effects. Acute – Impaired balance (49% all, 50% women, 48% men), restless legs (40% all, 40% women, 41% men), sensitivity to cold (41% all, 50% women, 37% men), dizziness (38% all, 40% women, 38% men), palpitations (35% all, 50% women, 30% men), restless (34% all, 35% women, 33% men), being cold (34% all, 45% women, 30% men), sweating (30% all, 20% women, 35% men), forgetfulness (28% all, 40% women, 24% men), heavy legs (21% all, 50% women, 19% men), fatigue (26% all, 35% women, 22% men), weakness (26% all, 35% women, 22% men). Listed by >25% of 74 subjects: hot flushes, parasthesia, tremor, inner tension, brooding, nausea, lack of energy, exhaustability, (listed by >15% of 74) frequent urge to urinate, headache, anxiety, irritability, increased appetite, muscle ache
Short Term Sequelae – See above for commonly reported sub-acute effects. Exhaustibility (19% all, 30% women, 15% men), brooding (18% all, 20% women, 16% men), hot flushes (15% all; 20% women, 13% men), sweating (12% all; 5% women, 15% men), restless legs (11% all, 5% women, 13% men), heavy legs (12% all, 20% women, 9% men), restlessness (12% all, 15% women, 11% men), sensitivity to cold (12% all, 10% women, 13% men), forgetfulness (11% all, 10% women, 11% men). Listed by >10% of 74: Being cold, tremor, inner tension, impaired balance, dizziness, palpitations, bad dreams, irritability. Listed 3% or less: muscle aches, increased appetite, anxiety, parasthesia, and nausea
Comments: While a couple of retrospective studies of ecstasy users have found gender differences the effects of MDMA, this is the first paper that has found gender differences in the effects of MDMA in controlled clinical studies. The higher frequency of acute adverse effects and short-term sequelae reported in women than men has been reported in retrospective studies. Other gender differences in this paper could not be predicted by examining past reports. Specifically, the differences in subjective effects reported by women were not simply greater than those reported by men, but possibly qualitatively different as well. While women were found to be more sensitive to the acute effects of MDMA on perception and thought, men seemed to be more sensitive to the sympathomimetic effects of MDMA. These findings are likely to stimulate further research into gender differences in the effects of MDMA and how these differences may influence the course of use in therapeutic and non-medical settings. One limitation of this report is the disparate number of men to women in this sample. By pooling and presenting data from three previously published studies, this paper is also notable as a clinical report with a large sample size.

Liechti et al. (2001) Effects of MDMA (Ecstasy) on pre-pulse inhibition.

Liechti, M. E., Geyer, M. A., Hell, D. & Vollenweider, F. X. (2001). Effects of MDMA (Ecstasy) on pre-pulse inhibition and habituation of startle in humans after pretreatment with citalopram, haloperidol, or ketanserin. Neuropsychopharmacology, 24, 240-252.

Purpose: Neuropsychological, psychopharmacological; investigation undertaken to replicate an earlier study that found an MDMA-induced increase in pre-pulse inhibition (PPI) in humans and an investigation of the neurotransmitter systems responsible for this increase. Specific hypotheses tested – 1). That MDMA would produce an increase in PPI in humans 2). That the SSRI citalopram would attenuate the MDMA-induced increase in PPI in humans and 3). That psychological changes produced by MDMA would be associated with differences in percentage of PPI (%PPI) or habituation (% habituation).
Design: All 3 studies used experimental 2 x 2,within-subjects designs, with pretreatment (placebo versus pretreatment drug) and treatment (placebo versus 1.5 mg / kg MDMA) each serving as within-subject factors. All subjects participated in 4 treatment conditions (placebo / placebo, pretreatment / placebo, placebo / MDMA, and pretreatment / MDMA), with intervals of at least two weeks between each experimental session. Each study featured a different pretreatment: 16 / 44 received citalopram pretreatment (40 mg IV), 14 / 44 received haloperidol (D2 antagonist) pretreatment (1.4 mg IV) and 14 / 44 received ketanserin ($5HT2_{A/C}$ antagonist) pretreatment (50 mg PO). Data were pooled across all

studies and comparisons were made between MDMA and placebo when investigating the effects of MDMA alone.
Subjects: 44 mostly MDMA-naïve subjects (34 men, 10 women, ages 21-41) recruited from the medical school or from hospital staff, with 42 / 44 being either students or physicians. 5 of 44 volunteers had used ecstasy once or twice in their lives. Startle was successfully measured in 38 / 44 subjects (31 men, 7 women, ages not provided). Data from 6 subjects was not included in PPI studies either due to insufficient startle response or to artifacts in data. (Same samples featured in Liechti, Baumann et al, 2000, Liechti, Saur et al, 2000, Liechti & Vollenweider, 2000a, and Liechti & Vollenweider, 2000b)
Criteria for Inclusion - Healthy according to physical examination, psychiatric interview, ECG and blood analysis. No history of major psychiatric disorders in subject or first-degree relatives, and no history of alcohol or substance abuse. Normal "neuroticism" scores on FPI (no more than 2 standard deviations above norm).
Measures: Pre-pulse Inhibition (PPI) – A measure of sensorimotor gating. Eyeblink component of acoustic startle response to noise bursts measured through EMGs of the obicularis orculi muscle. Startle trials consisted of 1) 115 dB 40-ms noise alone (no pre-pulse), 2) the same stimulus followed by pre-pulse stimulus of 20 ms duration or 3) no-stimulus trials, with trials presented in pseudorandom order. Pre-pulses consisted of 16 dB pulses appearing 30, 60, 120, 240, or 2000 ms before the pulse. PPI measured 90 after drug administration (placebo or MDMA).
Mood – Mood was measured by the AM, administered at time of peak MDMA effects, at 120 min after drug administration (either placebo or MDMA).
Alterations in Consciousness - Alterations in consciousness were measured via the ASC at the time of peak MDMA effects, at 120 min after drug administration.
Physiological Measures – HR, systolic and diastolic BP, and BT continuously monitored throughout the session.
Adverse Effects – Self-reported side effects and short-term sequelae were measured via LC, administered while subjects experienced acute effects, 24 h and 72 h (3 days) after drug administration.
Analyses: PPI – After calculating % habituation and % PPI, with % PPI calculated for each pre-pulse condition (30, 60, 120, 240 & 2000 ms before pulse) 2-way analyses of variance (ANOVAs) were performed to exclude treatment order effects, comparing MDMA versus placebo first and MDMA + pretreatment versus pretreatment first. The effect of MDMA on startle reactivity was examined via 2-way ANOVAs with drug condition (placebo or MDMA) and block (first, middle and last block) as within-subjects factors. A 2-way within-subjects ANOVA was performed with drug (placebo or MDMA) and pre-pulse type (30, 60, 120, 240 or 2000 ms before pulse) on % PPI. Pretreatment effects on % PPI were examined via 3-way within-subjects ANOVA, with pretreatment (placebo or pretreatment drug), treatment (placebo or MDMA) and pre-pulse type (30, 60, 120, 240 or 2000 ms before pulse) all serving as within-subjects factors. Separate analyses were conducted for each of the three drug pretreatment studies. Post-hoc comparisons were performed via Tukey's LSD test.
Mood – Data were pooled across drug treatment study to examine MDMA-induced changes in mood, via 1-way ANOVA, with drug treatment (MDMA or placebo) used as a within-subjects factor. Pretreatment moderation of MDMA-induced changes in mood were examined via 3 separate 2-way ANOVAs, with pre-treatment (placebo or pretreatment) and treatment (placebo or MDMA) both serving as within-subjects factors. Post-hoc comparisons were made via Tukey's test.
Alterations in Consciousness – Data were pooled across studies and examined via 1-way ANOVA with drug treatment (placebo or MDMA) serving as a within-subjects factor. 3 separate 2-way ANOVAs were conducted to examine pretreatment effects on MDMA-inducted alterations in consciousness, with pretreatment (placebo or pretreatment) and treatment (placebo or MDMA) serving as within-subjects factors. Post-hoc comparisons were made with Tukey's test.
Adverse Effects (LC) – Data were pooled across studies and examined via 1-way ANOVA, with drug treatment (placebo or MDMA) serving as a within-subjects factor. 3 separate 2-way ANOVAs were conducted to examine pretreatment moderation of MDMA-induced side effects, with pretreatment

(placebo or pretreatment) and treatment (placebo or MDMA) serving as within-subjects factors. Post-hoc comparisons were made via Tukey's test.
% Habituation, %PPI and MDMA-Induced Psychological Changes – Spearman's rank-order correlations were performed on psychological peak changes (MDMA value – placebo value) and changes in %habituation and %PPI, with separate correlations performed for pre-pulses appearing 60, 120 and 240 ms before pulse, using data from 43 / 44 subjects and with p. set at .05.
Results: Effects, Duration – MDMA effects first appeared 45 – 60 minutes after drug administration and peaked 90 – 120 minutes after drug administration. On average, duration of effects was 3.5 h.
PPI, MDMA Alone - MDMA did not significantly alter %habituation, as indicated by a lack of difference in startle response between first and last blocks of trials, when compared with placebo. There were no gender differences in startle reactivity. There was a significant main effect for % PPI indicating importance of duration of interval before pulse. MDMA significantly increased %PPI when compared with placebo. MDMA increased %PPI for pre-pulses appearing 60, 120 and 240 ms before pulse, but not for pre-pulses appearing 30 ms before pulse. A pre-pulse presented 2000 ms before pulse facilitated startle, both in placebo and MDMA conditions. Data from pre-pulses appearing 60, 120 and 240 ms before pulse were collapsed into a mean %PPI score for further analyses.
PPI, MDMA + Citalopram – Citalopram pretreatment did not affect %habituation. Citalopram alone and MDMA alone increased startle magnitude, but they did not produce additive increases in startle magnitude (sign of startle reactivity). Citalopram alone did not alter % PPI, but citalopram pretreatment significantly reduced the MDMA-induced increase in %PPI. Reduction in MDMA-induced %PPI by citalopram was strongest for pre-pulses occurring 60 and 240 ms before pulse, and there was little reduction in %PPI with pre-pulses presented 120 ms before pulse.
PPI, MDMA + Haloperidol – Haloperidol pretreatment did not affect % habituation. Haloperidol did not alter startle magnitude or habituation when given alone, and it did not change the effects of MDMA on startle magnitude. Haloperidol did not reduce the MDMA-induced increase in %PPI.
PPI, MDMA + Ketanserin – Ketanserin alone reduced startle magnitude, but did not reduce startle magnitude when combined with MDMA. Ketanserin did not alter %habituation. Though there was a trend for both MDMA alone and ketanserin alone to increase %PPI when compared with placebo, the increase was not significant. MDMA + ketanserin increased %PPI more than MDMA alone, but this difference just failed to reach significance (p. = .06).
Mood – MDMA significantly elevated scores for "self-confidence," "heightened mood," "extroversion," "introversion," "sensitivity," "emotional excitability," and "thoughtfulness-contemplation." MDMA significantly increased scores on "inactivation" and "dazed state," but also produced a non-significant reduction in "tiredness." More details on pre-treatment moderation of MDMA-induced changes in mood. Presented in previously published studies.
Alteration in Consciousness – MDMA increased scores on all 3 OAV scales, including OB, AED and VR. Increased OB scores were largely due to increases in reported positive mood, positively experienced derealization and "mania-like experience." Increased AED scores were mainly due to increases in reported thought disorder, and slight fear of loss of body control and fear of loss of thought control. (Thought disorders moderate, including difficulty concentrating, accelerated thinking, thought blocking and impaired decision making). Increased VR were scores were mainly due to reported increases in "changes in the meaning of percepts," "facilitated recollection" and "facilitated imagination." Participants reported that colors were more vivid, sense of touch was altered and sounds seemed closer or farther away.
Alterations in Consciousness, MDMA + Pretreatment – Citalopram reduced MDMA-induced increases on all 3 ASC scales (OB, AED and VR). Haloperidol reduced OB scores only, and ketanserin reduced VR scores only. More details of pretreatment moderation of MDMA-induced alterations in consciousness found in previously published studies.
Physiological Effects – MDMA significantly elevated systolic and diastolic BP and HR. MDMA did not produce a significant increase in BT. Detailed accounts of MDMA-induced changes in physiological

measures and pretreatment moderation of MDMA-induced changes can be found in previously published studies.
Adverse Effects – The most commonly reported acute side effects (reported in at least half of the subjects, 22 / 44) were "difficulty concentrating," "dry mouth," "impaired balance," "dizziness," "lack of appetite" and "jaw clenching." More detailed account of pre-treatment moderation of side effects and side effects reported 24 h and 72 h post-drug found in previously published studies.
Adverse Effects, Pretreatments – Nausea was the most commonly reported side effect of citalopram pretreatment. Drowsiness was the most commonly reported side effect for haloperidol and for ketanserin pretreatment. More details in previously published studies.
Psychological Ratings and %PPI – MDMA-induced changes in all 3 scores of the ASC (OB, AED and VR) were positively associated with changes in %PPI. %PPI for pre-pulses 60 ms and 240 ms before pulse (conditions most effected by MDMA) produced strongest correlations. Increased OB and VR scores were correlated with MDMA-induced changes in %PPI with pre-pulses 60 and 240 ms before pulse. Increased AED score was correlated with changes in %PPI in the pre-pulse 60 ms before pulse. Correlations were significant for male subjects but they did not reach significance for females.
Psychological Ratings and % Habituation – MDMA-induced changes in the OB and VR scales of the ASC were negatively associated with MDMA-induced reductions in %habituation. MDMA-induced changes in AED were not significantly related to changes in % habituation. There were no gender differences in relationship between change scores for ASC scales and % habituation after MDMA.
Overall Effects: MDMA elevated mood and altered consciousness, as reported in previous studies by this team. Most of these subjective effects were reduced by citalopram pretreatment, and some of these effects were altered by haloperidol or ketanserin pretreatment. Haloperidol reduced the increase in positive mood reported after MDMA, and ketanserin reduced changes in perception produced by MDMA. MDMA increased systolic BP, diastolic BP and HR, and produced a number of acute side effects, such as difficulty concentrating, dry mouth and lack of appetite. MDMA increased startle reactivity (startle magnitude) when compared with placebo. While citalopram alone increased startle reactivity and ketanserin alone reduced it, neither drug altered the effects of MDMA on startle magnitude. Haloperidol alone did not affect startle magnitude and did not alter the MDMA-induced increase in startle magnitude. Habituation to acoustic startle trials did not differ between MDMA and placebo conditions, and none of the 3 pre-treatments (citalopram, haloperidol or ketanserin) affected habituation. When given alone, MDMA facilitated pre-pulse inhibition; pre-pulses are more effective at reducing startle with MDMA than with placebo. The results of this study replicate findings from an earlier study conducted by the same team. Only citalopram significantly reduced the effects of MDMA on PPI. Haloperidol did not alter the effects of MDMA on PPI. While ketanserin did moderately enhance the effects of MDMA on PPI, this effect was not significant. When correlated, changes produced by MDMA on all 3 scales of a measure of alterations in consciousness had a significant positive relationship with changes in %PPI produced by MDMA, indicating a relationship between the intensity of the subjective effects of MDMA and the degree to which it increased PPI. The MDMA-induced increase in %PPI was strongest in people experiencing the strongest psychological effects after MDMA. Correlations between peak changes ASC scores and %PPI was not significant for female participants, probably due to there being far fewer females than males in this study. While MDMA did not have any effects upon % habituation, there was a negative relationship between MDMA-induced changes in mood and perception and changes in % habituation. This findings suggest that people experiencing strong psychological effects from MDMA were also liable to experience some disruptions in % habituation. MDMA-induced changes in fear of ego dissolution were not associated (either negatively or positively) with MDMA-induced changes in %PPI, indicating that the intensity of this subjective effect of MDMA is not associated with changes in % habituation after MDMA. All 3 of the authors' hypotheses are confirmed in this study. MDMA increased %PPI in humans, as was found in an earlier study. Citalopram attenuated the increase in %PPI produced by MDMA. The intensity of the MDMA-induced changes on scores measuring alterations in consciousness were associated with increased %PPI after MDMA, and the intensity of MDMA-induced

changes in positive mood and perception were both negatively associated with decreased %habituation after MDMA.
Adverse Effects: See above: details featured in 3 previous studies (Liechti, Saur et al, 2000, Liechti & Vollenweider, 2000a, Liechti & Vollenweider, 2000b).
Comments: This study replicates an earlier investigation of the effects of MDMA on PPI in humans, and its results replicate the findings of the first study. Both studies found that MDMA increased PPI rather than reducing it. This is surprising because in rodents, MDMA and other serotonin releasers apparently reduce PPI. The authors present evidence that serotonin release is largely responsible for the MDMA-induced increase in PPI, and not dopamine release (or at least activity at D2 receptors) or activation of 5HT2 receptors through comparing the effects of three relevant pretreatments on PPI. The reduction in MDMA-induced increase in % PPI produced by citalopram is in turn used as evidence that MDMA produces most of its effects by carrier-mediated release of serotonin (5HT). Since people who experience greater elevation in mood, fears of ego dissolution and alterations in perception also experience the greatest changes in %PPI, the two effects may be related to the same process or processes, such as serotonin release. Finding a negative relationship between the intensity of the subjective effects of MDMA and %habituation also suggests that as intensity in subjective effects are further increased (as they may be with higher doses), MDMA may reduce habituation to startle. The authors conclude that MDMA increases PPI in humans and decreases PPI in rodents due to indirect activation of 5HT1 receptors (various types) via serotonin release, with differences in the distribution of these receptors in humans and rodents responsible for differences in the effects of MDMA on PPI seen in the two species.

Mas et al. (1999). Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans.

Mas, M., Farre, M., de la Torre, R., Roset, P. N., Ortuno, J., Segura, J. & Cami, J. (1999). Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. Journal of Pharmacology and Experimental Therapeutics, 290, 136-145.

Purpose: Pharmacokinetic, neuroendocrine, neurophysiological: "To determine cardiovascular and neuroendocrine effects and pharmacokinetics of MDMA in healthy volunteers…" (p. 137).
Design: Randomized double-blind crossover within-subjects design, with drug (40 mg amphetamine, 75 mg MDMA, 125 mg MDMA or placebo) as a within-subjects factor. Volunteers participated in all four sessions, (placebo, 40 mg amphetamine, 75 mg MDMA and 125 mg MDMA, all p. o. Sessions took place two weeks apart.
Subjects: 14 MDMA-experienced males, aged 21-30), recruited via "word of mouth" All had used cannabis, cocaine and methamphetamine at least once, and average alcohol consumption was (estimated at) 2 units of alcohol, or 16 g.
Criteria for Inclusion – Lack of major psychiatric or medical illness as assessed through interview and physical examination, routine laboratory tests, urinalysis and ECG. Lack of substance abuse (except for nicotine dependence). Past use of MDMA at least 5 times. Urinary drug screens for opioids, cocaine, amphetamines conducted before and after study; all were negative. Identified as extensive metabolizers (measure of CYP2D6) via dextromethorphan / dextorphan assay.
Measures: Physiological Effects: Vital signs – HR, BP (systolic and diastolic) and BT measured 30 min pre-drug, immediately after drug administration and at 15, 30, 45, 60 and 90 minutes after drug administration, and after 2, 3, 4, 6, 8, 10, and 24 hours after drug administration. Cardiac activity monitored through ECG.
Pupillary diameter – Subjects' pupillary diameter measured by pupil gauge, with measurements made at 0, 15, 30, 45, 60, 90 min, 2, 3, 4, 6, 8, 10 and 24 h after drug administration..

Chemical assays – Subjects' blood assayed for MDMA (or amphetamine) and metabolites through gas chromatography. Blood samples drawn immediately after drug administration and 15, 30, 45, 60, 90 min and 2, 3, 5, 6, 8, 10, and 24 h post-drug.
Hormones – Plasma cortisol concentration was detected with fluorescence polarization immunoassay, with assay sensitivity reported at .45 Ug / dl. Prolactin concentration measured through microparticle enzyme immunoassay. Plasma growth hormone concentration measured through solid-phase two-site chemiluminescence enzyme immunoassay, with assay sensitivity reported at .003 ng / ml. Hormones measured in blood drawn before drug administration, immediately after drug administration, and at 15, 30, 45, 60 and 90 min and 2, 3, 4, 6, 8, 10 and 24 h after drug administration.
Pharmacokinetics – Peak concentration (Cmax), time to reach peak concentration (Tmax) and area under curve (AUC0-24) calculated for MDMA and MDA. Using pharmacokinetics software, absorption and elimination half-life computed for MDMA and MDA.
Analyses: Physiological measures (HR, BP, BT, pupillary diameter and hormone concentrations all transformed into differences from baseline. Peak effect until six hours (absolute value of maximum change until 6 h post-drug) and 6-hour AUC calculated by trapezoidal rule for each variable. The transformed data were analyzed via 1-way within-subjects ANOVA with drug condition (placebo, 40 mg amphetamine, 75 mg MDMA or 125 mg MDMA) as within-subjects factor, with p. set at .05. Post-hoc comparisons made with Tukey's test.
Results: Physiological Effects – Both doses of MDMA (75 mg and 125 mg) and 40 mg amphetamine significantly increased BP and HR compared to placebo. Increase in BP greater for amphetamine and 125 mg MDMA than for 75 mg MDMA, but difference not statistically significant. Maximum peak for both systolic and diastolic BP appeared 90 minutes post-drug for all active drugs. Maximal increase in HR seen 60 minutes after MDMA administration and 8 hours after amphetamine administration. Criteria for hypertension met in 4 volunteers in each of the MDMA conditions and in amphetamine conditions. Three volunteers met criteria for sinus tachycardia, two after 125 mg MDMA and one after 75 mg MDMA. All drugs (amphetamine, 75 mg and 125 mg MDMA) slightly raised BT, but BT not significantly increased by any drug. Pupils more dilated after both doses of MDMA, compared with placebo or with amphetamine. MDMA induced maximal changes in pupil size between 1 and 2 h post-drug, whereas amphetamine produced maximal change in pupil size at 10 h post-drug.
Neuroendocrine Effects – Cortisol concentration significantly higher after both doses of MDMA when compared with placebo (both peak and AUC), and 125 mg MDMA produced increase in cortisol higher than 40 mg amphetamine. Cortisol concentration peaked 2 h after MDMA and 60 min after amphetamine. Prolactin concentration only significantly increased with 125 mg MDMA when compared with all other treatments (placebo, amphetamine or 75 mg MDMA) for both peak and AUC, with prolactin peaking 2 hours after 125 mg MDMA. Growth hormone concentration not influenced by any active treatment (amphetamine or either dose of MDMA).
Pharmacokinetics – Tmax was observed at 2 hours for both doses of MDMA, with plasma levels declining at a mono-exponential level. Average elimination half-life was 7.9 h for 75 mg MDMA and 8.7 h after 125 mg MDMA. MDA (in plasma) appeared slowly shortly after MDMA administration. Cmax of 7.8 ng /l for 75 mg MDMA and 13.7 ng /1 for 125 mg MDMA, with peaks reached at 5 to 7 h after drug administration. Formation rate constant for MDA is .75 h(-1) and elimination half life of MDA at 16 to 28 h. Amphetamine Tmax was 2 h after administration, and Cmax was 65 ng / l. Amphetamine had a half-life of 15.3 h (range 9.5-22.5 h).
Overall Effects: While MDMA and amphetamine appeared to have very similar physiological and neuroendocrine effects (increase in heart rate and blood pressure, increase in cortisol) there were some significant qualitative and quantitative differences between amphetamine and MDMA. While both drugs produced an increase in cortisol, only 125 mg MDMA produced a significant increase in prolactin. MDMA at both doses caused more pupillary dilation than did amphetamine. Amphetamine had a longer half-life than MDMA. Systolic and diastolic BP peaked at 90 min post-drug for both doses of MDMA and amphetamine. Yet while HR peaked at 60 min post-drug for MDMA, it peaked at 8 h after drug for amphetamine. Authors note that plasma MDMA concentration with 125 mg MDMA was greater than

would be expected from observing plasma MDMA with 75 mg MDMA, leading them to suggest nonlinear functions in pharmacokinetics for MDMA. None of the drugs produced a significant increase in body temperature, and neither drug stimulated growth hormone secretion. MDA appeared to be a minor metabolite of MDMA, making up 8 to 9% of metabolized MDMA in plasma.
Adverse Effects: None measured or reported. However, diagnostic criteria for hypertension (4 / 14) or tachycardia (3 /14) appeared after either dose of MDMA. No need for clinical intervention reported in any of these cases.
Comments: This paper is a companion paper to the Cami et al. (2000) paper comparing 2 doses of MDMA with amphetamine on psychological effects and effects on psychomotor performance. Both papers may assist in differentiating between entactogens (MDMA-like drugs) and stimulants. The authors explain drug-related differences in HR (earlier with MDMA than with amphetamine) as arising from "baroreceptive reflex bradycardia" produced by amphetamine, and state that MDEA (a congener of MDMA) and methylphenidate (Ritalin, a stimulant) have heart rate profiles similar to that of MDMA. Mas et al. employ a larger sample size than previous pharmacokinetic studies of MDMA, and their findings are comparable to those of Helmlin et al. (1996) and Fallon et all (1999). On the basis of finding an unexpected increase in plasma MDMA with the 125 mg dose when compared with the loser dose, the authors hypothesize that there are non-linear dynamics in MDMA pharmacokinetics.

Pacifici et al. (1999). Immunomodulating properties of MDMA alone and in combination with alcohol; A pilot study.

Pacifici, R., Zuccaro, P., Farre, M., Pichini, S., Di Carlo, S., Roset, P. N., J. Ortuno et al. (1999). Immunomodulating properties of MDMA alone and in combination with alcohol; A pilot study. Life Sciences, 65, 309-316.

Purpose: Immunological, neuroendocrine: "Total leukocyte counts, blood lymphocyte subsets, and lymphocyte proliferative response to mitogenic stimulation, as well as plasma drug and cortisol concentrations, were investigated after the administration of MDMA alone and in combination with alcohol." (p. PL-310).
Design: Randomized, double blind, placebo-controlled cross-over (mixed, within subjects-between subjects) design, with four conditions: placebo, MDMA alone, .8 mg / kg alcohol alone, or MDMA + alcohol, with 1 week between sessions. All volunteers took part in all 4 conditions, but 2/4 volunteers received 75 mg MDMA and 2/4 received 100 mg MDMA in MDMA and in MDMA + alcohol conditions.
Subjects: 4 MDMA-experienced males. Age and recruitment method not reported. May have been recruited through "word of mouth" as were men in Mas et al., 1999.
Criteria for Inclusion – Not reported beyond "healthy." Other studies performed by this group used these criteria; lack of major psychiatric or medical illness as assessed through psychiatric interview and physical examination, routine laboratory tests, urinalysis and ECG and lack of substance abuse (except for nicotine dependence).
Measures: Immunological Function, – Complete blood profile and cell count conducted on blood drawn from each subject, with samples drawn 1, 2, 6 and 24 h post-drug. Subjects' lymphocytes cultured in vitro, and lymphocyte proliferation in response to phytohaemoaglutinin A measured via radioimmunassay. Number of lymphocytes counted by cytometer. Dual-color immunophenotyping used to detect immune cell types; helper-inducer, cytotoxic-suppressor, natural killer, mature B and T lymphocytes).
Plasma MDMA – MDMA concentration measured with gas chromatography from samples drawn at preadministration, 15, 30, 45, 60, 75, 90 min, 2, 3, 4, 6, 8, 10 and 24 h post-drug.
Plasma Cortisol – Using same set of samples described above (Plasma MDMA), performed a fluorescence polarization immunoassay (FPIA), with assay sensitivity set at .45 Ug / dL.

Analyses: No formal tests of statistical significance reported. Cell counts and tests of immune function apparently compared with published norms available for these procedures.
Results: All volunteers had normal immunological parameters (measured pre-drug). All treatments produced changes in immune function, and immune function partially restored to normal 24 h post-drug after all 3 drug treatments.
Immunological, MDMA Alone - MDMA produced a time-dependent decrease in CD4 / CD3 cell ratio. Fewer mature T and B lymphocytes were found in samples drawn after MDMA administration, and MDMA reduced lymphocyte response to PHA stimulation. MDMA increased numbers of natural killer cells (NK) in plasma. Change in immune function parallels blood MDMA and blood cortisol levels (with cortisol concentration increased by MDMA), and all changes in immune parameters peaking 1 to 2 h post-drug. Volunteers given 100 mg MDMA had greater reductions in CD4 T-cell counts and lymphocyte stimulation than volunteers given 75 mg MDMA (no tests of significance applied; comparing percentages).
Immunological, alcohol Alone - Alcohol alone produced decreased T helper cells (CD4) and B-lymphocytes (CD19), and reduced lymphocyte response to PHA. Time of peak changes in immunological function not reported for alcohol, but extrapolating from charts and alcohol + MDMA, peak change appeared at 1 – 2 h post-drug.
Immunological Function, Alcohol + MDMA - Alcohol + MDMA produced greatest reduction in CD4 count and greatest reduction in PHA-stimulated lymphocyte proliferation compared to all other conditions. Time of peak changes in immunological function not reported, but appears to be between 1 h – 2 h post-drug.
Cortisol, MDMA Alone – Both doses of MDMA produced a mean rise in plasma cortisol concentration at 2 h post-drug.
Cortisol, Alcohol Alone – Alcohol alone did not alter plasma cortisol concentration.
Cortisol, MDMA + Alcohol – Alcohol appears to blunt MDMA-induced rise in plasma cortisol.
Overall Effects: Doses of MDMA comparable to doses used recreationally induced changes in immune function, including reduced CD4 count, fewer T lymphocytes, less proliferation in response to PHA stimulation and greater numbers of NK cells. Authors refer to this as "immune dysfunction," since they are uncertain as to whether the net result of these changes will suppress or enhance immune response. MDMA-induced changes in immune function seemed to be time-dependent and dose-dependent and the course of effects ran parallel to MDMA and cortisol concentration in blood. A combination of MDMA and alcohol produced a more pronounced suppression of CD4 cells and a greater reduction in lymphocyte proliferation after stimulation via PHA for both doses. In all conditions, normal immune function was partially restored 24 h post-drug.
Adverse Effects: None described beyond reduction in amount of immune cells and responsiveness to mitogen stimulation (PHA stimulation).
Comments: This study is a preliminary investigation conducted by the same team that examined cardiovascular and psychological effects of MDMA in MDMA-experienced men. Findings have not yet been put to tests of significance and the small sample size will not allow for generalizing about immune response in the population. However, the results suggest that MDMA's immunological effects should be pursued further, particularly if therapeutic use of MDMA is given to people with immunological problems (either immune hyperfunction or hypofunction). The findings for acute modulation of immune function is consistent with several studies using rodents (e.g. Connor, Kelly & Leonard, 2000). Authors state that MDMA-induced changes in immune function resemble those produced by (unspecified) psychological stressors, and suggest that MDMA may be viewed as a "chemical stressor." MDMA did increase cortisol, but it should be noted that while alcohol blunted MDMA-induced rise in cortisol, immune function was most reduced in the alcohol + MDMA condition, suggesting that changes in immune function are not solely regulated via cortisol.

Pacifici et al. (2000). Immunomodulating activity of MDMA.

Pacifici, R., Zuccaro, P., Farre, M., Pichini, S., Di Carlo, S., Roset, P. N., Hernandez Lopez, C., Ortuno, J., Segura, J., Cami, J. & De La Torre, R. (2000). Immunomodulating activity of MDMA. In Ali, S.F. (Ed). Neurobiological Mechanisms of Drugs of Abuse; Cocaine, Ibogaine and Substituted Amphetamines. New York; New York Academy of Sciences., pp. 215-224. Annals of the New York Academy of Sciences, vol. 914.

Purpose: Immunological: The paper summarizes three lines of research investigating the effects of MDMA on immune response, including in vivo studies performed with human volunteers. MDMA is also compared with the immunological effects produced by amphetamines and amphetamine derivatives.
Design: Pilot Study – Randomized, double blind cross-over study, with each subject receiving placebo in one session and MDMA in another session, with half of the subjects receiving 75 mg MDMA and half receiving 100 mg MDMA. (Data presented in Pacifici et al, 1999; half of the complete design, which crossed MDMA administration with ethanol administration). Definitive Clinical Trial – Randomized double blind cross-over design, wherein each subject took part in two experimental conditions, including placebo and 100 mg. MDMA. (Data presented in Pacifici, 2001 but with 2 additional subjects included). A week was scheduled between each session for both the pilot and the definitive trials.
Subjects: Pilot – 4 MDMA-experienced men, ages not described. Method of recruitment not described, but previous publications indicate that authors recruited subjects through "word of mouth." Definitive Trial – 8 MDMA-experienced men, ages not provided. 6 / 8 were aged 19-36, with a mean age of 23. Recruitment method not described here, but presumably through "word of mouth," as was the case for Pacifici, 2001.
Criteria for Inclusion – Not described for either study beyond "healthy." Previous papers (e.g. Mas, 1999) state health was assessed through medical examination and psychiatric interview. Having used ecstasy at least five times in the past and no history of substance abuse, save nicotine dependence. Subjects may also have been typed for CYP2D6 responses, with all subjects required to be extensive metabolizers.
Measures: Plasma MDMA and Cortisol – Plasma MDMA concentration was measured using gas chromatography coupled with a nitrogen-phosphorus detector. Plasma cortisol concentration was assessed through fluorescence polarization immunoassay (FPIA). Measures of plasma MDMA and cortisol were performed on blood samples drawn at 0, 15, 30, 45, 60, 75 and 90 min post-drug, and 1, 2, 3, 4, 6, 8, 10 and 24 h after drug administration. (Both studies).
Cell Counts - A complete blood profile and cell count was performed on samples from each subject. Lymphocytes typed by staining with monoclonal antibody reagent. Lymphocytes counted with a flow cytometer. (Both studies) Pilot Study – Cell counts were performed on blood samples drawn before drug administration and at 1, 2, 6 and 24 h after drug administration. Definitive Trial – Cell counts were performed on blood samples drawn before treatment and at 1, 1.5, 2, 6 and 24 h after drug administration.
Lymphocyte Mitogen Stimulation - Lymphocytes' response to PHA tested with a [3H]thymidine test. Lymphocytes were gathered from series of samples described above (0, 1, 2, 6 and 24 h after drug administration for the pilot study and 0, 1, 1.5, 2, 6 and 23 h after drug administration for the definitive trial).
Analyses: Pilot Study – No formal tests of significance performed. Definitive Trial – Cell counts and degree of mitogen stimulation in lymphocytes analyzed via repeated-measures ANOVA, with drug condition (placebo or 100 mg MDMA) as one within-subjects factor and time of sample (0, 1, 1.5, 2, 6, and 24 h after drug administration) as the other within-subjects factor. Post-hoc comparisons were performed with Tukey's HSD test.
Results: MDMA and Cortisol – Pilot Study - Immunological alteration paralleled MDMA pharmacokinetics. No information reported on cortisol production. Definitive Trial – Immunological changes paralleled plasma concentrations of MDMA and cortisol, with immunological dysfunction appearing 1 to 1.5 h after drug administration. Plasma MDMA values appeared to peak between 1 and 2 h post-drug, and cortisol values peakedat 2 h after drug administration.

Cell Counts and Percentage of Immune Cell Types – Pilot Study – Total leukocyte count did not differ between MDMA condition and placebo. There was a decrease in CD4 T-cell / CD8 T-cell ratio and a reduction in mature T lymphocytes. When compared with placebo, MDMA increased number of natural killer (NK) cells. Definitive Trial – Results similar to those reported in pilot study; when compared with placebo, MDMA reduced number of CD4 T-cells, reduced CD4/CD8 T-cell ratios and increased numbers of NK cells. In addition, MDMA appeared to decrease the number of CD3 cells when compared with placebo. MDMA did not appear to affect number of CD8 T-cells or B lymphocytes. These changes in cell count were time-dependent, with number of various immune cells partially returned to normal values by 24 h after drug administration.
Lymphocyte Mitogen Stimulation – Pilot Study - MDMA apparently produced a decrease in lymphocyte mitogen stimulation, with the decrease more apparent in people receiving 100 mg MDMA when compared with people receiving 75 mg MDMA. Reduction in lymphocyte mitogen stimulation appeared at 1 h after drug administration in 2 / 4 receiving 100 mg. MDMA. Definitive Trial – Either this test not conducted or data not provided in this publication.
Overall Effects: MDMA in doses of 75 and 100 mg produced time-dependent changes in immune function in otherwise healthy male humans. Specifically, number of CD4 cells, number of mature lymphocytes, and CD4 / CD8 T-cell ratios were all decreased while number of NK cells is increased. There is also a decrease in lymphocyte mitogen stimulation after MDMA administration. These changes appeared at 1 hour after drug administration and they seemed to be associated with the effects of MDMA on cortisol and CRF secretion. The MDMA-induced changes in immune function appeared to parallel plasma MDMA and cortisol values. Normal immune function was partially restored 24 hours after MDMA administration. Findings with human volunteers are comparable to similar findings from in vitro studies using mouse immune cells and in vivo studies with rats. The authors state that similar changes in immune function also appear after psychological stress. Currently, there is no clear indication as to the consequences of these changes in immune system function.
Adverse Effects: None specifically reported in this paper beyond alterations in immunological function.
Comments: A large part of this paper consists of a review of data that has already been presented in two separate papers. The other papers also addressed the immunological effects of coadministering ethanol with MDMA. This study also compares findings in humans with findings from in vitro studies using mouse cells and in vivo studies with non-human animals, mostly rats. In vitro and in vivo rat studies also found that MDMA selectively reduced some T—cells and increasing NK cells. The consequences of these changes in immunological function are currently unknown, but the authors remark that chronic consumption of MDMA may be a health hazard for individuals with compromised immune systems. After comparing the effects of MDMA with the effects produced after psychological stressors, the authors suggest that MDMA is a "chemical stressor." This last finding may prove interesting to researchers investigating the effects of stress in humans, especially as MDMA may produce a dissociation between feelings of stress or anxiety (generally not present during acute MDMA intoxication) and the physiological stress response. Such a dissociation would allow researchers to examine the "psychological" and "physiological" aspects of stress separately. However, the sample size in the studies with human volunteers remains small, making it difficult to draw definitive conclusions about the effects of MDMA upon the immune system.

Pacifici et al. (2001). Acute effects of 3,4-methylenedioxymethamphetamine alone and in combination with ethanol on the immune system in humans.

Pacifici, R., Zuccaro, P., Lopez, C. H., Pichini, S., Di Carlo, S., Farre, M., Roset, P. N., Ortuno, J., Segura, J., De La Torre, R. (2001). Acute effects of 3,4-methylenedioxymethamphetamine alone and in combination with ethanol on the immune system in humans. Journal of Pharmacology and Experimental Therapeutics, 296, 207-215.

Purpose: Immunological, pharmacological: "…to examine acute immunological changes after administration of MDMA alone and in combination with ethanol" in humans.
Design: Randomized, double blind, placebo controlled within-subjects with 2(ethanol: placebo, 0.8 mg / kg ethanol) x 2(MDMA; placebo / 100 mg MDMA) design. All subjects took part in each of the four conditions (placebo / placebo, ethanol / placebo, MDMA / placebo**,** ethanol / MDMA**).**
Subjects: 6 MDMA-experienced volunteers, ages 19-36, mean age 23, with average weight of 67 kg and average height of 175.4 cm., recruited via "word of mouth."
Criteria for Inclusion – Being in good health, as assessed through psychiatric interview and physical examination, smoking no more than 20 cigarettes per day and no more than 60 g of ethanol a day, having used ecstasy / MDMA at least 5 times in the past, no history of substance abuse except nicotine dependence and typed as an extensive metabolizer for CYP2D6.
Measures: Plasma MDMA and Ethanol - Plasma levels of MDMA and ethanol were measured in blood samples taken before treatment and at 1, 2, 4, 6, 8, 10 and 24 h after drug administration, with MDMA and ethanol detected through gas chromatography.
Cortisol – Plasma cortisol concentrations were measured with fluorescent polarization immunoassay, with measures taken from blood samples drawn before treatment and at 1, 2, 4, 6, 8, 10 and 24 h after drug administration.
Peripheral Blood Mononuclear Cell Stimulation – Mononuclear cells were cultured, stimulated with PHA and centrifuged after 72 h incubation. Blood used in all blood cell preparations drawn before treatment and at 1, 1.5, 2, 6 and 24 h after drug administration.
Cytokines – IL-1Beta, IL-4, IL-6, IL-10, TNFAlpha and IFNGamma were analyzed via solid phase sandwich enzyme linked immunoabsorbent assay. IL-2 and TGFBeta analyzed via solid phase enzyme amplified sensitivity immunoassay. Cytokines measured in blood drawn before treatment and at 1, 1.5, 2, 6, and 24 h after drug administration.
Leukocyte Immunophenotyping – Forms of leukocyte counted with a fluorescence-activated cell sorting analysis. Cells analyzed were helper / inducer cells, suppressor cells, B cells, B lymphocytes and natural killer (NK) cells.
Analyses: Values for lymphocyte subsets, plasma cortisol concentrations and cytokines were transformed into differences from baseline, and maximum change from baseline was calculated for these variables. AUC was calculated for reach variable via trapezoidal rule. A repeated measures ANOVA was performed on these variables, with ethanol (present or absent) and MDMA (present or absent) as the two within-subjects factors. Post-hoc tests using Tukey's HSD test were conducted on any statistically significant differences. Changes over time course were analyzed with a 2(Time, 0 h to 6 h after drug) x condition (conditions 1 through 4) within-subjects ANOVA was conducted, with post-hoc analyses conducted via Tukey's HSD test.
Results: MDMA – Alterations in immune function peaked between 1 and 2 h post-drug and had returned to baseline or near-baseline 24 h post-drug. Total leukocyte count was unchanged, but there was a decrease in CD4 / CD8 T cell ratio indicating a decrease in helper cells. There were no differences in amount of suppressor cells or B lymphocytes. The number of NK cells increased. MDMA produced a decrease in the production of the cytokines IL-2 and IFNGamma, both Th1 type cytokines. MDMA increases production of IL-4 and IL-10, both Th2 cytokines. Alterations in immune function paralleled plasma MDMA concentration. MDMA produced a decrease in TNFAlpha and IL-6 and an increase in TFGB1 produced by stimulated mononuclear cells.
Ethanol – Alterations in immune function produced by ethanol also peak within 1 – 3 h post drug and return to baseline or near baseline at 24 h post-drug. Ethanol produced a decrease in number of helper cells and B lymphocytes. Ethanol did not alter amount of suppressor cells or NK cells. Ethanol produced a reduction in the Th1 cytokine IL-2 and an increase in the Th2 cytokine IL-10.
MDMA + Ethanol – When combined, MDMA and ethanol produced changes in immune function that peaked at about 1 h post-drug. This combination had an additive effect on amount of helper T cells, with the greatest decrease in helper T cells produced at this level. The effects of ethanol on B lymphocytes were attenuated by MDMA, with a lesser decrease in B lymphocytes experienced with the MDMA-

ethanol combination. MDMA + ethanol disrupted the balance between pro-inflammatory and anti-inflammatory cytokines, There was a general trend for an increase in anti-inflammatory cytokines and a decrease in pro-inflammatory cytokines. Alterations in immune function paralleled plasma MDMA concentration. Combining ethanol with MDMA had no further effects on stimulated mononuclear cells.
Cortisol – Cortisol levels did not change in either the placebo / placebo or the ethanol conditions. A statistically significant rise in cortisol appeared in both the MDMA and MDMA + ethanol conditions, with the rise peaking at 2 h post-drug.
Overall Effects: Both MDMA and ethanol produced time-dependent changes in immune function in human subjects. Specifically, MDMA alone decreased the amount of CD4 cells and increased the amount of NK cells. Ethanol alone decreased the amount of CD4 cells and decreased B lymphocytes as well. Combined, MDMA and ethanol produced an even greater decrease in T helper cells while producing less of a change on B lymphocytes. At least in the case of MDMA, these changes paralleled plasma MDMA values, suggesting that MDMA produced these changes in immune function via actions on the CNS, such as monoamine release or increases in cortisol. MDMA shifted the balance of cytokines by decreasing the amount of proinflammatory cytokines in relation ot the amount of anti-inflammatory cytokines. The authors compare alterations in immune function after MDMA to the effects of a psychological stressor, and they refer to MDMA as a "chemical stressor." It is also suggested that combining MDMA with alcohol amplified the immunological disruptions produced by MDMA alone.
Adverse Effects: None reported in this paper beyond alterations in immune function.
Comments: This is the third in a series of publications investigating the effects of MDMA, given alone and with alcohol (ethanol), on the immune system. So far, it appears that MDMA at various doses produces the same effects upon the immune system. The authors compare the effects of MDMA to that of psychological stressors, suggesting that MDMA may be a "chemical stressor." Since MDMA appears to reduce the number of helper cells, it is possible that recreational users face an increased risk of infection from temporary but frequently reduced numbers of CD4 cells. However, the outcome of the immunological changes produced by MDMA are currently unclear, and the sample size used in this study remains very small (six individuals). This research may be relevant when examining the effects of MDMA in people with compromised immune systems or people with auto-immune diseases.

Shulgin & Nichols (1978). Characterization of three new psychotomimetics.

Shulgin, A. T. & Nichols, D. E. (1978). Characterization of three new psychotomimetics. In Stillman, R. C. & Willette, R. E. (Eds). The Psychopharmacology of hallucinogens. (New York; Pergamon Press). pp. 74-83.

Purpose: Pharmacological, psychological; to describe the chemistry and the effects of MDMA (and two other compounds) in humans.
Design: Uncontrolled within-subjects design, wherein all volunteers received various unspecified doses of MDMA, including doses of 75 mg - 150 mg (effective dose range).
Subjects: An unspecified number of human volunteers, all experienced with the effects of psychedelic drugs, gender information and age range not provided. No information on subject recruitment provided.
Criteria for Inclusion – Prior experience with psychedelic drugs.
Measures: The time course and effects of MDMA were measured through unspecified means, apparently including reports either written throughout the period of intoxication or immediately afterwards. Reports contained information on the duration of the drug's effects and a narrative description of the drug's subjective effects.
Analyses: No formal tests of significance were performed. Information on the time course of MDMA and its effects is apparently summarized across volunteers.
Results: The chemistry and synthesis of MDMA are described, as are the chemistry and effects of two other compounds, para-DOT and alpha-methyl-5-tryptamine. The authors report that MDMA had a higher threshold level (dose at which effects are apparent) than the related compound MDA, but potency

was similar to that of MDA. The effective dosage range was 75-150 mg in humans when it was administered orally. Volunteers reported the first effects within a half-hour of drug administration, and most volunteers (unspecified number) reached a plateau at 1 h – 1.5 h post-drug. The effects dissipated 3 h after drug administration (2 h after plateau) except for residual "sympathomimetic arousal" lasting several hours (up to 5 or 6 h post-drug). Physical effects were not reported in this paper, and none of the volunteers reportedly experienced any sub-acute psychological effects. The state was described as an "easily controlled altered state of consciousness with emotional and sensual overtones," and volunteers compared it with marijuana, psilocybin without its hallucinogenic effects or to low doses of MDA.
Overall Effects: Volunteers in this study reported the time course of MDMA to be 3 – 6 hours, with most drug effects dissipating at 3 h after drug administration. The first effects were felt .5 h after taking an oral dose of MDMA, and a plateau was reached between 1 h-1.5 h after drug administration. Volunteers reported that MDMA produced an "easily controlled" altered state of consciousness with emotional and sensual overtones, a description that compares well with more recent descriptions of MDMA's subjective effects. Volunteers rated MDMA as being similar to hallucinogens but without the hallucinogenic effects. None of the volunteers reported unspecified psychological sequelae after drug administration.
Adverse Effects: None reported in this paper.
Comments: This is the first published report of the effects of MDMA in humans. It is also one of the least detailed. Absent from the paper are any details about the number of volunteers or their recruitment, the nature of the measure, the time or times at which volunteers completed the measure or the manner in which information was summarized across subjects. This paper provided future authors with an oft-quoted phrase describing subjective effects of MDMA in humans. Also contained in the paper is an argument for continued studies of psychedelic drugs using human volunteers.

Stolaroff & Wells (1993). Preliminary Results with New Psychoactive Agents 2C-T-2 and 2C-T-7.

Stolaroff, M. J. & Wells, C. W. (1993). Preliminary Results with New Psychoactive Agents 2C-T-2 and 2C-T-7. Yearbook for Ethnomedicine, 99-117.

Purpose: Psychological, exploratory; To describe and explore the acute subjective effects of 2 psychoactive phenethylamines by comparing the self-reported subjective effects of the 2 drugs with the self-reported subjective effects of the well-known compound MDMA.
Design: Uncontrolled prospective between-subjects (across groups) study design, with drug administered (MDMA, 2CT2 or 2CT7) serving as a between-subjects factor. All subjects completed questionnaires concerning the subjective effects of the specific drug received (MDMA, 2CT2 or 2CT7) and provided open-ended comments about their experiences. Each subject was assessed after receiving 1 drug; there was no placebo condition. MDMA subjects received 120 mg MDMA with 40 mg supplements in requested. 2CT2 subjects received 10-30 mg 2CT2, including supplement, with average dose = 15.7. 2CT7 received 20-25 mg 2CT7, including supplement, average dose 23.1 mg.
Subjects: 55 drug-naïve subjects (28 men, 19 women, 8 gender unknown, ages 18-67) where drug-naïve refers only to the substance assessed via questionnaire, depending upon condition); at least 50 / 55 were experienced users of psychedelic drugs. MDMA – Effects assessed in 7 subjects, 3 men, 3 women, 1 gender unknown, ages 32-63, median = 48. 2CT2 – Effects assessed in 40 subjects (21 men, 13 women, 6 gender unknown, ages 18-67, median = 40. 2CT7 – Effects assessed in 8 subjects, 4 men, 3 women, 1 gender unknown, ages 30-57, median = 42. No information on recruitment provided; at least some subjects may have been friends or acquaintances of the researchers or had heard about the study via word of mouth. Criteria for Inclusion – No experience with the specific drug assessed, and a stable personality. While familiarity with psychedelic drugs was not a requirement of study participation, a large majority of the subjects were experienced users of psychedelic drugs.
Measures: Author-devised questionnaire, with items addressing physical symptoms, level of intensity, subjective psychological effects concerning emotion, perception and cognitive processes, overall evaluation of drug, evaluation of dosage and desire to repeat the experience. Drug intensity rating scale

devised by Shulgin, Shulgin & Jacob. Subjects completed questionnaire several days after drug administration. Some subjects provided verbal responses rather than completing the questionnaire.
Analyses: No formal analyses were performed to compare responses across groups or within groups. Means and percentages are calculated for each response for each of the 3 drugs separately, and non-statistical comparisons are made concerning physical symptoms, areas of functioning, preferred dosage and desire to repeat experience.
Results: Onset and Intensity – No measure of onset and intensity is taken for MDMA. However, 3 subjects rated MDMA as very intense, 3 rated it as moderately intense and 1 rated it as not very intense. (2CT2 and 2CT7 tended to have longer onset than MDMA and tended to have a longer plateau, but they were no more nor less likely to be rated as intense as MDMA).
Physical Symptoms – MDMA, 2CT2 and 2CT7 were all rated as producing a similar amount of "distracting" symptoms, with low amounts of physical symptoms reported in all 3 cases. The most frequently cited physical effects were self-perceived increase in HR, BT, nausea and "other" (2 / 7, rating distracting, short duration). 2 / 7 rated muscle tension as "distracting and long-lasting," and 1 / 7 rated muscle tension as noticeable. Vomiting, self-perceived increase in BP, perspiration, and eye darting were not listed. (2CT2 generated the most physical complaints and 2CT7 the least amount. MDMA produced the most "distracting" effects (11.3% short-term distracting, 7.6% long-term distracting after MDMA vs. 6.6% short term, 1.7% long-term 2CT2 and 4.8 short-term, 4.8 long-term distracting 2CT7. Both 2CT2 and 2CT7 differed from MDMA in producing more nausea and vomiting as noticeable, short-duration or long-duration effects.)
Psychological Effects – All subjects (7 / 7) rated MDMA as producing a positive feeling tone, improved clarity of thought and greater perception of higher order meaning . 5 / 7 reported improved flow of insight, and 6 / 7 rated MDMA as improving communication with others while 1 / 7 rated MDMA as producing deterioration in communication with others. 3 / 7 reported improvement in recall of past events and visual perception. 3 / 7 rated physical skills, energy level and sense of elapsed time as deteriorating after MDMA, but 1 / 7 felt physical skills improved after MDMA. 1 / 7 reported an improvement in general fear after MDMA and 1 / 7 reported an increase in general fear after MDMA. Closed-eyes visual imagery was largely absent, with 6 / 7 reporting no closed-eye imagery after MDMA, but it was present in 1 / 7 individual. No open-eyes visual imagery or hallucinations were present in any subject after MDMA (7 / 7 reported absence of both). (In comparison, 2CT2 was middling to good in producing insights, ability to perceive higher order meaning while it decreased ability to communicate with others and decreased energy level. 2CT7 was best at improving overall functioning, produced the most euphoria, was both best and worst at producing clarity of thought, was middling at facilitating communication with others and produced a reduction in flow of insights and perception of higher order meaning. Both 2CT2 and 2CT7 produced closed-eye imagery and open-eye visual imagery and hallucinations, but the presence of open-eye visual imagery was more common or prominent with 2CT7.)
Evaluation and Desire to Repeat Experience – All subjects expressed a wish to repeat the experience after MDMA. 2 / 7 wished to repeat the experience with the same dose, 3 / 7 wished to repeat the experience with a higher dose and 1 / 7 wished to repeat the experience with a lower dose. (Nearly all (84% wanted to take 2CT2 again and most, but not all, wanted to take 2CT7 again (75%), with 2CT7 eliciting the largest number of people who did not wish to repeat the experience. A majority of the subjects taking 2CT2 and 2CT7 wished to use a higher dosage if they took it again, and only a few from each group wished to use lower dosages.)
Overall Effects: Subjects who had completed a questionnaire a few days after receiving MDMA in an informal setting reported that MDMA produced a number of "distracting" physical effects, including muscle tension, perception of increased heart rate, perceived changes in body temperature and nausea. General feeling tone, clarity of thought and perception of higher order meaning were facilitated by MDMA. While most individuals reported that MDMA improved communication with others, 1 (of 7) reported that MDMA reduced the ability to communicate with others, and 2 of 7 reported decrements in physical skills and energy level. None of the subjects reported increases in energy level, though 3 of 7 reported no change. A small number of subjects reported decreased general fear after MDMA and a small

number reported increased general fear after MDMA. Subjects did not report any visual imagery with open eyes or hallucinations with MDMA, and only 1 of 7 reported some closed-eye imagery. All subjects wished to repeat their MDMA experience, with 2 satisfied with the dose they took, 3 desiring a higher dose and 1 a lower dose. MDMA produced more positive general feeling tone and improved or left intact clarity of thought when compared with 2CT2 and 2CT7. However, MDMA also produced a comparably large number of physical symptoms in contrast to the other 2 drugs, and it did not allow for exploring as wide an array of emotions or feelings.
Adverse Effects: See above for self-reported acute physical symptoms and decrements some aspects of functioning. Authors also remark that some subjects experience discomfort after taking MDMA or other psychedelic drugs from confronting "repressed material" or uncomfortable thoughts and feelings.
Comments: This paper described a study intended to describe and compare the effects of the phenethylamine hallucinogens 2CT2 and 2CT7, with MDMA serving as a comparison drug. Hence more attention is devoted to elucidating the effects of 2CT2 and 2CT7 than is devoted to considering the responses made after MDMA. Sample sizes for this study are very uneven, with the greatest number of people assessed after first use of 2CT2 and the smallest number assessed after first use of MDMA. Since the vast majority of people participating in this study were familiar with psychedelic drugs, the subjective effects and physical symptoms they experienced may differ substantially from the effects experienced in the population at large during the first exposure to MDMA. Specifically, a greater number of distracting physical symptoms, alterations in perception and disruptive changes in cognitive processes acutely after MDMA might be reported in a sample with little or no experience with psychedelic drugs. It is also unclear whether all subjects completed the questionnaire shortly after receiving the specified drug, or whether there was a great deal of variability in the period of time elapsed between drug administration and completion of the questionnaire. It is possible that the presence or intensity of some subjective effects were forgotten over time or were recalled to conform to peer experiences with the drug or to preconceived ideas concerning its effects. However, the setting employed in this study probably bears a greater resemblance to settings where MDMA is used recreationally than settings employed in controlled laboratory studies.

Verebey et al. (1988). The complications of "Ecstasy" (MDMA).

Verebey, K., Alrazi, J., & Jaffe, J. J. (1988). The complications of "ecstasy" (MDMA). Journal of the American Medical Association, 259, 1649-1650

Purpose: Pharmacokinetic: "…a controlled study of MDMA metabolism and disposition in a single patient…" (p. 1649).
Design: Single dose study with one subject; authors refer to it as "controlled," but not enough information provided to confirm accuracy of statement; 50 mg. MDMA administered to subject, with blood samples collected over a 24 h period and urine samples collected over a 72 h period.
Subjects: 1 man, aged 40. No information on previous experience with MDMA or of subject recruitment provided.
Criteria for Inclusion – Healthy, information on assessment not provided, willing to ingest MDMA as part of controlled study.
Measures: MDMA and MDA measured in plasma and urine with gas chromatography/ mass spectrometry. Plasma MDMA and MDA measured in blood sampled at 1, 2, 4, 6, 8, 12, 18, 22 and 24 h post-drug and. Urine MDMA and MDA m fractional urine samples taken at 0-2 h, 2-4 h, 6-8 h, 8-12 h, 12-16 h, 16-24 h, 24-48 h and 48-72 h post-drug.
Analysis: No tests of significance over time course: only descriptives and comparison of peak concentration provided.
Results: Plasma – MDMA concentration peaked at 2 h post-drug, at 105.6 ng / mL, with values declining mono-exponentially to levels of 5.1 ng / mL. MDMA half-life calculated at 7.6 h. Peak plasma MDA

concentration at 3 h post-drug = 28.4 ng / mL, and declining to 2.4 ng / mL at 12 h post-drug, levels undetectable after 12 h post-drug.
Urine – Unchanged MDMA = major excretion in urine. Over 72 h, 36 mg / 50 mg (72%) MDMA recovered in urine (65% as MDMA, 7% as MDA) , and 28% excreted as other (unmeasured) metabolites. 3.52 mg MDA excreted in urine. In urine, MDMA concentration peak at 2 h post-drug (10.77 ng / mL) and MDA concentration peak at 3 h post-drug, at .75 ng / mL. MDMA content declined but remained detectable at 24 h – 72 h post-drug (.026 ng / mL) and MDA still detectable 24 h – 72 h post-drug (.22 ng / mL).
Overall Effects: Peak concentrations of MDMA in plasma and urine occurred at approximately same time, 2 h post-drug, with peak concentrations of the metabolite MDA appearing in plasma and urine at 3 h post-drug. MDMA continued to appear in plasma 24 h post-drug, but MDA was no longer detectable in plasma after 16 h. Both MDMA and MDA were found in urine up to 72 h post-drug. In this single-subject study, MDA was the major detected metabolite of MDMA, but more unchanged MDMA was excreted in urine than MDA.
Adverse Effects: None reported in this study.
Comments: This appears to be a recounting of an early unpublished single-case, single-dose study of MDMA metabolism in humans, conducted in 1985 as part of a doctoral dissertation. The half-life reported here (7.6 h) compares well with the half-life reported by Mas et al. in 1999 for 75 mg MDMA (7.9 h), assessed in 14 male subjects. At this dose and in this subject, a large quantity of MDMA was not metabolized at all before excretion in urine, and only 7% was metabolized into MDA. The remaining 28% was excreted as other metabolites, and these were likely to have been metabolites mentioned in later papers, such as HMMA and HMA.

Vollenweider (1998). Recent advances and concepts in the search for biological correlates of hallucinogen-induced altered states of consciousness.

Vollenweider, F. X. (1998). Recent advances and concepts in the search for biological correlates of hallucinogen-induced altered states of consciousness. Heffter Review of Psychedelic Research, 1, 121-132. *(This is a review paper containing information on research performed by the author and his colleagues prior to and during 1998).*

Purpose: Neuropsychological; To investigate brain modules and neurotransmitter systems involved in producing drug-induced altered states of consciousness, specifically psychosis-like features produced by hallucinogens and related drugs and to present a model of brain activity during the altered states of consciousness present after use of hallucinogens, entactogens or dissociative anesthetics. (Review paper).
Design: Comparison across studies. Most studies used a double-blind, placebo controlled experimental design, with at least 2 conditions (placebo or treatment) and occasionally with 4 conditions (placebo / placebo, pretreatment / placebo, placebo / treatment and pretreatment / treatment). Studies that use different treatments and similar measures are compared across drug (ketamine, psilocybin, MDMA, d-amphetamine and placebo), and studies investigating the same drug across different measures are also compared. Nearly all studies reviewed were performed on human subjects, but some studies assess how drugs affect PPI (pre-pulse inhibition) in rats.
Subjects: All studies performed on "healthy human subjects." Subjects in studies involving the measures of the effects of MDMA on PPI and the psychometric effects of MDMA were conducted on a sample of 13 MDMA-naïve subjects. 10 men, 3 women, aged 23-47, recruited from among university students and hospital staff. Imaging studies with MDMA appear to post-date this paper and are not addressed here. (One paragraph refers to an electroencephalographic investigation of the acute effects of MDMA, using LORETA, but little information is given about this study or the individuals participating in it).
Measures: Alterations in Consciousness – Via ASC, a self-report measure containing 3 scales, OB ("oceanic boundlessness), VR, "visionary restructuring" and AED, "fear of ego dissolution."

Pre-Pulse Inhibition – Measured in humans via the eye-blink component of the human startle response to noise bursts presented binaurally, with eye-blink measured with EMGs of the obicularis oculi muscle.
Imaging – Performed via PET. This paper addresses PET studies of the acute effects of psilocybin and ketamine, and does not address imaging after MDMA.
EEG – Performed via low resolution electromagnetic tomography (LORETA), a form of EEG that can locate electrical activity in the brain. LORETA allows for locating differences in distribution of active neuronal populations with high time resolution.
Drug-Drug Interaction Studies – The effects of a test drug on specific neurotransmitter systems are measured by combining the test drug with pre-treatments hypothesized to alter the drug's actions. Pretreatment drugs mentioned in this paper include 5HT2 antagonists (ketanserin, risperidone) and D2 antagonists (haloperidol, risperidone). This paper does not address the drug-drug interaction studies performed with MDMA as the test drug; studies with psilocybin and ketamine are addressed.
Analyses: NA. (Individual investigations with MDMA used either a 1-way or a 2-way repeated measures ANOVA with post-hoc comparisons made via Tukey's test. Other studies also used correlations. One study used a factor analysis of PET brain activity and performed a multiple regressions, associating ASC scores with distinct factors of brain activity.)
Results: Alterations in Consciousness – MDMA was compared with other drugs with respect to changes produced in the 3 ASC scale scores (OB, VR and AED). Ratings on all 3 ASC scales were higher after MDMA than after placebo. Comparing across studies, ASC scores after MDMA were different from scores produced after a stimulant (d-amphetamine), a hallucinogen (psilocybin) and a dissociative (ketamine). Ratings of OB, or pleasant derealization and changes in sense of self were high after MDMA, but with only moderately increased scores on VR (changes in perception) or AED (fear of ego-dissolution or loss of control). Psilocybin and ketamine both produced similar OB scores to those produced after MDMA, but the hallucinogen and the dissociative produced higher ratings of VR and AED, indicating a greater degree of altered perceptions and more fear of losing control or of losing the "self." Subjects who had received amphetamine had AED scores similar to subjects who had received MDMA, but their scores on the VR And OB scales were lower after amphetamine than after MDMA.
Pre-Pulse Inhibition – MDMA reduces PPI in rats, but in humans, MDMA increases PPI. Studies had not been performed on the effects of hallucinogens on PPI, though studies with non-human animals suggest that PPI is reduced by hallucinogens, with 5HT2 antagonists attenuating the reduction in PPI.
Imaging – No information directly relevant to studies involving MDMA. Review addresses studies that find similar patterns of hyperfrontality after the hallucinogen psilocybin and the dissociative ketamine. Using PET conducted with S-ketamine, R-ketamine, psilocybin and amphetamine, the authors found a five-factor model of brain activity, including these factors: "frontal parietal," "temporal," "occipital cortex," "striatum" and thalamus. Overall cortical / sub-cortical organization did not differ between people receiving placebo and drug treatments (psilocybin, R-ketamine, S-ketamine or amphetamine). Yet subjects experiencing hallucinations had higher scores on the "frontal-parietal" and "striatal" networks and lower scores on the "occipital" network. Subjects experiencing hallucinations or changes in perception had alterations in the fronto-parietal, temporal, striatal and occipital network. Positive derealization (OB) was associated with changes in the fronto-parietal, temporal and occipital networks, and fear of ego dissolution (AED) was associated with changes in thalamic activity.
EEG – A study was recently conducted or is nearing completion that has or will investigate the relationships between the thalamus and cortical regions (especially frontal regions) acutely after MDMA administration and psilocybin administration. The results were not available or complete at the time of publication.
Drug-Drug Interactions – The author does not report on data gathered from drug-drug studies with MDMA (these were published in 2000). Most of the effects of psilocybin could be attenuated by pretreatment with ketanserin (5HT2 antagonist) or risperidone. Haloperidol pretreatment lowered ratings of OB after psilocybin pretreatment, but increased ratings of AED on the ASC.
Overall Effects: MDMA produced measurable differences in responses to a psychometric measure of alterations in consciousness. Moreover, the acute effects of MDMA were distinguishable from those of a

stimulant, a hallucinogen and a dissociative. Specifically, the acute effects of MDMA were marked by high levels of "oceanic boundlessness" (pleasant derealization and loosening of ego boundaries) and low to moderate levels of "visionary restructuring" (alterations in perception) and "fear of ego dissolution." By contrast, psilocybin and ketamine produced higher scores on alterations in perception and fear of ego dissolution and amphetamine produced lower scores on all 3 scales than MDMA. While MDMA reduced PPI in rats, it facilitated PPI in normal human subjects. While the author had not yet investigated the acute effects of MDMA with PET or other imaging methods, he reported an association between different ASC scale scores and brain activity in people given various drugs, including psilocybin and amphetamine. These models found that positive derealization and changes in the sense of self or ego and fear of ego control seemed to arise from different cortical networks. Oceanic boundlessness was associated with changes in the fronto-parietal, temporal and occipital areas, while fear of ego dissolution was associated with changes in the thalamus. Drug-drug interaction studies found that pre-treatment with 5HT2 antagonists, but not D2 antagonists, decreased most of the effects of psilocybin. In contrast, haloperidol increased fear of ego dissolution. Though the author reported that he had conducted or was in the process of conducting a study using LORETA as a means to map brain activity after MDMA, no data was presented concerning the acute effects of MDMA or psilocybin on brain electrical activity as measured through LORETA.
Adverse Effects: Hallucinogens, dissociatives and entactogens all produce an increase in fear of ego dissolution or fear of losing control. MDMA produces far less fear of ego dissolution when compared with a hallucinogen or a dissociative. For more details, see above.
Comments: This paper reviews a number of studies conducted by the author and his colleagues in an attempt to better understand the effects of hallucinogens and related drugs, including MDMA. The author describes the "cortico-striatal-thalamo-cortical circuit" and its hypothesized relevance to psychosis and the acute effects of hallucinogens. In this framework, MDMA is investigated and used as a comparison drug when examining the effects of other drugs. Because this paper was published in 1998, it does not contain information on more recent studies of the effects of MDMA. Recent studies that measured blood flow acutely after MDMA with PET found that the drug also activates some frontal and temporal areas, as well as the cingulate and the cerebellum. The author does not present a clear role for MDMA in the model of brain activity during altered states of consciousness in this paper, perhaps because many of the studies investigating the effects of MDMA had not been conducted at the time this paper was published.

Vollenweider et al. (1998). Psychological and cardiovascular effects and short-term sequelae of MDMA ("Ecstasy") in MDMA-naïve healthy volunteers.

Vollenweider, F. X., Gamma, A., Liechti, M., & Huber, T. (1998). Psychological and cardiovascular effects and short-term sequelae of MDMA ("Ecstasy") in MDMA-naïve healthy volunteers. Neuropsychopharmacology, 19, 241-251.

Purpose: Neuropsychological, neurophysiological: "To determine the acute psychological and physical effects, as well as short-term sequelae of a typical recreational dose of MDMA in MDMA-naïve normals in a clinical setting." (p. 242).
Design: Randomized double-blind within-subjects design. Each subject participated in 1 placebo and 1 MDMA session (receiving 1.7 mg / kg MDMA p.o.), with sessions scheduled approximately one month apart.
S**ubjects**: 13 MDMA-naïve subjects. 10 men, 3 women, aged 23-47, recruited from university and from hospital staff.
Criteria for inclusion – Lack of personal or family history (in first-degree relatives) of psychiatric disorder, no history of substance abuse, healthy as assessed through physical exam, ECG, blood and urine analysis. Scoring in normal range for "openness" and "neuroticism" on personality survey (no more than 2 standard deviations above norm for "neuroticism" and no more than 2 standard deviations below norm for "openness."

Measures: Mood – AM. Measures taken at baseline and 75 min. post-drug (placebo or MDMA), 75 min post-drug predicted peak for MDMA effects.
Alteration in Consciousness – ASC, measured at baseline and 75 min post-drug (MDMA or placebo).
Stroop Task – Measure of attentional processes. Color words either printed in same color as word (congruent) or in different color (incongruent). Subject names aloud the color the word is printed in). Time between word presentation and speaking aloud (response time or latency) measured for congruent, incongruent and other conditions and these compared. Facilitation = percentage of time reduction in congruent condition compared with control conditions. Interference = percentage of increase in time in incongruent condition compared with control word condition and with control "string" condition.
Adverse effects – The VL, throughout session and 24 h (1 day) post-session.
Physiological Effects – Measures of BP, pulse and BT taken at zero, 75, 150 and 300 minutes after drug ingestion.
Analysis: 2-way within-subjects ANOVA with drug state (placebo versus MDMA) and time (baseline versus measures after ingestion) as within-subjects factors. Post-hoc comparisons performed with Tukey's test.
Results: Mood – MDMA produced an increase in extroversion, well being, emotional excitability (emotionality, sensitivity) and anxiety as measured by AM. Well-being high due to high ratings of "self-confident" and "heightened mood" and anxiety high due to increases in "thoughtfulness" component of scale.
Alterations in Consciousness – MDMA increased ratings on all 3 item-clusters of the ASC; OB, VR and AED. Increased OB was due to high scores on positive mood, derealization, depersonalization, change in perception of time and space and mania-like experience. Increased VR was due to increased ratings of changed meaning of percepts, illusions, facilitated recall and facilitated imagination, but without increase in hallucinations or synesthesias. Increased AED was due to increased ratings of thought disorder (thought blocking, accelerated thinking and impaired decision-making, but not delusions or paranoia) and loss of body control.
Physiological Effects – MDMA increased systolic and diastolic BP. For systolic BP, greatest changes were between zero minutes and 75 minutes and between 75 minutes and 150 minutes after drug administration. For diastolic BP, greatest changes were between 75 and 150 minutes and between 150 minutes and 300 minutes, with BP peaking at 2 h post-drug. 12 / 13 only mildly hypertensive after MDMA, but BP increased to 240 / 145 in 1 / 13 (age 49), without any signs of hypertensive crisis. Pulse rate was elevated in all subjects, A third (4-5/13) reported experiencing palpitations, but little discomfort. Increase in BT after MDMA was present but not statistically significant.
Adverse Effects – Volunteers experienced side effects acutely and a day later (24 hours post drug), with fewer sub-acute effects versus acute effects. Most of these classed as (acute) stimulant effects, bodily sensations and (24 hours later) lack of appetite, continued jaw clenching, fatigue. Not all volunteers experienced these effects. See below for more details.
Overall Effects: MDMA increased positive mood, extroversion and emotionality. MDMA produced moderate derealization and altered perception without hallucination or confusion. MDMA also increased BP, and pulse, and non-significantly increased BT. Jaw clenching and lack of appetite were the most commonly reported acute adverse effects, lack of appetite and energy were most commonly reported adverse effects 24 h post-drug.
Adverse Effects: Acute: Jaw clenching (8/13), lack of appetite (8/13), difficulty concentrating (8 / 13), impaired balance / gait (8/13), restless legs (6 / 13), perspiration (5 / 13), heavy legs (5 / 13), increased sensitivity to cold (5 / 13), thirst (5 / 13). Others lower than 5 / 13 include forgetfulness, palpitations, restlessness, insomnia, dizziness, and tremor. Less than a third of the volunteers experienced parasthesias, weakness, hot flashes, feeling cold or inner tension. As noted above, BP in 1 / 13 increased to hypertensive range but without signs of hypertensive crisis, and no intervention necessary to reduce BP.
24 h later – Lack of appetite (6 / 13), lack of energy (6 / 13), thirst (6 / 13), fatigue (5 / 13), feeling restless (5 / 13), heavy legs (5 / 13), insomnia (5 / 13), Below 5 / 13 of the volunteers experienced feeling

weak, urge to urinate, difficulty concentrating, decreased libido. Less than a third of the volunteers experienced: jaw clenching, perspiration, increased sensitivity to cold, brooding or job-related worries.
Comments: This study is the first to administer MDMA to MDMA-naïve subjects. The psychometric profile supports the existence of an "entactogen" classification for MDMA and like drugs that separates them from stimulants and classical hallucinogens, since MDMA's effects on mood and consciousness were measurably different from changes produced by stimulants and hallucinogens (measured in other papers). This paper demonstrates that MDMA can be administered to healthy MDMA-naïve volunteers (if selected for normal neuroticism and openness scores) without severe acute adverse reactions or psychological distress.

Vollenweider et al. (1999). Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans.

Vollenweider, F. X., Remensberger, S., Hell, D. & Geyer, M. A. (1999). Opposite effects of 3,4-methylenedioxymethamphetamine (MDMA) on sensorimotor gating in rats versus healthy humans. Psychopharmacology, 143, 365-373

Purpose: Neuropsychological, psychopharmacological: To compare "the effects of a 5HT releaser, MDMA on [pre-pulse inhibition, PPI] and habituation of acoustic startle in normal laboratory rats versus healthy human volunteers."
Design: A randomized, double blind within-subjects design, wherein volunteers received either placebo or 1.7 mg / kg MDMA during each experimental session, with sessions taking place 2-4 weeks apart. All volunteers underwent PPI testing at baseline and at 75 min post-drug during each session. (Study with rats used similar design, but with different groups of rats receiving different doses of MDMA).
Subjects: 13 MDMA-naïve volunteers, 10 men, 3 women, aged 23-47, recruited from university and from hospital staff. (Same sample as used in Vollenweider et al., 1998).
Criteria for inclusion – Healthy, as assessed via physical examination, ECG, blood and urine analysis. Lack of personal or family history (in 1st –degree relatives) of psychiatric disorder and no history of substance abuse. Normal range for "openness" and "neuroticism" as scored on FPI.
Measures: Mood – AM administered at baseline and approximately 75 min post-drug, (placebo or MDMA), with 75 min post-drug predicted peak time of MDMA's psychological effects.
Alteration in Consciousness – ASC, with measure administered at baseline and approximately 75 min post-drug.
Pre-Pulse Inhibition (PPI) – A measure of sensorimotor gating. Eyeblink component of acoustic startle response to noise bursts measured through EMGs of the obicularis orculi muscle. Startle trials consisted of 1) 115 dB 40-ms noise alone (no pre-pulse), 2) the same stimulus followed by pre-pulse stimulus of 20 ms duration or 3) no-stimulus trials, with trials presented in pseudorandom order. Pre-pulse stimuli appeared either 30 or 120 ms before the pulse and either 8 or 16 dB in volume; all pre-pulses lasted 20 ms. (Similar procedure used with rats except whole-body flinch startle response measured and noise presented through speakers placed above rats).
Analyses: PPI– % pre-pulse inhibition (PPI), % habituation calculated and compared with absolute scores for PPI and habituation, and both scores found to be similar. After confirming absence of order interactions and presence of treatment effects, % PPI and % habituation analyzed in 2-way ANOVA with drug condition (placebo versus MDMA) and block as within-subjects variables, with post-hoc comparisons made via Tukey's test. (Rat data analyzed similarly, but with drug dose as a between-subjects factor).
Mood and Alterations in Consciousness – A 2-way ANOVA was conducted on measures of mood and alterations in consciousness, with treatment (MDMA versus placebo) and psychological dimension as within-subjects factors. Post-hoc comparisons were made with Tukey's tests.
Results: PPI – MDMA increased startle reactivity and habituation in all 3 blocks, with strongest increase occurring in middle block of trials. MDMA increased % PPI, and this especially so for 16 dB pre-pulse

presented 120 ms before pulse. (In rats, MDMA decreased % PPI at higher doses and did not change % PPI at 1.7 mg / kg dose, same dose as increased PPI in humans.)
Mood – MDMA increased AM scores for extroversion, well-being, heightened mood, emotional excitability (emotionality, sensitivity) and thoughtfulness. Volunteers also reported experiencing enhanced insightfulness, self-confidence and closeness to others.
Alterations in Consciousness - MDMA increased all clusters of ASC (OB, VR and AED). Increase in OB due to increased ratings of "positive mood" (much higher than placebo), "derealization" and "depersonalization" (moderately higher) and "alteration in the sense of space and time." VR scores increased due to increased ratings of "changed meanings of percepts," "illusions" and "facilitated recall." AED scores increased due to increased ratings of "loss of body control" and "thought disorder" (but not delusions).
Overall Effects: 1.7 mg / kg MDMA in humans increased startle reactivity, habituation and % PPI. While MDMA increased pre-pulse inhibition in humans, it either had no effect on PPI in rats (at 1.7 mg / kg) or reduced it (at 5.4 mg / kg and at 17 mg / kg). MDMA did not seem to impair normal sensorimotor gating in humans, and it may have increased sensorimotor gating in humans, at least at the dose examined. Humans who ingested 1.7 mg / kg MDMA experienced an increase in positive mood, extroversion, emotionality, thoughtfulness, some perceptual alterations, facilitated recall, derealization, depersonalization, thought disorder and loss of body control.
Adverse Effects: Adverse effects not reported in this paper. See Vollenweider et al., 1998 for report of adverse effects in this sample.
Comments: In contrast to psychotomimetic drugs such as ketamine, MDMA (at those dose used in this study) did not reduce PPI. This paper is also notable in finding interspecies differences in the effects of MDMA, since it is usually assumed that mammals will respond similarly upon receiving a drug. The paper's findings indicate that while MDMA might disrupt sensory gating in rodents, it does not do so in humans. Alternately, another effect of MDMA in humans may have counteracted reduction in PPI, or differences between rats and humans might have been an artifact of measurement conditions. This paper is one of the first in an ongoing series of studies examining the neurochemical correlates of PPI in rodents and humans, particularly changes produced by serotonergic agents such as MDMA.

Appendix B: Structured Abstracts of Reports on Human Ecstasy Neurotoxicity Research

Lisa Jerome, Ph.D.

Contains: summaries of all 38 available studies published as of June 1, 2001 in the English-language literature that examined ecstasy users for evidence of neurotoxicity.

Allen et al. (1993). Persistent effects of (+/-)3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") in human sleep.

Allen, R. P., McCann, U. D., & Ricaurte, G. A. (1993). Persistent effects of (+/-) 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") on human sleep. Sleep, 16, 560-564.

Purpose: Sleep study: to investigate whether ecstasy use affects sleep or specific aspects of sleep architecture. Specific Hypotheses Tested – that MDMA users would have decreased total sleep time (TST) and that reduction in TST would be related to reductions in NREM and REM sleep.
Design: Non-experimental (retrospective) 2-group between-subjects (across group) design, with sleep variables measured in ecstasy users and matched non-user controls. All subjects spent 2 nights in a sleep laboratory. Only data gathered from the 2nd night was used in this study.
Subjects: 23 regular ecstasy users and 22 non-users. Recruitment information is not provided in this study, but since ecstasy users came from different geographic locations, recruitment of ecstasy users was not restricted to one locality. Matching – Ecstasy users and non-user controls matched on gender and age. Criteria for Inclusion – Ecstasy Users – Having used ecstasy on more than 25 separate occasions. Controls – No prior history of ecstasy use. All Groups – Absence of any major medical or psychiatric illness, no personal history of major medical illness, absence of current depressive disorder, alcohol dependence or psychosis and no history of sleep disorders. All subjects required to abstain from any psychoactive substances for at least two weeks before the study days, with compliance verified through analysis of blood and urine performed on first study day.
Drug Use Parameters – Ecstasy users reported using ecstasy on an average of 79.4 occasions (25-300). No information is provided on duration of use, typical dose used or frequency of ecstasy use.
Group Demographics and Matched Variables – Ecstasy users matched with non-user controls on age and sex, but not on place of residence. Gender, as M / F ratio – Ecstasy users, 15/8: non-users, 17/5. Age. Ecstasy users, average age 26.7 ± 6, no range provided: non-users, 26.1 ± 4.5, no range provided. Other Variables - Place of Residence. 11 ecstasy users resided in locations in the Eastern and Central time zones, and 12 ecstasy users resided in locations in the Mountain and Pacific time zones. 17 non-users resided in locations in the Eastern and Central Time zones and 3 non-users resided in locations in the Mountain and Pacific Time zones. The study was performed in the Eastern time zone. 6 ecstasy users diagnosed with conditions that might affect sleep and 4 non-users diagnosed with conditions that might affect sleep.
Measures: Sleep EEG recordings, including 2 EEG channels, 2 channels for eye movements, and 1 submental EMG channel. Respiratory activity measured via oximetry, measures of airflow from mouth and nose and respiratory effort measured through abdominal and thoracic strain gauges. Sleep time was from 11:00 to spontaneous waking after 6:00 AM, with a maximum of 8 h sleep permitted. Polysomnograms taken on both nights, but only night 2 analyzed in this study. Sleep stages visually scored for sleep on night 2 by 2 independent raters.
Analyses: Analysis of variance (ANOVA) performed on TST (in minutes) and all stages of sleep save Stage 1 (Stages 2, 3, 4 and REM) sleep. Drug use (ecstasy user versus non-user), time zone of origin (from East to West), age and presence (versus absence) of diagnoses, like alcohol dependence, that might affect sleep all served as independent (subject) variables.

Results – Significant Differences: Ecstasy users had less TST, spent less time in non-REM sleep and had less Stage 2 sleep than non-users.
Results – No Differences Found: Total time spent in REM sleep did not differ between ecstasy users and non-users. There were no differences between ecstasy users and non-users in time spent in Stages 1, 3 or 4 sleep. Though Stage 2 sleep was reduced in ecstasy users, there were no differences in structural features of Stage 2 sleep between ecstasy users and non-users. No sleep abnormalities in sleep records of ecstasy users.
Results – Additional: Older subjects in both groups (ecstasy users and non-users) had less slow-wave sleep (SWS), measured as Stages 3 + 4. Analyses yielded the same differences between drug use groups when 11 / 45 subjects with possible psychiatric diagnoses associated with changes in sleep were removed from the sample. Conducting analyses on 28 / 45 subjects who resided in the Eastern and Central time zones (closest to study location) also yielded the same results.
Overall Effects: Ecstasy users were found to spend less time asleep, as measured via total sleep time (TST) when compared with non-user controls. Ecstasy users also spent less time in non-REM (NREM) sleep. When compared with non-users, ecstasy users spent less time in Stage 2 sleep. Despite these differences in sleep pattern, ecstasy users and non-users did not appear to differ in time spent in any other sleep stages, and no sleep abnormalities were recorded for any of the ecstasy-user participants. In order to account for differences between the two groups in time zone of origin, analyses took this variable into account. Both the differences in TST and Stage 2 sleep and the lack of significant differences in all other sleep variables remained when the analysis was restricted to individuals residing no farther than 1 time zone from the study location. The same results were yielded when age was used as a between-subjects factor. The authors' hypotheses were partially confirmed: Ecstasy users did exhibit less TST and NREM sleep than did control subjects, but they did not exhibit less REM sleep or in any other facet of NREM sleep.
Comments: To date, this is the only study comparing sleep architecture in ecstasy users and non-users. Ecstasy users were matched with non-users on age and gender, but many more of the ecstasy users resided in an area three time zones away from the study location. However, an analysis that only considered individuals living in the same time zone still found differences in TST and Stage 2 sleep without finding any other differences in sleep pattern. The authors are unable to generate any explanations for the differences they found between ecstasy users and non-users. The results of the only follow-up to this study (presented as part of a review paper not summarized here) did not match these results; ecstasy users in the more recent study spent more time asleep, with increase due to more Stage 3 and 4 sleep, and had greater sleep efficiency than non-users.

Bolla et al. (1998). Memory impairment in abstinent MDMA ("Ecstasy") users.

Bolla, K., McCann, U. D., Ricaurte, G. A. (1998). Memory impairment in abstinent MDMA ("ecstasy") users. Neurology, 51, 1532-1537.

Purpose: Cognitive function (memory); Investigation to determine whether regular ecstasy use is associated with memory deficits by comparing drug-free ecstasy users with non-user controls, with an examination of any possible relationships between levels of the serotonin metabolite 5HIAA in CSF and memory scores.
Design: Non-experimental (retrospective) 2-group between-subjects (across-group) design, with regular ecstasy users and matched controls compared on performance on memory tests. The relationship between ecstasy dose and performance on memory tests and between 5HIAA and memory score performance were also examined. Each subject underwent one series of neuropsychological assessments.
Subjects: 24 regular ecstasy users and 24 non-user controls, with ecstasy users recruited via word of mouth and non-users recruited via local advertisements (subjects a sub-set of people participating in McCann et al, 1994). Matching – Groups matched on gender, age, education, other drug use, and WAIS vocabulary score.

Criteria for Inclusion, Ecstasy Users – Having used ecstasy on at least 25 separate occasions. Non-Users – No history of prior ecstasy use. All Groups – English as first language, below age 50, WAIS-Vocabulary raw score between 24 and 67, absence of past or present major medical illness, no current major psychiatric illness as determined by psychiatric interview, absence of current alcohol dependence and negative screens for psychoactive or prescribed medications. Abstinence from all recreational drugs for up to 2 weeks prior to the study day, with compliance verified through analysis of urine and blood. Drug Use Parameters – Ecstasy users reported using approximately 1.6 tablets per occasion (.6-5), and they had used ecstasy an average of 60 times (25-300). Average frequency of use (per month) was 2 times per month (0-20 times), and average duration of use (in months) was 57 months (12-204 months). Average dose of ecstasy per month was approximately 4.4 tablets (.6 – 40 tablets per month). Average self-reported length of drug-free period before study day, in days, 30 days (14-252). Use of Other Drugs – Ecstasy users reported using any of these substances at least once: alcohol (24 / 24), cannabis (22 / 24), cocaine (20 / 24), hallucinogens (19 / 24), nicotine (14 / 24), benzodiazepines (13 / 24), opiates (13 / 24), other amphetamines (10 / 24), sedatives (9 / 24), solvents (4 / 24) and PCP and related drugs (4 / 24). Non-users reported using any of these substances at least once: alcohol (23 / 24), cannabis (14 / 24), nicotine (9 / 24), hallucinogens (6 / 24), benzodiazepines (5 / 24), sedatives (5/ 24), cocaine (4 / 24), opiates (3 / 24), other amphetamines (2 / 24), solvents (2 / 24), and PCP and related drugs (1 / 24).
Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender, age, education and WAIS-Vocabulary score, with use of other drugs permitted in both groups. Gender, as M / F ratio – Ecstasy users, 14 / 10: non-users, 18 / 6. Age, Ecstasy users, 20-44, mean = 30: non-users, 19-49, mean = 27. Educational Level, in years – Ecstasy users, 12-21, mean = 15 ± 2: non-users, 12-23, mean = 17 ± 3. WAIS-Vocabulary Score – Ecstasy users, 24-64, mean = 54 ± 1: non-users, 24-67, mean = 57 ± 9. Use of Other Drugs – Ecstasy users, 24 / 24 had used alcohol or at least one other illicit drug: non-users, 24 / 24 non-users had used alcohol or at least one other illicit drug (except ecstasy). However, a greater number of ecstasy users than non-users had used every drug listed except for alcohol.
Measures: Measures of Memory - Measured via WMS (13 subtests), RAVLT (verbal memory test), Rey-Osterrieth Complex Figure (RCT) (visual memory test). Individual memory tests reduced to 4 major factors: immediate verbal memory (RAVLT-Logical memory, Digit Span total and verbal paired associates), delayed verbal memory (RAVLT-Recall, RAVLT-Recognition, logical memory-recall and verbal paired associates-recall), immediate visual memory (RCF, visual reproduction, visual paired associates and figural memory) and delayed visual memory (RCF-Recall, visual paired associates-recall and visual reproduction-recall).
Vocabulary – Measured via WAIS-R Vocabulary sub-test, said to be insensitive to changes produced by neurotoxins.
5HIAA in Cerebrospinal Fluid – Concentrations of the 5HT metabolite 5HIAA measured via high-performance liquid chromatography coupled with electrochemical detection.
Analyses: Separate multiple linear regressions were performed on each of the 4 memory factors (immediate and delayed verbal memory, immediate and delayed visual memory). Exploratory analyses were also conducted to find possible relationships between gender, age, vocabulary score, ecstasy dose and performance on memory tests. Regression analyses performed with estimated ecstasy dose (in milligrams) used rather than discrete group membership (ecstasy user versus non-user), with 1 tablet or capsule estimated at 100 mg.
Results – Significant Differences: Tests of Memory – When the influence of gender and vocabulary score removed from analysis, estimated dose was found to be related to decreased performance on immediate paired verbal associates, delayed paired verbal associates and delayed visual paired associates, with performance decreasing as dose increased. When the influence of gender and vocabulary score removed from analysis, estimated dose was found to be related to decreased performance on immediate paired verbal associates, delayed paired verbal associates and delayed visual paired associates, with performance decreasing as dose increased. Significant differences between groups only found when average monthly estimated dose of ecstasy (estimated dose of ecstasy in mg x frequency of use per month) added into the model. (Model also included gender and vocabulary score). Ecstasy dose was

associated with performance on tests of immediate verbal memory and delayed visual memory, with dose associated with poorer scores on these tests. Interaction between vocabulary score and dose on performance on delayed verbal memory, with estimated ecstasy dose associated with poorer performance on delayed verbal memory for subjects with low vocabulary scores, but with no association between dose and poorer performance on delayed verbal memory test for subjects with high vocabulary scores. When the influence of gender and vocabulary score removed from analysis, estimated dose was found to be related to decreased performance on immediate paired verbal associates, delayed paired verbal associates and delayed visual paired associates, with performance decreasing as dose increased. A vocabulary x dose interaction was found for immediate paired visual associates, with decrement in test performance associated with increasing dose affecting those with low vocabulary scores more than those with higher vocabulary scores. There was an interaction between ecstasy dose and gender on performance on immediate verbal associates, immediate and delayed paired visual associates and delayed RAVLT-Recognition, with higher doses of ecstasy positively related to poorer performance for men, but relationship between dose and performance on these tests less strong for women.
Correlations between Performance on Memory Tests and CSF 5HIAA – Concentration of 5HIAA was lower in ecstasy users than in controls. As estimated average monthly dose increases, concentration of 5HIAA in CSF decreases. Lower concentrations of 5HIAA in CSF associated with lower performance on delayed visual memory when effects of gender and vocabulary score are removed from model. Lower concentrations of 5HIAA in CSF associated with lower performance on immediate figural memory and delayed visual reproduction.
Results – No Differences Found: Tests of Memory – First analysis found no differences between ecstasy users and non-using controls on performance on memory tests, as measured through all four factors (immediate and delayed verbal memory, immediate and delayed visual memory). In the analysis using average dose per month rather than group membership, a relationship between dose and poorer scores on delayed verbal memory approached but did not reach significance.
Correlations between Performance on Memory Tests and CSF 5HIAA – There was no relationship between 5HIAA concentration and performance on tests of memory when effects of gender and vocabulary score remained in model. When gender and vocabulary score were entered into model, concentration of 5HIAA was not related to performance on tests of immediate or delayed verbal memory or immediate visual memory.
Results, Other: There was no significant relationship between subject age and performance on any of the four memory factors. Gender and vocabulary score were significantly related to performance on tests of memory (relationships not specified here).
Overall Effects: No differences in performance on tests of memory were found between ecstasy users and matched non-user controls when comparisons were made across groups. There were also no differences in performance on tests of immediate verbal memory and delayed verbal memory when group membership was replaced with estimated monthly dose. There was a trend for a relationship between higher dose and poorer performance on tests of delayed verbal memory, without this reaching statistical significance. The relationship between dose and poor performance on tests of memory (delayed verbal memory) was stronger for people with lower vocabulary scores than for people with higher vocabulary scores. The relationship between increasing ecstasy dose and decreased performance on tests of delayed verbal and visual memory was stronger for men than for women. Ecstasy users were found to have lower concentrations of 5HIAA in their cerebrospinal fluid than non-user controls. While 5HIAA concentration was unrelated to vocabulary score, 5HIAA concentration was related to performance on tests of delayed visual memory, with lower 5HIAA associated with poorer performance on immediate and delayed visual memory.
Comments: Rather than presenting a simple comparison between memory performance in ecstasy users and in matched controls, this paper examines linear relationships between estimated monthly ecstasy dose and performance on tests of memory. While some non-user controls used alcohol and a number of other drugs, a larger number of ecstasy users had tried all drugs measured except for alcohol, indicating that the two groups are not matched with respect to general drug use. Hence it is possible that people who use a

greater number of drugs recreationally also tend to use higher doses of ecstasy, and that increased drug use, and not ecstasy dose, explains decrements in memory. The results from analyses that used gender and vocabulary score as main variables were not presented in this paper.

Boone et al. (In preparation). Neuropsychological Effects of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy).

Boone, K. B., Chang, L., Grob, C. S., & Poland, R. E. (In Preparation). Neuropsychological Effects of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy). Manuscript obtained from C. S. Grob, August, 2000.

Purpose: Cognitive function (general); to investigate the effects of regular ecstasy use on cognitive functions measured in a comprehensive neuropsychological test battery. (Also compares performance on a subset of neuropsychological tests before and after the administration of MDMA in a laboratory setting. See "Clinical Study Summaries" for more details).
Design: Non-experimental (retrospective) 1-group design, with performance of ecstasy users on tests of cognitive function compared with published norms, largely matched by age. (Paper also employs comparison between performance at baseline and performance after MDMA administration for a sub-set of the sample. See "Clinical Study Summaries" for details.)
Subjects: 24 regular ecstasy users recruited through local advertisements. Matching – None. There were no controls. However, test scores were mostly compared with age-matched published norms.
Criteria for Inclusion – Having used ecstasy at least three times and for at least 1 year. Good health as assessed through medical examination, psychiatric interview and neurological examination. Lack of personal or family history of major medical or psychiatric illness. No history of substance abuse (except for MDMA or nicotine) and no history of head trauma with loss of consciousness over 30 min. At least 1 month free of psychoactive medications or illicit drugs, with compliance verified on study day by urinary screen conducted before or on study day.
Drug Use Parameters – Subjects reported using ecstasy on an average of 203.8 ± 334 times over a lifetime (3-1500 times) over an average period of 96 ± 57.6 months (12- 204 months). No information on frequency of use is provided. Average dose used per occasion ranged from approximately .6 to 1.75 tablets (or 62.5 to 175 mg). The last reported use of ecstasy before the study, in days, was 193 ± 225.3 days (7.5 – 780 days). Other Drugs – Subjects reported using marijuana (83%), LSD (71%), magic mushrooms (46%) and other amphetamines (29%). 3 / 24 reported using cocaine on > 3 occasions, but were not dependent on it.
Group Demographics and Matched Variables – There were no controls participating in this study. Gender, as M / F ratio – 16/8. Age. Average = 38 ± 12.6 years, no range provided. Education Level. Average education level was 15.8 ± 3.01 years of education.
Measures: MRI – Performed via clinical 1.5 Tesla scanner.
Neuropsychological Assessment – Tests of Intelligence – WAIS-R (Satz-Mogel format).
Tests of Attention – WAIS-Digit Span (recall and recite digits forwards and backwards). Speed of Information Processing – Stroop A (read color words in black ink) and B (speak aloud color of words printed in same or differently colored ink), WAIS-Digit Symbol (Learn and translate digits into symbols). Tests of Language – Boston Naming Test. Tests of Constructional Ability – Rey-Osterrieth Complex Figure (Draw complex abstract figure immediately after viewing it). Verbal Memory – WMS-Logical Memory, Warrington Recognition Memory Test-Words (Select one target previously presented out of new list or array) and RAVLT. Non-verbal Visual Memory – WMS-Visual Reproduction, Warrington Recognition Memory Test-Faces (Select one target previously presented out of a new array), Rey-Osterrieth Complex Figure-3 Min Delayed Recall (Reproduce complex abstract figure after delay), Continuous Visual Memory Test (CVMT). Executive Function – Stroop C (color interference), Auditory Consonant Trigrams, Wisconsin Card Sort (WSC) (Derive rules about sorting cards through feedback

from experimenter), and Verbal Fluency-Words (or Controlled Oral Word Association Test) (Generate as many words as possible in 60 s starting with selected consonant).
Analysis: Test Performance - Performance on each test scored for 24 subjects at baseline. (14 / 24 subjects re-tested and scored after MDMA administration). Performance scores on each test compared with published norms matched by age group, except for Copy and Recall scores for Rey-Osterrieth figure, which were matched for sample education. Performance below the 25th percentile or above the 75th percentile considered significantly different from published norms.
Drug Use Parameters and Test Performance – Spearman correlation coefficient was used to assess relationship between MDMA user parameters (duration, frequency and recency of use) and performance on each test. (Pre-drug performance compared with post-drug performance for 14 / 24 subjects on each test via paired t-test, see "Clinical Study Summaries.")
Results – Significant Differences: Neuropsychological Tests: Tests of Intelligence – Ecstasy users scored higher than published norms on WAIS-R Full-scale and Verbal IQ scores (FIQ at 87th percentile and VIQ at the 87th Percentile). Tests of Executive Function – Ecstasy users performed below published norms on all trials of the WCS (categories, 11th Percentile, "pers. Response," 25th Percentile, FTM, below 16th Percentile, errors, 32nd Percentile, %concept, 34th Percentile, Trials, 6th – 11th Percentile). Ecstasy users performed above published norms on Auditory Trigrams, at the 87th Percentile.
Drug Use Parameters and Test Performance – Frequency of MDMA use negatively correlated with scores on tests of visual memory and verbal recognition memory, and frequency of use positively correlated with speed in test of mental speed and cognitive inhibition. Length of abstinence prior to assessment positively correlated with performance on measures of divided attention / working memory and visual memory. Though cumulative number of ecstasy doses was not significantly correlated with performance on the WCS, it did account for 10% of the variance on WCS scores.
Results – No Differences: MRI – MRI scans normal for all subjects.
Neuropsychological Assessment – Tests of Intelligence – Ecstasy users did not differ from published norms for the WAIS-R Performance IQ (though they did perform above the 75th percentile). Tests of Attention – No difference from published norms for Digit Span. Speed of Information Processing – No difference from published norms for Digit Symbol, Stroop A or Stroop B (though performance on Stroop B at 48th percentile). Language – Ecstasy users did not differ from published norms for Boston Naming Test (though performance at 48th Percentile). Tests of Constructional Ability (Visual-Spatial) – Ecstasy users did not differ from published norms on Rey-Osterrieth Complex Figure-Immediate Recall. Verbal Memory – There were no differences from published norms for WMS-Logical Memory, Warrington Recognition Memory-Words or RAVLT scores (though scores on RAVLT over trials varied and fell below 50th percentile). Tests of Non-Verbal Visual Memory – Ecstasy uses did not differ from published norms for WMS-Visual Reproduction, Immediate Recall and Retention (though performance on Immediate was > 75th percentile), CVMT (though "recognition" score at 41st percentile), Warrington Recognition Memory-Faces or Rey-Osterrieth-Delayed. Tests of Executive Function – Performance scores did not differ from published norms on Stroop C or Verbal Fluency-First Consonant (though performance was at 43rd and 47th percentile, respectively.
Overall Effects: When tested on a comprehensive test battery assessing cognitive function, a sample of ecstasy users performed in the range expected of their age group in the majority of tests. They performed above published norms on the WAIS-R, a test of general intelligence, and they performed somewhat below published norms (below 50th percentile) on specific tests of verbal and non-verbal memory. Yet performance on most tests, including tests of attention, information processing, visual constructional ability, language and memory, were within the range of normal performance. However, performance on two of three tests of executive function was far below published norms, even while performance on one test was slightly above published norms. Frequent use of MDMA was associated with poorer performance on tasks involving memory, with visual memory being particularly affected, and more recent use of MDMA was associated with poorer performance on a test of divided attention and working memory. On the other hand, frequency of use is associated with faster performance on a test of mental

speed. (Test performance measured 2 to 4 weeks after MDMA administration did not significantly differ from baseline performance).
Comments: This study makes a stronger contribution as the first prospective study of cognitive function measured acutely after MDMA administration, with comparisons made at baseline and after MDMA administration in 14 of the 24 subjects. Findings from the prospective study suggest that up to 2 doses of MDMA administered in a controlled setting have little effect on cognitive function, as post-MDMA performance does not differ greatly from baseline performance. Because it lacks a non-user control group and relies on comparisons with published norms, it is difficult to interpret findings concerning test performance in regular ecstasy users. It seems particularly surprising that a group of individuals who score at or above norms on general intelligence do so poorly on tests of executive function. Overall, the findings suggest that ecstasy use is associated with specific deficits in executive function, and that frequent and recent use may affect memory and attentional mechanisms.

Brody et al. (1998). Cardiovascular autonomic dysregulation in users of MDMA.

Brody, S., Krause, C., Veit, R. & Rau, H. (1998). Cardiovascular autonomic dysregulation in users of MDMA. Psychopharmacology, 136, 390-393.

Purpose: Physiological, cardiology study; to investigate whether regular ecstasy use affects autonomic tone and function. Specific Hypothesis Tested – That ecstasy users would have less bradycardia after performing the Valsalva maneuver, and that they would also exhibit less resting heart rate variability (HRV), an index of parasympathetic tone.
Design: Non-experimental (retrospective) 2-group between subjects (across groups) design, with drug-free ecstasy users and matched non-user controls compared on HRV and performance on the Valsalva maneuver, with drug use serving as a between-subjects factor. All subjects underwent cardiovascular monitoring, performed the Valsalva maneuver and completed questionnaires.
Subjects: 12 regular ecstasy users and 12 non-user controls, with ecstasy users recruited by word of mouth and "snowball technique" from the local "techno scene." Recruitment information on controls is not provided. Matching – Ecstasy users were matched with non-using controls on age, sex, weight, extent of cigarette smoking and on amount of exercise.
Criteria for Inclusion, Ecstasy Users – Not specified, but having used ecstasy on a regular basis (more often than once). Non-Users – Not specified beyond absence of any history of ecstasy use. All Groups – Abstinence from ecstasy for at least 6 days prior to study day, with compliance verified through self-report only.
Drug Use Parameters – No information is provided on average dose per use or number of days elapsed since last use. Average frequency of ecstasy use reported for the last 6 months was approximately 3.5 times a month ("a little less than once a week") (approximately .125 – 20 times a month, reported as once in 8 mo – 20 times a month), and average duration of use in months was 48 months (18-84). All ecstasy users had also used marijuana, LSD, botanical hallucinogens and other amphetamines, and all but one had used cocaine. 8 / 12 had tried heroin and 6 / 12 had tried amyl nitrite.
Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender, age, weight, cigarette smoking and amount of weekly exercise. Gender, as M / F ratio – Ecstasy users, 8/4: non-users, 8/4. Age. Not provided separately, but mean = 25.3 (22-38). Weight (not provided separately), in body mass index (kg/m^2 – 22.3. Cigarette Use – (not provided separately), 11 cigarette smokers. Exercise – Information for either group not provided.
Measures: Cardiovascular Measures – Resting blood pressure was measured 3 times, with median used in analysis. Heart rate measured via ECG. Standard deviation for HR over 5 min served as HRV value. Valsalva Maneuver – A measure of autonomic tone. Subjects breathe continuously into a tube with a slight leak to produce pressure on a manometer for 20 seconds. Valsalva ratio = Maximum interval between R waves / minimum R-R interval during the blowing (strain) phase plus measure 20 seconds afterwards. Subjects performed 2 Valsalva maneuvers, with a 5-min rest period between each

performance. The greater value was used in analysis (ambiguous, but seems to refer to the greater pressure exerted by blowing).
Personality – German-language version of the Eyesenck Personality Questionnaire (EPQ) was administered to ecstasy users and non-user controls.
Drug Use – Author-designed measure of drug use administered to ecstasy users, including items for the drugs listed in "Drug Use Parameters," fluoxetine and a fictitious drug, KLZ, intended as a measure of self-report honesty. Ecstasy users also asked if they ever experienced any cardiovascular symptoms after ecstasy use. Non-user drug use survey only contained items on alcohol and cigarette use.
Analyses: Cardiovascular measures - Valsalva ratios for ecstasy users and non-users were compared via t-test, with further comparisons made via chi-square statistic. T-tests were also used to compare resting HRV, systolic and diastolic BP in ecstasy users and non-users. A correlational analysis (probably Pearson's correlation coefficient) was performed on resting HRV and Valsalva ratio.
Personality – Not enough information provided; If the same procedures used as in other cases, then the EPQ scores of ecstasy users compared with non-users via t-test.
Results – Significant Differences: Cardiovascular Measures - Users differed from non-users on Valsalva ratio, with ecstasy users having decreased Valsalva ratio. 3 / 12 ecstasy users, but no controls, had Valsalva ratios below 1.5, the cut-off point for normal autonomic function (suggesting the Valsalva ratios for these users could be indicative of autonomic dysfunction). 5 / 12 ecstasy users but no controls had low Valsalva ratios. HRV differed between ecstasy users and non-users, with ecstasy users having smaller HRV values than non-users. This indicates a lack of bradycardia during the "release" (rest) of the Valsalva maneuver. 9 / 12 ecstasy users had low HRV values, whereas 3 / 12 non-user controls had low HRV values. Resting heart rate and systolic BP were higher in ecstasy users than in non-user controls.
Results – No Differences Found: Cardiovascular Measures – Resting diastolic BP did not differ between ecstasy users and non-user controls.
Personality – While there was a trend for ecstasy users to have higher extraversion and lower neuroticism scores than non-users, the difference did not reach statistical significance.
Results, Other: Correlations - A significant positive correlation was found between Valsalva ratio and HRV for both ecstasy users and non-user controls. Questionnaire – 8 of 12 ecstasy users reported experiencing tachycardia or circulatory problems acutely after taking ecstasy.
Overall Effects: Regular ecstasy users differed from a group of non-user controls matched on a number of variables, with ecstasy users demonstrating a lower Valsalva ratio and lower HRV. They also had higher values for resting HR and systolic BP. Since these measures are used as indicators of autonomic dysfunction, ecstasy users in this sample were considered more likely to have some form of autonomic dysfunction. Specifically, they showed less bradycardia during the rest phase after performing the Valsalva maneuver, which the authors interpret as a sign of decreased parasympathetic tone. The authors' hypotheses were confirmed, with ecstasy users demonstrating less bradycardia after performing the Valsalva maneuver and having less heart rate variability than non-users.
Comments: Currently, this is the only paper examines cardiovascular function in regular ecstasy users. Other papers have either presented case reports of cardiovascular problems occurring acutely after ecstasy use or have investigated acute cardiovascular responses to MDMA in humans. This study suggests that ecstasy may alter autonomic function in otherwise healthy young humans, either through increased sympathetic tone or decreased parasympathetic tone. Sample size is small, with 12 subjects in each of the two conditions, making it more difficult to rely on the findings in this study to make predictions about the general population.

Chang et al. (2000). Effect of Ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow; A co-registered SPECT and MRI study.

Chang, L., Grob, C. S., Ernst, T., Itti, L., Mishkin, F. S., Jose-Melchor, R., & Poland, R. E. (2000). Effect of ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow; A co-registered SPECT and MRI study. Psychiatry Research; Neuroimaging Section, 98, 15-28.

Purpose: Brain imaging (SPECT) "This study evaluates the chronic and sub-acute effects of MDMA on brain function as measured by regional cerebral blood flow." (p. 16). The study compared scans of MDMA users with scans from controls with no history of MDMA use, and also compared scans taken before MDMA administered in a clinical setting and scans taken after MDMA administration (See "Clinical Study Summaries.")
Design: Non-experimental 2-group between-subjects design to compare scans of ecstasy users with scans of matched non-user controls, with drug use as between-subjects variable. (A randomized, double blind, placebo controlled within-subjects experimental design was used to compare pre-MDMA scans with scans performed after MDMA administration in sub-set of 10 ecstasy users).
Subjects: 21 ecstasy users and 21 non-users recruited through local advertisements (in California area). Matching – Groups matched on gender, age and socioeconomic status. (Some individuals participating in this study also participated in studies reported in Chang et al, 1999 and Boone et al, in preparation). Criteria for Inclusion, Ecstasy Users – Reported using low doses of MDMA, with low doses defined as (< 3 mg / kg per occasion, with occasions occurring at least 6 times a year for at least one year. Non-Users – No prior history of ecstasy use. All Groups - Good health as assessed through medical examination, psychiatric interview and neurological examination, and not pregnant. Lack of personal or family history of major medical or psychiatric illness. No history of substance abuse (except for MDMA or nicotine) and no history of head trauma with loss of consciousness for more than 30 min, no metallic objects in body. Abstinent from psychoactive medications or illicit drugs for at least 1 month prior to study day, with compliance verified by urinary screen conducted before or on study day.
Drug Use Parameters - Ecstasy users reported using ecstasy on a median of 75 occasions or 211 ± 340 times (6-1500), and they used an average of approximately 1.25 – 2.25 tablets per use. Average frequency of use not provided. Duration of use, in months, was an average of 103.2 ± 58.8 months, median 120 months, range 12 -204). Average lifetime exposure, in grams, estimated at 13.1 g (.5-263 g). Self-reported length of drug free period before study day, in days, was an average of approximately 198 ± 231 days (15-425, median of 120 days). Use of Other Drugs – 83% of ecstasy users had used marijuana at least once, 71% had used LSD at least once, 46% had used hallucinogenic mushrooms at least once and 29% used other amphetamines at least once. No one reported dependence on these other substances and use was minimal to moderate.
Group Demographics and Matched Variables – Ecstasy users matched with non-user controls on gender, age and socioeconomic status (as indicated through education). Gender, as M / F ratio – Ecstasy users, 17 / 4: non-users, 17/ 4. Age – Ecstasy users, 43.4 ± 12.5 years, range not provided: non-users, 43.7 ± 11.7 years, range not provided. Education – Ecstasy users had an average of 15.9 ± 2.2 years of education and non-users had an average of 16.2 ± 2.3 years education. Other Variables – All subjects were employed or attending school and none had a criminal record.
Measures: Imaging – Via [99mTc]-HMPAO SPECT scan co-registered with MRI scan. MRI performed with 1.5 T scanner. SPECT procedure relied on inhaled [133]-xenon for absolute CBF and [99mTc]-HMPAO for higher resolution images. (A sub-set of 10 ecstasy users was scanned again after MDMA administration in a controlled clinical setting).
Analysis: Regions of interest (ROIs) selected by investigator blinded to drug use condition. Scans from ecstasy users compared with controls via 3-way mixed model ANOVA, with drug use (ecstasy use or non-use) as a between-subjects factor and brain hemisphere (L or R) and brain region as within-subjects factors.
Drug Use Parameters and Brain Image Variables – Multiple linear regressions were used to assess the existence of any possible relationships between 3 drug use parameters (cumulative lifetime exposure, frequency of use and time since last use) and cerebral blood flow (global and regional CBF). Multiple regressions were performed to assess the relationship between cumulative lifetime exposure, frequency of use and time since last use global brain volume, global CSF and %CSF.

Results – Significant Differences: Imaging – None found. (Differences were found in rCBF in 8 ecstasy users scanned approximately 2 wks after MDMA administration, including decreased rCBF in visual cortex, caudate, superior parietal and dorsolateral frontal cortex, and increased global CBF found in 2 ecstasy users scanned a month after MDMA administration, see "Clinical Study Summaries"). Drug Use Parameters and Brain Imaging Variables - Multiple linear regressions found a negative correlation between brain volume and cumulative lifetime exposure to ecstasy (duration of use), with brain volume decreasing with increased duration of use. The association remained even when controlling for age.
Results – No Significant Differences: – Imaging – No differences in MRI between ecstasy users and non-users, with all images normal. Global CBF lower in ecstasy users than in non-user controls (2.3% lower), but this difference was not significant. Global brain volume, global %CSF and %CSF were similar in ecstasy users and non-users. Drug Use Parameters and Brain Imaging Variables – Global and rCBF were not associated with duration of ecstasy use, frequency of use or recency of use.
Overall Effects: A comparison of SPECT scans of ecstasy users and age and gender-matched controls failed to find any significant differences in global CBF, rCBF, brain volume, global CSF or percentage of CSF. While global and rCBF were mildly decreased in ecstasy users, the decrease was small and did not reach statistical significance. Frequency and recency of ecstasy use were not associated with differences in CBF, brain volume or %CSF. Duration of ecstasy use (cumulative lifetime exposure) was associated with brain volume, with duration negatively correlated with brain volume. Regular ecstasy use did not produce changes in cerebral blood flow, and only duration of use affected one brain-related variable.
Comments: This paper reports findings from a SPECT study that did not employ radioligands. The lack of any significant differences in CBF between ecstasy users and non-user controls is more surprising given the fact that changes in CBF were found to occur 2 weeks and 1 month after MDMA administration. These findings are reported in the same paper and refer to a sub-set of ecstasy users given 2 doses of MDMA in controlled clinical settings. These findings suggest the possibility that ecstasy / MDMA produces change in CBF that are persistent but not permanent. However, the lack of an association between recency of ecstasy use (time since last use) and changes in CBF, reported in the same paper, does not support this conclusion. The consequences of reduced brain volume with increasing duration of use are unclear, but are consonant with other studies that find associations between duration of use or cumulative exposure and decrements in cognitive function.

Chang et al. (1999). Cerebral H-MRS alterations in recreational 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") users.

Chang, L., Ernst, T., Grob, C. S., Poland, R. E. (1999). Cerebral H-MRS alterations in recreational 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") users. Journal of Magnetic Resonance Imaging, 10, 521-526.

Purpose: Brain imaging (MRS), to investigate neurochemical abnormalities in the brains of ecstasy users.
Design: Non-experimental (retrospective) 2-group between-subjects (across groups) design, with drug-free regular ecstasy users compared with matched non-user controls, with all subjects receiving MRI and 1H-MRS imaging.
Subjects: 22 regular ecstasy users and 37 non-user controls consecutively recruited from the local community (Southern California). Matching – Groups matched on age and sex. (A sub-set of this sample also participated in the studies reported in Chang et al, 2000 and Boone et al, in preparation).
Criteria for Inclusion – Ecstasy Users – Having used ecstasy at least 6 times a year for 1 year and abstinence from ecstasy for at least 2 weeks before study day, with compliance verified via drug screen (screen not described, but Chang et al, 2000 relied on urinary screen). Non-Users – No history of prior ecstasy use. All Groups – Healthy as assessed through medical and psychiatric examination, with no history of past or present medical or psychiatric illness, not taking prescribed medication for medical or psychiatric illness, no history of alcohol or substance abuse (other than ecstasy for ecstasy users), no history of head trauma with unconsciousness lasting over 30 min and no metallic objects in body.

Drug Use Parameters – Ecstasy users reported using ecstasy on a median of 75 occasions (6-1500), and they used an average of approximately 1.25 – 2.25 tablets per use. Average frequency of use not provided, but reported duration of use, in months, with a median value of 120 months, (12 -204). Average lifetime exposure, in grams, estimated at 13.1 g (.5-263 g). Self-reported length of drug free period before study day, in days, was approximately 120 days (15-425 days). Use of Other Drugs – 83% of ecstasy users had used marijuana at least once, 71% had used LSD at least once, 46% had used hallucinogenic mushrooms at least once and 29% used other amphetamines at least once. No one reported dependence on these other substances and use was minimal to moderate.
Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender and age. Gender, as M / F ratio: Ecstasy users, 15 / 6, non-users, 22 / 15. Age. Ecstasy users, 19-75, median = 43 ± 14.6: non-users, 22-80, median = 38 ± 14.7. Other Demographic Variables – Median educational level reported by ecstasy users was 15.8 years (12-20 years). All ecstasy users were either employed or enrolled in school, and none reported having a criminal record.
Measures: Imaging – MRI – Performed via 1.5 T scanner. 1H-MRS – 1H-MRS performed in the mid-occipital gray matter, mid-frontal gray matter and R parietal white matter. Substances assessed in brain via MRS were N-acetyl-L-aspartate (NA), creatine (CR), choline compounds (CHO), myo-inositol (MI) and glutamate / glutamine ratios (GLX), with all substances converted from "institutional units" to millimolar concentrations using published norms for each brain area.
Analyses: Imaging - Two-tailed unpaired t-tests were performed on concentrations of all metabolites listed in each brain region, with comparisons made between ecstasy users and non-user controls. An analysis of covariance (ANCOVA) was also performed upon brain metabolite concentrations in ecstasy users and non-users, with age serving as covariate.
Metabolite-Ecstasy Use Parameter Relationships – Linear regressions were performed on brain metabolite concentrations in each selected brain region in ecstasy users only. Cumulative lifetime dose transformed into logarithm.
Results – Significant Differences: 1H-MRS – MI and MI / CR ratios in parietal white matter were elevated in ecstasy users. MI elevated in parietal white matter of ecstasy users when age was controlled for via ANCOVA with age as covariate. CHO / CR ratio in mid-occipital gray matter, elevated in ecstasy users, due to less CR found in ecstasy users.
Metabolite-Ecstasy Use Parameters – Positive relationship between concentration of MI in both parietal white matter and occipital gray matter and log of cumulative lifetime dose, with higher cumulative doses associated with greater MI in parietal white matter and mid-occipital cortex when compared with values in non-user controls. Duration of ecstasy use was positively correlated with MI concentration in parietal white matter and mid-frontal gray matter, with trend for significant relationship in occipital gray matter, with greater MI associated with longer duration of ecstasy use. Positive relationship between choline compounds (CHO) in parietal white matter and duration of ecstasy use, with elevated choline compounds associated with longer duration of ecstasy use.
Results – No Differences Found: MRI – No differences in brain structured between ecstasy users and non-users, with all images normal. 1H-MRS – Concentrations of NA, choline compounds, creatine compounds, glutamate / glutamine ratio in all three brain regions (mid-occipital gray matter, mid-frontal gray matter and R parietal white matter. No lactate or excess lipids found in brains of either group. (Amount of CR may be decreased in ecstasy users in mid-occipital gray matter only.)
Metabolite-Ecstasy Use Parameters – No relationship between log of cumulative lifetime ecstasy dose and concentration of NA, creatine-containing compounds, choline containing compounds or glutamate/glutamine ratio in all 3 selected areas (mid-occipital gray matter, mid-frontal gray matter and R parietal white matter). No relationship between log of cumulative lifetime ecstasy dose and MI concentration in mid-frontal gray matter. Figures not reported on relationships between duration of ecstasy use and other brain metabolites, indicating no significant relationships found between duration of use and NA, creatine compounds or glutamate / glutamine ratio in all three brain areas. No significant relationship between recency of ecstasy use and any of the brain metabolites (NA, MI, CHO, CR, GLX) in any of the three areas (mid-occipital gray matter, mid-frontal gray matter, R parietal white matter).

Overall Effects: When compared with non-using controls, ecstasy users had elevated concentrations of myo-inositol (MI), a tentative glial marker, in parietal white matter, and they also have elevated MI / creatine levels. Ecstasy users have elevated CHO / CR levels in mid-occipital gray matter when compared with non-user controls, with this difference chiefly due to lower levels of creatine compounds. However, there is no sign of increased N-acetyl-L-aspartate (NA), considered an indicator of cell death, in ecstasy users. For the most part, concentration of various markers within the brain were found to be similar in ecstasy users and non-user controls, and this remains true when controlling for age. However, some parameters of ecstasy use were associated with higher or lower levels of specific markers. Cumulative exposure to ecstasy was associated with higher levels of MI in parietal and occipital areas, and duration of ecstasy use was associated with higher levels of MI in parietal and mid-frontal areas, and perhaps with elevated MI in mid-frontal areas as well. Duration of ecstasy use was also associated with greater amounts of choline compounds in parietal white matter when compared to non-user controls. Recency of ecstasy use was not associated with amount of any marker measured in brain.
Comments: To date, this is the only paper that uses MRS Imaging to examine brain metabolites in ecstasy users and non-users. While lack of elevated NA values indicated lack of cell death arising from ecstasy use, an increase in MI in ecstasy users suggests that ecstasy use might still produce some form of harm to the brain. The findings in this paper suggest that regular ecstasy use may have an additive effect on specific markers of brain activity, with cumulative lifetime exposure and duration of use both associated with increased MI in selected brain areas. However, the authors did not conduct regressions using average dose per use, so it is possible that people who have used ecstasy for a longer time also tend to use higher doses. Because this is a new area of research, and the significance of elevated NA, MI or CR is not entirely clear, it is somewhat difficult to draw definite conclusions on the basis of these findings.

Croft et al. (2001). The relative contribution of Ecstasy and cannabis to cognitive impairment.

Croft, R. J., Mackay, A. J., Mills, A. T. D., & Gruzelier, J. G. H. (2001). The relative contribution of ecstasy and cannabis to cognitive impairment. Psychopharmacology, 153, 373-379.

Purpose: Cognitive function (general), personality: to investigate the respective effects of ecstasy and cannabis on human cognitive function using measures comparable with those employed in previous investigations of the effects of regular ecstasy use on cognitive function.
Design: Non-experimental (retrospective) 3-group between subjects (across groups) design comparing drug-free ecstasy users with cannabis using and non-using controls, with drug use (ecstasy + cannabis, cannabis only or control) serving as a between-subjects factor. All subjects completed the same set of neuropsychological tests.
Subjects: 11 regular ecstasy users, 18 regular cannabis user controls and 31 non-user controls residing in the London (England) area, recruited via word of mouth, advertisements posted in the local area and in the London magazine "Time Out." Matching – Authors did not appear to explicitly match subjects on any one variable. However, all 3 groups are matched for estimated full-scale IQ (via NART score), education and (approximately) on age. Non-user controls and ecstasy + cannabis groups were approximately matched in gender.
Criteria for Inclusion, Ecstasy Users – Having used ecstasy at least once and abstaining from ecstasy or cannabis use at least 48 h before study day, with abstinence confirmed by self-report only. Cannabis Users – Having used cannabis at least once, no prior history of ecstasy use, and abstinence from cannabis for at least 48 h prior to study day. Non-Users – Not currently using cannabis and little or no prior history of cannabis use or ecstasy use. All Groups – Absence of current or past neurological or psychiatric illness.
Drug Use Parameters – Ecstasy Use – Users reported taking an average of 41.9 ± 49.3 tablets over lifetime, range not provided. Information on duration or frequency of ecstasy use not provided. Information on average dose per use not provided. Cannabis users reported an average lifetime ecstasy

use of .6 ± 1.3 tablet. Cannabis Use – Ecstasy users reported an average lifetime use of 10,964.9 ± 13,235.5 joints. Cannabis users reported average lifetime use of 7762.4 ± 14,480.9 joints. Non-users reported an average lifetime use of .5 ± .8 joints. Other Drugs – Average lifetime use of cocaine was 6.4 ± 6.1 grams, 5.7 ± 13.3 grams for cannabis users and no exposures for non-user controls. Average lifetime exposure to speed was 20.4 ± 29.7 tablets for ecstasy + cannabis users, 12.1 ±19 for cannabis users and no lifetime use for non-users. Ecstasy users had an average lifetime use of alcohol at 3484 ± 3254 "standard units" alcohol, cannabis users reported lifetime use of alcohol at 5309.8 ± 6517.5 "standard units" and non-users reported total lifetime alcohol use at 3875.3 ± 4407.8 "standard units."
Group Demographics and Matched Variables – Authors did not report matching groups by any variable. However, ecstasy + cannabis, cannabis and non-user groups seem to be matched on the basis of estimated general IQ, education level and age, and the ecstasy + cannabis group is approximately matched with non-users on gender. Estimated General IQ, estimated via National Adult Reading Test score, a measure of vocabulary and verbal intelligence, with values presented as IQ: Ecstasy users, 116.2, cannabis users, 115.2, non-users, 115.2. Age. Ecstasy users, 25.7 ± 4.7, no range provided: cannabis users, 26.6 ± 8.1, no range provided: non-users, 23.5 ± 6.8, no range provided. Education Level – Coded as 1 = O levels (educational exam at 15 years old), 2 = A Level (examination at 17 years), 3 = university degree: Ecstasy + cannabis users had an education level of 2.5 ± .65 (approximately 15.5 years), cannabis users had an educational level of 2.43 ±.79 (approximately 14.8 years) and non-users had an educational level of 2.57 ±.63 (approximately 15.7 years). Gender, as M / F ratio, Ecstasy + cannabis users, 14 / 17: cannabis users, 5 / 6: non-users, 14 / 4.
Measures: Warrington Recognition Memory Tests, for Words and Faces (Select one target previously presented out of new list or array.) Grooved Pegboard (Rapidly place 25 pegs into non-uniform matching holes, performed with one hand, with test conducted with each hand. Authors distinguish performance by hemisphere presumably involved, not hand, so Left Pegboard performed by right hand). Spatial and Non-Spatial Associative Learning Test (Learns association between pairs, with subject first guessing and receiving feedback. Task complete when 18 associations reported and score = number of guesses). Digit Span (Forward and backward). Verbal Fluency (Generate words starting with consonant or belonging to category in 6 sec). Stroop A, Stroop B (Color words printed in black ink, read aloud in Stroop A; color words printed in same and different colored ink, name color ink (incongruent). Stroop A measures speed of reading, Stroop B measures cognitive interference. Coughlan List and Design Learning (Learn first list of 15 words through repetition of list and recall of all items (list 1to5), and interference measured with second list presented after first is learned (list B) and delayed recall measured on list (list6). Recall for design measured by redrawing design, also has interference and delayed recall.) National Adult Reading Test (NART) – Read 50 words aloud, where pronunciation cannot be derived from standard rules of pronunciation.
Other Measures – Several personality questionnaires, with results not reported in this paper. Half the subjects paid for participation to measure effects of motivation on performance. Authors reported that there were no differences between paid and unpaid subjects on any of the tests, nor any interaction between monetary incentive and drug use, indicating little or no effects of motivation.
Analyses: Across-Group Comparisons - Scores on several tests transformed before analyses. Scores from each test analyzed via between subjects ANCOVA (analysis of covariance), with drug use group (ecstasy + cannabis, cannabis or non-user) serving as between subjects factor and with age, gender or NART score serving as covariates if they were found to be significant in earlier analyses. Directional tests were used, with predicted outcome that ecstasy + cannabis group would perform worse than cannabis or non-user group.
Drug Use Parameters and Test Performance – 4 additional ANCOVAs were performed an all test scores where differences between drug user groups and control groups found. A separate ANCOVA performed, with one of the variables listed serving as the covariate: total lifetime ecstasy use, frequency of ecstasy use, total cannabis use and frequency of ecstasy use.

Results – Significant Differences: Both Drug User Groups vs. Non-Users - Warrington Recognition Memory-Faces, non-spatial association, Stroop A (reading speed), Digit Span-Forward, Digit Span-Backward, Coughlan-List1to5 (initial recall, list learning), Grooved Pegboard-Left Pegboard (right handed performance) and Verbal Fluency-Animals: Ecstasy + cannabis and cannabis < non-user controls. Ecstasy + Cannabis vs. Cannabis Users – Coughlan-Design1to5 (Immediate recall and design learning): Cannabis users < Ecstasy + Cannabis Users.
Drug Use Parameters and Test Scores, Ecstasy Use – Stroop A, total ecstasy use, correlated at .31, and frequency of ecstasy use, correlated at .24. Cannabis Use. Total cannabis use correlated with test scores on: Warrington-Faces (.21), spatial associative learning (.38), non-spatial associative learning (.29), and Digit Span-Backwards (.43). The following test scores are correlated with frequency of cannabis use: Stroop A (.21), Warrington Faces (.38), spatial associative learning (.23), Digit Span-Forward (.43), Digit Span-Backward (.32) and Verbal Fluency-Animals (.39).
Results – No Differences Found: Warrington Recognition Memory-Words, Spatial Associative Learning, Stroop B (interference), Verbal Fluency-First Consonant, Coughlan-List B (interference), Coughlan-List 6 (delayed recall), Coughlan-Design B (interference), Coughlan-Design 6 (Delayed recall for design), Grooved Pegboard-Right (Left-handed performance). No differences between performance of ecstasy + cannabis, cannabis or non-user groups.
Drug Use Parameters and Test Scores, Ecstasy Use – None of the following test scores correlated with either total ecstasy use or frequency of ecstasy use at values above .2: Warrington-Faces, Spatial-Associative Learning, Non-spatial Associative Learning, Digit Span-Forward, Digit Span-Backward, Verbal Fluency-Animals, Coughlan-List1to5 or Pegboard-Left. Cannabis Use – The following test scores did not correlate with total cannabis use at values above .2: Stroop A, Digit Span-Forward, Verbal Fluency-Animals, Pegboard-Left. The following test scores did not correlate with frequency of cannabis use at values above .2: Non-spatial associative Learning, Coughlan-List 1to5, Pegboard-Left.
Overall Effects: Both cannabis users and ecstasy + cannabis users performed less well than did non-user controls matched by age, education level and NART score on an array of neuropsychological tests measuring verbal and visual memory, verbal and visual learning, manual dexterity and executive function. Cannabis users did not perform as well as ecstasy + cannabis users on one test (Coughlan-Design1to5), a test of immediate recall and learning. Analyses that employed lifetime exposure to ecstasy and frequency of ecstasy use as covariates found that only Stroop A performance, assessing reading speed, is related to ecstasy use variables. Analyses that employed total lifetime cannabis use and frequency of cannabis use as covariates found that both lifetime cannabis use and frequency of use affected performance on tests of immediate and delayed recall, cognitive interference, manual dexterity, learning and perhaps executive function. The authors conclude that cannabis use made a significant contribution to decrements in test performance, and that ecstasy use was generally less related to test performance than cannabis use.
Comments: This is one of a few investigations featuring both non-user controls and cannabis using controls to address the issue of cannabis use in ecstasy users. In this study, the authors found that ecstasy + cannabis users and cannabis users performed similarly on tests, with both groups scoring lower than non-users on many tests. While the authors note that Digit Span test performance (said to test working memory) was correlated with MDMA use, the correlation presented in the paper is below 0.2. The authors state that while cannabis is not neurotoxic, it is known to affect hippocampal neurons and that the residual drug effects of cannabis may produce reduction in memory and learning. However, the authors also suggest that ecstasy might produce decrements in performance on cognitive tests, but that concomitant cannabis use reduces the MDMA-induced deficits in performance. The findings in this study suggest that the relationships between ecstasy use, cannabis use and performance on tests of cognitive skills are complex, and that future studies should pursue the contribution made by cannabis use by employing a cannabis using control group in their design.

Dafters et al. (1999). Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence.

Dafters, R. D., Duffy, F., O'Donnell, P. J., & Bouquet, C. (1999). Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence. Psychopharmacology, 145, 82-90

P**urpose**: Electroencephalography, cognitive function, mood: investigation performed to discover whether a correlation exists between extent of ecstasy use and quantitative EEG variables (spectral EEG power and coherence), and whether a correlation exists between quantitative EEG variables in ecstasy users and measures of mood and cognitive function. Specific Hypothesis Tested – That ecstasy use should produce reduced coherence, with coherence considered an indicator of synchronous activity in different locations.
Design: Non-experimental (retrospective) 1-group correlational design, with parameters of self-reported ecstasy use in past year serving as predictors and EEG power and coherence, mood scores, scores on tests of verbal intelligence, memory and executive function serving as dependent measures. Investigators conducting the EEG and neuropsychological tests were blind to subject drug history. All subjects underwent quantitative EEG and completed measures of mood and cognitive performance.
Subjects: 23 university students who were self-reported ecstasy users residing in the Glasgow (Scotland) area, recruited via snowball technique. Matching – No controls and correlational design, hence no matched variables.
Criteria for Inclusion – Having used ecstasy at least once, no history of neurological or medical disorder (such as cardiovascular disease or diabetes) that might affect EEG, no history of head injury, not currently taking prescribed medication and abstinence from ecstasy or other substances (except alcohol or nicotine) within 7 days of the study day, with compliance verified through self-report only.
Drug Use Parameters – No information provided on typical ecstasy dosage or frequency of usage. Subjects reported using, on average, 14.04 tablets in the year preceding the study (1-60 tablets). 12 subjects had taken less than 20 tablets across the lifetime ("low" users) and 11 used over 20 ecstasy tablets over a lifetime ("high" users). Other Drugs – 23 reported using alcohol (148.6 drinks in year), 21 used cannabis (154 joints in year), 20 used amphetamines (10.91 tablets in year) 16 used cigarettes (3173.8 in year), and 9 used LSD (2.82 "tablets" in a year).
Group Demographics and Matched Variables – This is a correlational study without controls, hence no matched variables. Gender – Information on gender not provided in this paper (personal communication from author indicates that gender was "approximately 50 / 50, but with more women than men). Age – Range 18-42 years, average = 24. Education – All subjects were either university students or their friends, hence estimated education between 12-16 years.
Measures: EEG – Measured on 128 channel electrode array with 125 samples taken per second. An artifact-free 60 s period located visually and analysis conducted on 1-second epochs. Spectral Power – Calculated for left frontal, right frontal, left posterior and right posterior quadrants and across each frequency band (alpha, beta, delta, theta). Coherence – Electrode pairs selected on the basis of connection via presumed white-matter fiber tracts (method of Leuchter et al, reduces chance for Type I error), Coherence was measured for fascicular tract, visual association pathways (visual tract) and trans-callosal interhemispheric tract (trans-callosal tract).
Mood – Assessed via BDI and PANAS (Positive Affect Negative Affect Scale), two self-report measures of mood and affect, after EEG recordings were made.
Cognitive Function – NART (Read aloud 50 words of decreasing frequency that do not follow standard rules of pronunciation), Rivermead Behavioral Memory Test (Immediate and delayed recall for story), Behavioral Assessment of Dysexecutive Syndrome (BADS) Card Sort Task (Similar to WCS, determine rule change in card sorting), and an author-derived test of working memory (recall for words presented between math problems used as distracters), with subject asked to recall words several times throughout task (delayed recall).

Analyses: Performed individual Pearson correlation coefficients calculated for all annual drug use measures, age and gender. EEG variables analyzed via multiple regression, with ecstasy use parameters and other drug use variables all included (with effects of other drugs controlled for in model by using partial correlations), with regressions performed for each EEG frequency band. Separate analyses performed on log 10 transformed EEG data as a means of reducing effects of skew and kurtosis in power data. (Results not reported, with findings not significantly different from findings arrived at with untransformed data). Regressions with the effects of other drugs removed (partialed out) performed on measures of mood and cognitive function, with ecstasy use as the predictor variable.
Results – Significant Differences: EEG – Extent of ecstasy use (number of tablets in year) was positively correlated with global increase in alpha rhythm power, with association weakest in right frontal quadrant, (just reaches significance). Extent of ecstasy use positively associated with increased beta rhythm power in the left posterior quadrant, and negatively associated with delta rhythm power averaged over whole scalp. Extent of ecstasy use (number of tablets used in a year) weakly but significantly negatively correlated with coherence in the visual tract.
Cognitive Function – Extent of ecstasy use associated with decrease in performance on BADS card sort.
Results – No Differences Found: EEG – Extent of ecstasy use was not correlated with theta rhythm power in any quadrant of the brain. Extent of ecstasy use not correlated with beta rhythm power in the left or right quadrants, or in the right posterior quadrant. Extent of ecstasy use not correlated with coherence in the fascicular or the trans-callosal tracts.
Mood – No significant correlations between extent of ecstasy use and scores on BDI, PA score of PANAS or NA score of PANAS (though NA correlation is .33).
Cognitive Function – Extent of ecstasy use not significantly associated with performance on NART, immediate or delayed scores for Rivermead Behavioral Memory Test or Word Memory test (though Word Memory correlates at .34).
Overall Effects: Degree of ecstasy use, measured here as number of tablets consumed in past year before study day (a combination of cumulative dose and frequency), is correlated with an increase in global alpha power in the left posterior quadrant, with alpha power usually considered an indicator of decreased mental activity. Delta activity is globally reduced. The authors state that there are some similarities with this spectral power profile and the profile seen in normal aging. Decreased coherence is seen in what the authors define as the visual tract, indicating there is less synchronized activity in this tract. However, while there are associations between extent of ecstasy use and changes in EEG measures, the authors did not find any significant associations between extent of ecstasy use and any of the measures of mood or cognition except for the card sort task, a measure of executive function. In this case, decreased performance on the card sort task was associated with greater extent of ecstasy use. These findings indirectly suggest that differences in spectral power and coherence are not associated with any changes in mood or cognitive function, with the possible exception of executive function.
Comments: This paper is the first to examine the effects of ecstasy use on electrical activity in the brain and how these effects relate to changes in mood and cognitive function, if present. Its weakness is that the authors do not employ a control group, but its strength is that the authors employ a correlational design rather than arbitrarily dividing up the sample into use categories. The paper is also notable for its attempt to control for the effects of other drugs through the use of partial correlations. The authors state that the spectral power profile associated with extent of ecstasy use bears some similarity to shifts in spectral power seen in normal aging. However, the reduction in coherence seen after regular ecstasy use differed from the pattern of reduced coherence seen in Alzheimer's disease. Specifically, Alzheimer's disease is associated with reduction in the fascicular tract while regular ecstasy use was associated with reduced coherence in the visual tract. This area of research is relatively new, and further research is needed to understand the significance of the changes in EEG activity and their relation to measurable changes in cognition or affect. Gamma et al. (2000) also measured EEG in ecstasy users.

Gamma et al. (2001). No difference in brain activation during cognitive performance between Ecstasy (MDMA) users and controls: A [$H_2{}^{15}0$]-PET study.

Gamma, A., Buck, A., Berthold, T. & Vollenweider, F. X. (2001). No difference in brain activation during cognitive performance between Ecstasy (MDMA) users and controls: A [$H_2{}^{15}0$]-PET study. Journal of Clinical Psychopharmacology, 21, 66-71

Purpose: Brain imaging (PET), cognitive function (visual search), mood: To investigate possible differences in mood and cerebral blood flow (CBF) between ecstasy users and controls, and to see whether differences in mood, if they are present, are related to differences in brain activity as measured by [H2"-PET. Specific Hypothesis Tested – That if ecstasy users are found to differ from non-user controls on measures of mood, that these differences in mood would correlate with differences in rCBF as measured through PET scan.
Design: Non-experimental (retrospective) 2-group between subjects (across groups) / within-subjects design, with ecstasy users compared with matched non-user controls on measures of mood and PET, and with resting PET scan compared with PET scan taken during task performance. All subjects completed measures of mood. 11 / 15 subjects underwent resting PET scans and all subjects underwent task-performance PET scans.
Subjects: 16 regular ecstasy users recruited from local raves (in the Zurich area) and from postings at the university and 17 non-user controls recruited from postings at the university. Matching – Groups matched on age, education and drug use, though non-user controls were slightly older and had attained slightly more education.
Criteria for Inclusion, Ecstasy Users – Having used ecstasy on at least 100 occasions (with the exception of 2 / 16 ecstasy users, with no information provided on drug use patterns in these subjects). Non-users – Never having used ecstasy, with use of other substances permitted. All Groups – Good health as assessed via physical examination, psychiatric interview, ECG and blood analyses. No past or current major medical or psychiatric illnesses, and no family history of psychiatric illness. Abstention from all psychoactive substances save alcohol or nicotine for at least a week prior to study day, with compliance verified through self-report only.
Drug Use Parameters – Ecstasy Users - Ecstasy users reported an average lifetime use of 270 ± 397.2 tablets. No information is provided on duration (in years) of use, frequency of use, average dose consumed per occasion or time since last use (recency of use). According to personal communication with A. Gamma, frequency of ecstasy use reported over 2 years, per month, was 8 – 12 tablets per month (4 – 60). Average lifetime use of cannabis was reported at 332 ± 349.1 joints, and lifetime use of amphetamines was reported at an average overall use of 309 ± 757 mg. Average lifetime use of cocaine was reported at 615 ± 715 mg, average use of LSD over a lifetime was reported at 5 ± 7.5 "trips, and average lifetime use of magic mushrooms was reported at 3 ± 5.3 occasions. Non-Users – Non-users did not use ecstasy. Average lifetime use of cannabis was reported at 85 ± 173.2 "joints", average lifetime use of amphetamines was reported at 0 mg, and average lifetime use of cocaine was reported at 161 ± 624 mg. Non-users reported an average lifetime use of LSD at 0 ± .3 "trips," and an average lifetime use of magic mushrooms at 1 ± 1.9 occasions.
Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender and approximately matched with non-users on age, education and drug use. Gender, as M / F ratio – Ecstasy users, 8 / 8: Non-users, 10 / 7. Age. Ecstasy users, average age = 22.6 ± 2.6, range not provided: non-users, average age = 26 ± 2.4. Education Level – Where 1 = junior high, 2 = high school, 3 = undergraduate, 4 = university: Ecstasy users had approximately 15 years (2.6 ± 1), non-users had approximately 17 years (3.8 ± .4). Use of Other Drugs – Both ecstasy users and non-users reported using cannabis, cocaine and magic mushrooms, with a few non-users reporting occasional experimentation with LSD. However, in all cases, ecstasy users had higher lifetime exposure to every drug measured than non-users, and this was particularly true for cannabis and amphetamine.

Measures: Mood and Depression – Mood was measured by the AM, administered immediately after PET scans were performed. Depressed mood and signs of depression were measured via HAM-D administered on a day previous to or after conducting PET scans.
CPT – A visual version of the Continuous Performance Task, a measure of vigilance in which subjects indicate the presence of target letters in an array of letters by pressing a button, with multiple trials presented. Control task presented arrays without target letters or requirement to attend or respond to arrays.
PET – 4 scans performed, 2 during performance of the CPT and 2 during the control task. Control task scans performed on a sub-set of subjects, with manuscript unclear on exact number. Either 22 / 33 received control task scans (11 from each group) or 11/ 33 received control task scans (11 overall, group membership distribution unknown).
Analyses: Mood – Psychological tests were examined via MANOVA, with drug use (ecstasy user versus non-user) as a between-subjects factor and scale scores as dependent factors. Post-hoc comparisons made via Tukey's LSD test, with p. set at .05.
PET – Images were normalized and global counts were corrected via ANCOVA. Analyses performed on individual mean scans (2 task-equivalent scans averaged into 1 via t-test). CPT task scans were compared across groups (ecstasy users versus non-users) with a single-voxel statistic, and control task scans were compared with CPT scans within each group using single-voxel statistics, with p. at .05.
Drug Use Parameters and PET scans – Analysis of covariance (ANCOVA) was performed on rCBF and drug use and overall lifetime use of ecstasy and other drugs, with analyses only performed on ecstasy users.
Results – Significant Differences: Mood and Depression – Ecstasy users scored higher than non-users on the following AM scales: inactivation, emotional excitability (nervousness, vulnerability) and depressed mood. Ecstasy users had higher HAM-D scores than non-users, though no scores were within the range considered diagnostic of clinical depression. 5 / 16 ecstasy users reported experiencing pre-existing depression before ecstasy use and 2 of 5 reported that their symptoms of depression, including suicidality, were alleviated and eventually vanished after commencing ecstasy use.
PET – No significant differences found between two groups. CPT significantly different from control task for both groups, with increased rCBF in the R medial occipital area, the L precentral area, R postcentral area and R superior frontal lobe, and decreased rCBF in L and R superior and medial temporal lobe and R precueneus.
Results – No Significant Differences: Mood and Depression – Ecstasy users did not differ from non-users on the following AM scores: efficiency, extroversion / introversion, well-being and anxiety.
PET – CPT task performance produced similar pattern of brain activity in ecstasy users and non-users. No differences found when CPT scans directly compared between ecstasy users and non-users.
CPT – No differences found in performance of ecstasy users and non-user controls on CPT, either in number of errors of omissions (missed targets) or errors of commission (false alarms).
Drug Use Parameters and rCBF – No relationships were found between total lifetime use of any other drug and patterns of rCBF.
Overall Effects: Ecstasy users reported a greater number of depression-related symptoms, as indicated in higher HAM-D scores, and they scored higher on measures of inactivation, emotional excitability and depressed mood. Yet there were no differences in rCBF recorded during performance of a vigilance task. Both groups showed increased activation in the same areas and less activation in other areas during task performance. Patterns of rCBF were unrelated to overall lifetime drug consumption for ecstasy, cannabis, amphetamines, cocaine, LSD or magic mushrooms, as measured in ecstasy users. The authors' hypothesis was not confirmed; while ecstasy users had higher scores on measures of depressed mood and depression, there was no evidence of changes in rCBF in ecstasy users when compared with controls. Hence elevated scores on measures of depression could not be correlated with any changes in rCBF for ecstasy users.
Comments: This is one of several papers (e.g., Reneman et al., 2000a,b) seeking to compare cerebral blood flow in ecstasy users with that of non-user controls, with the findings being similar to that of Chang

et al, 2000. The authors acknowledge that normalizing the imaging data may have reduced or eliminated evidence for global differences in CBF across groups. Since scans for ecstasy users and non-users were similar, it appears that the increased depressed mood and inactivation reported by ecstasy users is not correlated with any specific changes in brain activation. While there are no differences between the two groups on task performance, the authors acknowledge that the CPT may not be as complex as other tasks of sustained attention, and that it does not necessarily measure memory or other functions. The sample used in this study is nearly identical to that used in Gamma, 2000a.

Gamma et al. (2000). Mood state and brain electric activity in Ecstasy users.

Gamma, A., Frei, E., Lehmann, D., Pascual-Marqui, R., Hell, D. & Vollenweider, F. X. (2000). Mood state and brain electric activity in Ecstasy users. NeuroReport, 11, 1-6.

Purpose: Electroencephalography, mood: To investigate whether regular ecstasy use is associated with changes in brain electrical activity and distribution of spectral band power, as measured through LORETA (low resolution brain electromagnetic tomography) and spectral analysis, respectively, and to investigate differences between ecstasy users and non-users in mood state during EEG. Specific Hypothesis Tested – That chronic (regular) ecstasy use would be related to changes in brain electric activity and spectral band distribution, and that differences in brain electric activity, if present, would parallel changes in mood state.
Design: Non-experimental (retrospective) 2-group between subjects (across groups) design where ecstasy users were compared with matched non-user controls, with drug use (ecstasy use versus no ecstasy use) serving as the between subjects factor. All subjects underwent quantitative EEG and completed measures of mood immediately after EEG was performed.
Subjects: 16 regular ecstasy users and 16 non-user controls (all university students), with ecstasy users recruited from local raves and postings at a university in Zurich, Switzerland and non-user controls recruited via word of mouth and by postings at the university. Matching – On gender and roughly matched on age and education
Criteria for Inclusion, Ecstasy Users – Having used ecstasy at least 100 times prior to study participation. Non-users – No prior history of ecstasy use (use of other drugs allowed). All Groups – Having no past or current major medical or psychiatric disorders, as assessed via physical examination, psychiatric interview, ECG and blood analysis. Abstinence from all psychoactive substances except alcohol and nicotine for the week prior study day, with no information provided on how abstinence would be verified).
Drug Use Parameters – (Information only presented for 15 ecstasy users and 14 controls with artifact-free EEG recordings) Ecstasy Users – Ecstasy users had taken an average of 222 ± 358.5 ecstasy tablets over a lifetime. No information is provided about duration (in years) of use, frequency of use, average dose consumed per occasion or time since last use (recency of use). Average lifetime use of other drugs by ecstasy users: cannabis, 320 ± 357.6 joints, amphetamines, 320 ± 782.3 mg, cocaine, 506 ± 586 mg, LSD, 6 ± 7.7 "trips", magic mushrooms, 3 ± 5.4 occasions. Non-Users – Average lifetime use of other drugs reported by non-user controls: ecstasy, 0 tablets, cannabis, 46 ± 137 joints, amphetamine, 0 mg, cocaine, 198 ± 692 mg, LSD, 0 "trips," magic mushrooms, 1 ± 2.2 occasions.
Group Demographics and Matched Variables – (Information reported only for 15 ecstasy users and 14 controls with artifact-free EEG recordings). Regular ecstasy users matched with non-user controls on age, and approximately matched on gender and educational level. Gender, As M / F ratio – Ecstasy users, 8/7: Non-user controls, 8/6. Age. Ecstasy users, 22.5 ± 2.7 years: Non-users, 26 ± 2.7 years. Education Level. Education rated from 1 (junior high) to 4 (graduate school). Ecstasy users, 2.5 ± 1 (approximately 14 years): Non-users, 3.7 ± .5 (approximately 16 years).
Measures: EEG and Spectral Band Power – Measured via 31 scalp electrodes placed according to the international 10 / 20 system. 3-min recordings made for all subjects under eyes-open and eyes-closed

conditions. As many artifact-free 2-s epochs as possible used in analysis. EEG data filtered into 7 independent frequency bands: alpha1, alpha2, beta1, beta2, beta3, delta and theta. (Artifact-free epochs could only be obtained from 15 ecstasy users and 14 controls).
LORETA – Intracerebral electric sources derived from computations performed by LORETA. Time-averaged LORETA images used in analysis, with each image representing 1-s (256 images produced per sec).
Mood – Measured by AM, completed immediately after subjects underwent EEG recording.
Analyses: EEG – Localized activity analyzed via voxel by voxel t-tests comparing ecstasy users with non-user controls, with one LORETA image used from each subject, each frequency band and each condition. Spectral Band Power – All data log transformed to address deviation from normal distribution. Each frequency band analyzed separately via mixed-model ANOVA, with condition (eyes open versus eyes closed) as a within-subject factor and drug use (ecstasy use versus no ecstasy use) as a between groups factor. Mood – Multivariate analysis of variance (MANOVA) was used to compare AM scores in ecstasy users and non-user controls, with drug use serving as a between-group factor and with each scale on the AM serving as a dependent measure, with post-hoc comparisons made via Tukey's HSD test.
Results – Significant Differences: LORETA – Cluster analysis of non-normalized LORETA images found that ecstasy users had significant increases in theta, alpha1, beta2 and beta3, but only in the eyes-open condition.
EEG and Spectral Band Power – (Absolute power higher under eyes closed condition for both ecstasy users and non-users). Ecstasy users had higher beta2 power than non-users in the eyes-open condition, though both groups had similar beta2 power in eyes-closed condition. Trend for ecstasy users to have greater beta1 power than non-users in eyes open condition and lower beta1 power than non-users in eyes closed condition. Analyses of channel-wise EEG power found trend for globally higher power in ecstasy users in the theta, alpha1, beta2 and beta3 bands, with trend reflecting increases in these bands found with cluster statistics performed on non-normalized data. Beta1 – Higher in controls in eyes-closed condition, higher in ecstasy users in eyes-open condition. Beta2 – Higher beta1 power in ecstasy users, but only in eyes open condition. Ecstasy users had a trend for higher beta3 power than controls in both eyes-open and eyes-closed condition, but with difference between groups greatest in eyes-open condition. Alpha2 – Higher power in ecstasy users in right temporal-occipital region and left occipital region, with increased alpha2 in right temporal-occipital region associated with eyes open condition and increased alpha2 in left medial occipital region associated with eyes closed condition. Analyses with normalized data for alpha2 band used to clarify localization of this difference.
Mood – Ecstasy users different from non-users on the following AM scales: depression (ecstasy users > non-users), inactivation (ecstasy users > non-users) and emotional excitability, defined as nervousness or vulnerability (ecstasy users > non-users). Ecstasy users scored higher on anxiety scale than non-users, but at a level just short of statistical significance.
Results – No Differences Found: LORETA – No differences between ecstasy users and non-users in normalized images, whether analyzed by single-voxel statistics or cluster analyses, indicating similar distribution of brain electrical activity. No differences between ecstasy users and non-users found with non-normalized data in single-voxel statistics.
EEG and Spectral Band Power – No difference between ecstasy users and non-users in spectral power for any frequency band, though there was a tendency for ecstasy users to have higher overall power. Ecstasy users and non-users had similar beta2 power in the eyes-closed condition, but ecstasy users had higher beta2 power in eyes-open condition. No significant differences for any specific frequency band found in analysis of channel-wise EEG power. While ecstasy users had higher beta2 power in eyes-open condition, ecstasy users and non-users did not differ in beta2 power in eyes-closed condition. No difference in delta frequency band.
Mood – Ecstasy users did not differ from non-users on the following scales of the AM: Efficiency, extroversion / introversion and well-being.
Overall Effects: Ecstasy users did not differ from non-user controls in global EEG distribution as measured via LORETA, at least when analysis was performed with normalized data. While there was a

tendency for ecstasy users to have higher global EEG power than non-users, there were few differences in global power in any frequency band. Yet ecstasy users were found to have increased power in the theta, alpha1, beta2 and beta3 bands, but only in the eyes-open condition. Separate channel-wise analyses found that ecstasy users had higher beta1, beta2 and beta3 power than non-users in the eyes-open condition, but that band power was the same (beta2, beta3) or lower (beta1) in ecstasy users and controls in the eyes-closed condition. There may be some differences in localization of the alpha2 band, with ecstasy users showing greater alpha2 in the right temporal-occipital region in the eyes-open condition and greater alpha2 in the left medial occipital region in the eyes-closed condition. Ecstasy users had higher scores for depression, inactivation and emotional excitability than non-users on a measure of mood while reporting similar values for efficiency, extroversion / introversion and well-being. It is not clear whether differences in spectral power seen in the eyes-open condition is related to changes in mood state in ecstasy users, since no analyses related the two sets of variables to each other. The authors' hypothesis is partially confirmed, as ecstasy users show some differences in EEG patterns and spectral band frequency when compared with controls, but there is no indication that these changes in EEG pattern are related to elevated scores on scales measuring depression, inactivation and emotional excitability.
Comments: Along with the work of Dafters, this is one of the few studies examining changes in EEG variables in ecstasy users. Unlike Dafters et al, Gamma et al are comparing across groups of ecstasy users and non-user controls rather than conducting correlational analyses within a sample of ecstasy users. It is interesting to contrast the findings of Dafters et al with those of Gamma et al. While Dafters found that total number of ecstasy tablets taken per year was not associated with changes in mood, Gamma et al found that ecstasy users may be more depressed and less activated than non-users. The two papers report related findings; Dafters found that greater lifetime ecstasy use was associated with increased beta power, and Gamma found that ecstasy users had greater beta power in three statistically independent bands, specifically when eyes were open. The authors interpret increases in spectral power during the eyes open condition as evidence of disturbances of arousal or attention, and associate this with increased depressiveness and inactivation in ecstasy users. Currently, there have been few quantitative EEG studies conducted with ecstasy users, and interpreting the results is difficult without understanding the full context of each variable measured.

Gerra et al. (2000). Long-lasting effects of 3,4-methylenedioxymethamphetamine (Ecstasy) on serotonin system function in humans.

Gerra, G., Zaimovic, A., Ferri, M., Zambelli, U., Timpano, M., Neri, E., Marzocchi, G. F., Delsignore, R. & Brambilla, F. (2000). Long-lasting effects of 3,4-methylenedioxymethamphetamine (Ecstasy) on serotonin system function in humans. Biological Psychiatry, 47, 127-136.

Purpose: Personality, neuroendocrine challenge: to investigate possible long-term changes seen in recreational ecstasy users after 3 weeks and after 12 months of abstinence from ecstasy, with changes in personality and response to d-fenfluramine used as measures of serotonin system function.
Design: Non-experimental (retrospective) 2-group mixed (between subjects / within-subjects) design, with comparisons made between drug-free ecstasy users and matched non-user controls 3 weeks after ecstasy users stopped using ecstasy and again 12 months after ecstasy users had stopped using ecstasy. Each subject underwent d-fenfluramine challenge and completed measures of personality and affect.
Subjects: 15 abstinent regular ecstasy users and 15 non-user controls residing in the Parma (Italy) area, with ecstasy users recruited from individuals who had contacted the Drug Addiction Service, and controls recruited from a local high school and from the hospital. Matching – Ecstasy users matched with non-user controls on gender, age, height and possibly socioeconomic status.
Criteria for Inclusion, Ecstasy Users – Having used ecstasy at least 25 times, remaining abstinent from ecstasy for the period between both tests (12 months) with abstinence verified through twice-weekly urinary analyses, little or no use of other drugs besides ecstasy, and having contacted Drug Addiction Services. Non-users – Having never used ecstasy or any other psychoactive drug, absence of alcohol

abuse, and being similar to ecstasy users on matched variables. All Groups – Male, no current or past major medical disorders, including severe liver and renal disorders, significant weight loss, obesity, endocrinopathies or immune dysfunction. No history of major (Axis 1) psychiatric disorders as detected through psychiatric interview: 3 ecstasy users diagnosed with personality disorders were included in study.
Drug Use Parameters – Ecstasy users reported using ecstasy on an average of 69.3 ± 38 occasions (25-95), with usual dose per use reported as being approximately 1 ± .9 tablets per use (approximately .25 – 2.5 tablets). Average frequency of use was reported at 4.7 ± 2.7 times a month (2.5 – 8.2 times monthly), and average duration of use was reported to be 15 ± 9 months (8-25 months). The length of drug-free period before the study times ranged from 21 days to 365 days.
Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender, age, height and possibly socioeconomic status. Gender, as M / F ratio – Ecstasy users, 15 / 0: non-users, 15 / 0. Age – Ecstasy users, 18-26, average = 21.8, non-users, 19-24, average = 21.5. Height, in cm. Ecstasy users, average = 175 ± 12.9 cm, non-users, average = 175 ± 9.9 cm. Socioeconomic Status – Ecstasy users, "middle or high" socioeconomic status. Information not provided for non-users, but authors assert non-users matched for socioeconomic status. Other variables – No information provided about education, but 10 ecstasy users were "students," 3 were "workers," and 2 were unemployed.
Measures: Mood and Personality – Personality measured via MMPI 2 and TPQ (Tridimensional Personality Questionnaire). Aggression and hostility measured via Italian-language version of BDHI (Buss-Durkee Hostility Inventory). Subjects monitored for depression through the HAM-D. All measures were administered at 3 weeks after abstinence from ecstasy (Time 1) and again 12 months after abstinence (Time 2).
Plasma Cortisol and Prolactin after d-Fenfluramine Challenge – Measures of plasma cortisol and prolactin after d-fenfluramine challenge, with samples drawn at –15, 0, 30, 60, 90, 120 and 180 min after d-fenfluramine administration. Challenge performed once at 3 weeks after abstinence from ecstasy (Time 1) and again 12 months after abstinence from ecstasy (Time 2). Prolactin – Plasma prolactin measured via specific radioimmunoassay. Cortisol – Plasma cortisol measured via specific radioimmunoassay.
Analyses: Mood and Personality – Psychometric measures analyzed via 2-way between subjects / within subjects ANOVA, with ecstasy users versus non-users as a between-group factor and value at Time 1 (3 weeks) and value at Time 2 (12 months) as within-group factors. Psychometric measures were correlated with cortisol and prolactin AUC (area under curve) at Time 1 (3 weeks) and Time 2 (12 months).
Plasma Cortisol and Prolactin after d-Fenfluramine – Cortisol and prolactin release after d-fenfluramine were both analyzed via MANOVA, with drug use (ecstasy user versus non user) as a between group factor, time of measurement (Time 1 versus Time 2) as a within-subjects factor and with plasma cortisol and prolactin at each time point as dependent variables. Duration of ecstasy use and number of lifetime occasions of ecstasy use (total lifetime exposure) correlated with prolactin and cortisol values after d-fenfluramine challenge, presumably via Pearson correlation coefficients (method not described).
Results – Significant Differences: Mood and personality – Ecstasy users scored higher than controls on the MMPI D scale, both at 3 weeks and 12 months of abstinence from ecstasy. Ecstasy users scored higher than non-users on the BDHI Direct Aggression and Guilt scales at 3 weeks of abstinence from ecstasy, but not at 12 months of abstinence. Ecstasy users scored higher than controls on the HAM-D at 3 weeks and at 12 months of abstinence from ecstasy use. Ecstasy users scored higher than controls on the Novelty Seeking sub-scale of the TPQ at 3 weeks and at 12 months of abstinence from ecstasy. 8 ecstasy users reported dysphoric mood after 3 weeks of abstinence from ecstasy, and 4 ecstasy users reported tiredness and fatigue at the 3 week point. 4 reported subtle, unspecified cognitive impairment or confusional episodes.
Plasma Prolactin and Cortisol after d-Fenfluramine – Increase in plasma prolactin in ecstasy users was not as great as in controls after d-fenfluramine (blunted response) both at 3 weeks and at 12 weeks of abstinence from ecstasy. Increase in plasma cortisol after d-fenfluramine was lower in ecstasy users than non-user controls at 3 weeks of abstinence from ecstasy (blunted cortisol response) but not at 12 months

of abstinence. Strength of prolactin response to d-fenfluramine (prolactin AUC) in ecstasy users was negatively associated with Direct Aggressiveness scores on the BDHI and Novelty Seeking scores on the TPQ at 3 weeks of abstinence from ecstasy. (Negative association implies that less prolactin release after d-fenfluramine associated with higher direct aggression and novelty seeking scores.) After 12 months of abstinence from ecstasy, there was only a negative association between prolactin after d-fenfluramine and direct aggression; novelty seeking and prolactin response to fenfluramine challenge was no longer associated. Duration of ecstasy use was inversely related (negatively correlated) with strength of prolactin response to d-fenfluramine at 12 months of abstinence from ecstasy, but apparently not at 3 weeks of abstinence from ecstasy.

Results – No Differences Found: Mood and Personality – Ecstasy users did not differ from controls on any other MMPI scale at either the 3 week or 12 month point after abstinence from ecstasy. Ecstasy users no longer had higher Direct Aggression and Guilt scores than controls on the BDHI at 12 months of abstinence from ecstasy, though scores were elevated at 3 weeks abstinence. Ecstasy users did not score differently from non-user on Reward Dependence and Harm Avoidance scales of TPQ at either 3 weeks or 12 months of abstinence from ecstasy.

Plasma Prolactin and Cortisol after d-Fenfluramine – Ecstasy users did not differ from controls on basic prolactin levels (before fenfluramine) either at 3 or 12 months of abstinence from ecstasy. Ecstasy users did not differ from non-user controls in basal cortisol levels at 3 weeks of abstinence from ecstasy. Cortisol was non-significantly higher in ecstasy users than controls at 12 months of abstinence. Scores on the HRS-D, Reward Dependence and Harm Avoidance scores on the TPQ and other BDHI and MMPI scores not correlated with strength of prolactin response (prolactin AUC) to d-fenfluramine in ecstasy users. Strength of cortisol response (cortisol AUC) to d-fenfluramine in ecstasy users was not significantly associated with any score on any of the psychometric measures employed (MMPI, BDHI, TPQ or HRS-D), either at 3 weeks of abstinence from ecstasy or at 12 months of abstinence from ecstasy. Strength of prolactin response after d-fenfluramine was not significantly correlated with either total occasions of ecstasy use or duration of use at 3 weeks of abstinence from ecstasy.

Overall Effects: Some differences between ecstasy users and non-user controls persisted after 12 months of abstaining from further ecstasy use, while other differences were only present recently after discontinuing ecstasy use. Ecstasy users scored higher on measures of depression and novelty seeking even after discontinuing ecstasy use for a year. Blunted prolactin response to d-fenfluramine challenge was also present in ecstasy users a year after abstinence from ecstasy. On the other hand, ecstasy users had higher scores on sub-scales for direct aggression and guilt from the BDHI only after 3 weeks of discontinuing ecstasy. After a year of abstinence from ecstasy, ecstasy users and non-users did not differ on direct aggression or guilt scores. Blunted cortisol response after d-fenfluramine challenge in ecstasy users was only seen after 3 weeks of abstinence from ecstasy. Ecstasy users and non-users no longer differed on cortisol response to d-fenfluramine after a year of abstinence from ecstasy use. (Basal cortisol levels were somewhat higher in ecstasy users at the 12-month point, but the difference was not significant). Duration of use was inversely related to prolactin response to d-fenfluramine, but only after 12 months of abstinence from ecstasy, and lifetime use (total number of doses) was not related to either neuroendocrine response to d-fenfluramine challenge. Novelty seeking was consistently and negatively related to strength of prolactin response to d-fenfluramine, both after 3 week and after 12 months of discontinuation of ecstasy use. There was a negative association between strength of prolactin response at the 3-week point and direct aggressiveness score, but this relationship was no longer present at the 12-month point.

Comments: This paper is notable for employing frequent drug-screening, hence reducing the likelihood of recent ecstasy use. Findings are relatively consistent with other papers that have measured plasma cortisol and prolactin after challenge with various serotonergic drugs. However, it should be noted that no differences were found in prolactin release after tryptophan challenge in one paper (McCann et al, 1994). The findings of persistent effects can either be interpreted as arising from regular ecstasy use or as pre-existing differences leading to ecstasy use (as may be true for novelty seeking). On the other hand, transient changes on measures of aggression and guilt and blunted cortisol response may either be signs of

reversible change, drug withdrawal effects, or residual drug effects. Since the authors only use male participants in their study, caution should be used in generalizing study findings to females. All ecstasy users in this sample contacted local addiction-related social services, so that it is possible that some of the effects seen in this sample may be more specifically associated with people who contact social services about their drug use. However, the paper is notable in its attempt to select ecstasy users with little or no exposure to drugs other than ecstasy. Five of the subjects in this study also participated in an earlier study performed by Gerra and colleagues in 1998. The fenfluramine challenge was not placebo-controlled, though comparisons were made between baseline and post-drug values.

Gerra et al. (1998). Serotonin function after (+ / -) 3,4-methylenedioxymethamphetamine ("Ecstasy") in humans.

Gerra, G., Zaimovic, A., Giucastro, G., Maestri, D., Monica, C., Sartori, R., Caccavari, R. & Delsignore, R. (1998). Serotonin function after (+ / -) 3,4-methylenedioxymethamphetamine ("ecstasy") in humans. International Clinical Psychopharmacology, 13, 1-9

Purpose: Personality, pharmacological challenge: to investigate possible short-term changes seen in recreational ecstasy users who have abstained from ecstasy use for 3 weeks, with changes in personality and response to d-fenfluramine used as measures of serotonin system.
Design: Non-experimental (retrospective) 2-group between-subjects (across groups) design, with drug-free ecstasy users compared with matched non-user controls, and with drug use (ecstasy use versus non-use) serving as a between-subjects factor. All subjects completed psychometric measures of mood and personality and underwent d-fenfluramine challenge.
Subjects: 15 abstinent regular ecstasy users and 15 non-user controls residing in the Parma (Italy) area, with ecstasy users recruited from individuals who had contacted local Drug Addiction Service, and controls recruited from a local high school and from the hospital. Matching – On gender, age, height and possibly socioeconomic status.
Criteria for Inclusion - Ecstasy Users – Having used ecstasy at least 25 times, remaining abstinent from ecstasy for 3 weeks prior to study day, with abstinence verified through twice-weekly urinary analyses, little or no use of other drugs besides ecstasy, and having contacted Drug Addiction Services. Non-users – No past or current use of ecstasy or any other psychoactive drug, absence of alcohol abuse, and being similar to ecstasy users on matched variables. All Groups – Male, current or past major medical disorders, including severe liver and renal disorders, significant weight loss, obesity, endocrinopathies or immune dysfunction. No history of major (Axis 1) psychiatric disorders as detected through psychiatric interview: 2 ecstasy users diagnosed with personality disorders were included in study.
Drug Use Parameters – Ecstasy users used ecstasy on an average of 62.7 ± 34.2 occasions over a lifetime (25-90), with usual dose per use reported as being approximately 1 ± .9 tablets per use (approximately .25 – 2.5 tablets). Average frequency of use was reported at 4.7 ± 2.7 times a month (2.5 – 8.2 times monthly), and average duration of use was reported to be 14 ± 8 months (8-24 months). Length of drug-free period before study day was 21 days.
Group Demographics and Matched Variables - Ecstasy users matched with non-users on gender, age, height and possibly socioeconomic status. Gender, as M / F ratio – Ecstasy users, 15 / 0, non-users, 15 / 0. Age. – Ecstasy users, average age = 20.6 ± 2.9 years (18-24): non-users, average = 21.5 ± 2.9 (20-25). Height, in cm. Ecstasy users, average = 177 ± 10.4 cm, non-users, average = 175 ± 9.9 cm. Socioeconomic Status – Ecstasy users, "middle or high" socioeconomic status. Information not provided for non-users, but authors assert non-users matched for socioeconomic status. Other variables – No information provided about educational levels, but 11 ecstasy users were "students," 3 were "workers" and 1 was unemployed.
Measures: Mood and Personality – Personality measured via MMPI 2, the PDQ-R (Personality Diagnostic Questionnaire) and TPQ (Tridimensional Personality Questionnaire). Aggression and hostility

measured via Italian-language version of BDHI (Buss-Durkee Hostility Inventory). Subjects monitored for depression through the HAM-D. All measures were administered at 3 weeks after abstinence from ecstasy.
Plasma Cortisol and Prolactin after d-Fenfluramine Challenge – Measures of plasma cortisol and prolactin after d-fenfluramine challenge, with samples drawn at –15, 0, 30, 60, 90, 120, 180 and 240 min after d-fenfluramine administration, with challenge performed at 3 weeks after abstinence from ecstasy.
Prolactin – Plasma prolactin measured via specific radioimmunoassay. Cortisol – Plasma cortisol measured via specific radioimmunoassay.
Analyses: Mood and Personality – Analyzed via 1-way between-subjects ANOVA, with drug use (ecstasy use versus non-use) serving as between-group factor. Pearson correlation coefficients performed between psychometric measures and strength of neuroendocrine response to d-fenfluramine, with strength of response measured as prolactin and cortisol AUC.
Plasma Prolactin and Cortisol after d-Fenfluramine – A 2-way repeated measures ANOVA was used to analyze plasma prolactin and cortisol levels after d-fenfluramine, with drug use (ecstasy use versus non-use) as a between group factor and time of blood sample as a within-group factor.
Results – Significant Differences: Mood and Personality - Ecstasy users scored significantly higher than controls did on the MMPI-2 D scale. Ecstasy users had higher Direct Aggression and Guilt scores on the BDHI than controls, and ecstasy users had a higher score on the Novelty Seeking sub-scale of the TPQ than did non-users. When compared with non-users, ecstasy users obtained significantly higher HAM-D scores. 7 ecstasy users reported dysphoric mood, 5 reported tiredness or fatigue and 2 reported subtle, unspecified cognitive impairment and confusional episodes.
Plasma Prolactin and Cortisol Response after d-Fenfluramine – Increase in prolactin and increase in cortisol were both not as great in ecstasy users when compared with non-user controls (blunted prolactin response to d-fenfluramine and blunted cortisol response to d-fenfluramine). Strength of prolactin response after d-fenfluramine (AUC) was negatively correlated with direct aggression score on the BDHI (less prolactin release, higher direct aggression score). There was a trend for ecstasy users with decreased prolactin response to d-fenfluramine to score higher on the Novelty Seeking scale of the TPQ.
Results – No Differences Found: Mood and Personality – There were no differences between ecstasy users and non-users on all other MMPI-2 scale scores except for the D scale. Overall BDHI scores were higher in ecstasy users than in controls, but this difference was non-significant. While ecstasy users had higher overall PDQ-R scores than controls, the difference was not significant. Ecstasy users did not differ from controls on the Harm Avoidance and the Reward Dependents sub-scales of the TPQ.
Plasma Prolactin and Cortisol After d-Fenfluramine – Ecstasy users did not differ from non-users on baseline values for prolactin or cortisol. Strength of prolactin response to d-fenfluramine was not significantly associated with any MMPI score or any other BDHI scores except direct aggression score, HRS-D score or the Harm Reduction and Reward Dependence scores on the TPQ. Strength of cortisol response (cortisol AUC) to d-fenfluramine in ecstasy users was not significantly associated with any score on any of the psychometric measures employed (MMPI, BDHI, TPQ or HRS-D). Neither duration of ecstasy use nor total lifetime exposures (number of ecstasy tablets used) correlated with prolactin or cortisol response to d-fenfluramine. There was a very weak inverse relationship (negative correlation) between duration of use and reduced prolactin response to d-fenfluramine, with longer duration of use associated with lower prolactin response to d-fenfluramine.
Overall Effects: When compared after 3 weeks of abstinence from ecstasy, ecstasy users had higher MMPI D (Depression) scores than controls, and they had higher scores on the Hamilton depression scale (the HRS-D). When compared on a measure of aggression and hostility (the BDHI), ecstasy users obtained higher scores for direct aggression and guilt than did non-user controls. Ecstasy users had higher Novelty Seeking scores on the TPQ when compared with controls, but their scores, while obtaining scores similar to those of controls on harm avoidance and reward dependence. Prolactin and cortisol release were both blunted after d-fenfluramine challenge in abstinent ecstasy users when compared with controls. Blunted prolactin response to d-fenfluramine was associated with increased Direct Aggression scores. There were no significant relationships between duration of use or lifetime

number of doses and either prolactin or cortisol response to d-fenfluramine, though there was a weak inverse correlation between duration of ecstasy use and degree to which prolactin release was blunted after d-fenfluramine.
Comments: Like the study performed subsequent to this one, this study is notable for the authors' frequent drug-screens. Since the two papers only share 5 subjects in common, the later paper confirms findings in this paper for the 3-week time period. Findings of increased hostility in ecstasy users stand in contrast to other studies that either found lower scores on some BDHI scores in ecstasy users (McCann et al, 1994) or no differences between ecstasy users and non-users on measures of anger and hostility (Morgan et al, 1998). As was noted for the later study, all subjects in this study were male, and all ecstasy users had contacted the local drug addiction services. Hence caution should be used in generalizing study findings across gender or to other groups of ecstasy users who do not contact social services. Data from 5 subjects in this study are included in the second study. The fenfluramine challenge did not employ a placebo control.

Gouzoulis-Mayfrank et al. (2000). Impaired cognitive performance in drug free users of recreational Ecstasy (MDMA)

Gouzoulis-Mayfrank, E., Daumann, J., Tuchtenhagen, F., Pelz, S., Becker, S., Kunert, H.-J., Fimm, B., & Sass, H. (2000). Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). Journal of Neurology, Neurosurgery and Psychiatry, 68, 719-725.

Purpose: Cognitive function, general: comparative study assessing various cognitive abilities in abstinent moderate ecstasy users, cannabis users and non-users.
Design: Non-experimental (retrospective) 3-group between subjects (across group) design, with ecstasy users compared with matched cannabis-user and non-user controls, with drug use as a between subjects factor.
Subjects: 28 ecstasy users, 28 cannabis users and 28 non-users in the Aachen (Germany) area, with subjects recruited directly by students participating in the dance scene or through word of mouth.
Matching – On gender, age and education. Ecstasy users and cannabis users matched on extent of cannabis use.
Criteria for Inclusion – Ecstasy Users – Regular ecstasy use for 6 months or longer, minimum frequency of use; twice a month or 25 instances in 2 years. No regular use of other legal or illegal drugs except cannabis, with regular use defined as at least once a month in past 6 months, and no heavy use of alcohol, defined as severe drunkenness 2 or more times a month. Cannabis Users – No use of ecstasy, all other criteria above concerning drug and alcohol use. Non-Users – No past or current use of cannabis, ecstasy or any other illicit substance, and lack of heavy alcohol use. All Groups – Absence of any major medical or psychiatric disorder (excepting substance abuse for drug user groups), ascertained through medical and psychiatric interview, and abstinence from ecstasy or cannabis for at least 7 days before study day, with compliance verified through urinary analysis on the study day.
Drug Use Parameters – Ecstasy users took ecstasy, on average, 93.4± 119.9 times over a lifetime (20-500), using an average dose of 1.4 ± .9 tablets per use (.5 – 3.5 tablets per occasion). Average frequency of use was 2.4 ± 1.6 times per month (.75 – 8 times), and average duration of use in months was 27 ± 18 months (6-60). Self-reported length of drug-free period before study day, in days was 41 ± 71 days (7-356 days). 26 / 28 were regular ecstasy users and 2 / 28 were sporadic users. The average age when ecstasy was first used = 19.4 ± 3.3 years (14-27 years). Cannabis use – 22 ecstasy users were regular cannabis users, 1 used cannabis sporadically and 5 did not use cannabis. In matched cannabis user group, 23 were regular cannabis users, 2 were sporadic cannabis users and 3 did not use cannabis. Cannabis was used on 20.7 ± 11.5) days a month by ecstasy users and 20.9 ± 10.2 days per month by cannabis users. Duration of cannabis use extends for 66.6 ± 37 months for ecstasy users and for 35.1 ±24 months for cannabis users. Ecstasy users had last used cannabis 4.3 ± 5.3 days before the study day and cannabis

users last used cannabis 4 ± 15.5 days before the study day. 17 ecstasy users and 20 cannabis users tested positive for presence of THC in urine on study day, and 11 ecstasy users and 8 cannabis users tested negative for THC in urinary analysis. Average age of first cannabis use for ecstasy users = 16.6 ± 2.9 years, and the average age of first cannabis use for cannabis users = 17.1 ± 2.4 years.
Group Demographics and Matched Variables – Ecstasy users matched with both cannabis user and non-user controls on gender, age and education level. Gender, as M / F ratio – ecstasy users, 16/12: cannabis users, 15/13: non-users, 17 / 11. Age. Ecstasy users, 18-29, mean = 23.25, cannabis users, 18-31, mean = 22.9, non-users, 18-30, mean = 23.5. Education level. Little / no secondary school – 1 ecstasy user, 0 cannabis users, 0 non-users: "Basic" school-leaving exam – 2 ecstasy users, 2 cannabis users, 0 non-users: "intermediate" school-leaving exam – 8 ecstasy users, 5 cannabis users, 8 non-users: "highest" school-leaving exam – 16 ecstasy users, 20 cannabis users, 20 non-users: university degree – 1 ecstasy user, 1 cannabis user, 0 non-users. Average education, ecstasy users = 3.5 (approx. 11 years), cannabis users = 3.7 (approx. 12 years), non-users = 3.7 (approx. 12 years). Cannabis Use – Ecstasy users matched with cannabis using controls on cannabis use. Regular cannabis use – 22 ecstasy users, 23 cannabis users: sporadic cannabis use – 1 ecstasy user, 2 cannabis users: No cannabis use – 5 ecstasy users, 3 cannabis users.
Measures: Tests of Attention – TAP Subtest 1 (Simple RT), TAP Subtest 6 (Selective visual attention, matching to sample), TAP Subtest 5 (RT, simultaneous visual and auditory stimuli), TAP Subtest 8 (Intermodal integration RT; matched visual and auditory stimuli), TAP Subtest 12 (Visual scanning; Locate target in array), Stroop test (cognitive interference). Tests of Memory – Corsi block tapping test (Reproduce sequences of taps on blocks performed by experimenter), Digit Span, WAIS-R, German language (Verbal memory, working memory). Tests of Memory and Learning – VMLT (Immediate and delayed recall, recognition, similar format to RAVLT), VIG Visuospatial Memory (Immediate and delayed recall for geometric figures). Prefrontal and General Intelligence – Word fluency (Word generation; executive function), LPS-4-Abstract Logical Thinking (Discover rule for series of letters, digits and indicate "wrong" element, test of fluid intelligence), Mosaic Test, WAIS-R, German language (Subjects reproduce patterns with cubes, test of fluid intelligence, visuomotor performance, problem solving), General Knowledge, WAIS-R, German language (Crystallized intelligence). Self Report Questionnaire – Asked to report any difficulties in concentration or memory experienced in everyday life.
Analyses: Performance scores analyzed via 1-way between subjects ANOVA, with user group (ecstasy user, cannabis user, non-user) as between-group factor, post-hoc comparisons made with Scheffe test. A canonical discriminant analysis performed on entire data set. Relationship between ecstasy and cannabis use and performance scores on assessments made via Pearson correlation coefficient. Performance scores analyzed via ANCOVA, with general knowledge score serving as covariate. If findings were significant in tests of attention and memory, the relevant scores were correlated with 3 intelligence scores via Pearson correlation.
Results – Significant Differences: Tests of Attention – Increased RT on TAP6 (Selective Visual Attention), with ecstasy users > non-users, cannabis users. TAP5 (Divided Attention), with ecstasy users > cannabis users). TAP8 (Intermodal Integration) – ecstasy users > cannabis users. Tests of Memory – Digit Span-Backwards, poorer performers, with non-users > ecstasy users. Tests of Memory and Learning – VLMT-Immediate recall, poorer recall, with non-users > ecstasy users, VLMT interference, with non-users > ecstasy users, VLMT-Recall after 30 min, with non-users > ecstasy users. VIG-immediate recall, with cannabis users, non-users > ecstasy users. Executive Function and General Intelligence – LPS-4, with cannabis users, non-users > ecstasy users. Mosaic test, with cannabis users, non-users > ecstasy users, General Knowledge, with cannabis users, non-users > ecstasy users.
Results – No Differences Found: Tests of Attention – TAP1 (Simple RT, Alertness), TAP2 (Visual Scanning), Stroop Test, Digit Span-Forward Tests of Memory – VLMT-Learning, Corsi Block Tapping, VIG-Learning and Number of Repetitions. Tests of Executive Function, General Intelligence – Word fluency. Self-Report – None of the 3 groups reported experiencing greater difficulty in concentrating or with memory.

Results – Correlations, Significant: Longer RTs on divided attention task associated with longer duration of ecstasy use. Poor digit span performance associated with larger cumulative ecstasy doses and with younger age of first cannabis use. Poor performance on VLMT associated with heavier ecstasy use (immediate recall associated with emulative dose, interference of second list associated with frequency of use and number of repetitions associated with estimated usual dose per use). Poor VLMT performance also associated with heavy cannabis use (number of repetitions associated with frequency of cannabis use).
Results – Correlations, Not Significant: All other test scores (Selective attention, intermodal integration, VIG-Immediate recall, LPS-4, Mosaic Test, General knowledge).
Results – ANCOVA With General Knowledge as Covariate: All significant findings remained the same except VLMT-Interference, with differences between non-users and ecstasy users only approaching significance. With ANCOVA, all 3 intelligence measures slightly to moderately associated with each other, but not with performance on other assessments.
Results – Canonical Analysis: Canonical analysis successfully classified 90.36% of all participants on the basis of performance scores, with 92.9% of ecstasy users successfully classified, 85.7% of the cannabis users successfully classified and 92.6% of the non-users successfully classified.
Overall Effects: Ecstasy users performed less well than either cannabis users or non-users on measures of fluid and crystallized intelligence, and they did not attain as high scores as non-users on various tests of working memory. However, members of all three groups did equally well with simple RT tasks, and findings are inconclusive on tasks of executive function, with differences appearing between groups on some assessments and not on others. Long reaction time and poor performance on measures of divided attention, working memory and memory and learning were related with longer duration of ecstasy use and higher cumulative ecstasy dose. However, a specific assessment of working memory and the "number of repetitions" score in another assessment of memory and learning were also associated with age of onset of cannabis use and frequency of cannabis use, respectively. The authors appear to favor an explanation for their findings via ecstasy-related deficits in working memory, with deficits in working memory affecting performance on other tests besides those directly measuring working memory. The authors hypothesize that the decline is related to serotonergic neurotoxicity, possibly in combination with or in addition to the effects of regular cannabis use.
Comments: This paper is one of several that employ cannabis-user control as well as non-user control, perhaps sampled from the same "dance scene" population, though information in text makes this uncertain. This paper is also notable in its attempt to select a sample of ecstasy users who were not polydrug users. Study findings indicate that cannabis use and ecstasy use may both affect cognitive function. While they found that ecstasy users performed less well on a greater number of measures than did cannabis users, the authors also found that cannabis use might be due in part to poor performance on some tests of learning and memory. Authors describe ecstasy use as "moderate," though parameters indicate that their ecstasy use is heavier than ecstasy use in other studies. It is interesting that different drug use parameters appear to be associated with poorer performance on measures of different cognitive functions. Other studies have not found such distinct associations between specific drug use parameters (like duration of use or dose per use) and specific cognitive functions, but it is also true that not all researchers measure the same drug use parameters.

Klugman et al. (1999). Toxic effects of MDMA on brain neurons (Letter).

Klugman, A., Hardy, S., Baldeweg, T. & Gruzelier, J. (1999). Toxic effects of MDMA on brain neurons (Letter). The Lancet, 353, 1269-1270.

Purpose: Mood, cognitive function, general: To investigate whether long-term consumption of ecstasy affects cognitive function, with cognitive function measured via neuropsychological test. .
Design: Non-experimental (retrospective) 2-group between-subjects (across group) design where ecstasy users were compared with an unequal number of matched non-user controls, and with drug use (ecstasy

use versus non-user) serving as a between-subjects factor. All subjects underwent assessments of cognitive function.
Subjects: 36 ecstasy users and 19 controls recruited through advertisements in popular magazines and through the internet. Matching – Groups matched on age.
Criteria for Inclusion, Ecstasy Users – Regular and "predominant" ecstasy user, with specifications not reported here, and no use of ecstasy or other psychoactive drugs less than 2 days prior to the study day; no information on verification of drug-free status. Non-user – No past or current use of used ecstasy or other psychoactive drugs. All Groups – Further requirements for inclusion not specified. Subjects were screened for psychiatric disorders via psychiatric interview, but those found to have "neurotic depression" were not excluded from study.
Drug Use Parameters – Ecstasy users reported an taking an average of 235 doses of ecstasy over a lifetime (12-2600 doses), with no information provided concerning average dose per use. Ecstasy users reported that they had used ecstasy for an average duration of 48 ± 31.2 months, with information not provided concerning frequency of use. Average time elapsed between last use of ecstasy and study day was 79 days (2-400 days).
Group Demographics and Matched Variables – Ecstasy users were matched with non-user controls on age. Age – Ecstasy users = 24.1 ± 4.9 years, range not provided; non-users = 22.7 ± 2.3 years, range not provided. Gender – No information provided about gender composition of either group (ecstasy users or non-users). Other Variables – No information is provided concerning education level, socioeconomic status or use of other drugs for ecstasy users or for non-user controls.
Measures: Mood – Depressed mood or signs of depression measured via BDI.
Tests of Cognitive Function – No information is provided concerning identity of any test employed in this study. Measures listed included tests of learning, recognition, and recall, and tests of executive function. Tests of learning included test of list learning and possibly the Digit Span test, and tests of spatial and perhaps non-spatial learning and memory. Tests of recognition and recall employed at least a test for recall of faces and perhaps words, possibly the Warrington Recognition Memory test. Tests of executive function included tests of verbal fluency and tests of verbal and non-verbal working memory.
Analyses: Performance on tests of cognitive function analyzed via multiple analysis of variance (MANOVA). No further details given; presumably drug use (ecstasy user versus non-user) served as a between-subjects variable and each test score served as a dependent variable. Unspecified form of correlation performed on use of other drugs (with other drugs unspecified, but including cannabis) and scores on test of performance.
Results – Significant Differences: Tests of Cognitive Function – Ecstasy users had lower scores than non-users on tests of learning, recognition and recall. Ecstasy users had lower immediate recall of words from list. Ecstasy users recognized fewer target faces on a test of face recognition. Ecstasy users performed less well than non-users on learning a repeatedly administered list of words or a list of digits. Ecstasy users did less well learning spatial information than did non-users. 3 ecstasy users scored 2 standard deviations below presumed published norm for 2 tests, and 8 users scored 2 standard deviations below presumed published norms on 1 test, whereas only one non-user control scored more than 1 standard deviation below presumed published norms, with nature of test unspecified. There was a positive correlation between cannabis use and performance on unspecified tests of cognitive function, where more cannabis use was associated with poorer test performance.
Results – No Differences Found: Mood – No differences between BDI scores of ecstasy users and BDI scores of non-user controls.
Tests of Cognitive Function – There were mo difference between the scores of ecstasy users and non-users on unspecified tests of executive function (described as tests of verbal fluency and verbal and non-verbal working memory). Extent of using unspecified other drugs were not associated (either positively or negatively) with performance on most tests of cognitive function.
Overall Effects: When compared on tests of learning, recognition and recall, ecstasy users did not perform as well as a group of non-user controls matched on age. Performance lower than published norms was more likely for ecstasy users than for non-users, though the authors did not specify the tests

for which this is the case. However, performance on tests of verbal and non-verbal working memory and tests of verbal fluency were similar in ecstasy users and non-users. The authors describe the tests listed above as tests of executive function. Cannabis use may be correlated with a decrement in performance on an unspecified number of tests of executive function, but use of all other drugs did not correlate with performance on any test of cognitive function.
Comments: The findings reported by Klugman et al are contained in a letter to the medical journal, The Lancet. As such, the information provided in this report was sparse. Attempts to contact the authors have thus far been unsuccessful. The identities of the tests used were unspecified, and information on the gender composition and on other demographics beyond subject's age was not provided. In contrast with other studies, this study did not find that ecstasy users differed from controls in their performance on tests of working memory or verbal fluency. Instead, they differed on tests of learning and both verbal and non-verbal recall. This report has not been through the process of peer review, and it lacks information in a number of important areas, so caution should be used in interpreting the findings.

Krystal et al. (1992). Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: Effects on mood and neuropsychological function?

Krystal, J. H., Price, L. H., Opsahl, C. Ricaurte, G. A., Heninger, G. R. (1992). Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: Effects on mood and neuropsychological function? American Journal of Drug and Alcohol Abuse, 18, 331-341.

Purpose: Mood, cognitive function, general: To investigate the long-term consequences of ecstasy use by assessing mood and examining performance on tests of cognitive function in a group of ecstasy users.
Design: Non-experimental (retrospective) 1-group design without controls. Performance of ecstasy users on tests of cognitive function compared with published age-matched norms. All subjects completed test battery and measures of depressed mood.
Subjects: 9 regular ecstasy users recruited nationally, with recruitment criteria unspecified except "current or recent history of substantial" ecstasy use, with substantial use undefined. Matching – No matched groups: 1-group design.
Criteria for Inclusion – None explicitly specified beyond "substantial" use of ecstasy, with ecstasy being main drug of choice, and abstention from psychoactive drugs for at least 3 weeks prior to study day, with compliance verified through self-report. (3 / 9 reported infrequent marijuana use during 3-week period). However, all subjects underwent a psychiatric interview, including a personal and family history of major psychiatric disorders. However, it is not reported whether only subjects without a personal or family history of psychiatric illness were accepted into the study.
Drug Use Parameters – Subjects reported an average total lifetime use of approximately 130 tablets (estimated from cumulative exposure, 13.3 g) (range 120 – 440 tablets, 12 – 44 g), and an average frequency of use of 1.9 ± 1.7 times a month (.3 – 5 times a month). Average duration of use, in months, is 61 ± 27.6 months (24 – 84 months), and subjects reported using, on average, approximately 1.35 tablets (135 mg) (.5 – 2.5 tablets, 50 – 250 mg). "Many" subjects (unspecified) reported using much higher doses on occasion, reporting doses up to 500 mg (approximately 5 tablets) per occasion. The average last reported use prior to study day was 66 ± 50 days (20-180 days). Use of Other Drugs – Data collected on 8 / 9 subjects. 6 / 8 reported previous experimentation or use of alcohol, amphetamines, cocaine and marijuana. 5 / 8 reported using LSD, and 2 / 8 reported using DMT, PCP or psilocybin. 1 / 8 reported using additional hallucinogens and dissociatives (harmaline, mescaline, 5-Meo-DMT, ibogaine and ketamine).
Group Demographics and Matched Variables – Only 1-group design, so no matching occurred. Performance on tests of cognitive function compared with age-matched norms.
Gender, as M / F ratio: 7 / 2. Age. Average age = 34 ± 7 (22-47 years). Education Level – Information on subjects' level of education not provided. Psychiatric Diagnosis – No current reports of major

psychiatric illness. However, 7 / 9 subjects reported previous experiences of anxiety or depression. Diagnosis of previous psychiatric illnesses: Anxiety disorder: 3 / 9, panic disorder: 1 / 9, depression: 3 / 9, dysthymia: 1 / 9, self-reported "identity problem": 1 / 9. Family history of alcohol or substance abuse present in 1st degree relative of 6 / 9 subjects. Family history of depressive disorder reported in 3 / 9 subjects and of GAD in 1 / 9 subject.

Measures: Tests of Cognitive Function – WAIS-R (general intelligence), Paragraph and Figural Recall sections of WMS (memory, immediate and delayed recall), Boston Naming Test (?unspecified, others indicate a test of language), multiple choice version of Benton Visual Retention Test (visual memory), the Token test (language and transformational grammar, not described in paper) and Trail Making Test. Tactual Performance test, Finger Oscillation Test, the Lafayette Pegboard Test, and Grip Strength test (manual grip). "Mild" impairment defined as scoring 1 SD below age-matched norm and "moderate" impairment defined as scoring 2 SDs below age-matched norm. Tests of cognitive function administered at least 3 h after subjects underwent tryptophan challenge, with details of tryptophan challenge not presented in this paper.

Depression / Depressed Mood – Measured via the BDI and an extended version of the HAM-D, administered at least 3 h after tryptophan challenge (tryptophan challenge reported elsewhere).

Mental Status Examination and Neurological Examination – Conducted as part of screening.

Prolactin response After Tryptophan Infusion – Procedures not described in this paper. Prolactin measured at baseline and then after tryptophan infusion.

Analyses: Possible relationships between scores on tests of memory (specifically the WMS) and cumulative dose of ecstasy were examined via correlation. Prolactin levels at baseline and prolactin response to tryptophan infusion also reported (procedure not described in full). Comparisons on tests of performance were made on the basis of age-matched norms, and measures of depression scored via published norms. Number of subjects with impairment on each test reported. Otherwise, no formal analyses performed on data.

Results – Significant Differences: Tests of Cognitive Function – 5 / 9 subjects showed at least mild impairment on the WMS-Initial paragraph test compared with norms. 4 / 9 (all belonging to group who showed impaired performance on Initial Paragraph) also showed deficits in the Delayed paragraph test, and 3 / 9 had definite mild impairment on the WMS-Delayed Paragraph test. In comparison, 2 / 9 showed mild (1) or moderate (1) impairment on Trail Making test, 4 / 9 showed mild impairment on Tactual Performance test (1, dominant hand, 2, non-dominant hand, 1, both hands), 2 showed mild impairment on location performance test in Tactual Performance test and 1 / 9 was mildly impaired on performance of Lafayette Pegboard test. Because of small sample size, authors only consider the findings for the WMS to be significant.

Prolactin Response to Tryptophan and Test Performance – Prolactin response to tryptophan was associated with impaired performance on the WMS-Delayed Figural test, suggesting that tryptophan infusion itself, or prolactin response to tryptophan, might have interfered with test performance.

Results – No Differences Found: Mental Status Examination and Neurological Examination – All subjects found to be functioning normally, and no sign of clinical impairment in cognitive function, as evidenced through mean full-scale IQ: (115 ± 9.5) and no difference between verbal and performance IQ. There were no group-related patterns on WAIS-R, Boston Naming Test, Benton Visual Retention Test, Trail Making Test, Tokens Test, Lafayette Pegboard Test, Tactual Performance Test, Finger Oscillation Test, or Grip Strength

Depression / Depressed Mood – None of the subjects had elevated scores on either the BDI or the HAM-D, with all scores below indicators of clinical depression.

Drug Use Parameters and Test Performance – No relationship between cumulative ecstasy dose (lifetime exposure) and performance on the WMS. There were no associations between prolactin at baseline or in response to tryptophan and performance on the Paragraph tests of the WMS.

Overall Effects: A small sample of regular ecstasy users performed within the normal range on tests of general intelligence, learning, language, manual dexterity, eye-hand co-ordination, 5 of 9 subjects performed at least 1 standard deviation below published age-matched norms on tests of immediate and

delayed memory. (Specific references are made to the test of immediate and delayed verbal memory). There is some indication that a small number of subjects were impaired on various tests of manual speed, manual dexterity and (possibly) executive function, but there were too few of them in a small sample for this to be considered a "group specific pattern." Impaired performance on tests of memory was not correlated with cumulative lifetime exposure to ecstasy and it was not associated with prolactin response to tryptophan challenge. None of the subjects participating in this study were diagnosed with affective or anxiety disorders, though they frequently reported previous experiences with depression or anxiety, and BDI and HAM-D scores were well within normal range.
Comments: This paper is one of the first to document possible deficits in cognitive performance in regular ecstasy users. The paper seems to have the qualities of a preliminary study in that the sample size is very small and no matched controls were employed. Unlike later studies without control groups, little use is made of correlational analyses. Correlations were only performed between performance and cumulative exposure to ecstasy (number of lifetime exposures). Because tests of cognitive function were conducted a few hours after tryptophan infusion, it is possible that performance on one or more test was either made worse or better by the tryptophan challenge. The paper is unusual in the number of tests employed for measuring manual dexterity and eye-hand co-ordination. Subjects taking part in this study were selected from another study on the basis of their low levels of 5HIAA in CSF, so caution should be used in generalizing from this study. Study sample is identical to the sample taking part in Price et al.

McCann et al. (1994). Serotonergic neurotoxicity after 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"): A controlled study in humans.

McCann, U. D., Ridenour, A., Shaham, Y., & Ricaurte, G. A. (1994). Serotonergic neurotoxicity after 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"): A controlled study in humans. Neuropsychopharmacology, 10, 129-138.

Purpose: Neuropsychological, including pharmacological challenge and personality measures: To measure CSF monoamines in ecstasy users and to examine whether differences in amount of 5HIAA in CSF are related to differences in functional domains presumed to be related to serotonergic function.
Design: Non-experimental (retrospective) 2-group between subjects (across groups) design, with drug-free ecstasy users compared with matched non-user controls, with drug use (ecstasy use versus non-use) serving as a between-subjects factor. All subjects underwent measurements of monoamine metabolites in CSF, prolactin response to tryptophan infusion and measures of response to ischemic pain, and all completed measures of personality.
Subjects: 30 regular ecstasy users recruited nationally through self-referral and 28 non-user controls either recruited by ecstasy user subjects or recruited through local advertisements in the Baltimore / Washington DC area. Matching – On gender, height and weight, and approximately matched on age and education.
Criteria for Inclusion, Ecstasy Users – Having used ecstasy on at least 25 different occasions over lifetime. Non-users – No past or current ecstasy use, but use of psychoactive drugs other than ecstasy permitted. All Groups – Good health as assessed through physical examination, psychiatric interview, ECG and laboratory analysis. No history of major medical disorder, including neurological, renal, endocrine or hematological illness) and no history of psychiatric disorders, including psychosis or depression, alcohol or substance abuse. Not pregnant, and negative urine and blood screen for major psychiatric drugs. Abstinence from any psychoactive drug for at least 2 weeks prior to study day, with compliance verified by drug screens described above, performed on 1st study day.
Drug Use Parameters – Ecstasy Users – Ecstasy users reported that, on average, they had used ecstasy on 94.4 ± 90.6 occasions over a lifetime (25-300), and that average frequency of use was 4.16 ± 4.79 times a month (.15-20 times monthly.) Average dose of ecstasy taken per occasion was approximately 1.7 ± .8 tablets (.5 – 4 tablets), and average duration of use was approximately 59.8 ± 35.52 months (6 – 192

months (16 years)). Average time of last use prior to 1st study day was reported as approximately 125.3 ± 172.9 days (14 – 728 days). Number of ecstasy users reported using the following drugs: cannabis, 28 / 30: LSD, other hallucinogens, 26 / 30: cocaine, 24 / 30: benzodiazepines, 18 / 30: opiates, 16 / 30: other amphetamines, 13 / 30: sedative hypnotics, 10 / 30: solvents, 8 / 30 and PCP and related drugs, 4 / 30. Non-Users - Number of non-user controls reported using the following drugs: cannabis, 22 / 28: LSD, other hallucinogens, 9 / 28: cocaine, 8 / 28: benzodiazepines, 6 / 28: opiates, 9 / 28: other amphetamines, 9 / 28: sedative hypnotics, 1 / 28: solvents, 8 / 28 and PCP, related drugs, 2 / 28.
Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender, height and weight, and ecstasy users were approximately matched on age and education level. Gender, as M / F ratio – Ecstasy users, 18 / 12: non-users, 17 / 11. Height, in cm – Ecstasy users, 174.8 ± 9.2 cm: non-users, 175.4 ± 9.5. Weight, in kg – Ecstasy users, 69.9 ± 14.9 kg: non-users, 70.4 ± 10.7 kg. Age. Ecstasy users, no range provided, mean = 32.3 ± 13.6: non-users, no range provided, mean = 27.8 ± 7.8. Educational level – On average, ecstasy users had 15.2 ± 2 years' education, and non-users had, on average, 16.5 ± 2.8 years' education.
Measures: Monoamine Metabolites in CSF – Subjects received lumbar puncture on the morning of 3rd study day after overnight fast. Monoamine metabolites in CSF measured via high performance liquid chromatography with electrochemical detection. Metabolites measured were 5HIAA (serotonin metabolite), HVA (dopamine metabolite) and MHPG (norepinephrine metabolite).
Prolactin Response to Tryptophan Challenge – 7 g L-tryptophan i. v. infused over 20 min, and plasma prolactin concentration was measured in blood samples drawn at 15 and .5 minutes before tryptophan infusion and 30, 40, 50, 60, 70, 90 and 120 min after infusion. Date of tryptophan challenge unspecified. Serum prolactin determined via radioimmunoassay.
Pain Measurements – Measured via maximum effort tourniquet technique, used to induce ischemic pain in humans. Pain assessed through 3 measures. Pain Sensitivity – Numerical value of 1st self-rating of pain. Pain Endurance – Time elapsed between start of test and time when subject requested end of test. Pain Tolerance – Total pain scores (sum of all pain ratings recorded at 30 sec intervals for duration of test. Date of pain measurements unspecified.
Personality Assessment – Personality traits measured via MMPI and EPQ, both of which contain scales referring to impulsivity and control. Aggression and hostility was measured via BDHI. Time of administration unspecified.
Analyses: CSF Monoamine Metabolites – Amount of monoamine metabolites initially analyzed via ANCOVA, with age and height serving as covariates and with drug use (ecstasy user versus non-user) serving as a between-subjects variable. Second analysis attempted to control for seasonal variation in monoamine metabolites by analyzing data via 2(drug use) x 4(season) ANCOVA, with age and height serving as covariates. Because raw scores indicated possibility of gender differences in monoamine concentration, CSF monoamine metabolites also analyzed via 2(drug use) x 2(gender) ANCOVA, with age and height serving as covariates. Post-hoc comparisons made with Duncan's multiple range test.
Prolactin after Tryptophan Infusion – Prolactin values at 15 and .5 minutes before tryptophan infusion averaged. Peak change scores were calculated by subtracting baseline prolactin value from highest prolactin value after tryptophan infusion, and AUC was calculated using the trapezoidal method. Prolactin response to tryptophan challenge measured via ANCOVA, with drug use (ecstasy user versus non-user) as a between-subjects factor and with age, basal prolactin level and plasma L-tryptophan values serving as covariates. Duncan's multiple range test was used for post-hoc comparisons.
Pain Measures – All 3 measures of pain (sensitivity, endurance and tolerance) analyzed via 2(drug use) x 2(gender) ANOVAs, with drug use and gender serving as between-group factors, and with post-hoc comparisons made via Duncan's multiple range test.
Personality Assessments – Scores on the MMPI, BDHI and EPQ were analyzed via 2(drug use) x 2(gender) ANCOVA, with age and education as covariates, and with analysis corrected for Type 1 error via Bonferroni method, and with post-hoc comparisons made via Duncan's multiple range test.
Correlations – All correlations calculated were Pearson correlations (product moment).

Results – Significant Differences: CSF Monoamine Metabolites – When age and height used as covariance, ecstasy users had lower 5HIAA in CSF than did non-user controls. A drug use x gender ANOVA found that while 5HIAA levels lowest in females in ecstasy user group, non-user males had lower 5HIAA levels than non-user females. Female ecstasy users had lower CSF HVA than female non-users, but there was no difference in CSF HVA for males.
Personality Assessments – Ecstasy users scored higher on MMPI Control scale, indicating that ecstasy users were less impulsive than non-users. While there were drug use x gender effects on the alienation, harm avoidance and constraint scales of the MMPI, these are not described. Ecstasy users scored lower on the Indirect Hostility scale of the BDHI than did non-users.
Results – No Differences Found: CSF Monoamine Metabolites – Duration of ecstasy use and CSF 5HIAA were uncorrelated. While number of lifetime doses (cumulative exposure) was negatively correlated with CSF 5HIAA, the correlation was not statistically significant. A drug use x season analysis found no interactions with season. Ecstasy users and non-users did not differ in amount of CSF MHPG. While CSF HVA was lower in ecstasy user females versus non-users, male ecstasy users and non-users had similar values of CSF HVA.
Prolactin after Tryptophan Infusion – Ecstasy users did not differ from non-users in their prolactin response to tryptophan infusion, whether measured as peak change or as AUC.
Pain Measures – Ecstasy users did not differ from non-users on any of the 3 measures; pain sensitivity, pain endurance or pain tolerance.
Personality Assessments – Ecstasy users did not differ from non-users on other MMPI scales, other BDHI scales (such as direct hostility, direct aggression and indirect aggression) and any of the EPQ scales.
Overall Effects: Ecstasy users had lower levels of 5HIAA in their cerebrospinal fluid (CSF), and there was a gender-specific decrease in HVA in ecstasy users, with female ecstasy users having decreased HVA compared to female controls while HVA values were similar for male ecstasy users and non-user controls. Despite the lower 5HIAA values, ecstasy users did not differ from controls on two measures selected for their presumed connection with serotonergic function. Ecstasy users did not have a blunted (or stronger) prolactin response to tryptophan infusion when compared with controls, and all measures of pain reaction, including pain sensitivity, endurance and tolerance were similar for ecstasy users and non-user controls. Non users and ecstasy users differed in some personality scale scores, with ecstasy users scoring higher on the MMPI control scale (meaning they were less impulsive) and lower on the BDHI Indirect Hostility scale. However, the two groups scored similarly on all other MMPI, BDHI and EPQ scales.
Comments: This paper sought to establish links between ecstasy use, lower serotonin metabolites and changes in functions selected for their presumed association with serotonergic function. The findings are thus surprising in that lower levels of the serotonin metabolite 5HIAA was found in ecstasy users, but there were few behavioral correlates of this difference, and the differences that were found between ecstasy users and non-users were opposite those predicted on the basis of theory. Either the assumptions about the strong relationship between the selected functions were incorrect or incomplete, or the measures chosen were not accurate or effective measures. There is also some suggestion that some of the personality differences between the 2 groups were a reflection of the personality characteristics of regular ecstasy users in the late 1980s or early 1990s. The authors explain the discrepancy between their findings of reduced 5HIAA without any behavioral correlates as evidence for selective damage to ascending, but not descending, serotonergic axons. Gender seems to be a more powerful predictor of outcome than past use of ecstasy in several measures, suggesting that it is important to examine studies that rely on data from one gender only (as with Gerra). Such studies may not accurately reflect either serotonergic function or the effects of regular ecstasy use in both genders.

McCann et al. (1998). Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings.

McCann, U., Szabo, Z., Scheffel, U., Dannals, R. F. &, Ricaurte, G. A. (1998). Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. The Lancet, 352, 1433-1437.

Purpose: Brain imaging (PET with ligand binding): To investigate whether MDMA use produces long-term changes in number of serotonin transporter sites by performing PET with a radioligand for the serotonin transporter site.
Design: Non-experimental (retrospective) 2-group between subjects design that compared drug free ecstasy users with matched non-user controls, with drug use (ecstasy use versus no ecstasy use) as a between-group factor, and with all subjects receiving PET scans.
Subjects: 14 regular ecstasy users and 15 non-users recruited via advertisements in local (Baltimore, MD / Washington, DC) newspapers and on the internet, and referrals. Matching – On gender, age and education.
Criteria for Inclusion, Ecstasy Users – Having used ecstasy on at least 25 occasions over a lifetime. Non-users – No past or current ecstasy use, but use of other drugs permitted. All Groups – No past or current major medical or psychiatric illness as assessed through physical examination and psychiatric interview, ECG and standard urinary and blood analyses. Abstaining from all psychoactive drugs for at least 3 weeks prior to study period, with compliance verified by urinary and blood screening for drugs on day of admission to study. No claustrophobia, absence of any neuropsychiatric disorders where serotonin function might be impaired, and no cardiac pacemaker.
Drug Use Parameters – Ecstasy Users – On average, ecstasy users reported taking ecstasy on 228 occasions (70-400 occasions), with an average dose per use of approximately 3.8 tablets (1.5 – 12.5 tablets). Ecstasy users had an average frequency of use of 6 times a month (1-16 times monthly), and average duration of use, in months, was 55.2 months (18-120 months). Number of days from last use until study day was 133 days (21- 1029 days)
Group Demographics and Matched Variables – Ecstasy users matched with non-user controls on gender, age and education. Gender, as M / F ratio – Ecstasy users, 9 / 5: non-users, 9 / 6. Age. Ecstasy users average age = 26.6 ± 10.5 (range not provided): non-users average age = 28.3 ± 11.7 (range not provided). Education Level – Ecstasy users average education level, in years, was 15 ± 2, and non-users average education level, in years, was 16 ± 4. Use of Other Drugs – Information on number of other psychoactive drugs used by ecstasy users or non-users not provided, but members of both groups had negative screens for marijuana, amphetamines, opiates, barbiturates, PCP and benzodiazepines on the study day.
Measures: PET was performed, with PET co-registered with MRI to more clearly locate and define regions of interest. PET was conducted after injection of [11C]McN-5652. 2 sets of scans were performed on each subject; one with (+)McN-5652 and one with (-)McN-5652. Regions of interest were drawn on PET scans by an experimenter blind to subject's drug history, with regions being frontal cortex, parietal cortex, temporal cortex, occipital cortex and cingulate, caudate, putamen, thalamus, midbrain, pons, hypothalamus and cerebellum.
Analyses: Analyses were performed on model for (+)McN-5652 that consisted of specific binding, non-specific binding and free ligand, and the model for (-)McN-5652 consisted of non-specific binding and free ligand only. Ligand binding data was transformed to log to achieve normal distribution, and data for all regions in controls used to create a pooled coefficient of variation of 22%. Log transformed ligand binding data for 12 brain regions were analyzed via MANOVA, with drug use (ecstasy user versus non-user) as between-group variable, ligand binding data as dependent variables and age and gender as covariates. A 1-way ANOVA was used to examine differences in ligand binding in individual regions, presumably with drug use (ecstasy use versus non-use) serving as a between-subjects factor. Correlations – Possible relationships between time since last use, extent of previous use (total lifetime use) and ligand binding data were examined via Pearson's correlations, with p. set at .05.
Results – Significant Differences: Ecstasy users had lower global specific binding for [11C]McN-5652, indicating lower numbers of serotonin (5HT) transporter sites in brain. Decreased serotonin transporter

binding in ecstasy users was found when comparisons were made between [11C]McN-5652 binding in the following brain regions: frontal cortex, parietal cortex, occipital cortex and cingulate, caudate, putamen, midbrain, pons, hypothalamus and cerebellum. Correlations – Extent of ecstasy use (presumably total number of lifetime doses) was negatively correlated with extent of transporter binding, with greater extent of use associated with less serotonin transporter binding.
Results – No Differences Found: Serotonin binding in the temporal cortex and the thalamus, as measured through [11C]McN-5652 binding, was similar for ecstasy users and non-users. Correlations – Time between last use and study day was not related to number of serotonin transporter sites, as measured through [11C]McN-5652 binding.
Overall Effects: When measured via PET with the radioligand [11C]McN-5652 (specific for the serotonin transporter site), ecstasy users had fewer serotonin binding sites than non-user controls. Number of serotonin transporter sites was reduced in a global comparison of ecstasy users and non-users, and number of serotonin transporter sites were also reduced in 10 of 12 ROIs (regions of interest), including most cortical and sub-cortical regions except for the temporal cortex and thalamus. Greater extent of ecstasy use was associated with fewer serotonin transporter sites, but number of days since last use was not associated with quantity of serotonin transporter sites.
Comments: This paper is one of the first to use PET imaging with a radioligand specific for the serotonin transporter site to compare serotonergic functioning in regular ecstasy users and non-user controls. While findings cannot be interpreted as irrefutable evidence of serotonergic neurotoxicity of ecstasy, they do support this hypothesis. Given some of the findings for region-specific differences in cerebral glucose utilization (Obrocki et al., 1999), cerebral blood volume (Reneman et al, 2000a,b), and presence of myo-inositol (e.g. Chang et al, 1999) in ecstasy users versus non-user controls, it is surprising that reduction in serotonin transporter sites is nearly global, affecting 10 of 12 regions of interest. Sample size is small, and so caution should be used in generalizing to the population at large.

McCann et al. (1999). Altered neuroendocrine and behavioral responses to m-chlorophenylpiperazine in 3,4-methylenedioxymethamphatemine (MDMA) users.

McCann, U. D., Eligulashvili, V., Mertl, M., Murphy, D. L., & Ricaurte, G. A. (1999). Altered neuroendocrine and behavioral responses to m-chlorophenylpiperazine in 3,4-methylenedioxymethamphatemine (MDMA) users. Psychopharmacology, 147, 56-65.

Purpose: Pharmacological challenge: To determine whether differences between ecstasy users and non-user controls would be revealed after administering the mixed serotonin agonist mCPP, with differences presumably referring to changes in serotonergic function after regular ecstasy use. Specific hypothesis tested – that if ecstasy users had sustained serotonergic injury, they would exhibit altered neuroendocrine and behavioral responses to mCPP. (Does not specify nature of difference).
Design: Non-experimental (retrospective) 2-group between groups design, wherein drug-free ecstasy users were compared with matched non-user controls on their physiological and subjective responses to mCPP (.08 mg / kg in 20 cc NS). Drug use (ecstasy use versus non-use) was a between-subjects factor. All subjects received mCPP and completed self-report measures of subjective drug effects for mCPP. Design of mCPP Administration – mCPP was administered via a placebo controlled, single-blind, fixed order design, with all subjects receiving saline at Time 1 and mCPP at time 2.
Subjects: 25 regular ecstasy users and 25 non-user controls. Information not provided on recruitment for ecstasy users, but another related study used advertisements in newspapers and the internet and self-referrals. Non-user controls were recruited via advertisements. Matching – On gender, age, education and use of other drugs.
Criteria for Inclusion, Ecstasy Users – Having used ecstasy at least 25 times over lifetime. Non-users – No past or current use of ecstasy, though use of other psychoactive drugs permitted. All Groups – Absence of past or current major medical or psychiatric illness as assessed through physical examination and psychiatric interview, ECG and standard urinary and blood analyses. Abstinence from all

psychoactive drugs for 3 weeks prior to study period, with compliance verified by urinary and blood screening for drugs on day of admission to study. Sample in this study appears to be similar to the sample used in McCann et al, 1999b.
Drug Use Parameters – Ecstasy Users – On average, ecstasy users reported that they took ecstasy on 196 ± 24 occasions over the lifetime (30 – 400 times), and that the average dose per occasion was approximately 3.2 ± 2.8 tablets (1-12.5 tablets). Ecstasy users reported that on average, they took ecstasy 5 ± 1 times a month (.6 – 11 times monthly) and that they had used ecstasy for an average of 60 ± 36 months (12 – 168 months). The average period between the last use of ecstasy and the first study day was 98 ± 203 days (21- 973 days). Other drugs reportedly used by ecstasy users: Cannabis (25 / 25), LSD, other hallucinogens (24 / 25), amphetamines (24 / 25), cocaine (23 / 25), solvents (18 / 25), sedative hypnotics (19 / 25), opiates (14 / 25), PCP, related drugs (5 / 25). Non-users – Other drugs reportedly used by non-users: cannabis (20 / 25), LSD, other hallucinogens (11 / 25), amphetamines (10 / 25), cocaine (10 / 25), opiates (10 / 25), sedative hypnotics (7 / 25), solvents (7 / 25), PCP, related drugs (4 / 25)
Group Demographics and Matched Variables – Ecstasy users were matched with non-user controls on gender and approximately matched on age and education. Gender, as M / F ratio – Ecstasy users, 17 / 8: non-users, 17 / 8. Age. Average age of ecstasy users = 26.92 ± 1.95 (men, 28 ± 4, women, 27 ± 2, no range provided). Average age of non-users = 30.36 ± 1.84 (men, 28 ± 2, women, 34 ± 4, no range provided). Education Level, in years - Ecstasy users, 13.36 ± .59: non-users, 15.28 ± .42. Use of Other Drugs – While both groups had tried the same types of drugs, save ecstasy, with the same proportion of each group generally using each drug, a smaller number of non-users had tried each drug when compared with ecstasy users in every case (see above). Other Variables – Ethnic / racial make-up of ecstasy users, 23 White, 1 African American, 1 "other: non-users, 15 White, 6 African American, 4 "other." Past psychiatric history – Ecstasy users, dysthymia = 1, PTSD = 1: Non-users, dysthymia = 0, PTSD = 3.
Measures: Neuroendocrine Response to mCPP – Fasting subjects received placebo infusion at Time 1 and (approximately 2 h later) received mCPP infusion, with subjects believing randomized presentation of drug. Plasma cortisol and prolactin measured from blood samples drawn at 30 and 15 min pre-drug and 30, 60 and 90 min post-drug, with drug either placebo or mCPP. Cortisol and prolactin concentrations measured via immunoassays.
Mood – Lader's Mood Scale and 8 author-generated 100-mm visual analog scales (VAS) measuring mood states, with each measure administered at 15, 30, 60 and 90 min post-drug (either placebo or mCPP), and all measures administered at baseline (before placebo).
Panic Symptoms – Measured via NIMH Panic Symptoms Scale, administered at baseline and 90 min post-drug (placebo or mCPP). Subjects asked to rate symptoms "at their worst" as mild, moderate or severe; presence of panic attacks also recorded within each group.
Self-reported Drug Effects ("Side Effects") – Measured via NIMH Self-Rating Symptom Scale, measuring emotional and physiological drug effects and author-devised 21 item questionnaire designed to measure self-reported physical effects, with measures administered at baseline (pre-placebo) and at 15, 30, 60 and 90 min post-drug (placebo or mCPP).
Analyses: Neuroendocrine Response to mCPP – Only male subjects included in analyses of cortisol and prolactin response to mCPP. Cortisol and prolactin response analyzed with a repeated measures ANCOVA, with drug use (ecstasy user versus non-user) as a between-group factor, drug infusion (placebo versus mCPP) and time (time of sample) as within-subjects factors and with one covariant (baseline cortisol or prolactin). Post-hoc comparisons made via Bonferroni method and p. set at .05. Correlates made between "extent of ecstasy use" (definition unspecified, but may refer to overall lifetime occasions or estimated cumulative dose) and prolactin response to mCPP infusion.
Mood – Mood analyzed via repeated measures ANCOVA with one between-group factor, with drug use (ecstasy user versus non-user) as between-group factor and with drug infusion (placebo or mCPP) and time (time of sample) as within-subjects factors, and with baseline mood measures as covariates. Post-hoc comparisons made via Bonferroni method, with p. set at .05.

Panic Symptoms – Subjects scored positively on panic symptom scale if they rated 4 or more panic-related symptoms as moderate or severe. Ecstasy users compared with non-users using Fisher's exact test, with comparisons made at placebo and after mCPP infusion.
Self-reported Physiological Effects ("Side Effects") – Self-reported side effects analyzed via repeated measures ANCOVA, with drug use (ecstasy use versus non-use) as a between-group factor and with drug infusion (placebo or mCPP) and time (time of sample) as within-subjects factors, and with baseline side effect / symptom measures as covariates. Post-hoc comparisons made via Bonferroni method, with p. set at .05.
Results – Significant Differences: Neuroendocrine Response to mCPP – All findings relating to neuroendocrine response to mCPP refers to analyses employing male subjects only. Baseline cortisol was lower in ecstasy users than in controls. Cortisol response to mCPP infusion blunted in ecstasy users compared with controls (lower cortisol after mCPP). Prolactin response to mCPP infusion was blunted in male ecstasy users compared with same-sex controls.
Mood – Lader Mood Scales: Ecstasy users had higher scores on Lader "attentiveness" scale at baseline than non-users. After mCPP infusion, ecstasy users rated selves higher than non-user controls on Lader Mood "content," "energetic," "happy," and "quick-witted" scales. Overall, ecstasy users rated mood more positively than did non-users after mCPP. Ecstasy users rated themselves higher on Lader Mood "alert," "content," "amicable," "tranquil," "quick-witted" after mCPP, with scale ratings increasing over time after mCPP infusion, but not after placebo. Analyses using peak changes from baseline found that after placebo, ecstasy users rated selves higher on Lader Mood "interested" but on no other scales. After mCPP infusion, ecstasy users rated selves higher on 11 of 16 Lader Mood scales compared with controls.
VAS: After mCPP infusion, ecstasy users rated selves less sad and less tired on VAS measures when compared with non-user controls. When ecstasy users and non-users were compared on peak change scores after mCPP, ecstasy users rated selves as less tired and less sad on VAS compared with controls.
Panic Symptoms – Non users were more likely to meet criteria for panic attacks than were ecstasy users after mCPP infusion. 1 ecstasy user and 8 controls experienced a panic attack after mCPP infusion.
Drug Effects, "Side Effects" – NIMH Self-Rating Scale: At baseline, ecstasy users rated themselves as more "elated" and less" worried" than non-user controls. After mCPP, ecstasy users had higher scores on "elated" and lower scores on "sad," "slowed down" "uncomfortable mentally" and "worried." Overall ecstasy users reported more pleasant effects after mCPP than did non-users, and fewer unpleasant effects, and the same pattern of self-ratings was true when ratings were compared over time of sample (30, 60, 90 min post-drug). After placebo, ecstasy users only differed in self-rating of "feel mistrustful or suspicious," with direction of difference unspecified. Physical Symptoms: Ecstasy users differed from non-users on ratings of "dry mouth," (lower rating), "nausea" (lower rating) and "poor appetite" (no information provided, probably lower rating). After mCPP infusion, ecstasy users reported less of these symptoms than did non-users: drowsiness, poor appetite, increased appetite, stiffness, tiredness, weakness. After mCPP infusion, ecstasy users reported more sexual thoughts or interest than did non-users.
Results – No Differences Found: Neuroendocrine Measures – All findings refer to analyses employing male subjects only. No difference in plasma cortisol values between male ecstasy users and same-sex non-users after placebo. There were no differences between the 2 groups in prolactin concentration at baseline, or in prolactin response to placebo. Extent of ecstasy use was not correlated with changes in prolactin after mCPP or with changes in cortisol after mCPP, with extent of ecstasy use undefined; in prior studies, defined as total lifetime occasions used). Ecstasy users and non-users had similar plasma mCPP values.
Mood – Lader Mood Scales: Ecstasy users and non-users did not differ on all other Lader Mood scales (clear-headed, content, energetic, gregarious, happy, interested, proficient, relaxed, strong, tranquil) at baseline. After mCPP, ecstasy users and non-users rated selves similarly on some (unspecified) Lader Mood scales. When peak change from baseline analyzed after placebo, ecstasy users and non-users rated selves similarly on all Lader Mood scales except "interested," and after mCPP, ecstasy users and non-users rated selves similarly on 4 of 16 Lader Mood scales. VAS: There were no differences between

ecstasy users and controls on all VAS at baseline or after placebo. After mCPP, ecstasy users and non-users provided similar VAS ratings on 6 (undescribed) VAS scales.
Panic Symptoms – There were no differences between ecstasy users and non-users on number of panic symptoms after placebo. No subjects from either group experienced a panic attack after placebo.
Drug Effects and Side Effects – NIMH Self Rating Scale: Ecstasy users and non-users did not differ in their self-ratings on 19 (undescribed) other items on the NIHM Self-Rating measure. Ecstasy users did not differ from non-users on 23 of the 24 items on the NIMH self-Rating Scale or any of 6 sub-scales.
Physical Symptoms: Ecstasy users and non-users reported a similar number of physical symptoms after placebo and baseline on 23 of 26 items. After mCPP, ecstasy users and non-users did not differ in their reports of experiencing 19 other physical symptoms on the NIMH Self-Rating scale.
Overall Effects: Prolactin and cortisol response to mCPP was blunted in ecstasy users, and this remained true even though ecstasy users had lower cortisol levels at baseline. Differences in neuroendocrine response to mCPP could not be explained via plasma mCPP level, as they were similar in both groups. However, extent of ecstasy use was not associated with extent of blunted prolactin or cortisol response after mCPP. Ecstasy users were more likely to experience mCPP as producing positive effects, such as alertness, contentedness and feeling quick-witted. They were less likely than non-users to report feeling tired or sad after mCPP, and they were less likely than non-users to report feeling slowed down, mentally uncomfortable or stiff. While the two groups did not differ in reports of panic symptoms at placebo, non-users were more likely than users to report panic symptoms and to experience panic attacks after mCPP infusion. Non-users reported a greater number of unpleasant physical symptoms after mCPP infusion, such as weakness, nausea and drowsiness, while ecstasy users reported fewer negative symptoms and greater sexual thoughts after mCPP. Since ecstasy users also rated themselves as less "worried" and more "elated" in general, and described their mood as more positive generally, they may have had fewer concerns about the effects of mCPP than the non-user controls. The authors' hypothesis was partially confirmed. Ecstasy users demonstrated blunted neuroendocrine response to mCPP, and their experience of the subjective effects of mCPP was different from that reported by non-users. However, the hypothesis is bi-directional, and did not specify expectations about the nature of the predicted change. The results do not rest on confirmed serotonin injury, as stated in the hypothesis, as serotonin injury has only been implied via by blunted neuroendocrine response to mCPP challenge, and not confirmed.
Comments: This paper attempts to replicate and expand upon earlier findings comparing ecstasy users with non-user controls on a challenge with a serotonin releaser. (An earlier study used d-fenfluramine challenge, and the subjective effects of the challenge drug were not measured in that study). Neuroendocrine responses are measured in male subjects only, because the authors were concerned with fluctuations in prolactin related to the menstrual cycle. The authors propose that the differences in neuroendocrine and behavioral responses to mCPP in ecstasy users are evidence for altered serotonin systems. The major alternative hypotheses they mention are greater exposure to drugs and greater sensation seeking in ecstasy users. However, it is also possible that ecstasy users may have reported a "conditioned" response to mCPP, as some of its physical effects are similar to those reported for ecstasy. Non-users, who were specifically selected for lack of experience with ecstasy, would not have "learned" to associate these physical effects with elevated mood or positive effects. Some of the individuals participating in this study also participated in a paper from the same year that assessed cognitive performance.

McCann et al. (1999). Cognitive performance in 3,4-methylenedioxymethamphetamine (MDMA) users: A controlled study.

McCann, U., Mertl, M., Eligulashvili, V. & Ricaurte, G. A. (1999). Cognitive performance in 3,4-methylenedioxymethamphetamine (MDMA) users: A controlled study. Psychopharmacology, 143, 417-425.

Purpose: Cognitive function (general): To examine whether ecstasy use affects other cognitive functions besides or in addition to visual and verbal memory and to see whether cognitive functions other than those mediated by the serotonin system might be affected by regular ecstasy use
Design: Non-experimental (retrospective) 2-group between-subjects design where drug-free ecstasy users were compared with matched non-user controls. Drug use (ecstasy use versus no use) served as a between-subjects factor. All subjects completed test battery designed to assess cognitive functions. (Test administration was part of a more extensive study of neuroendocrine and other functions in ecstasy users and non-users).
Subjects: 22 regular ecstasy users recruited by word of mouth / self-referral and 22 non-user controls recruited via local advertisements in the Baltimore / Washington DC area. Matching – On age, gender, education and use of other drugs. Sample seems to be similar to that used in McCann et al, 1999a. Criteria for Inclusion, Ecstasy Users – Having used ecstasy at least 25 times over lifetime. Non-users – No past or current ecstasy use, though use of other psychoactive drugs permitted. All Groups – Absence of past or current major medical or psychiatric illness as assessed through physical examination and psychiatric interview, ECG and standard urinary and blood analyses. Abstinence from all psychoactive drugs for 3 weeks prior to study period, with compliance verified by urinary and blood screening for drugs on day of admission to study. (Nicotine use permitted before and during study to avoid effects due to nicotine withdrawal).
Drug Use Parameters – Ecstasy Users – On average, ecstasy users reported that they took ecstasy on 215 ± 33 occasions over a lifetime (30 – 725 times), and that the average dose per occasion was approximately 2.7 ± .4 tablets, or 272± 40 mg (1-10 tablets). Ecstasy users reported that on average, they took ecstasy 5.72 ± .61 times a month (.8 – 15 times monthly) and that they had used ecstasy for an average of 54.24 ± approx. 9 months (12 – 168 months). The average time since last use of ecstasy and the first study day was 97.37 ± 45.78 days (21- 1029 days). Other Drugs – Other drugs reportedly used by ecstasy users: Cannabis (22 / 22), LSD, other hallucinogens (22 / 22), amphetamines (21 / 22), cocaine (21 / 22), solvents (17 / 22), sedative hypnotics (15 / 22), opiates (13 / 22), PCP, related drugs (6 / 22). Non-users – Other drugs reportedly used by non-user controls: cannabis (19 / 23), LSD, other hallucinogens (11 / 23), amphetamines (10 / 23), cocaine (10 / 23), opiates (10 / 23), sedative hypnotics (7 / 23), solvents (7 / 23), PCP, related drugs (4 / 23).
Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender, and approximately matched on age, education level and use of other drugs. Gender, as M / F ratio – Ecstasy users, 15 / 7: Non-users, 16 / 7. Age. – Ecstasy user average age = 26.23 ± 1.99 (range not provided). Non-user average age = 30.35 ± 1.98. (Non-users older than ecstasy users). Education Level, in years: Ecstasy users had, on average, 13.36 ± .63 years, non-users had 15.22 ± .45 years. Use of Other Drugs – Both ecstasy users and non-users had tried other psychoactive drugs, but in nearly all cases, a greater number of ecstasy users had tried other drugs than had non-users. Only use of opiates and PCP roughly equivalent in both samples.
Measures: CSF Monoamine Metabolites – CSF extracted through lumbar puncture (Day of study and time of puncture not provided). Monoamine metabolites in CSF measured via high performance liquid chromatography with electrochemical detection. Metabolites measured were 5HIAA, HVA and MHPG. Samples were assayed without awareness of participant drug history.
Tests of Cognitive Function – Measured via Walter Reed Army Institute of Research Performance Assessment Battery (WRAIR-PAB), a computerized test battery designed for testing people with wide range of reading and arithmetic skills, including people who only possess basic skills. This test battery contains: Time Wall task (time estimation), Serial Add and Subtract (machine-paced mental arithmetic), Logical Reasoning (self-paced, subjects indicate which of two target statements is incorrect), Manikin task (visuospatial rotation, subject indicates hand that a human figure is using to hold target), Code Substitution (similar to WAIS Digit Symbol: self-paced, indicate learn number-code correspondence, then translate code without key for maximum points, but can press button to view key), Matching to Sample (Pick 1 of 2 visual arrays that match previously presented target), and Delayed Recall (At conclusion of

test battery, perform Code Substitution again without code). WRAIR-PAB administered 3 times daily for all 5 study days, with test battery taking approximately 20-30 min to complete.
Analyses: CSF Monoamine Metabolites – Analysis of 5HIAA in ecstasy users and controls compared with 2-tailed student's t-test. CSF 5HIAA value also correlated with peak accuracy, speed and "throughput" scores (see below) on all 7 cognitive tasks.
Tests of Cognitive Function – Analyses excluded test performance on 4th day of study due to administration of mCPP on 4th day. All 3 daily administrations of the WRAIR-PAB were averaged within each day, producing 3 time points (1 per day). Baseline = Performance on Day 1, learning curve = performance on Day 2 and peak = Performance on Day 3. Data then analyzed via 2(Drug use: ecstasy user versus non-user) x 3(Time: Day 1 vs. Day 2, Day 3) repeated measures ANOVA, with drug use serving as between-group factor and time of administration as within-subjects factor. Post-hoc comparisons made via Bonferroni method. Comparisons also made on speed, accuracy and "throughput" score, where throughput = number of questions answered per minute (speed) x number of correct answers (accuracy). If significant effects due to drug use were found on any one task, those test scores were further analyzed separately for speed and accuracy of response. Regressions – Baseline (Day 1) and peak (Day 3) performance scores (accuracy, speed, throughput) regressed on drug use status, lifetime (total) ecstasy dose, weekly dose and monthly dose.
Results – Significant Differences: CSF Monoamine Metabolites – Ecstasy users and non-user controls differed on amount of CSF 5HIAA, with ecstasy users < controls.
Tests of Cognitive Function – Ecstasy had lower test scores overall on the Logical Reasoning and the Code Substitution task (for all 3 days). Ecstasy users had lower test scores on Serial Add and Subtract on Learning (Day 2) and Peak (Day 3) days. Ecstasy users had lower test scores for Delayed Recall at Baseline (Day 1), but not for Learning or Peak days. Accuracy – Ecstasy users were less accurate (made more errors) on Code Substitution and Delayed Recall on Baseline day. Speed – Ecstasy users performed the Serial Recall task more slowly on Learning (Day 2) and Peak (Day 3) days than did non-user controls. Regression – Total lifetime number of ecstasy doses was associated with performance on Code Substitution task only, with greater number of doses associated with lower speed and "throughput" scores on the Peak day (Day 3).
Results – No Differences Found: CSF Monoamine Metabolites – Ecstasy users and non-user controls had similar amounts of CSF HVA and MHPG. CSF 5HIAA values were found to be unrelated to task performance on any of the 3 study days measured.
Tests of Cognitive Function – Performance measured on Time Wall, Manikin and Matching to Sample tasks were similar in ecstasy users and non-users, with similar performance seen on all 3 days (baseline, learning and peak). Ecstasy users and non-users had similar Baseline (Day 1) performance scores on Serial Add and Subtract task. Ecstasy users had similar scores on Learning and Peak days on Delayed Recall task. Accuracy – Ecstasy users were as accurate on Serial Add and Subtract and Logical Reasoning tasks as non-users (members of both groups made similar numbers of errors). Speed – There were no differences between speed of performance for ecstasy users and controls for Code Substitution, Delayed Recall or Logical Reasoning. Regression – There were no associations (positive or negative) between performance on all other WRAIR-PAB tests and total number of ecstasy doses, weekly dose or monthly dose of ecstasy.
Overall Effects: Ecstasy users had comparatively less 5HIAA, a serotonin metabolite, in CSF than did non-user controls. When compared on a test battery designed to measure cognitive performance, it was found that ecstasy users performed worse on all testing days on two of seven tests (Logical Reasoning and Code Substitution). Ecstasy users performed poorly on two other tests, but only on some testing days. While ecstasy users did less well on Delayed Recall (performing the Code Substitution task again, without code, at the end of the test battery) on the first day, the two groups maintained similar performance on Days 2 and 3. On the other hand, both groups showed similar performance on Serial Add and Subtract for Day 1, but ecstasy users performed less well (or non-users performed better) on Days 2 and 3. While ecstasy users had lower CSF 5HIAA and performed less well on certain tasks, amount of 5HIAA was not correlated with task performance on any of the 3 days. Decrements in performance by

ecstasy users on some tests (Code Substitution, Delayed Recall) was due to greater number of errors on baseline day, whereas poor performance on another task (Serial Add and Subtract) was due to slower responses compared to those of non-users on Days 2 and 3. The two groups did not differ on task performance for a task of visuospatial rotation (Manikin task), task of time estimation (Time Wall) or a Matching to Sample task. Total number of lifetime doses was negatively correlated with peak performance on Code Substitution, but it not with any other task, and number of days since last use was not associated with performance on any of the WRAIR-PAB tests. The lack of association between lower levels of 5HIAA and decrements in test performance can be interpreted as evidence that regular ecstasy use affects cognitive functions not directly mediated by the serotonin system. Decreased performance on at least one test (Logical Reasoning) suggests decrements in areas outside of verbal or visual memory, but the number of functions assessed by any one test is less clear.
Comments: This paper appears to be a combined replication of several studies performed by the same authors, including a comparison of CSF monoamine metabolites and performance on cognitive tests. In contrast to a previous study measuring monoamine metabolites, this study only found decreased 5HIAA in ecstasy users, and it did not find gender differences with respect to HVA concentration. The findings in this paper can be interpreted as evidence for a dissociation between the effects of regular ecstasy use on the serotonin system and on cognitive function. However, evidence concerning deficits in cognitive function outside of memory seems less certain. It would appear that performance on 2 of the 4 tests relies upon memory (Code Substitution and Delayed Recall) and performance on a third test might involve immediate recall (Serial Add and Subtract). This seems to leave only one task demonstrating performance decrements in ecstasy users that is truly unrelated to memory (Logical Reasoning.) The authors remark that differences in performance are subtle, and that ecstasy users do not report any difficulties with everyday functioning. As was true in other user comparison studies performed by the same author, use of other drugs in ecstasy users is much higher than drug use in the non-user sample.

Morgan (1998). Recreational user of "Ecstasy" (MDMA) is associated with elevated impulsivity (Study 1).

Morgan, M. J. (1998). Recreational user of "Ecstasy" (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology, 19, 252-264. (Study 1).

Purpose: Neuropsychological, including mood, personality and cognitive function: To determine whether a history of recreational ecstasy use is specifically associated with changes in functional domains believed to be associated with serotonin (5HT) function by comparing ecstasy users with polydrug user and no drug user controls.
Design: Non-experimental (retrospective) 3-group between subjects (across groups) design, with ecstasy users compared with 2 groups of matched controls, polydrug users who had never used ecstasy (polydrug user controls) and individuals who had never used illicit drugs (no-drug user controls), with drug use as a between subjects factor. All groups were compared on measures of mood, anxiety, anger / hostility, impulsivity (psychometric and behavioral) and cognitive function, and all subjects completed questionnaires and test batteries.
Subjects: 16 ecstasy users, 12 polydrug users and 16 no-drug users residing in the Swansea (Wales) area, with members of all 3 groups recruited via posters and advertisements and by word of mouth. Matching – On gender, age, height, weight, education level and estimated IQ (NART score).
Criteria for Inclusion, Ecstasy Users – Had used ecstasy on at least 20 separate occasions. Polydrug Users – No past or current use of ecstasy, but drug use pattern that is otherwise similar to that of ecstasy users. No-drug controls – No prior history of ecstasy use and no use of other drugs save alcohol and nicotine. All Groups – No past or current major medical or psychiatric illnesses, not pregnant, and no alcohol or substance abuse. No more than 25 incorrect answers on NART and attending university or being a university graduate. No information on required drug-free period, but Morgan, 1999 (containing

Study 2 data) required subjects to abstain from psychoactive substances on the study day, with compliance verified via self-report only.
Drug Use Parameters – Ecstasy Users – On average, ecstasy users reported that they had taken an average of 35.6 ± 17.5 tablets over the lifetime (range not provided), and that the average dose used per occasion was 1.12 ± .34 tablets (range not provided). Ecstasy users reported that on average, they took ecstasy 2.94 ± .93 times a month (range not provided) and that they had used ecstasy for an average of 25.44 ± 16.32 months (range not provided). The average period between the last use of ecstasy and the first study day was 20.4 ± 33.6 days (range not provided). The average maximum amount of ecstasy used on 1 occasion, in tablets = 2.28 ± 1.25 tablets. Other drugs used by ecstasy users, reported as average amount per wk / per month / per year, and duration of use, in years: Alcohol, 67.12 units per month, duration 8.31 years, cigarettes, 64.81 per wk, no duration information, cannabis, 59.75 joints per month, 5.69 years, amphetamines, 17.2 grams per year, 2.56, LSD, 6.19 trips per year, no duration information. Polydrug Users – Drug use reported as average amount per wk / per month / per year, and duration of use, in years: Alcohol, 85.67 units per month, duration 7.25 years, cigarettes, 71.67 per wk, no duration information, cannabis, 50.5 joints per month, 4.67 years, amphetamines, 19.2 grams per year, 2.42, LSD, 18.33trips per year, no duration information. Both MDMA users and polydrug users also used psilocybian mushrooms and benzodiazepines infrequently. Ecstasy users more likely to use cocaine than polydrug users, though use was low (exact figures not presented here).
Group Demographics and Matched Variables – Ecstasy users, polydrug users and no-drug users were matched on gender, age, weight, height, education level and NART score. Ecstasy users were matched with polydrug users on use of other (non-ecstasy) drugs. Gender, as (approximate) M / F ratio: Ecstasy users, 8 / 8: polydrug users, 7 / 5: no-drug users, 7 / 9. (Author presented data as average of binary coded data where 1 = male and 2 = female, with ecstasy users = 1.50, polydrug users = 1.42, no-drug users = 1.62.) Age. Ecstasy users' average age = 20.94 ± 1.88, polydrug users average age = 20.25 ± 1.48, no-drug users average age = 21.87 ± 6.09. Height, Weight – Height in cm, weight in kg: Ecstasy users, 170 ± 10 cm, 61.26 ± 9.63 kg, polydrug users, 172.3 ± 7.65 cm. 62.22 ± 7.18 kg, no-drug users, 171.3 ± 9.99 cm, 69.15 ± 12.91 kg. Education Level – Ecstasy users had approximately 15.5 years education, polydrug users had approximately 14.5 years education and no-drug users had approximately 14.5 years education. (Original data coded 1 = passed basic high school exam, 2 = passed advanced high school exam, 3 = university degree, with ecstasy users = 2.94 ± .25, polydrug users = 2.67 ± .49, no-drug users = 2.69 ± .6).
Estimated IQ (from NART Score) – Ecstasy users = 114.9 ± 5.6, polydrug users = 112.3 ± 4.76, no-drug users = 113.5 ± 6.41
Measures: Mood – Current (state) mood measured via author-devised self-report questionnaire with 9 items, with some items addressing positive mood (happy, joyful) and others addressing negative mood (depressed, frustrated). Anxiety was measured via STAI and anger was measured with the State-Trait Anger Expression Inventory (STAXI).
Personality: Psychometric – Trait anxiety measured via STAI and trait anger / hostility measured through STAXI. Impulsiveness, venturesomeness (risk taking) and empathy measured via IVE.
Executive Function / Cognitive Function – Measured through the Cambridge Neuropsychological Test Automated Battery (CANTAB), a suite of tests performed on touch-screen computers. CANTAB tests intended to assess cognitive function associated with frontal lobe function. The CANTAB includes:
Tower of London (TOL) – Variation of "Tower of Hanoi" puzzle. Subject asked to move balls from "pockets" on screen using the smallest number of moves, with each set presenting an increasingly difficult task (2 moves – 5 moves). TOL also compares "yoked control" where each step of self-generated solution is replayed and subject follows each move). Subjects scored on "number of excess moves" (more than minimum required), "proportion of perfect solutions" (number of solutions using minimum moves), 'initial thinking time" (time elapsed from presentation to first touch of screen), "subsequent thinking time per move" (time between first move and completion of problem). "Pure planning" scores calculated by subtracting simple movement time from "initial thinking" ("motor initiation") and "subsequent thinking" ("motor execution") time. Spatial Span – Test of visual working

memory. Subjects asked to reproduce sequence of events via touch-screen, with test terminated if subject unable to correctly reproduce all sequences at one level, with 3 presentations given for each level. Spatial span scored for highest possible span, number of sequence errors made and number of usage errors made (pressing a box not illuminated during presentation). TOL and Spatial Span tasks counterbalanced to prevent order effects.
Impulsivity, Behavioral Measure – Impulsivity measured via another CANTAB test, the Matching Familiar Figures Test (MFF20. Sample and 6 potential matches presented simultaneously, with only one correct response (identical match), and sample must be matched with target. If incorrect, asked to try again. Subjects scored on time to first response, the first alternative indicated and number of errors before correct response. Scores used in analysis were: mean latency to first response, total number of errors, and "I score, " calculated as Z score of Total Errors – Z score of Mean Latency Before First Response.
Analyses: All measures (mood, personality, cognitive function, impulsivity) analyzed via separate multiple analyses of variance (MANOVAs) with drug use (ecstasy versus polydrug versus no-drug) serving as between-subjects factor and each score serving as a dependent variable. Post-hoc comparisons made via Duncan's multiple range test.
Results - Significant Differences: Personality – Both ecstasy users and polydrug users were more venturous (risk-taking, novelty-seeking) than no-drug subjects (ecstasy users = polydrug users > no-drugs),
Impulsivity, Behavioral – There were differences in number of errors and in "I score" (impulsivity) due to drug use, with ecstasy users < polydrug users = no drug subjects.
Results - No Differences Found: Mood – No differences on the author-devised mood measure, with all 3 groups (ecstasy users, polydrug users, no-drugs) making similar responses. There were no differences in STAI (anxiety) scores due to drug use; STAI scores for ecstasy users, polydrug users and no-drug subjects did not differ. There were no differences in STAXI (anger / hostility) scores due to drug use (ecstasy users, polydrug users and no-drug subjects had similar scores).
Personality – As noted above, 3 groups did not differ in STAI (anxiety) or STAXI (anger / hostility) scores. There were no differences in "impulsiveness" or "empathy" scores of the IVE, with ecstasy users, polydrug users and no-drug subjects had similar scores.
Cognitive Function (Executive Function) – There were no differences in total spatial span, number of sequence errors or number of usage errors between all 3 groups (ecstasy users, polydrug users, no drugs). No difference in scores of "number of excess moves," "initial thinking time," "proportion of perfect solutions," or "thinking time per move," so that all 3 groups (ecstasy users, polydrug users and no drug subjects) performed similarly on TOL task.
Impulsivity, Behavioral - Ecstasy users, polydrug users and no-drug subjects did not differ in latencies to first response on MFF20.
Overall Effects: Ecstasy users, polydrug users who had never taken ecstasy and a set of controls without any history of drug use scored similarly on measures of mood and personality and on two measures associated with frontal lobe function. Specifically, they reported similar current mood states on a self-report questionnaire, and members of all 3 groups had similar levels of trait and state anxiety. None of the groups differed in degree of state or trait anger or hostility, and all three groups reported similar levels of impulsivity and empathy on a self-report measure. As might be expected, given their drug history, both polydrug users and ecstasy users scored similarly on a measure of venturousness. All three groups performed similarly on the "spatial span" and "Tower of London" tasks featured in the CANTAB, a test battery designed to measure frontal lobe function (apparently including attention, memory and executive function). However, when compared on the "Matching Familiar Figures" test, considered a behavioral measure of impulsivity, ecstasy users committed more errors than polydrug user or no-drug controls, and they had higher "impulsivity" scores on the MFF20.
Comments: Study 1 in this paper is as surprising for what it failed to find as it is for what it did find. While other studies have found altered mood or cognitive function in ecstasy users, the ecstasy users in this study only differed in impulsivity, and only when it was assessed via behavioral measure. The findings in this study suggest that behavioral measures may not be measuring the same construct tapped

by self-report measures. However, that does not mean that the behavioral measure is necessarily "better" than the self-report measure, as a task involving matching to sample could also serve as an assessment of visual search strategy or even of visual non-spatial memory. Differences in age and education were minimal in this study (in fact, all participants were either university students or graduates), reducing the potential influence of differences in educational level. Perhaps the lack of many differences between the 3 groups indicates that differences found in other studies may have arisen from other factors, such as differences in age, education or drug use patterns. A few individuals reported using ecstasy within a week of the study, so that the difference in impulsivity could potentially be due to residual drug effects.

Morgan (1998). Recreational user of "Ecstasy" (MDMA) is associated with elevated impulsivity (Study 2).

Morgan, M. J. (1998). Recreational user of "Ecstasy" (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology, 19, 252-264. (Study 2).

Purpose: Neuropsychological, including mood, personality and cognitive function: To determine whether preliminary findings concerning the effects of ecstasy use on various domains (including increased impulsivity) could be replicated in a second study using the same study design but with a larger sample.
Design: Non-experimental (retrospective) 3-group between subjects (across-groups) design, with drug ecstasy users compared with 2 groups of matched controls; polydrug users with no history of ecstasy use (polydrug user controls) and people with no history of illicit drug use (no-drug users), with drug use as a between subjects variable. All groups completed self-report measures of impulsivity and health complaints, and all groups underwent behavioral assessments of impulsivity.
Subjects: 25 ecstasy users, 20 polydrug (no ecstasy) users and 19 no-drug (drug-free) users residing in the Swansea (Wales) area, with members of all 3 groups recruited via posters, advertisements and word of mouth. Matching – On gender, age, education, height, weight, and estimated IQ. Ecstasy users and polydrug users approximately matched on use of other drugs, excluding ecstasy.
Criteria for Inclusion, Ecstasy Users – Having used ecstasy on at least 20 separate occasions. Polydrug Users -–No past or current use of ecstasy, but similar drug use histories to those reported by ecstasy users. No-drug Users – No past or current use of ecstasy and little or no past or current use of other psychoactive drugs, but similar on other matched variables to ecstasy users and polydrug users. All Groups – In good health, including absence of current or past major medical or psychiatric illness (verification unspecified, either through examination or through self-report). Absence of asthma, dyslexia and migraine, and no alcohol or opiate dependence, and not pregnant. Attending university or being a university graduate, making no more than 25 errors on the NART test. Abstinence from any psychoactive drug except for nicotine on the study day, with compliance verified by self-report on study day
Drug Use Parameters – Ecstasy Users – On average, ecstasy users reported that they had taken an average of 49.6 ± 33.2 tablets over a lifetime (20-160), and that the average dose per occasion was 1.47 ± .78 tablets (range not provided). Ecstasy users reported that on average, they took ecstasy 4.36 ± 1.15 times a month (range not provided) and that they had used ecstasy for an average of 49.4 ± 15.2 months (range not provided). The average period between the last use of ecstasy and the study day was 65.1 ± 85.7 days (range not provided). The average maximum amount of ecstasy used on 1 occasion, in tablets, 3.78 ± 2.17. Other drugs used by ecstasy users, reported as average amount per wk / month/ year, and duration of use, in years: Alcohol, 34.94 units per wk, 7.9 years, cigarettes, 65.8 per wk, 6.07 years, cannabis, 13.74 joints per week, 6.14 years, amphetamines, 1.97 grams per month, 4.46, psilocybe mushrooms, 204 per year, no duration information, LSD, 2.63 trips per year, 4.23 years, inhalants, 2.5 a month, no duration information, cocaine, 2.6 grams a year, no duration information. 8 subjects reported some use of benzodiazepines, 3 reported some use of barbiturates and 2 reported taking ketamine with ecstasy.
Polydrug Users – Average drug use per week / month/ year and duration of use per year: Alcohol, 43.25 units per wk, 8.67 years, cigarettes, 73.71 per wk, 6.17 years, cannabis, 9.31 joints per week, 5.17 years,

amphetamines, 1.2 grams per month, 2.65, psilocybe mushrooms, 124 per year, no duration information provided, LSD, 2.95 trips per year, 2.12 years, inhalants, 1.13 "hits" per month, no duration information, cocaine, .3 grams a year, no duration information.
Group Demographics and Matched Variables – Ecstasy users, polydrug users and no-drugs groups matched on gender, age, height, weight, and estimated IQ (via NART score). Ecstasy users and polydrug users matched on use of other drugs (except ecstasy). Gender, as approximate M / F ratio – Ecstasy users, 13 / 12, polydrug users, 8 / 12, no-drug controls, 8 / 11 (see note for Study 1 on gender coding scheme: here, ecstasy users = 1.48, polydrug users = 1.70, no-drug = 1.63). Age. Ecstasy users, average age = 22.28 ± 2.48, polydrug users, average age = 23 ± 4.71, no-drugs, average age = 21.74 ± 2.94. Height, Weight – Height in cm, weight in kg: Ecstasy users, 173.3 ± 8.88 cm, 65.1 ± 9.9 kg, polydrug users, 170.3 ± 8.42 cm, 62.2 ± 9.3 kg, no-drugs controls, 172.3 ± 7.91 cm, 67.4 ± 10.8 kg. Education Level – Average number of years of education, in approximate years: Ecstasy users, 15.5 years, polydrug users, 15.5 years, no-drug controls, 14.5 years. (See note on "Study 1" for education level coding: ecstasy users = 2.8 ± .5, polydrug users = 2.95 ± .22, no-drugs = 2.68 ± .58). Estimated IQ, as derived from NART score: Ecstasy users = 113.1 ± 3.13, polydrug users = 116.1 ± 5.06, no drug controls = 115.1 ± 5.15. Ecstasy users have lower NART scores (hence lower estimated IQ) than members of the other 2 groups.
Measures: Mood / Health Complaints – Measured via GHQ, a measure of current psychological health, containing 12 mood and health-related items.
Personality Traits – Measured via IVE, a self-report measure with scales for empathy, impulsivity and venturesomeness.
Cognitive Function – Measured via Tower of London, described in "Study 1" (Solve puzzle in minimum of moves, thinking time, errors and planning measured). TOL administered on twice, with the MFF20 placed between the 2 administrations, to see whether groups could be differentiated after subjects had grown familiar with task. Test of memory (Rivermead Behavioral Memory Test Battery) also employed, but method and results not described in this paper).
Impulsivity, Behavioral – Measured via Matching Familiar Figures (MFF20) described above (Subject matches stimulus to 1 among 6 targets, with latency to first response, number of errors and "I score" (impulsivity score) calculated for each subject.
Analyses: Same procedure described for Study 1. Data analyzed via MANOVA, with drug use as between-groups variable, and with post-hoc comparisons made with Duncan's multiple range test. Relationships between variables analyzed via Pearson correlation coefficient.
Results: Significant Differences: Mood / Mental Health – Ecstasy users and polydrug users scored lower on the GHQ than did no-drug subjects, but ecstasy users did not have significantly lower GHQ scores than no drug subjects. (Ecstasy users = polydrug users < no-drug controls). However, ecstasy user scores were lower than polydrug user scores.
Personality - Ecstasy users and polydrug users scored higher on measures of trait impulsivity and venturousness than did non-users, but ecstasy users did not have significantly higher impulsiveness or venturesomeness scores than polydrug users (ecstasy users = polydrug users > no-drugs).
.**Results: No Differences Found**: Personality – There were no between-group differences on empathy scores, with ecstasy users, polydrug users and no drug subjects scoring similarly.
Cognitive Function / Executive Function – No drug controls had a longer "initial thinking time" on the TOL than did ecstasy users or polydrug users, but only on the first administration of the TOL, and the difference was a trend only and did not reach statistical significance. There were no differences in "number of excess moves," "proportion of perfect solutions" or "thinking time per move" for either the first or the second administration of the TOL. Ecstasy users, polydrug users and no drug controls scored similarly on this measure.
Impulsivity, Behavioral Measure – Ecstasy users made a greater number of errors than did polydrug users on the MFF20, though ecstasy users' number of errors were not significantly different from the number of errors made by no-drug controls. Ecstasy users, polydrug users and no-drug controls did not differ on mean latency to first response or on "I score" on the MFF20.

Overall Effects: Ecstasy users and polydrug users had higher scores on trait impulsivity and venturousness than no-drug users. (In study 1, ecstasy users and polydrug users only had higher venturesomeness scores). Ecstasy users and polydrug users scored significantly lower on a measure of psychological health than no-drug users. All three groups performed equally well on the Tower of London (TOL) task, though there was a tendency for non-drug users to take more time thinking before the first move during the first, but not the second, administration of the TOL. Ecstasy users made more errors than polydrug users on the MFF20, a behavioral measure of impulsiveness, but the number of errors they made was not significantly different than the number of errors made by no-drug controls.
Comments: Some of the findings first seen in Study 1 are confirmed in this replication, while there are differences in other areas. Ecstasy users are again found to be more impulsive than the no-drug group, but Study 2 results are less certain, since ecstasy users did not differentiate themselves from polydrug users on the self-report measure of impulsivity and they did not have higher "I scores" than the other 2 groups. The lower scores on a measure of psychological health found in this study are more consonant with findings in other studies, yet they stand in contrast with the lack of difference in current mood state reported in Study 1. Even after employing larger samples and a greater number of ecstasy users who had not recently used the drug before the study, Study 2 finds differences between the self-report and behavioral measures of impulsiveness. However, in this study, it seems that there is slightly more similarity between the self-report and the behavioral measure of impulsiveness.

Morgan (1998). Recreational user of "Ecstasy" (MDMA) is associated with elevated impulsivity (Analysis of pooled data from Studies 1 and 2).

Morgan, M. J. (1998). Recreational user of "Ecstasy" (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology, 19, 252-264. (Analysis of pooled data from Studies 1 and 2).

Purpose: Neuropsychological, with focus on impulsivity: To use the larger sample provided by pooling data from Study 1 and Study 2 to investigate the effects of ecstasy on impulsivity and cognitive function and to clarify the relationship, if any, between self-report and behavioral measures of impulsivity.
Design: Analysis using data pooled from Study 1 and Study 2, using a 2 (Study) x 3(Group) design. Both studies used retrospective 3-group designs with drug use (ecstasy use, polydrug use without ecstasy use or no drug use) as a between-subjects factor.
Subjects: 41 regular ecstasy users, 32 polydrug users with no past or current ecstasy use and 35 non-users residing in the Swansea area, with participants in all 3 groups recruited via local advertisements and word of mouth. Matching – See Study 1 and Study 2; subjects matched within study on gender, age, education level, height, weight, and estimated IQ. Ecstasy users and polydrug users approximately matched on use of other drugs, excluding ecstasy.
Criteria for Inclusion – See criteria used for including subjects in Study 1 and Study 2.
Drug Use Parameters – See information on drug use parameters within Study 1 and Study 2.
Group Demographics and Matched Variables – Ecstasy users, polydrug users and non-user controls matched on gender, age, education level, height, weight and estimated IQ, but matching took place within each study.
Measures: Personality Traits – Measured via IVE, as described above.
Impulsivity, Behavioral – Measured via MFF20, previously described (subject matches stimulus to 1 among 6 targets, with latency to first response, number of errors and "I score" calculated for each subject.
Cognitive Function / Executive Function – Measured via TOL, as previously described, (solve puzzle in minimum of moves, with thinking time, number of errors and planning measured). Only the first administration of the TOL in Study 2 used for pooled analysis.
Analyses: IVE scores, MFF20 scores and TOL scores analyzed via MANOVA, with a 2(study: study 1 versus study 2) x 3(Group: ecstasy users, polydrug users, no-drug users) between-factor design. Correlations performed with Pearson correlation coefficient.

Effects of Overall Ecstasy Consumption on Impulsivity - Using data pooled from both studies, ecstasy users divided on the basis of lifetime ecstasy consumption (in tablets) of 20-30 tablets (n = 15), 30-60 tablets (n = 10) and 60-160 tablets (n = 16). IVE impulsivity scores and MFF20 performance analyzed via 1-way ANOVA with lifetime ecstasy consumption as between-group variable.
Results – Significant Differences: Study Effects – The polydrug users and non-drug users of Study 2 made more errors on the MFF20 than did polydrug users and non-drug users in Study 1.
Personality Traits – Ecstasy users had higher impulsivity scores than polydrug users or no-drug controls (ecstasy users > polydrug users, non-users). Ecstasy users and polydrug users had higher scores on the Venturesomeness scale than did non-users (ecstasy users, polydrug users > non-users).
Impulsivity, Behavioral – Ecstasy users committed a greater number of errors and thus attained higher "I scores" on the MFF20 than either the polydrug users or no-drug controls (ecstasy users > polydrug users, non-users).
Effects of Overall Ecstasy Consumption on Impulsivity – Subjects with overall consumption of 30-60 tablets of ecstasy had higher scores on trait impulsivity than those who had taken 30 tablets or less.
Correlational Analyses – On the MFF20, "mean latency to first response" scores and total numbers of errors were negatively correlated (shorter latency associated with more errors).
Results – No Differences Found: Study Effects – Performance was similar for each of the 3 drug use groups across the 2 studies on the IVE, the TOL, and 2 scores on the MFF20 (Latency to 1st response and "I score"). This means that groups can be successfully combined across study (i.e. ecstasy users in study 1 with ecstasy users in study 2).
Personality Traits – Non-users, polydrug users and ecstasy users all scored similarly on the Empathy scale of the IVE.
Cognitive Function / Executive Function – Ecstasy users, polydrug users and no-drug controls all scored similarly on all of the TOL performance scores (number of excessive moves, thinking time, or planning time).
Impulsivity – Members of the 3 groups (ecstasy users, polydrug users, no-drug controls) did not differ on latency to first response on the MFF20.
Effects of Overall Ecstasy Consumption on Impulsivity – There were no differences on MFF20 performance between ecstasy uses who had taken 20-30 tablets, those who had taken 30-60 tablets those who had taken over 60 tablets.
Correlational Analyses – While "initial think time" in TOL was positively correlated with "mean latency to first response" in MFF20 before Bonferroni corrections, the two scores were no longer significantly correlated after Bonferroni method corrections used. There were no other significant correlations between IVE scores, TOL scores or MFF20 scores. Trait impulsivity measured via IVE was not correlated with "I score" or number of errors committed on the MFF20.
Overall Effects: Subjects from Study 1 and Study 2 could be safely pooled, as there was only one difference in performance across studies, with polydrug users and no-drug controls in Study 2 making more errors than did members of these groups in Study 1. Ecstasy users and polydrug users in the combined analysis had higher scores on the IVE venturesomeness scale than did non-drug users. The pooled group of ecstasy users had higher impulsivity scores than did polydrug users or no-drug controls, and they also demonstrated more impulsivity when performing the MFF20 task. There still were no differences in performance on the TOL task, said to be a test of executive function. When ecstasy users were categorized on the basis of lifetime tablet consumption, lifetime ecstasy consumption was related to trait impulsivity, as measured via IVE, but not to behavioral impulsivity, as measured through MFF20.
Comments: Aside from offering further confirmation of increased behavioral, and perhaps trait, impulsiveness in ecstasy users, analysis of the pooled data allows for an examination of the relationship between overall ecstasy use and degree of impulsiveness. Furthermore, the lack of a correlation between trait and behavioral measures of impulsivity suggests that the two measures are not tapping into the same construct. The combined analysis is notable for using relatively large sample sizes in a between-group comparison study. Employing a larger sample size and the addition of a group of polydrug user controls

gives strength to the findings of increased impulsivity, but not decreased executive function, in regular ecstasy users.

Morgan (1999). Memory deficits associated with recreational use of "Ecstasy" (MDMA).

Morgan, M. J. (1999). Memory deficits associated with recreational use of "ecstasy" (MDMA). Psychopharmacology, 141, 30-36.

Purpose: Cognitive function (Memory): To investigate whether a history of ecstasy use, and not polydrug use, is specifically associated with deficits in immediate and delayed recall by comparing test performance by ecstasy users, polydrug users who have not used ecstasy and people who have not used any illicit drugs on a measure of memory. Specific hypothesis tested: that ecstasy users would perform less well than polydrug user and non-user controls.
Design: Non-experimental (retrospective) 3-group between subjects (across groups) design wherein drug-free ecstasy users are compared with two groups of matched controls, one polydrug user group and one no-drugs user group. All subjects completed a test for immediate and delayed recall.
Subjects: 25 ecstasy users, 22 polydrug (no ecstasy) users and 19 no-drug (drug-free) users, with members of all 3 groups recruited via posters, advertisements and word of mouth. Matching – On gender, age, education level, height, weight, and estimated IQ. Ecstasy users and polydrug users approximately matched on use of other drugs, excluding ecstasy.
Criteria for Inclusion, Ecstasy Users – Having used ecstasy on at least 20 separate occasions. Polydrug Users -–No past or current use of ecstasy, but with drug use histories similar to those reported by ecstasy users. No-drug Controls– No prior history of ecstasy use, little or no past or current use of other psychoactive drugs, but similar on other matched variables to ecstasy users and polydrug users. All Groups – In good health, including absence of current or past major medical or psychiatric illness (verification unspecified, either through examination or through self-report), and not pregnant. Absence of asthma, dyslexia and migraine, and no alcohol or opiate dependence. Attending a university student or being a university graduate, Making no more than 25 errors on the NART test. Abstinence from any psychoactive drug except for nicotine on the study day, with compliance verified by self-report on study day.
Drug Use Parameters – Ecstasy Users – On average, ecstasy users reported that they had taken an average of 49.6± 33.2 tablets over the lifetime (20-160), and that the average dose per occasion was 1.47 ± .78 tablets (range not provided). Ecstasy users reported that on average, they took ecstasy 4.36 ± 1.15 times a month (range not provided) and that they had used ecstasy for an average of 49.4 ± 15.2 months (range not provided). The average period between the last use of ecstasy and the study day was 65.1 ± 85.7 days (range not provided). The average maximum amount of ecstasy used on 1 occasion, in tablets, 3.78 ± 2.17. Other drugs used by ecstasy users, reported as average amount per wk / per year, and duration of use, in years: Alcohol, 34.94 units per wk, 7.9 years, cigarettes, 65.8 per wk, 6.07 years, cannabis, 13.74 joints per week, 6.14 years, amphetamines, 23.68 grams per year, 4.32, psilocybe mushrooms, 203.6 per year, 2.44 years, LSD, 2.63 trips per year, 3.19 years, inhalants, 30.03 "hits," per year, 2.02 years, cocaine, 2.6 grams a year, 1.36 years. Polydrug Users – Average drug use per week / year and duration of use per year: Alcohol, 42.95 units per wk, 8.5 years, cigarettes, 67.3 per wk, 6.15 years, cannabis, 9.28 joints per week, 5.52 years, amphetamines, 12.09 grams per year, 2.73, psilocybe mushrooms, 112.3 per year, 1.25 years, LSD, 2.68 trips per year, 1.43 years, inhalants, 176 "hits," per year, 1.18 years, cocaine, .27 grams a year, .27 years. No Drug Controls – Average alcohol use, per wk = 14.97 units, duration of use in years, 5.79 and cigarettes, 36.75 per week, 3.18 years (1 non-user admitted 1 use of cannabis at least 1 year before study). Duration of LSD use longer in ecstasy users than in polydrug users, and some ecstasy users, but no polydrug users, had reported using benzodiazepines and barbiturates.
Group Demographics and Matched Variables – Ecstasy users, polydrug users and no-drug controls matched on gender, age, height, weight, education and NART score. Ecstasy users and polydrug users

matched for drug use, excepting ecstasy use. Gender, as approximate M / F ratio – Ecstasy users, 13 / 12: polydrug users, 10 / 12: no-drug subjects, 9 / 10 (Gender presented in text as "average" with 1 = M, 2 = F, but ratio for ecstasy users known from previous paper; Ecstasy users = 1.48, polydrug users = 1.68, non-users = 1.58). Age. Ecstasy users, average age = 22.28 ± 2.51 years: polydrug users, average = 22.86 ± 4.52 years: no-drug, average = 21.74 ± 2.94 years. Height, Weight, with height in cm and weight in kg – Ecstasy users, 172.3 ± 8.88 cm, 65.1 ± 9.9 kg: polydrug users, 170.3 ± 8.48 cm, 64.4 ± 14.2 kg: No-drug controls, 172.3 ± 7.91 cm, 67.4 ± 10.8 kg. Education Level – Ecstasy users, approximately 15.5 years (2.8 ± .5): polydrug users, approximately 15.5 years, (2.95 ± .21): no-drug, approximately 14.5 years (2.68 ± .58). Education level 1 = Basic high school exam, 2 = Advanced high school exam, 3 = University degree. NART Score – Average score for ecstasy users = 35.9 ± 2.52, average score for polydrug users, 39.1± 4.73, average score for no-drug user, 37.5 ± 4.15. When compared with polydrug users and no-drug users, ecstasy users were found to have significantly lower NART scores than the other 2 groups, indicating that they were not matched on this variable. Other Variables – 16 / 25 ecstasy users reported usually taking ecstasy when in a large group, 8 / 25 reported usually using ecstasy when in small groups and 1 / 25 reported usually using ecstasy when alone. 21 / 25 ecstasy users reported that there were long-term (sub-acute) side effects to ecstasy use, while 4 / 25 reported no long-term side effects. When asked whether they viewed ecstasy as safe, 5 / 25 responded "yes," 8 / 25 responded "no" and 12 / 25 responded "not sure."

Measures: Immediate and delayed recall measured via Rivermead Behavioural Memory Test (RBMT), with subjects writing down as much as they could recall from audiotaped story immediately after presentation and again 40-50 minutes after presentation, with subjects performing unrelated tasks between the measures. Recall scored by number of ideas correctly recalled.

Analyses: Recall scores analyzed via between subjects / repeated measures ANOVA with drug use (ecstasy use, polydrug use or no drug use) as a between-subjects variable and with immediate and delayed recall as within-subjects variables. Post-hoc comparisons made with Duncan's multiple range test, with p. set at .05. Possible relationships between drug use parameters and recall scores assessed via Pearson's correlation coefficient. Recall scores also analyzed via ANCOVA, with any items that appeared to be related to performance serving as covariates.

Post-hoc Analysis of Ecstasy Users by Time since Last Use – Ecstasy users divided into 3 groups with reference to period of time since last use, with subjects divided into those who had last used ecstasy within the month (13), those who last used ecstasy between 1 and 6 months before the study (9) and those who had last used ecstasy 6 months or earlier before the study (3). A between subjects / repeated measures ANOVA was performed, with time since last use as a between group variable and scores on immediate and delayed recall as within-subjects variables.

Results – Significant Differences: Ecstasy users had lower Immediate Recall scores than did polydrug users or no-drug controls (ecstasy users < polydrug users = no-drugs). Ecstasy users also had lower Delayed Recall scores than members of the other 2 groups (ecstasy users < polydrug users = no drug users). Cannabis consumption per week was negatively associated with performance on immediate recall for ecstasy users only, with greater cannabis use associated with decrements in performance. Duration of LSD use was positively associated with estimated lifetime consumption of ecstasy (total lifetime uses or cumulative dose). Duration of LSD use was also negatively correlated with performance on delayed recall for ecstasy users, but not for polydrug users, with longer duration of LSD use indicating decrements in delayed recall. While duration of LSD use proved to be a significant covariate, differences between ecstasy users and polydrug users on immediate and delayed recall scores remained when duration of LSD use entered into analysis. Performance on immediate recall, but not delayed recall, was negatively correlated with a composite of average dose per session and duration of use, with greater amount per month x duration associated with lower performance on the test of immediate recall.

Post-hoc Analysis of Ecstasy Users by Time Since Last Use – Those who had taken ecstasy at least 6 months before study performed better on both immediate and delayed recall than subjects who had last taken ecstasy within the month or those who had taken ecstasy 1 – 6 months ago.

Results – No Differences Found: NART score did not correlate with either immediate recall or delayed recall. Cannabis consumption per week did not correlate with performance on immediate or delayed recall for the polydrug users; the relationship between cannabis use and performance on delayed recall only existed for ecstasy users. Duration of LSD use was unrelated to performance on immediate or delayed recall for polydrug users. Duration or consumption of all other drugs (amphetamines, psilocybe mushrooms, alcohol, consumption of LSD per year, inhalants, cocaine) were all uncorrelated with performance on immediate or delay recall measures. Use of benzodiazepines and barbiturates (restricted to ecstasy users) was uncorrelated with immediate or delayed recall. Total lifetime consumption of ecstasy was not correlated with performance on measure of immediate or delayed recall. There were negative associations between average ecstasy dose per occasion and performance on the immediate recall measure, and between duration of ecstasy use (in years) and performance on immediate and delayed recall, but neither of these associations reached statistical significance. Performance on delayed recall was unrelated to the composite variable of average dose per session x duration of use.
Overall Effects: A group of ecstasy users matched for gender, age, education and (to some degree) use of other drugs did less well on measures of immediate and delayed recall when compared with polydrug users who had not used ecstasy and people who had never used any illicit drugs. Amount of cannabis consumed per week was associated with reduced performance on immediate recall, but only for ecstasy users, and not for polydrug users. However, amount of cannabis used per week was not associated with reduced or increased performance on delayed recall for either ecstasy users or polydrug users. Duration of LSD use, which is moderately related to lifetime ecstasy use, was negatively associated with performance on delayed, but not immediate, recall. However, there was no relationship between duration of LSD use and performance on either measure of recall for polydrug users. The author found some tentative evidence for a relationship between the combination of average dose per session and duration of use and effects on immediate, but not delayed, recall in ecstasy users. Ecstasy users who had abstained from ecstasy for at least 6 months before the study day did best on both measures of immediate and delayed recall when compared with those who had last used ecstasy within six months of the study day.
Comments: This is one of several (and possibly the first) paper that employed 2 comparison groups, polydrug users and non-user controls, when examining the effects of ecstasy use on performance on a test of memory. By restricting subjects to university students or graduates and by using a cut-off for NART score, the author also attempted to select subjects with the same level of education and general intelligence. This paper supports the existence of a relationship between ecstasy use and decrements in performance on tasks involving memory that is independent of polydrug use. The findings might even be interpreted as supporting an interaction between ecstasy and other drugs on memory, given the susceptibility of ecstasy using subjects, but not polydrug using subjects, to associations between weekly cannabis use or duration of LSD use and reductions in recall. The effects of ecstasy use on memory may be time-dependent, with people who had abstained from ecstasy for over 6 months performing better on tests of memory than those who had taken ecstasy within the month or between 1 and 6 months before the study day. However, since there were only 3 such users, compared with larger numbers of people taking ecstasy closer to the time of study, conclusions based on this analysis alone should be viewed with caution. Nearly all of the subjects participating in this study also participated in Study 2 of Morgan, 1998.

Obrocki et al. (1999). Ecstasy: Long term effects on the human central nervous system revealed by positron emission tomography.

Obrocki, J., Buchert, R., Vaterlein, O., Thomasius, R., Beyer, W., & Schiemann, T. (1999). Ecstasy: Long term effects on the human central nervous system revealed by positron emission tomography. British Journal of Psychiatry, 175, 186-188.

Purpose: Brain imaging (PET): To investigate whether long-term ecstasy use has any relationship with alteration in brain glucose metabolic rate, considered a marker of global and regional brain activity.

Design: Non-experimental (retrospective) 2-group between subjects (across groups) design, with ecstasy users compared with matched non-user controls, with drug use (ecstasy use versus non-use) serving as a between-subjects factor and with all subjects receiving brain scans.
Subjects: 7 ecstasy users recruited via out-patient substance abuse unit and 7 non-user controls recruited from a sample of patients with tumors who routinely received whole-body PET scans, with both samples probably residing in or near Hamburg (Germany). Matching – On age and gender.
Criteria for Inclusion, Ecstasy Users – No specific criteria for inclusion referring to parameters of ecstasy use provided; all subjects used ecstasy more than once over their lifetimes, and all used ecstasy more consistently than other drugs. Non-users – No past or current use of ecstasy, and no history of alcohol or substance abuse. All Groups – No past or current major neurological or psychological illness, as assessed through psychiatric interview, BDI and symptom checklist, and abstinence from psychoactive drugs before or on the study day (drug-free period not specified), with compliance verified through urine drug screen performed at unspecified time before or on study day.
Drug Use Parameters – Ecstasy users reported an overall lifetime use of 12-840 tablets, producing an estimated range of occasions of 12-620 uses (assuming a use pattern of 1 – 2 tablets per occasion). Information on average dose per use and frequency of use not provided. Average duration of ecstasy use not provided, but range of use was reported at 1-39 months. The time period between last use of ecstasy and the study day was 60-480 days. An unspecified number of ecstasy users also reported using cannabis, amphetamines and cocaine in "varying doses," but using these drugs less often (or in lesser amounts) than ecstasy use. Non-user controls – Selected for absence of history of drug use.
Group Demographics and Matched Variables – Ecstasy users matched on gender and age. Gender, as M / F ratio – Ecstasy users, 5 / 2: non-users, 6 / 1. Age. Ecstasy users' average age not provided, range was 19-29 years. Average age and precise age range for non-users not specified, but required age range to be 16-30. Other variables – No information on education level provided.
Measures: PET scans performed with 2[18F]-fluoro-2-deoxy-D-glucose (FDG), a radioactive tracer for glucose metabolism. Volumes of interest (VOIs) selected from both cortical and subcortical structures. VOIs were amygdala, caudate nucleus, cingulate, hippocampus, putamen, Brodmann 10 and Brodmann 11, with areas examined on both L and R hemispheres. Maximum FDG uptake measured in all individuals.
Analyses: Average maximum uptake was calculated for both groups (ecstasy users and non-users). Group means were compared via unpaired 2-tailed t-test. Possible correlations between PET data and two drug use parameters (number of tablets consumed over lifetime, time since last use) were examined via correlation, procedure not described but probably Pearson correlation coefficient.
Results – Significant Differences: Glucose metabolism in the L hippocampus was lower in ecstasy users than it was in non-users. Ecstasy users also had increased glucose metabolism when compared with non-users in Brodmann area 11, but only after increasing p. level.
Results – No Differences Found: While there was decreased glucose metabolism in the amygdala (L, R), cingulate (L, R) and R hippocampus in ecstasy users, compared with non-users, these differences did not differentiate all ecstasy users from all non-users. While ecstasy users experienced an increase in glucose metabolism when compared with controls in the caudate nucleus (L, R), the putamen (L, R) and Brodmann area 10, these differences did not reach statistical significance. Neither positive nor negative associations were found between overall ecstasy consumption and changes in brain glucose metabolism or between time since last use and changes in brain glucose metabolism.
Overall Effects: While differences between glucose metabolism in ecstasy users and non-user controls were found in every area studied (decreases in amygdala, cingulate and hippocampus, increases in Brodmann 10, Brodmann 11, caudate and putamen), the only differences that differentiated all ecstasy users from all non-user controls was decreased glucose metabolism in the left hippocampus and perhaps increased glucose metabolism in Brodmann area 11 The consequences of these differences in terms of mood or cognitive function is unknown, although the hippocampus plays a role in learning and memory. Overall ecstasy consumption, defined as number of tablets taken in a lifetime, did not predict the extent of the changes in brain metabolism, and neither did the time since last use of ecstasy.

Comments: To date, this is the only study employing PET scans with FDG rather than a serotonin-specific radioligand. However, the results may be somewhat comparable to SPECT scans that measure cerebral blood flow or volume. The authors did not examine what relationship, if any, these changes in regional cerebral glucose metabolism had on mood or cognitive function, though they did select for individuals with no psychiatric illness. The changes the authors found were persistent enough to remain at least 2 months after the last use of ecstasy. However, the sample size used in this study is very small, and controls were not matched with ecstasy users on the basis of drug use. Furthermore, members of both groups (ecstasy users and non-users) were selected from specific and potentially non-representative groups; ecstasy users were all enrolled in an outpatient substance abuse treatment program and non-users were all people with tumors. Caution should be used when generalizing to broader populations.

Parrott & Lasky (1998). Ecstasy (MDMA) effects on mood and cognition; Before, during and after a Saturday night dance.

Parrott, A. C., & Lasky, J. (1998). Ecstasy (MDMA) effects on mood and cognition; Before, during and after a Saturday night dance. Psychopharmacology, 139, 261-268.

Purpose: Mood and cognitive function acutely over time: To investigate the acute and chronic effects of ecstasy on mood and cognition in humans by taking measures at 4 time points occurring before and after ecstasy self-administration in a night-club environment.
Design: Non-experimental (retrospective) 3-group mixed between-subjects / within-subjects design, comparing self-selected regular ecstasy users, novice ecstasy users and matched non-user controls, with drug use (regular ecstasy use, novice ecstasy use, non-use) as a between-group variable, and time as a within-subjects factor. Measures were taken at baseline, at a night-club (on-drug for ecstasy users) and at 2 and 7 days post-club, with all subjects completing measures of mood, memory and visual search. (See also "Retrospective Studies" for an account of Parrott & Lasky focusing more on the acute and sub-acute effects of ecstasy over time).
Subjects: 15 regular ecstasy users, 15 novice ecstasy users and 15 non-user controls residing in the London (England) area, recruited through snowball technique. Matching – On age, gender, use of other drugs, and sub-culture (night-club patrons).
Criteria for Inclusion, Regular ecstasy users – Having used ecstasy 10 or more times in lifetime. Novice ecstasy users – Having used ecstasy 1-9 times in lifetime. Non-Users – No past or current ecstasy use. All Groups – Regularly visiting a large nightclub in London area. Use of alcohol and other drugs permitted in all groups, but not required. On baseline test, abstinence from ecstasy for 1 week prior to testing and abstinence from all other drugs for 24 h before testing, with compliance verified through self-report only.
Drug Use Parameters – No information is provided on number of occasions or tablets used over a lifetime, frequency of use per month or duration of use. As noted in "Criteria for Inclusion," novice ecstasy users reported using ecstasy on 1-9 occasions (no average provided) and regular ecstasy users reported using ecstasy on 10 or more occasions, no average or largest number of occasions for regular ecstasy users provided. Average dose per use for regular ecstasy users was 1.8 tablets: average dose per use in novice ecstasy users was 1.45 tablets. The day since last use before baseline is not reported: assessments were made acutely during / after ecstasy use, 2 days and 7 days after ecstasy use, with abstention from ecstasy and other drugs verified via self-report only. Information on use of other drugs not reported for overall use, but the text indicates that members all 3 groups had used cannabis, cocaine or amphetamines at least once in a lifetime. On assessment 2 (at club), subjects reported suing the following drugs: cannabis, (2 regular ecstasy users, 1 novice ecstasy user and 3 non-user controls), cocaine (4 regular ecstasy users, 2 novice ecstasy users and 2 controls) and amphetamines (1 novice user), alcohol (6 regular ecstasy users, 5 novice ecstasy users, 10 non-user controls). Number of drinks reported in each group: Regular users, 3.7 drinks, novice users, 2.7 drinks, controls, 5 drinks,

Group Demographics and Matched Variables – Regular ecstasy users, novice ecstasy users and non-user controls were matched on age, gender and sub-culture (patron at specific London night club). Gender, as M / F ratio – Regular ecstasy users: 7 / 8: novice ecstasy users, 7/ 8: non-users, 5/ 10. Age. Average age for regular ecstasy user = 21.4, no range provided, average age for novice ecstasy user = 22.8, no range provided, average age for non-user = 21.3, no range provided. Overall age range for 3 groups combined = 19-30. Sub-Group – Regular ecstasy users, novice users and non-users all recruited from population of individuals who frequented a large night club in London. Other Variables – Use of cannabis and other psychostimulants (amphetamines, cocaine) reported by members of all 3 groups on Assessment 2 ("club" night), and members of all 3 groups had used other illicit drugs at least once in a lifetime, with cannabis use, amphetamine use and cocaine use specifically reported. Non-user controls consumed more alcoholic drinks than regular or novice ecstasy users at assessment 2 ("club" assessment) and regular ecstasy users consumed more drinks than novice ecstasy users on assessment 2. No information provided about education level for any subjects in any of the 3 groups.

Measures: Mood – Author-generated visual analog scales (VAS) presented via palm-top computer, with scales containing 16 items addressing current mood, with VAS administered once at each session (baseline (1), at club (2), 2 days post-club (3) and 7 days post-club (4). On-drug measures for ecstasy users taken 2 to 4 h post-ingestion for 22/ 30 ecstasy users and 8-16 h post-ingestion in 8 / 30 ecstasy users.

Memory and Visual Search – Memory – Assessed via auditory word recall (listen to tape-recorded list, and after 30 sec, write down all words recalled from 20-word list in any order). 2 lists presented per session, with 8 different lists presented overall. Visual Search – (locate target embedded in array of distracters and touch with light pen as rapidly as possible). Test had "easy" and "difficult" form, with "easy" task using differently shaped distracters and difficult task using somewhat similarly shaped distracters. 4 increasingly large arrays presented, but only the smallest and largest arrays used for analysis. Both measures taken at baseline, at club (2), 2 days (3) and 7 days (4) post-club. On-drug measures for ecstasy users taken 2 to 4 h post-ingestion for 22/ 30 ecstasy users and 8-16 h post-ingestion in 8 / 30 ecstasy users.

Analyses: Mood – Each item on VAS analyzed separately via 2-way between subjects / within-subjects ANOVAs, with drug use (regular ecstasy use, novice ecstasy use and non-use) serving as between-group factor and session (Assessment 1, 2, 3 or 4) as a within-subjects factor. Within-session comparisons for each item on the visual analog scales made via 1-way ANOVA, with drug use serving as between-group factor. Post-hoc comparisons on within-session analysis made via Duncan's test.

Memory and Visual Search – Memory and visual search tasks analyzed via 2-way between subjects / within subjects ANOVA, with drug use (regular ecstasy use, novice ecstasy use or non-use) serving as a between-group factor and session (Assessment 1, 2, 3 or 4) as a within-subjects variable. Within-session performance was compared across 3 groups (regular ecstasy user, novice ecstasy user and non-user) via 1-way ANOVA with drug use serving as a between-group factor, with post-hoc comparisons made via Duncan's test.

Results – Significant Differences: Mood – At baseline, ecstasy users reported being more clear-headed than non-users (regular > novice > non-user) and novice ecstasy users reported being more sad than either non-users or regular ecstasy users. On assessment 2 (at club), both regular and novice ecstasy users reported feeling more abnormal, sober and steady than non-users. There was a trend for regular and novice ecstasy users to indicate they were less sad and depressed during Assessment 2 (at club). On Assessment 3 (2 days post-club), ecstasy users reported feeling more depressed, sad, unsociable, unpleasant, and abnormal; in most cases, regular ecstasy users and novice ecstasy users scored closer to each other than to controls (abnormal, sad, unsociable). Novice ecstasy users reported feeling more depressed, less good-tempered and more unpleasant than both regular ecstasy users and non-user controls. On Assessment 4 (7 days post-club), regular and novice ecstasy users reported feeling more drowsy than non-users (regular < novice < non-user). Overall, regular and novice ecstasy users reported being more sad than non-users. Members of all 3 groups felt more good tempered, sociable and less sad on Assessment 2 (at club) than at other times of assessment.

Memory and Visual Search – Members of all 3 groups recalled fewest words at club (Assessment 2) than during any other session (Baseline, Assessment 3 or Assessment 4). Regular and novice ecstasy users recalled fewer words than non-users across all 4 assessments (baseline, at club, 2 and 7 days post-club), but with regular ecstasy users performing worse than novice ecstasy users (regular users < novice users < non-users). Only on Assessment 2 (At club), ecstasy users took longer to perform the visual search task than non-users, with regular ecstasy users performing more poorly than novice ecstasy users.
Results – No Differences Found: Mood – At baseline, there were no significant differences between members of all 3 groups on 14/ 16 visual analog scale items. At assessment 2 (at club), there were no differences between members of all 3 groups on 13/ 16 scales. On assessment 3 (2 days post-club), there were no differences between all 3 groups on: calm, clear-headed, drowsy, energetic, ill, interested, quick-witted, sober, steady and well-coordinated. On Assessment 4 (7 days post-club), there were no differences between all 3 groups on 15 / 16 scales. There were no between-group differences in mood that extended across all 4 assessments.
Memory and Visual Search – Regular ecstasy users, novice ecstasy users and non-users performed at similar levels on the visual search days at baseline, at Assessment 3 (2 days post-club) and on Assessment 4 (7 days post-club).
Overall Effects: Ecstasy acutely reduced sadness and sub-acutely produced deterioration in mood two days after use, with mood returning to baseline 7 days after use. In several cases (feeling depressed, feeling less good tempered), scores of novice ecstasy users were more affected 2 days post-club than were those of regular ecstasy users. Ecstasy acutely reduced recall and visual search, with regular ecstasy users performing less well than novice users, and novice users performing less well than controls. Ecstasy users had lower performance scores on word recall than non-users in across-group comparisons at each assessment, with regular ecstasy users having the lowest recall scores and non-user controls the highest recall scores. Ecstasy acutely reduced attention (assessed in visual search), probably due to difficulty concentrating. Performance on the visual search task returned to baseline both at 2 days and 7 days post-drug.
Comments: While the overall design used in the study reported here was retrospective, with groups divided on the basis of drug-use rather than assigned to drug use condition, the authors attempt to use a prospective design to study the acute and sub-acute effects of ecstasy over time. The advantage of using this design in comparing users with non-users is that there is some chance of separating "residual drug effects" from more persistent ones. The authors also sought to compare people with a higher lifetime exposure to ecstasy with people who had a lower lifetime exposure. It is particularly interesting that while novice ecstasy users reported greater negative mood on Assessment 3 than did regular ecstasy users, regular ecstasy users recalled fewer words than did novice users on all sessions. These findings suggest that changes in mood and cognitive function after ecstasy use do not necessarily reflect changes in the same neural substrates. The authors believe that their data supports the case for alterations in memory even after using ecstasy on no more than 9 occasions, but they also believe that single large doses and frequency of use are the most important contributors to ecstasy related cognitive deficits. The sample size in this study is small, so some caution should be used in generalizing to the population at large. Regression analyses using drug use parameters may also be more informative means for learning about the effects of these parameters on cognitive function or other variables, particularly in a study where subjects were not formally assigned to a specific drug use condition.

Parrott et al. (1998). Cognitive performance in recreational users of MDMA or "Ecstasy": evidence for memory deficits.

Parrott, A. C., Lees, A., Garnham, N. J., Jones, M. & Wesnes, K (1998). Cognitive performance in recreational users of MDMA or "ecstasy": evidence for memory deficits. Journal of Psychopharmacology, 12, 79-83.

Purpose: Cognitive function, general: To investigate whether MDMA use affects cognitive functions.

Design: Non-experimental (retrospective) 3-group between subjects design comparing regular ecstasy users, novice ecstasy users and matched non-user controls, with drug use serving as a between-subjects factor. All subjects completed a battery of tests assessing several cognitive functions.
Subjects: 10 regular ecstasy users, 10 novice ecstasy users and 10 non-user controls residing in the London (England) area, with members of all 3 groups recruited via snowball technique (either through direct acquaintance with researchers or via word of mouth through friends). Matching – On age and approximately matched on gender and education.
Criteria for Inclusion, Ecstasy Users – Having used ecstasy on 10 or more occasions over a lifetime. Novice ecstasy users – Having used ecstasy on 1-9 occasions over a lifetime. Non-users – No past or current use of ecstasy. All Groups – Abstention from ecstasy or other psychoactive drugs on the study day, with compliance verified via self-report only.
Drug Use Parameters – No information provided concerning average dose of ecstasy per use, frequency of use or duration of use (in months). As noted above, novice ecstasy users reported using ecstasy 1-9 times (no average provided) and regular ecstasy users reported using ecstasy 10 or more times (no average provided, and greatest number of occasions per lifetime unknown). Time elapsed since last use is not provided, though subjects reported being drug-free on study day.
Group Demographics and Matched Variables – Regular ecstasy users, novice ecstasy users and controls matched on the basis of age and approximately matched on the basis of gender. Gender, as M / F ratio – Regular ecstasy users, 8 / 2, novice ecstasy users, 5 / 5, non-users, 4 / 6. Age. No average ages provided for any group. Regular ecstasy users ages ranged from 18-25 year, novice ecstasy users age range, 20-25, and non-users age range was 21-30 years. There were more women non-users than regular ecstasy users.
Other variables – While no information is formally provided on education level, author states that most subjects were university students or their friends; estimated education level in years across all 3 groups is approximately 14.5 years.
Measures: Cognitive function measured via sub-set of tasks selected from the Cognitive Drug Research (CDR) test battery, a computerized test battery consisting of speeded tasks. Simple Reaction Time – Press appropriate key as rapidly as possible after target word ("YES") appeared on screen. Choice Reaction Time – Press "Yes" key as rapidly as possible on appearance of "Yes" on screen and press "No" key as rapidly as possible when "No" appears on screen, with "Choice Reaction Time" presented at 2 points in assessment. Immediate Word Recall – Write down as many words as can recall immediately after viewing a 15-word list presented on computer screen, with score = total number of words recalled. Number Vigilance Task – Press "Yes" key as rapidly as possible when target number matches stimulus, with potential targets presented in succession, with target detection and reaction time scored. Sternberg task – Indicate presence of number in previously presented list by pressing "Yes" key, with potential targets presented after stimulus (not simultaneously, as in Number Vigilance), and with reaction time scored. Delayed recall – Write down as many words as can still recall from original "Immediate recall" list, with score = total number of words recalled
Analyses: All tasks on the cognitive test battery were analyzed via separate 1-way ANOVAs, with drug use (regular ecstasy use versus novice ecstasy use and non-use) as a between-group subject, with post-hoc comparisons made via Duncan's test.
Results – Significant Differences: Ecstasy users differed from non-users on performance on both the immediate and the delayed word recall task, with regular and novice ecstasy users recalling fewer words than non-users both on the immediate and the delayed recall task. Novice ecstasy users recalled significantly fewer words than non-users and regular ecstasy users recalled slightly (but not significantly) more words than regular ecstasy users.
Results – No Differences Found: There were no differences between regular ecstasy users, novice ecstasy users and non-users on the following tasks: simple reaction time, choice reaction time (at first or second time point), number vigilance task or Sternberg task response time. There were no differences between regular ecstasy users, novice ecstasy users and non-users on target detection in the number vigilance task.

Overall Effects: Regular ecstasy users, novice ecstasy users and non-uses all performed equally well on tests of simple and complex reaction time, vigilance and visual search and immediate visual recall. However, after being presented with a list of words, regular and novice ecstasy users recalled fewer words immediately after list presentation and at a later point in time. The effect of drug use was equally present for both novice and regular ecstasy users, but there was a tendency for regular ecstasy users to recall fewer words than novice users.
Comments: This paper is one of several that seeks to compare cognitive performance both between ecstasy users and non-user controls and between "regular" and "novice" ecstasy users, with categories defined via self-reported number of occasions where ecstasy was used over a lifetime. It is surprising to find that "novice" ecstasy users show the same pattern of deficits in immediate and delayed verbal recall as do "regular" ecstasy users. Either the effects of ecstasy on memory are produced after a small number of exposures or some other drug use parameter not measured here produced these effects. Unfortunately, the authors do not present information on other drug use parameters found to correlate with deficits in cognitive function in other studies, such as duration of use, frequency of use, or time elapsed since last use. Additionally, it is unclear whether use of other psychoactive drugs was similar across all 3 groups or whether there were differences in use of other drugs, such as cannabis. While the groups were approximately matched for gender, there were more men in the regular ecstasy group than in the novice user or non-user group, and non-users tended to be older than either group of users.

Parrott et al. (2000). Psychobiological problems in heavy 'Ecstasy' (MDMA) polydrug users.

Parrott, A. C., Sisk, E., & Turner, J. J. D. (2000). Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. Drug and Alcohol Dependence, 60, 105-110

P**urpose**: Psychiatric health (presence of symptoms): To investigate whether extent of ecstasy use affects presence of psychiatric symptoms in light ecstasy users, heavy ecstasy users and in non-user controls.
Design: Non-experimental (retrospective) 3-group between subjects design comparing groups of matched light ecstasy users, heavy ecstasy users and non-user controls, with drug use (light use, heavy use or no use of ecstasy) as a between-subjects factor, and with all subjects completing measures of mood and psychiatric symptoms.
Subjects: 12 heavy ecstasy users, 16 light ecstasy users and 22 non-users residing near Cork (Ireland), recruited via "snowball technique" (word of mouth and through direct acquaintance with researchers).
Matching – On age and gender.
Criteria for Inclusion, Heavy Ecstasy Users – Having used ecstasy on 20-1000 occasions. Light Ecstasy Users – Having used ecstasy on 1-20 occasions. Non-users – No past or current use of ecstasy, but use of other drugs permitted. All groups – Participation in "youth subculture" in small town near Cork, Ireland, and using no psychoactive drugs on study day, with compliance verified through self-report only. No other criteria given for inclusion, though it appears that members of all 3 groups are matched on use of drugs other than ecstasy.
Drug Use Parameters – Heavy ecstasy users reported using ecstasy on an average of 371 occasions in a lifetime (30-1000), with no information on average dose per session. Light ecstasy users reported using ecstasy on an average of 6.8 occasions (1-20), no information on dose per use provided. No information provided on frequency or duration of ecstasy use or time since last use. Other Drugs – Percentage of individuals in each group who used each drug listed: alcohol, heavy users 92%, light users 100%, non-users 100%, tobacco, heavy users 92%, light users, 82%, non-user, 50%, cannabis, heavy users, 100%, light users, 87%, non-users, 82%, amphetamines, heavy users, 83%, light users, 69%, non-users, 36%, cocaine, 75%, light users, 56%, non-users, 14%, LSD, heavy users, 83%, light users, 69% non-users, 18%, magic mushrooms, heavy users,75%, light users, 31%, non-users, 27%, barbiturates / benzodiazepines, heavy users, 33%, light users, 12%, non-users, O%, opiates, heavy users, 25%, light users, 25%, non-users, 14%, steroids, 8%, light users, 0%, non-users, 5%, solvents, heavy users, 50%,

light users, 31%, non-users, 14%. There were differences in drug use pattern for LSD and cocaine, and for amphetamines and magic mushrooms, with heavy ecstasy users > light ecstasy users > non-users.
Group Demographics and Matched Variables – Heavy ecstasy users, light ecstasy users and non-users matched on age, gender and approximately matched on use of drugs other than ecstasy. Gender, as M / F ratio – Heavy ecstasy users, 7 / 4, 1 undeclared: light ecstasy users, 6 / 10: non-users, 11 / 10, 1 undeclared. Age. Average age of heavy ecstasy users = 20.8 ± 2.2 (range not provided), average age of light ecstasy users = 20.9 ± 1.6 (range not provided), average age for non-users = 23.2 ± 4.9 (range not provided.)
Measures: Psychiatric Symptoms – Measured via SCL-90, a self-report measure addressing symptoms related to major psychiatric illnesses.
Daily Life Events – Author-designed Uplifts, Hassles, Stresses & Cognitive Failures questionnaire, designed to measure frequency of occurrence of the life events listed over the last month.
Personality – Impulsiveness, venturesomeness and empathy assessed via IVE.
Analyses: Psychiatric Symptoms – Data analyzed by 1-way ANOVA, with drug use (heavy ecstasy use, light ecstasy use, non-use) as between-subjects factor. Post-hoc comparisons made with Tukey's test.
Daily Life Events – Score on each scale analyzed via 1-way ANOVA with drug use (heavy ecstasy use, light ecstasy use, non-use) as between-subjects factor. Post-hoc comparisons made via Tukey's test.
Personality – Each scale on the IVE analyzed via 1-way ANOVA with drug use (heavy ecstasy use, light ecstasy use, non-use) serving as between-subjects factor. Post-hoc comparisons made via Tukey's test.
Results – Significant Differences: Psychiatric Symptoms – Heavy ecstasy users scored higher on specific SCL-90 scales than did non-users. These included somatisation, obsessionality, anxiety, hostility, phobic-anxiety, paranoid ideation, psychoticism, poor appetite and restless / disturbed sleep, with heavy ecstasy users > non-users. Light ecstasy users differed from non-user controls on 2 SCL-90 scales, paranoid ideation and psychoticism, with light ecstasy users > non-users.
Daily Life Events – None found. However, cognitive failure scores increased across groups (heavy ecstasy users > light users > non-users), but differences did not reach statistical significance.
Personality – Heavy ecstasy users scored higher on the Impulsivity scale on the IVE than did non-users, with heavy users > non-users.
Results – No Differences Found: Psychiatric Symptoms – No differences found between heavy users and non-users on only 2 SCL-90 scales (depression, interpersonal sensitivity). No differences found between light users and non-users on 8 of 10 SCL-90 scales, including depression, anxiety, somatisation, phobic-anxiety, obsessionality, interpersonal sensitivity, hostility, disturbed appetite / sleep). SCL-90 scores for light users intermediate between those of non-users and heavy users.
Daily Life Events – There were no differences between all 3 groups on the Uplifts, Hassles, Stresses & Cognitive Failures scale for all 4 scales. Heavy ecstasy users had higher scores on the cognitive failures scale than did light ecstasy users, and light ecstasy users scored higher on cognitive failures than non-users, but this difference in scores did not reach significance.
Personality – All 3 groups (heavy ecstasy user, light ecstasy user, non-user) did not differ on venturesomeness or empathy scale scores on IVE. Light ecstasy users did not differ from non-users on impulsivity scale, though scores were higher, and they also did not differ from non-users on empathy or venturesomeness scale scores.
Overall Effects: When compared on number of self-reported psychiatric symptoms, heavy ecstasy users reported a greater number of symptoms than did light ecstasy users and non-user controls. Self-reported symptoms covered a wide array of problems, including anxiety-related symptoms, hostility related symptoms, psychoticism and signs of disturbed appetite and sleep. Light ecstasy users reported symptoms at a level that was intermediate between heavy users and non-user controls, but this difference rarely reached statistical significance except in the case of symptoms of psychoticism and paranoid ideation, with both greater in light users than in non-user controls. Heavy ecstasy users scored higher on the IVE impulsivity scale when compared with non-users, but there were no differences in venturesomeness or empathy between the 3 groups. Heavy ecstasy users, light ecstasy users and non-users reported experiencing similar numbers of uplifts, hassles, stresses and cognitive failures in the past

month. While members of the 3 groups did not differ in the number of daily life stressors they experienced, there was a trend for self-reported cognitive failures to increase with ecstasy use.
Comments: This paper reports one of several studies that seeking to investigate differences arising from extent of ecstasy use as well as differences arising from ecstasy use in general. This paper presents more evidence in support of an association between ecstasy use and higher impulsivity. This paper also found that heavy ecstasy users experienced a greater number of psychiatric symptoms, despite their failure to report a greater number of daily life stressors (stresses and hassles) than light ecstasy users or non-users. It is surprising that one self-report measure of psychiatric symptoms found differences across groups while another self-report measure of daily life events did not produce across-group differences, since people experiencing symptoms of depression, anxiety, or paranoid ideation would be expected to report more daily life stressors than people without these psychiatric symptoms. Unlike a similar study conducted by Schifano et al. (1998, 2000), ecstasy users in this study had not sought medical help for their substance use. Members of all 3 groups, including the non-users were sampled from a population that is more representative of young ecstasy users than that of Schifano. Drug use was comparable in all 3 groups, yet ecstasy users, especially those classified as heavy users, did use more drugs than did non-users, and this was particularly true for use of stimulants and hallucinogens. Hence some caution might be used in generalizing study results to the population at large.

Peroutka et al. (1987). Monoamine metabolites in the cerebrospinal fluid of recreational users of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy").

Peroutka, S. J., Pascoe, N. & Paull, K. F. (1987). Monoamine metabolites in the cerebrospinal fluid of recreational users of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Research Communications in Substance Abuse, 8, 125-132.

Purpose: Measure of metabolites in CSF: to examine monoamine metabolites in ecstasy users and non-user controls to discover whether regular ecstasy use alters amount of brain monoamines.
Design: Non-experimental (retrospective) 2-group between-subjects (across groups) design comparing ecstasy users with matched non-user controls, with drug use (ecstasy use versus no ecstasy use) serving as between-subjects factor and with all subjects receiving lumbar puncture.
Subjects: 5 ecstasy users and 17 non-user controls. No information is provided on recruitment of ecstasy users; perhaps performed via word of mouth. Non-users recruited from a larger study previously conducted in the Palo Alto (California) area that already involved lumbar puncture. Matching – On age and perhaps gender (not enough information provided to be certain).
Criteria for Inclusion, Ecstasy Users – Having used ecstasy at least once in a lifetime. Non-users – No past or current use of ecstasy. All Groups – Abstinence from all psychoactive drugs for 6 weeks (ecstasy users) to 2 weeks (controls), with abstinence verified through self-report. No information provided concerning restrictions, if any, based on mental or physical health, though ecstasy users denied any long-term effects on their behavior or emotional state.
Drug Use Parameters – Ecstasy users reported taking ecstasy on 1 to 33 occasions over a lifetime, with average number of occasions approximately 22.5 (excluding subject reporting 1 use only) or 18.2 (including low-dose subject). Dose per use ranged from 1 tablet to approximately 1.6 tablets (converted from self-reported dosage by mg where 1 tablet estimated at 125 mg), no average value provided. No information is provided concerning frequency of use, but duration of use was approximately 18 months (no range provided). No information on number of days since last use; requested to be drug-free for 30-60 days before study day.
Group Demographics and Matched Variables – Ecstasy users and non-users matched on age, and perhaps matched on gender. Gender, as M / F variable. Ecstasy users, unknown. Possibly 5 / 0: non-users, 17 / 0. Age. Ecstasy users average age not provided, (20 – 33 years), non-users average age = 26 ± 3 (20-33 years). Other Variables – Controls were selected from larger pool of subjects from study conducted 7 years previous to study with MDMA users and matched via age.

Measures: Concentrations of 5HIAA, HVA and MHPG in CSF. Subjects underwent lumbar puncture in the morning after an overnight fast. Metabolite levels assessed via combined gas chromatography and mass spectrometry.
Analyses: No formal analyses reported; nature of data suggests either an unpaired t-test or a non-parametric test comparing means across groups (ecstasy users and non-users). A correlation (undescribed) was performed between extent of ecstasy use (number of occasions used over a lifetime) and concentration of 5HIAA in CSF.
Results – Significant Differences: None found.
Results – No Differences Found: There were no differences between ecstasy users and non-user controls in CSF concentration of 5HIAA, HVA or MHPG. Extent of ecstasy use did not correlate with amount of 5HIAA found in CSF.
Overall Effects: When values for the serotonin metabolite 5HIAA, the dopamine metabolite HVA and the norepinephrine metabolite MHPG were measured in a sample of 5 ecstasy users and an age-matched sample of non-user controls, comparisons across user groups found values for all 3 metabolites to be similar in both groups. There was no association between extent of ecstasy use and level of 5HIAA in CSF.
Comments: This is the first paper that attempted to detect alteration or damage of the serotonergic system in ecstasy users by measuring the concentration of 5HIAA in cerebrospinal fluid. The technique is used much less frequently in later papers, probably because of its invasiveness and unpleasantness for participants. Later papers (e.g. McCann et al., 1994; McCann et al., 1999; Ricaurte et al., 1990) in contrast with this paper, did find differences between 5HIAA in regular ecstasy users and 5HIAA values in non-user controls. The samples in this study are matched for age only, and little information is provided about other variables, such as general health or complete drug use history. It is even possible that the samples were not matched on gender, as information is only provided on the gender of non-user controls, who were all male. Non-user controls outnumber ecstasy users by a factor of 3, and controls were drawn from a study not specifically designed for comparisons between controls and ecstasy users. Caution should be used in generalizing from this study to the population at large.

Price et al. (1989). Neuroendocrine and mood responses to intravenous L-tryptophan in 3,4-methylenedioxymethamphetamine (MDMA) users: Preliminary observations.

Price, L. H., Ricaurte, G. A., Krystal, J. H. & Heninger, G. R. (1989). Neuroendocrine and mood responses to intravenous L-tryptophan in 3,4-methylenedioxymethamphetamine (MDMA) users: Preliminary observations. Archives of General Psychiatry, 46, 20-22.

Purpose: Pharmacological challenge: To investigate whether ecstasy use has altered serotonergic function through measuring prolactin response to L-tryptophan challenge in ecstasy users and controls.
Design: Non-experimental (retrospective) 2-group design, with ecstasy users compared with matched non-user controls, with drug use (ecstasy use versus no ecstasy use) as a between subjects factor, and with all subjects receiving L-tryptophan challenge.
Subjects: 9 regular ecstasy users and 9 non-users, with non-users recruited via local advertisements in the New Haven (Connecticut) area, and ecstasy users recruited nationally, perhaps through self-referral or via snowball technique (information not provided). Matching – On gender, age.
Criteria for Inclusion, Ecstasy Users – Current or past history of ecstasy use, specific extent, duration or cumulative dose requirements unspecified. Non-users – No current or prior history of ecstasy use, absence of substance abuse. All Groups – Good health as established via physical examination, neurological examination and standard laboratory tests, absence of major medical or psychiatric illnesses, and abstinence from use of psychoactive drugs for at least 3 weeks prior to study day, with compliance verified through self-report only. (Some ecstasy users reported infrequent marijuana use during this period).

Drug Use Parameters – No information is provided on number of times (occasions) ecstasy had been used in a lifetime, cumulative exposure (originally listed in grams) indicates ecstasy users took an average of 130 ± 131 tablets over a lifetime (13.3 ± 13.4 g). Ecstasy users reported taking approximately 1.3 ± .4 tablets per occasion (.5 – 2 tablets per occasion). Some ecstasy users (exact number of users not provided) reported taking occasional doses of 5 tablets or more per occasion. Average frequency of use was reported at 1.9 ± 1.7 times per month (.3 – 5 times per month) and duration of use was reported to be 61.2 ± 27.6 months (24 – 84 months). Day since last use not reported; if ecstasy users complied with requested drug-free period, last day of use estimated at 21 days prior to study day. An unspecified number of ecstasy users also used cannabis, as indicated in "Criteria for Inclusion" section.
Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender and age. Gender, as M / F ratio – Ecstasy users, 7 / 2: non-users, 7 / 2. Age. Ecstasy users, average age = 34 ± 7 (22-47 years): non-users, average age, 33 ± 8 years (22-48 years).
Measures: Prolactin Response to L-Tryptophan – Subjects received an infusion of 7 g tryptophan in 500 mL saline, with duration of infusion at 3 h. Blood samples taken at 15 and .5 min before infusion and at 30, 40, 50, 60, 70, and 90 min after start of infusion. Plasma prolactin assessed through radioimmunoassay. Different assays used for detecting prolactin in ecstasy users and controls, with low intra-assay and inter-assay coefficients of variation.
Mood – Current mood state experienced during tryptophan infusion measured via 11 visual analog scales (VAS(, with items for happy, sad, drowsy, nervous, calm, depressed, anxious, energetic, fearful, mellow, high). Measures administered at 15 and .5 minutes before infusion and at 30, 40, 50, 60, 70 and 90 minutes after start of infusion.
Analyses: Prolactin Response to L-Tryptophan – Baseline values averaged, and peak change scores calculated by subtracting baseline average from highest prolactin value after tryptophan infusion. AUCs calculated via trapezoidal rule. Because of non-normal data distribution, comparisons over time of sample (within subjects) analyzed via Wilcoxon signed-rank test (non-parametric test) and comparisons across group (between subjects) examined via Wilcoxon ranked sum (non-parametric test.) Correlations were performed using Spearman's P.
Mood – Analyzed via repeated-measures ANOVA, with group (ecstasy user versus non-user) as a between subjects factor and time of administration (15, .5 min before infusion and 30, 40, 50, 60, 70 and 90 min after start of infusion) as a within-subjects factor. No information provided on test used for post-hoc comparisons. Correlations were performed using Spearman's P.
Results – Significant Differences: Prolactin Response to Tryptophan Infusion – When compared with baseline values, peak prolactin levels after tryptophan infusion were significantly higher in non-user controls, but not in ecstasy users. Prolactin at baseline was positively correlated with peak prolactin values after tryptophan infusion, with higher baseline prolactin associated with higher peak prolactin after tryptophan infusion. Difference between AUC and baseline was significantly different for non-user controls, but not for ecstasy users.
Results – No Differences Found: Prolactin Response to Tryptophan Infusion – Ecstasy users and non-user controls did not differ on baseline prolactin concentration. Ecstasy users and non-user controls did not differ in peak plasma prolactin value after tryptophan infusion. When baseline plasma prolactin values were compared with peak prolactin values after tryptophan infusion, values were not significantly different in ecstasy users, though they were in non-user controls. There was no correlation between prolactin values at baseline and peak prolactin values after tryptophan infusion for ecstasy users. While the AUC values for ecstasy users' prolactin was higher than at baseline, this difference did not reach statistical significance. There were no significant differences between ecstasy users and non-user controls for prolactin AUC after tryptophan infusion. Baseline plasma prolactin, peak plasma prolactin after tryptophan infusion and prolactin AUC were not correlated with duration of ecstasy use, frequency of ecstasy use or estimated cumulative dose for ecstasy users.

Mood – There were no differences between ecstasy users and non-users in the subjective effects of tryptophan infusion as reported via visual analog scales. Members of both groups reported feeling more drowsy, less energetic and less happy during / after the infusion than before the infusion.
Overall Effects: Increased prolactin was seen in ecstasy users and in non-user controls. The difference between baseline prolactin values in non-user controls was great enough to be statistically significant, but the difference between baseline values and peak prolactin after tryptophan in ecstasy users was not great enough to be considered statistically significant. Ecstasy users appear to have a blunted prolactin response to tryptophan infusion, yet a formal comparison of the two groups concluded that prolactin response to L-tryptophan did not significantly differ between the two groups. Both ecstasy users and controls reported decreased happiness and energy and increased drowsiness after tryptophan infusion, with no differences in the subjective effects of tryptophan as experienced by members of either group.
Comments: This paper attempts to detect altered serotonergic function in ecstasy users via L-tryptophan challenge. However, there are a number of difficulties with the study. According to the authors, samples comprised of men tend to have modest prolactin values after tryptophan challenge, making it difficult to spot between-group differences in an already low value (a "floor effect.") Due to non-normative distribution, non-parametric tests were used instead of parametric tests. On the other hand, ecstasy user participants were selected on the basis of having low 5HIAA values in CSF. These individuals also appeared in Krystal et al, 1992. While most controls resided near the study location, some ecstasy users resided in different locations and had traveled to New Haven to participate in the study. Furthermore, not enough information is provided about use of other psychoactive drugs, such as cannabis, amphetamines or hallucinogens, in either group. Data concerning prolactin response after ecstasy use continues to be inconclusive, though later studies (i.e. Gerra, 1999, Gerra et al, 2000) suggest that ecstasy users have a blunted prolactin response to serotonergic drugs.

Reneman et al. (2000). Memory disturbances in "Ecstasy" users are correlated with an altered brain serotonin transmission.

Reneman, L., Booij, J., Schmand, B., van den Brink, W., & Gunning, B. (2000). Memory disturbances in "Ecstasy" users are correlated with an altered brain serotonin transmission. Psychopharmacology, 148, 322-324.

Purpose: Brain imaging (SPECT with ligand), cognitive function (memory): To see whether regular ecstasy use alters serotonergic function and performance on a test of memory, with density of $5HT2_A$ receptors measured via SPECT scans using the radioligand, [123-I]-5-I-R91150.
Design: Non-experimental (retrospective) 2-group between subjects design comparing ecstasy users with matched non-user controls, with drug use (ecstasy use versus no ecstasy use) serving as a between-subjects factor and with all subjects undergoing SPECT scans and completing measures of memory.
Subjects: 5 regular ecstasy users and 9 non-user controls residing in the Amsterdam (Netherlands) area, with subjects in both groups recruited via local advertisements. Matching – On age, approximately matched for gender and education.
Criteria for Inclusion, Ecstasy Users – Having used at least 50 tablets over lifetime. Non-users – No past or current use of ecstasy, no history of substance use or abuse for any other illicit drug. All groups – Healthy, not pregnant, absence of past or current major medical or psychiatric illness, including conditions that preclude informed consent. Absence of claustrophobia and conditions where serotonin function is implicated. Abstention from all psychoactive drugs for at least 2 weeks prior to study day, with compliance verified by urinary drug screen performed at unspecified time before or on study day.
Drug Use Parameters – Average number of tablets consumed over a lifetime was 218 tablets (50-500), with no information on average dose per use. No information is provided concerning frequency or duration of ecstasy use. Average time since last use, in days, was approximately 138 days (4.6 months), (approximately 60-360 days).

Group Demographics and Matched Variables – Groups matched on age and approximately matched on gender and education. Gender, as M / F ratio – Ecstasy users, 4 / 1: non-users, 4 / 5. Age. Ecstasy users average age = 23.6 ± 5.3 years, non-users 22.8 ± 2.9 years. Education level, in years – Average education level in ecstasy users = 13 ± 6 years: average education level in non-users = 15 ± 5 years. There were more female non-users than there were female ecstasy users, and ecstasy users had attained fewer years of education than non-users.

Measures: SPECT – Scans performed with the $5HT2_A$ receptor radioligand, [123-I]-5-I-R91150 co-registered with MRI scans. Frontal, parietal and occipital areas were selected as regions of interest (ROIs) and the cerebellum and temporal area selected as ROIs in another template. An investigator blind to subjects' drug use histories performed ROI analysis, with the cerebellum used as a reference due to presumed lack of $5HT2_A$ receptors. "Specific" binding for each ROI calculated as "mean" ROI binding / cerebellar binding = $5HT2_A$ binding ratio.

Memory – Assessed via RAVLT, a test of verbal memory, with immediate recall measured via Logical Memory sub-test and delayed memory measured via Delayed Recall and Recognition sub-tests. RAVLT administered day before conducting SPECT imaging. (Personal communication to R. Doblin indicates memory also assessed via WMS-Recall and Rivermead Behavioral Memory Test (RBMT)).

Analyses: SPECT – Specific binding figures derived from the formula above were compared between ecstasy users and non-users via Mann-Whitney U test (non-parametric test), with p. set at .05.

Memory – Analysis not specifically described. Each RAVLT sub-test score was compared between ecstasy users and controls, apparently also with the Mann-Whitney U test Other test scores (as with WMS-Recall and RBMT) probably treated to similar analyses.

Correlations between SPECT and Test Performance – Possible relationships between performance on RAVLT and [123-I]-5-I-R91150 binding (indicating $5HT2_A$ receptor density) performed via Spearman's R (ranked coefficient). Subsequent correlations also employed demographic variables (gender, age, education) and drug use parameters (extent of previous MDMA use).

Results – Significant Differences: SPECT – Specific [123-I]-5-I-R91150 binding in the occipital cortex was higher in ecstasy users than in non-users.

Memory – Ecstasy users had lower scores on RAVLT Recall than did non-users, indicating that ecstasy users recalled fewer words after a delay than did non-user controls.

Correlations between SPECT and Test Performance – Score on RAVLT-Recall sub-test were positively correlated with mean cortical $5HT2_A$ binding (as indicated through [123-I]-5-I-R91150 binding), with higher Recall scores associated with greater mean cortical $5HT2_A$ binding. Correlations also employing subjects' age, gender or education did not modify the relationship between RAVLT-Recall score and mean cortical $5HT2_A$ binding. Extent of past ecstasy use (unspecified, either total lifetime ecstasy consumption, duration of use or some combination of these drug use parameters) did not modify the relationship between RAVLT-Recall score and mean cortical $5HT2_A$ binding. Hence the relationship between increased $5HT2_A$ binding and memory scores is not strongly affected by age, gender, education or extent of ecstasy use.

Results – No Differences Found: SPECT – While specific [123-I]-5-I-R91150 binding was higher in ecstasy users across other ROIs, (frontal, temporal and parietal areas), these differences in binding did not reach statistical significance.

Memory – Ecstasy users and non-users did not differ on their performance on the Immediate Recall and Recognition sub-tests of the RAVLT. (Personal communication to R. Doblin indicates that there were also no differences between ecstasy users and non-users on test performance for the RBMT and the WMS, but this data is not presented in the paper).

Correlations between SPECT and Test Performance – Performance on RAVLT-Recall was unrelated to mean cortical $5HT2_A$ binding (as indicated through [123-I]-5-I-R91150 binding) in non-user controls, despite there being a relationship between recall score and $5HT2_A$ binding for ecstasy users.

Overall Effects: $5HT2_A$ receptor binding, assessed via SPECT using a radioligand specific to the $5HT2_A$ receptor, was greater in the occipital area for ecstasy users than for controls. Though ecstasy users and non-users performed similarly on measures of immediate recall and a test of visual and verbal memory,

ecstasy users also scored lower on a measure of delayed verbal recall. In ecstasy users, greater mean cortical $5HT2_A$ binding was associated with higher performance on the measure of delayed recall, yet mean cortical $5HT2_A$ binding was neither positively nor negatively correlated with performance on the test of recall in non-users. Gender, age, education and prior use of ecstasy were not correlated with performance on Recall and did not change the association between mean cortical $5HT2_A$ binding and Recall score.
Comments: This paper appeared as a "rapid communication," and the information here has been supplemented with further information sent as a personal communication to Rick Doblin. The relationship between mean cortical $5HT2_A$ binding and RAVLT recall score is especially interesting because the alteration in $5HT2_A$ binding is correlated with better performance rather than worse performance on a test of verbal memory. These findings could be used in support of a role for $5HT2_A$ receptor density either as a pre-existing protective factor or as an adaptive or compensatory factor that reduces the effects of ecstasy use on delayed recall. However, the sample size in this study is small, and insufficient information is offered concerning use of other psychoactive drugs in either group. Hence it is possible that the findings arose out of differences in use of other drugs. Caution should be used in generalizing from this small sample to the population at large.

Reneman et al. (2000). MDMA ("Ecstasy") and its association with cerebrovascular accidents; Preliminary findings.

Reneman, L., Habraken, J. B. A., Majoie, C. B. L., Booij, J. & der Heeten, G. J. (2000). MDMA ("Ecstasy") and its association with cerebrovascular accidents; Preliminary findings. American Journal of Neuroradiology, 21, 1001-1007.

Purpose: Brain imaging (SPECT with ligand): To investigate the effects of ecstasy on brain $5HT2_A$ receptor density by performing SPECT scans with {123-I]-R91150 on two groups of ecstasy users ("current" and "ex" users) and on non-user controls.
Design: Non-experimental (retrospective) 3-group between subjects (across groups) design comparing current ecstasy users with former ecstasy users and matched non-user controls, with drug use (ecstasy use or no ecstasy use) and recency of drug use (current ecstasy use, past ecstasy use, no ecstasy use) serving as between subjects factors, and with all subjects undergoing SPECT and MRI scans.
Subjects: 10 recent regular ecstasy users, 5 former regular ecstasy users and 10 non-user controls residing in the Amsterdam (Netherlands) area recruited via advertisements in local newspapers. Matching – On age.
Criteria for Inclusion, Current ecstasy users – Having used at least 50 ecstasy tablets over a lifetime and last use of ecstasy between 1 week and 2 months prior to study day. Former ("Ex") Ecstasy Users – Having used at least 50 ecstasy tablets over a lifetime and last use of ecstasy at least 2 months prior to study day. Non-users – No past or current use of psychoactive drugs, including ecstasy, though some reported using cannabis. All Groups – Healthy, not pregnant, absence of past or current major medical or psychiatric illness, including conditions that preclude informed consent. Absence of claustrophobia and conditions where serotonin (5HT) function is implicated. Abstention from all psychoactive drugs for at least 1 week prior to study day, with compliance verified by urinary drug screen performed at unspecified time before or on study day.
Drug Use Parameters – Current Ecstasy Users. Current ecstasy users took, on average, 139 ± 129 tablets over a lifetime (no range provided), with no information provided on average dose per use. Average frequency of use, assessed as use in last 3 months, was approximately .3 ± .26 tablets per month (1 ± .8 in 3 months), (range not provided) with no information on duration of use provided. Last use of ecstasy prior to study day, in days, 49 ± 35 days. Former (Ex) Ecstasy Users. Ex-ecstasy users reported taking, on average 218 ± 201 tablets over a lifetime (no range provided), with no information provided on average dose per use. Average frequency of use, assessed as use in last 3 months for ex-ecstasy users was

approximately .13 ± .2 tablets per month (.4 ± .6 tablets in last 3 months), (range not provided) with no information on duration of use provided. Last use of ecstasy prior to study day, in days, 126 ± 105 days. Other Drugs: For current users, average amount of alcohol drunk in last 3 months, in units = 27 ± 31 units, tobacco = 57 ± 45 cigarettes, cannabis = 20 ± 29 joints, cocaine, 6 ± 15 lines, LSD = 1 ± 1.7 times. For ex-users, average amount of alcohol drunk in last 3 months, in units (approximately) = 38 ± 33 units, tobacco = 54 ± 44 cigarettes, cannabis = 46 ± 39 joints, cocaine, .8 ± 2 lines, LSD = Either not reported or not used. Non-Users – Average amount used in last 3 months, alcohol, in units = 41 ± 38 in last 3 months, tobacco, in cigarettes = 17 ± 20 in last 3 months, cannabis, in joints = 3 ± 6 in last 3 months. Group Demographics and Matched Variables – All 3 groups matched on age. Age. Average age of current ecstasy users = 27 ± 5: average age of ex-ecstasy users = 24 ± 5: Average age of non-users = 23 ± 3 (Non-users slightly younger than either group of ecstasy users). Other Variables – Gender, as M / F ratio – Current ecstasy users, 7 / 3: ex-ecstasy users, 4 / 1: non-users, 4 / 6.

Measures: SPECT-Radioligand Binding – Scans performed with the $5HT2_A$ receptor radioligand, [123-I]R91150, co-registered with MRI scans. Frontal, parietal and occipital areas were selected as regions of interest (ROIs) and the cerebellum and temporal area selected as ROIs in another template. An investigator blind to subjects' drug use histories performed ROI analysis, with the cerebellum used as a reference due to presumed lack of $5HT2_A$ receptors. "Specific" binding for each ROI calculated as "mean" ROI binding / cerebellar binding = $5HT2_A$ binding ratio.

Regional Cerebral Blood Volume (CBV) – Performed on a sub-sample of 5 ecstasy users (4 men, 1 woman, average age = 25 ± 5, 3 (of 10) current users and 2 (of 5) former users and 6 controls (3 women, 3 men, average age = 22 ± 1. MRI scans made by 1.5 T scanner with gadolinium-based contrast material, with scans made 6 h before SPECT. rCBV maps derived on a voxel by voxel basis with dynamic imaging software, rCBV / white matter calculated for each ROI (L, R frontal and occipital cortices, white matter, putamen, globus pallidus), where mean CBV for region divided by unilateral mean white matter. High ratio = vasodilatation, low ratio = vasoconstriction.

Analyses: SPECT-Radioligand Binding – Examined via 1-way between subjects (across groups) ANOVA, with comparisons made between current ecstasy users, ex-ecstasy users and non-users, with p. value set at .05.

Regional CBV – CBV across groups (current ecstasy users, ex-ecstasy users and non-users) analyzed via unpaired student's t test, with p. value set at .05.

Relationship between Ligand Binding and rCBV – Mean radioligand binding was correlated with CBV values using Spearman's rank correlation. Correlations or regressions (unspecified) also performed where gender, age and extent of ecstasy served as covariates.

Results – Significant Differences: SPECT-Radioligand Binding – [123-I]R91150 binding in each of the 3 groups differed from ligand binding in 1 other group. Current ecstasy users had lower mean ligand binding values than ex-ecstasy users. Ex-ecstasy users had higher mean ligand binding values than did non-users, (ex-ecstasy users = > non-users = > current ecstasy users.)

Regional CBV – CBV was higher in ex-ecstasy users than in current ecstasy users. Ex-ecstasy users also had higher rCBV than non-users, but in certain (unspecified) brain areas only.

Relationships between Ligand Binding and rCBV – $5HT2_A$ receptor density (measured via ligand binding) was positively correlated with rCBV in the globus pallidus and occipital cortex in current ecstasy users, but not in non-users. Age, gender and extent of previous ecstasy use (presumably total number of tablets consumed over lifetime) did not modify the relationship between $5HT2_A$ receptor density and rCBV in either the globus pallidus or the occipital cortex.

Results – No Differences Found: No differences were found between CBV for current ecstasy users and controls in all brain regions studied (frontal, parietal and occipital regions).

Relationships between Ligand Binding and rCBV – $5HT2_A$ receptor density was uncorrelated with rCBV in any brain region studied in non-users.

Overall Effects: Density of $5HT2_A$ receptors was found to be lower in current ecstasy users, people who had last used ecstasy less than 2 months before the study day than in ex-ecstasy users, people who had last

used ecstasy more than 2 months before the study day. However, people defined as "ex-ecstasy users" had greater density of $5HT2_A$ receptors than did non-users. Thus the greatest difference in $5HT2_A$ receptor density, as measured through [123-I]-R91150 binding, was between "current" and "former" ecstasy users. Regional CBV was found to be higher in ex-ecstasy users than regional CBV in non-users or current ecstasy users, though it should be noted that the sample of ex-ecstasy users who underwent rCBV recording was very small (2 individuals). In current ecstasy users, but not in non-user controls, $5HT2_A$ receptor density is positively correlated with rCBV in the globus pallidus and the occipital cortex. Age, gender and number of ecstasy tablets taken over a lifetime did not moderate the relationship between $5HT2_A$ receptor density and rCBV in the areas listed above.
Comments: This paper could be considered a companion to the previous Reneman paper. The "ex-ecstasy users" who participated in this study appear to be the ecstasy user group featured in the first Reneman imaging paper. It should be noted that in contrast to findings with individuals who have not used ecstasy in at least 3 months, those who have used ecstasy more recently (within 2 months) show a decrease in $5HT2_A$ receptor binding density rather than an increase in $5HT2_A$ density. Because the authors did not report memory findings in this paper, it is hard to draw conclusions about the relationship between $5HT2_A$ receptor density and performance on measures of memory. Differences in CBV in ex-ecstasy users are used as the basis for hypotheses concerning associations between ecstasy use and cerebrovascular accidents, mentioned in the title of the paper. To date, there have been reports of cerebrovascular accidents acutely after ecstasy use, but no signs that chronic use of ecstasy increases risk of cerebrovascular accident. While matched for age, the samples were not matched for gender, and the sample of ex-ecstasy users is smaller than the other 2 samples (5 versus 10). Furthermore, conclusions drawn about regional cerebral blood volume are based on a sub-sample of 11 (3 current users, 2 ex-users and 6 non-users). Caution should be used in drawing conclusions about the general population from this study, particularly in the case of data on rCBV.

Ricaurte et al. (1990). Aminergic metabolites in cerebrospinal fluid of humans previously exposed to MDMA: Preliminary observations.

Ricaurte, G. A., Finnegan, K. T., Irwin, I. & Langston, J. W. (1990). Aminergic metabolites in cerebrospinal fluid of humans previously exposed to MDMA: Preliminary observations. Annals of the New York Academy of Sciences, 600, 698-707.

Purpose: Metabolites in CSF: To evaluate the neurotoxic potential of MDMA (ecstasy) in humans by comparing levels of 5HIAA in the cerebrospinal fluid of ecstasy users and non-using controls.
Design: Non-experimental (retrospective) 2-group between subjects (across groups) design with ecstasy users compared with matched non-user controls, with drug use (ecstasy use or no ecstasy use) as a between subjects variable. All subjects underwent lumbar puncture.
Subjects: 33 regular ecstasy users and 24 people with lower back pain who had not used ecstasy. No recruitment information provided for either group. However, other studies conducted by this author recruited ecstasy users nationally, while non-user controls probably resided in the Baltimore (MD) / Washington, DC area. Matching – On gender
Criteria for Inclusion, Ecstasy Users – Prior or current use of ecstasy, with no restrictions on extent of use stated (all users had taken >10 tablets, so using ecstasy on at least 10 occasions may have been a requirement.) Non-Users – No past or current use of ecstasy, undergoing myelography for diagnostic purposes relating to low back pain. All Groups – No current major medical or psychiatric illness, as assessed through physical examination, neurological examination and laboratory analyses. Abstinence from all psychoactive drugs for at least 2 weeks before study day, with compliance verified through self-report only.
Drug Use Parameters – On average, ecstasy users had used ecstasy on 52 ± 45 occasions (11-219), with average usual dose per use of 1.25 ± .4 tablets per use (may be 1 ± .3 due to subjects' belief that 1 tablet = 125 mg) (.5 – 2 tablets). 12 / 33 individuals reported using higher doses. Maximum dose used was

(approximately) 7 tablets (or 5.6 tablets, if 1 tablet = 125 mg) per occasion. Average frequency of ecstasy use was 1.25 ± .25 times a month, reported as intervals of 3.4 ± 1.8 weeks. 13 of 33 reported occasional daily use for 5-7 days. Average duration of use, in months, was 42 ± 22.8 months (6 – 96 months). Time elapsed, in days, since last use was, on average, 116.9 ± 163.1 days (14 – 728 days). Other Drugs – 'Most" ecstasy users were also polydrug users. Ecstasy users also used these drugs: marijuana, LSD, mescaline and psilocybin (no information on percentage of group using each), Occasionally used were: MDE ("Eve"), 2-CB, and sporadic use of cocaine, other stimulants.
Group Demographics and Matched Variables – Ecstasy users and non-users matched on gender. Gender, as M / F ratio – Ecstasy users, 21 / 12: non-users, 14 / 10. Other variables – Age. – Average age of ecstasy users = 36 ± 10 (19 – 71): average age of non-users = 45 ± 14 (21-73). Non-users were approximately 9 years older than ecstasy users.
Measures: Drug Analysis – 16 / 33 subjects brought 1 sample of ecstasy they had purchased (1 / 33 brought sample plus "suspect" pill sold as ecstasy, but producing different effects). Material analyzed via thin-layer chromatography, gas chromatography / mass spectrometry with nitrogen-phosphorus detector.
Clinical Assessment – Asked to report on functional domains believed to be associated with serotonergic function, including sleep, pain perception, sexual behavior, aggression, mood regulation, appetite and food preference. Subjects also asked about any recent (post-ecstasy) tendency toward impulsiveness, obsessiveness or cognitive decline. However, no psychometric measures used to assess any of the dimensions listed above.
Monoamine Metabolites in CSF – Lumbar puncture performed from morning until late afternoon, without any requirement for overnight fast or bed-rest, but with conditions of lumbar puncture matched between controls and ecstasy users. Concentrations of 5HIAA, HVA and MHPG measured through HPLC (high-performance liquid chromatography) with electrochemical detection.
Proteins and Cell Counts in CSF – Amount of total protein concentration and cell count (white blood cells, lymphocytes, polymorphnuclear cells) performed in CSF of ecstasy users only.
Analyses: (Metabolites in CSF only). Comparisons between ecstasy users and non-users made via 2-tailed Student's t-test. Correlations were carried out with Pearson's correlation coefficient. Correlations performed between CSF 5HIAA values and number of occasions of ecstasy use, duration of use and time since last use.
Results – Significant Differences: Monoamine Metabolites in CSF – Ecstasy users had lower levels of 5HIAA than controls (26% less 5HIAA).
Clinical Assessment – There was no formal comparison between non-users and ecstasy users, and most reported no problems in the functional domains asked about. However, 3 of 33 ecstasy users reported experiencing psychiatric symptoms. 1 complained of "depression," 1 of "poor concentration and bad memory" and 1 of "diminished creativity." All believed their ecstasy use played a role in producing symptoms but also identified other causes as well.
Results – No Differences Found: Monoamine Metabolites in CSF – Non-users and ecstasy users had similar levels of HVA and MHPG in CSF. While women in both groups had higher 5HIAA values than men in both groups, this difference did not reach statistical significance.
Protein and Cell Count in CSF (Ecstasy Users Only) – Total protein count for ecstasy users was within the normal range for ecstasy users. Protein level was slightly elevated in 5 / 33 subjects, but only 1 / 33 had protein level 2 times greater than upper limit of normal protein level. Cell counts (immune cell counts) were within normal limits for all but 1 subject (1 of 33). (This subject also had high protein levels in CSF, but no sign of meningeal irritation).
Correlations – 5HIAA level in CSF was neither positively nor negatively correlated with lifetime number of occasions of ecstasy use. Amount of 5HIAA in CSF was unrelated to duration of ecstasy use. Level of 5HIAA in CSF was neither positively nor negatively correlated with self-reported time since last use of ecstasy.
Clinical Assessment – No formal analysis compared non-users with ecstasy users on the basis of self-reported symptoms, and only 3 of 33 ecstasy users reported complaints concerning any of the functional

domains they were asked about. Ecstasy users did not have complaints about disturbed appetite or sleep, increased or decreased aggressiveness, changes in sexual behavior or in pain perception.
Results – Other: All ecstasy samples provided (16 / 16) contained MDMA. "Suspect" pill contained MDA.
Overall Effects: Regular ecstasy users had lower levels of 5HIAA than did people with lower back pain with no history of ecstasy use. However, both groups had the same levels of the dopamine metabolite HVA and the norepinephrine metabolite MHPG. Total protein level and cell counts, performed on ecstasy users only, found that the majority of the ecstasy users had values within the normal range. Only 1 subject had protein levels that were twice the normal level, and only 1 subject (also at the high end of elevated protein levels) had a high immune cell count, but no sign of infection. A majority of ecstasy users reported no symptoms related to serotonergic function (sleep disturbance, mood disorders, aggression, impulsivity, change in appetite, pain or sexual behavior). Only 1 of 33 complained of depression and 2 of 3 complained of decline in cognitive function (poor concentration, decline in creativity). Since these were not measured in non-user controls and normative data on these complaints not provided, it would appear that there is no significant increase in these complaints. All samples of material purchased as "ecstasy" (in the late 1980s – 1990) were identified as MDMA except for 1 pill, identified as MDA.
Comments: This is an early paper attempting to associate ecstasy use with alteration in serotonergic function, here measured via the fairly invasive and unpleasant method of measuring metabolites in cerebrospinal fluid via lumbar puncture, as well as a clinical assessment. Because of the invasiveness of this technique, the authors had to use non-user controls receiving the procedure for diagnostic purposes. It is possible that people with lower back pain might differ from healthy controls in cerebrospinal monoamine metabolites or in measures of psychological health. No formal comparisons were made between ecstasy users and non-users on assessment for psychiatric complaints, and so it is difficult to tell whether the number of complaints (3 of 33 in ecstasy users) is within the expected range for people of the same gender and age group. The paper is also notable for its attempt to identify at least some of the material people purchased as ecstasy, and it appears that most or all of the material was MDMA. While the findings in this paper might support the case for regular ecstasy / MDMA use producing reduction in serotonin turnover, these findings cannot support a relationship between reduced 5HIAA and changes in physiological or mental health.

Rodgers (2000). Cognitive performance amongst recreational users of "Ecstasy."

Rodgers, J. (2000). Cognitive performance amongst recreational users of "ecstasy." Psychopharmacology, 151, 19-24.

Purpose: Cognitive function, general: To investigate the effects of regular ecstasy use and regular cannabis use, independent of ecstasy use, on memory and attentional processes by comparing performance on tests of reaction time, memory and attention in ecstasy users, cannabis users and non-user controls.
Design: Non-experimental (retrospective) 3-group between subjects (across-groups) design comparing ecstasy users (who had all used cannabis) with 2 matched control groups; cannabis users and people with no history of drug use (non-users). All subjects completed a test battery assessing memory and attentional processes and the Cognitive Failures Questionnaire.
Subjects: 15 regular ecstasy users, 15 cannabis users who had never taken ecstasy and 15 individuals who had never taken any illicit drugs. All subjects resided near the Sunderland (England) area and members of all 3 groups were recruited via "snowball" technique (word of mouth and direct acquaintance with the researchers). Matching – On gender, age, socioeconomic status and educational level. Ecstasy users and cannabis users matched on cannabis use.
Criteria for Inclusion, Ecstasy Users – Having used ecstasy on at least 5 occasions. Abstinence from ecstasy for at least 2 months prior to study day and abstinence from cannabis for at least 1 month prior to

study day, with compliance with both requests verified via self-report only. Cannabis Users – Regular use of cannabis, with regular use undefined, perhaps using cannabis on 5 or more occasions. No past or current use of ecstasy, and abstinence from cannabis for at least 1 month prior to study day, with compliance verified via self-report only. Non-users – No use of any psychoactive drugs, including either ecstasy or cannabis. All Groups – Abstinence from any psychoactive substance on study day, with compliance verified through self-report only. Absence of psychiatric illness reported for all 3 groups, but unclear as to whether this was a criterion for study participation.
Drug Use Parameters – Ecstasy Users – Ecstasy users taken ecstasy on an average of 20 occasions (range not provided) over a 5 year period, with no information provided on average dose per use. Duration of use, on average, was 60 months, (range not provided) with no information provided concerning frequency of use, though using the numbers above provides a rough calculation of approximately .3 occasions per month. Time since last use was at least 60 days (precise information not provided). Other Drugs – Ecstasy users also reported using cannabis on an average of 4 days a week, with an average duration of use of 10 years. (No information on dose per use). Time of last use prior to study day was reported as at least 30 days. Use of these drugs reported on less than 5 occasions: LSD (3 / 15), amphetamines (2 / 15) and cocaine (3 / 15). Cannabis Users – Cannabis users reported using cannabis on an average of 4 days a week for an 11-year period. (No information on dose per use). Time of last use prior to study day was at approximately 30 days.
Group Demographics and Matched Variables – Ecstasy users, cannabis users and non-users all matched on gender, age, socioeconomic background and educational level. Ecstasy users and cannabis users matched on frequency of cannabis use. Gender, as M / F ratio – Ecstasy users, 8 / 7: cannabis users, 8 / 7: non-users, 9 / 6. Age. Average age of ecstasy users, 31 ± 4 years (23-44 years): cannabis users, 30 ± 6 years (21-43 years): non-users, 32 ± 4 years (26-39 years). Socioeconomic Status – Subjects in all groups reported to be working in "professional careers." Educational Level, as number of people with this amount of education and approximate years (provided via personal communication) – GCSE ("school leaving" exam), ecstasy users = 3, cannabis users = 2, non-users = 3 (approx. 10 years), "A" levels (high school pre-college), ecstasy users = 2, cannabis users = 3, non-users = 4 (approximately 12 years), undergraduate, first degree, ecstasy users = 7, cannabis users = 8, non-users = 7 (approximately 16 years), post-college, graduate school, ecstasy users = 3, cannabis users = 2, non-users = 1. Average education, ecstasy users = 2.6 (approx. 15), cannabis users = 2.6 (approximately 15 years), non-users = 2.4 (approximately 14.5 years).
Measures: Tests of Reaction Time – Via computerized tests devised specifically for this study. Subjects press spacebar after seeing or hearing a target (white circle for visual RT, simple tone for auditory RT). Subjects press number corresponding to number (from 1 to 9) displayed on screen for test of complex RT.
Tests of Memory – Assessed via WMS. This scale consists of Figural Memory (match to sample with designs as targets), Logical Memory (Subject listens to and retells story by memory, scored on total number of ideas recalled from story), Visual Paired Associates, Verbal Paired Associates (learn associations), Visual Reproduction (Draw picture from memory), Digit Span, Visual Memory Span (Subject watches and reproduces sequences of taps of colored squares). Delayed recall is tested by a second presentation of Logical Memory, Visual Reproduction, Visual Paired Associates and Verbal Paired Associates. Index Scores – Calculated using weights provided by the WMS record form. Index scores calculated for General Memory, Verbal Memory, Visual Memory, Delayed Recall and Attention and Concentration.
Self-Reported Cognitive Deficits – Measured via Cognitive Failures Questionnaire.
Analyses: All data (tests of reaction time, WMS Index scores, WMS sub-test scores and Cognitive Failures Questionnaires) analyzed via 1-way ANOVA, with drug use (ecstasy use, cannabis use or no drug use) as between-subjects factor. Post-hoc comparisons were made via Newman-Keuls procedure.
Results – Significant Differences: Tests of Memory – Both groups of drug users (ecstasy users and cannabis users) had lower General Memory index scores (ecstasy users, cannabis users < non-users), but since Verbal Memory is part of this score, the difference reflects differences in Verbal Memory. Verbal memory score differed across all three groups, with ecstasy users, cannabis users < non-users. Ecstasy

users and cannabis users performed less well on the Logical Memory sub-test than did non-users. There were differences in Delayed Recall index score, with ecstasy users, cannabis users < non-users. Ecstasy users and cannabis users did not perform as well on Logical Memory II. Ecstasy users performed less well on Verbal Paired Associates II and Visual Paired Associates II when compared with cannabis users and non-user controls (ecstasy users < cannabis users < = non-users).
Results – No Differences Found: Tests of Reaction Time – Ecstasy users, cannabis users and non-users performed similarly on all tests of RT: visual reaction time, auditory reaction time and complex reaction time.
Tests of Memory – There were no differences between any of the 3 groups on performance of the Verbal Associates sub-test. All 3 groups (ecstasy users, cannabis users, non-users) scored similarly on the Visual Memory Index of the WMS and on all sub-tests that made up this score (Figural Memory, Visual Associates-Immediate, Visual Reproduction). Attention and Concentration index score was similar for all 3 groups, including performance on all components (Mental Control, Digit Span, Visual Memory Span). All 3 groups scored similarly on Visual Reproduction II (delayed visual reproduction).
Self-Reported Cognitive Deficits – Ecstasy users, cannabis users and non-users all scored similarly on the Cognitive Failures Questionnaire, indicating that the 3 groups did not differ in respect to self-reported everyday difficulties with cognitive function.
Overall Effects: Immediate verbal recall, but not immediate visual recall, was worse in cannabis users and ecstasy users (who also used cannabis) when compared with controls who had never used either drug. However, ecstasy users, but not cannabis users, performed less well on tests of delayed recall, in the verbal and visual domain. Neither ecstasy use or cannabis use seemed to affect immediate visual recall or attention and concentration, with all three groups scoring similarly on index scores and tests of these areas. Members of all 3 groups also performed equally well on tests of simple and complex reaction time. While ecstasy users and cannabis users each performed less well on some tests of memory, neither group reported an increased number of difficulties related to problems with memory or cognition, as assessed in the Cognitive Failures Questionnaire.
Comments: Like Croft and Gouzoulis-Mayfrank, Rodgers has sought to separate the effects of cannabis from the effects of ecstasy on cognitive function by employing 2 matched control groups, one consisting of regular cannabis users who have never used ecstasy and one consisting of individuals with no history of drug use. The findings in this paper support the existence of two independent drug-related effects, with cannabis affecting immediate verbal recall and ecstasy (perhaps interacting with cannabis) affecting delayed recall. There were no attempts to correlate one or more parameter of ecstasy or cannabis use with performance on tests of cognitive function. The author suggests that some of the effects attributed to cannabis in both ecstasy and cannabis users may be related to cannabis withdrawal. The paper is notable in being moderately successful in matching ecstasy users and cannabis users on use of cannabis and other drugs, and making sure that members of both drug-using groups were not regular users of drugs other than ecstasy or cannabis. Samples used in this study are larger than those used in other studies, but the samples are small enough to warrant some caution when extrapolating the findings to larger groups of ecstasy and cannabis users.

Schifano et al. (1998). MDMA ("Ecstasy") consumption in the context of polydrug abuse; A report on 150 patients.

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

Purpose: Psychiatric health, cognitive function, general, epidemiological; to investigate the subjective effects of ecstasy and ecstasy usage patterns and possible psychopathological consequences of regular ecstasy use in the context of polydrug use. (See "Non-Clinical Studies" for a summary of the paper focusing on the subjective effects and epidemiology of ecstasy use in a sample of polydrug users).

Design: Non-experimental (retrospective) 2-group between subjects (across groups) design comparing drug free ecstasy users with matched non-user controls, with drug use as a between-subjects factor, and with all non-users and sub-set of users completing tests of memory and executive function. (Comparisons are also made between ecstasy users with and without psychiatric problems, also using a retrospective 2-group between subjects design wherein subjects are divided into "problematic" and "problem-free" ecstasy uses on the basis of diagnosis with at least one psychiatric problem).
Subjects: 10 out of 150 ecstasy users seeking treatment for substance abuse, consecutively presented in N. Italian addiction unit and 20 non-user controls. Matching – On age and education.
Criteria for Inclusion, Ecstasy Users – Using ecstasy at least once. Non-Users – No past or current of any illegal drugs, including ecstasy, but similar age and education as ecstasy users. All Groups – No other criteria stated, though all subjects received physical and psychiatric examinations.
Drug Use Parameters – Information for sub-set of 10 ecstasy users unavailable. Information here is for sample of 150 users sampled in study, with some information presented only after categorization by presence of psychiatric problems). Ecstasy users took an average of 11 tablets over a lifetime (1-125), 1 in 4 had taken 50 or more tablets overa lifetime; no information on average dose per use provided, though author reports that most "usually" used 1 tablet per occasion. Average duration of ecstasy use was 8.125 months (.25-24 months). Frequency of use, in tablets per month, ranged from approximately .48 to 6 tablets per month, with no overall average presented (problem-free users = 1 per month, problematic users = 4 per month). Largest single intake ranged from 1 to 5 tablets, with problem-free users average = 1 tablet, problematic users = 3 tablets. Time of last use prior to study day not provided. Age when First Used – Average age when ecstasy was first consumed = 19 years. Other Drugs Used – 58% had used opiates. Percentage of problematic and non-problematic users who also reported use of these substances: cannabis, 66% and 78%, cocaine, 56% and 63%, and 30% of problematic users and 57% of non-problematic users had used other drugs (nitrites, other amphetamines, and psychedelics).
Group Demographics and Matched Variables – While the author indicates that 10 ecstasy users and 20 non-users were matched by education, specific information is not provided about the demographics of either group or years of education attained by members of either group. Gender, overall, as M / F ratio is 124 / 26. Age, average age = 23.2. 48% of overall sample of ecstasy users were employed, 21% were students and 31% were unemployed. The degree to which ecstasy users and non-users were matched for age or education cannot be assessed, due to lack of information. About non-users
Measures: Memory – (10 ecstasy users and 20 non-users only) Assessed via RBMB (Rivermead Behavioral Memory Battery.
Executive Function (Planning Abilities) – (10 ecstasy users and 20 non-users only) Assessed via Tower of London (TOL) task.
Psychiatric Symptoms – (Overall ecstasy user sample only) Assessed via psychiatric interview, with focus on symptoms believed to be related to serotonin function, including mood, sleep, aggression, impulsivity and appetite disorders, and cognitive decline. Percentage of ecstasy users reporting psychiatric disorders compared with number of ecstasy users not reporting any psychiatric disorders.
Analyses: Memory and Executive Function – Not clearly reported, but probably unpaired Student's t test.
Psychiatric Symptoms – Relationship between being diagnosed with at least 1 psychiatric symptom and demographic variables analyzed via t-test. The effects of drug use parameters (lifetime use, frequency of use, duration of use, largest single intake) on presence versus absence of psychiatric complaints analyzed via Mann-Whitney U test. The effect of other drug use on diagnosis with at least 1 psychiatric symptom was analyzed via chi-square.
Results – Significant Differences: Memory – Ecstasy users had lower scores on the RBMB than did non-drug users.
Executive Function – Ecstasy users had lower scores on the TOL test than did non-drug users.
Psychiatric Symptoms – See "Non-Clinical Studies" for more detailed description of findings. Depression, psychotic disorders and cognitive decline were the most frequently diagnosed problems. 48% were categorized as "non-problematic users" and 52% were deemed to be problematic users. Ecstasy users diagnosed with at least 1 psychiatric symptom were more likely to report their first use of

ecstasy at a younger age than those without psychiatric symptoms were. Ecstasy users with at least 1 psychiatric problem had a taken ecstasy on a greater number of occasions than ecstasy users without psychiatric problems (lifetime use of 47 versus 3 tablets). Ecstasy users with psychiatric problems reported a higher frequency of use (weekly or more often) than ecstasy users without psychiatric problems who used ecstasy once per month or less often. Ecstasy users with psychiatric problems reported a longer duration of use (4-24 months) compared with users without any psychiatric symptoms (duration of .4-12 months). Ecstasy users diagnosed with at least 1 psychiatric problem more likely to have taken a larger "maximum dose" of ecstasy than those without psychiatric problems (average maximum use of 3 tablets versus maximum use of 1 tablet).
Results – No Differences Found: Psychiatric Symptoms – See "Non-Clinical Studies" for more details. Gender and weight did not increase or decrease likelihood of having at least 1 psychiatric symptom (though it appears that while men are equally split between "problematic" and "problem free" users, there are more women with psychiatric symptoms than there are women without them. There were no differences in lifetime use of benzodiazepines, opiates or cocaine and being diagnosed with at least 1 psychiatric symptom (i.e. being a problematic user). Overall use of other drugs neither increased nor decreased the likelihood of being diagnosed with at least 1 psychiatric symptom.
Overall Effects: A sub-set of 10 ecstasy users drawn from a larger sample of 150 did not perform as well on a test of memory (the RBMT) or a test of executive function (the TOL) as did 20 individuals with no history of drug use. 27% of a sample of 150 ecstasy users reported experiencing some cognitive decline after ecstasy use. 53% of larger sample (150 ecstasy users) also diagnosed with psychiatric problems after ecstasy use, with diagnoses correlated with subject's age, all parameters of ecstasy use examined (age at first use, frequency of use, duration of use, overall lifetime consumption and maximum dose per use). Ecstasy users with at least 1 psychiatric symptom were more likely to use some drugs (cannabis, alcohol, LSD and stimulants) but not others (benzodiazepines, opiates, cocaine), even though raw percentage data suggest that users with psychiatric problems use opiates at a much higher rate than ecstasy users who were not diagnosed without problems.
Comments: This paper is more notable for its exploration of the acute and sub-acute effects of ecstasy in polydrug users than it is for its exploration of the effects of ecstasy use on cognitive function. While the authors present findings supporting the existence of cognitive deficits after ecstasy use, they do not provide enough information about either group of participants for a thorough evaluation of these claims. Given the demographics of the entire sample, it seems highly likely that the sub-set of ecstasy users tested were polydrug users, while non-users had no history of illicit drug use. This raises the issue of whether differences in memory or executive function in this sample arise out of regular ecstasy use or from regular use of other drugs, such as stimulants or opiates. Since all ecstasy users came from a sample of polydrug users who were seeking help for substance abuse, it is unclear as to whether this sample is representative of ecstasy users in general. Because the sample in this paper is unlikely to be representative of ecstasy users in general, findings probably cannot be generalized to the population at large. Sample size is also small as well.

Semple et al. (1999). Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ("Ecstasy") users.

Semple, D. M., Ebmeier, K. P., Glabus, M. F., O'Carroll, R. E., Johnstone, E. C. (1999). Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ("ecstasy") users. British Journal of Psychiatry, 175, 63-69.

Purpose: Brain imaging (SPECT with ligand): To investigate the effects of regular ecstasy use on amount of serotonin and dopamine transporter binding, as measured via SPECT with a radioligand sensitive to both the serotonin and the dopamine transporter. Specific Hypothesis Tested – That regular ecstasy use would produce abnormalities in serotonin transporter (SERT) binding but would not produce abnormalities in dopamine transporter binding.

Design: Non-experimental (retrospective) 2-group between subjects (across groups) design comparing regular ecstasy users and a matched group of polydrug users with no history of ecstasy use, with drug use as a between-subjects variable, with all subjects completing tests of cognitive function and receiving SPECT scans.
Subjects: 10 regular ecstasy users and 10 polydrug users with no past or current use of ecstasy residing in the Edinburgh (Scotland) area. Members of both groups were recruited from amongst the dance event / rave community via advertisements, word of mouth and contact with independent (public health) drug agency volunteers. Matching – On gender, age, education, estimated IQ (through NART), drug use and lifestyle.
Criteria for Inclusion, Ecstasy Users – Lifetime consumption of at least 50 ecstasy tablets, having taken ecstasy for a year or longer and current regular use of ecstasy. Abstinence from ecstasy for at least a week prior to study day, with compliance verified by hair sample taken before study day. Non-Users – No past or current use of ecstasy, but use of other drugs permitted. All Groups – Being male, between ages of 18-35, and without past or current psychiatric or medical illnesses. No history of head injury or neurological health problems, as assessed via neurological examination.
Drug Use Parameters – Ecstasy users had taken, on average, 672 ± 647 tablets of ecstasy over a lifetime (50-1800), with no information provided on average dose per occasion. Average frequency of use not provided. Duration of use not reported, (estimated range, 12 – 120 months, from inclusion criterion and text). The time since last use of ecstasy, prior to study day, was 18 ± 8 days (6 – 28 days). Other Drugs – Average weekly use of cannabis in ecstasy users, in 1/ 16 oz = 3 16^{th} oz, in ecstasy users 2.3 16^{th} oz in non-users. Daily use: 6 / 10 ecstasy users, 4 / 10 non-users. Weekly use, 3 / 10 ecstasy users, 3 / 10 non-users. Monthly use, 0 ecstasy users, 2 / 10 non-users. Irregular, 1 / 10 non-users, 1 / 10 non-users. Amphetamine, mean weekly use for ecstasy users = 1.3 g and for non-users, .7 g. Weekly use of amphetamine, 3 / 10 ecstasy users, 0 non-users. Monthly use of amphetamine, 3 / 10 ecstasy users, 1 / 10 non-user. Irregular use 4 / 10 ecstasy users, 9 / 10 non-users. Ecstasy users drank 19.8 ± 10 units of alcohol weekly and smoked 15.4 ± 5.2 cigarettes a day: non-users drank 15.1 ± 12.8 units of alcohol weekly and smoked 11.5 ± 8 cigarettes a day. Both groups reported occasional use of LSD, "magic mushrooms" and cocaine (figures not reported).
Group Demographics and Matched Variables – Ecstasy users matched with non-users on gender (all male), age, height, weight, education, estimated IQ via NART score, drug use, personality factors and GHQ score responses. Gender, as M / F ratio – Ecstasy users, 10 / 0: Non-users, 10 / 0. Age. Average age of ecstasy users = 25.5 ± 4.4, average age of non-users = 24.2 ± 5.2. Height, Weight, Height in cm, weight in kg – Ecstasy users, 177 ± 8.6 cm, 72.1 ± 10.4 kg: Non-users, 174.5 ± 6.8 cm, 72.4 ± 9.1 kg. Education Level, in years – Ecstasy users = 14.7 ± 2.3 years, non-users = 15 ± 2.5 years. Estimated IQ from NART score: Ecstasy users, 107.6 ± 8.2, non-users = 109.7 ± 7.8. Personality Measures (Assessed via short form of Eyesenck Personality Questionnaire, or EPQ). Average extroversion score for ecstasy users = 8.4 ± 3.1 and for non-users 7.4 ± 3.6. Average neuroticism score for ecstasy users = 4.3 ± 3.3 and for non-users, 3.2 ± 3.1. Average psychoticism score for ecstasy users = 4.7 ± 1.7 and for non-users = 4.5 ± 2.2. "Lie" score, for ecstasy users = 2.4 ± 1.5, and for non-users = 3.7 ± 2.7. Authors report subjects matched on General Health Questionnaire score, but scores not provided.
Measures: Tests of Cognitive Function – Reaction time (RT) and psychomotor speed tested via Trails A and CANTAB simple RT tests. Visual memory tested via CANTAB Delayed Matching to Sample test. Verbal memory measured via California Verbal Learning Test (verbal memory test, similar to RAVLT with immediate and delayed recall of items). Attention measured via WMS-R Digit Span. Executive function assessed via CANTAB Spatial Working Memory test, Trails B, verbal fluency (FAS word generation) test and Stroop task.
Imaging – Performed via SPECT with the radioligand [123I]-betaCIT, which binds to serotonin and dopamine transporter. The first scan was performed 90 minutes after ligand injection and the second was performed 21-23 h after injection. Specific binding to serotonin and dopamine transporter was calculated. An ROI analysis was carried out by an individual blind to study hypotheses, using a reference ROI at

cerebellar area. ROI unspecified but included: Frontal (L, R), anterior cingulate (L, R), anterior temporal (L, R), middle temporal (L, R), occipital (L, R), calcarine (L, R), posterior cingulate (L, R), caudate (L, R), putamen (L, R), thalamus (L, R), caudate and putamen on Day 2 (L, R) and caudal midbrain / pons (R?).
Analyses: Tests of Cognitive Function – Not clearly reported, but involved a parametric between-group test of significance, such as ANOVA or Student's t-test, with drug use (ecstasy use versus no ecstasy use) as a between-groups factor. Number of tablets taken over a lifetime was correlated with scores on each test of cognitive function.
Imaging – ROI data examined via ANCOVA, with drug use (ecstasy use or non-use) as between-group factor and white matter or cerebellar binding counts as covariant.
Correlations – A correlation was performed on lifetime ecstasy dose and specific binding to the serotonin transporter site (SERT). A correlation was performed on time since last use and ligand binding.
Results – Significant Differences: Tests of Cognitive Function – In ecstasy users, larger lifetime doses of ecstasy were associated with reduced performance on CVLT (verbal memory). Larger lifetime doses of ecstasy were also associated with lower scores on the CANTAB Spatial Working Memory test (authors define as test of executive function), indicating deficits in verbal memory and either spatial working memory or executive function associated with lifetime dose of ecstasy. These negative associations between lifetime ecstasy use and performance on CVLT and Spatial Working Memory task are unmodified when estimated IQ is entered into equation.
Imaging – Ecstasy users had reduced binding for SERT sites in 4 of 22 brain regions (left occipital, calcarine (L, R) and R posterior cingulate. Time since last ecstasy use was correlated with extent of binding in many (unspecified) regions, and specifically L calcarine region. Statistical parameter modeling confirmed findings of ROI analysis and also revealed a positive correlation between time since last use of ecstasy and ligand binding in the mid-line limbic areas (but authors later report absence of correlation between time since last use and tracer binding in these areas).
Results – No Differences Found: Tests of Cognitive Function – There were no differences between ecstasy users and non-users on simple RT test, Trails A, Matching to Sample (visual memory), Digit Span (attention), Trails B (executive function), verbal fluency and Stroop task.
Imaging – Ecstasy users and non-users were found to have similar SERT binding in 18 of 22 brain regions examined via ROI, including frontal (L, R) anterior cingulate (L, R), anterior and middle temporal (L, R), R occipital, L posterior cingulate, caudate, putamen, thalamus (all 3 bilaterally), caudate and putamen on Day 2 (L, R) and R caudal midbrain / pons. There was no relationship between lifetime ecstasy dose (in tablets) and ligand binding at any brain region assessed. Ecstasy users did not differ in dopamine binding in any brain region examined.
Overall Effects: A SPECT scan using a radioligand apparently sensitive to both serotonin and dopamine transporter sites found reduced serotonin transporter binding in the left occipital area and bilaterally in the calcarine and cingulate area in ecstasy users, but not matched non-user controls. Time since last ecstasy use was negatively correlated with serotonin binding in some areas and perhaps positively correlated with binding in other areas. While there were differences between the two groups in serotonin binding, there were no differences between these groups in dopamine binding. Both ecstasy users and non-users scored similarly on tests of reaction time, attention, memory (visual and verbal) and executive function. Yet lifetime (overall) use of ecstasy was correlated with poorer performance in tests of verbal memory and a test of executive function or spatial working memory. The authors' hypothesis was confirmed; ecstasy users differed from polydrug users who had not used ecstasy on the basis of serotonin transporter binding and not dopamine transporter binding. However, the hypothesis did not predict where differences in serotonin transporter binding would appear.
Comments: This paper is notable for using two very carefully matched groups, both drawn from the same population (relatively young individuals involved in the dance event culture in the Edinburgh area). This strategy would seem to strengthen the validity of differences found between the groups. However, it should be noted that the study had a large attrition rate, with many potential subjects dropping out or being difficult to locate before the study was completed. It is interesting that the authors find differences

in serotonin transporter binding while finding no differences in cognitive function between the groups. Instead, overall lifetime use of ecstasy was more closely related to performance on tests of memory and executive function than simply using 50 or more tablets of ecstasy. The authors made an unusual choice of radioligand for their studies, choosing one that binds to both serotonin and dopamine transporter sites. They sought to distinguish binding at the 2 sites by performing scans at 2 different times, but the success of this procedure is unclear (see Heinz & Jones, 2000). Though the samples were carefully matched, they are small and contain males only; hence some caution should be used when generalizing from the findings in this study to the population at large or to both genders.

Tuchtenhagen et al. (2000). High intensity dependence of auditory evoked dipole source activity indicates decreased serotonergic activity in abstinent Ecstasy (MDMA) users.

Tuchtenhagen, F., Daumann, J., Norra, C., Gobbele, R., Becker, S., Pelz, S., Sass, H., Buchner, H. & Gouzoulis-Mayfrank, E. (2000). High intensity dependence of auditory evoked dipole source activity indicates decreased serotonergic activity in abstinent ecstasy (MDMA) users. Neuropsychopharmacology, 22, 608-617

Purpose: Electroencephalography (evoked potentials), personality: To investigate the effects of regular ecstasy use on serotonin system functioning by comparing ecstasy users with two control groups (cannabis users and non-drug users) on auditory evoked potentials and personality characteristics. Specific hypothesis tested – that ecstasy users should be more likely than cannabis users or non-user controls to exhibit a relationship between intensity (volume) of sound and aspects of AEP (tangential NI / P2 source activity).
Design: Non-experimental (retrospective) 3-group; between-subjects (across groups) design comparing regular ecstasy users with 2 matched control groups, cannabis users and people who used no drugs (non-users). Drug use (ecstasy and cannabis use, cannabis use alone or no drug use) served as between-subjects factor. All subjects underwent recording of auditory evoked potentials.
Subjects: 28 regular ecstasy users, 28 cannabis users and 28 individuals with no past or current drug use, with all subjects recruited via personal contacts with people in the Aachen (Germany) dance scene and via snowball technique. (Same sample studied in Gouzoulis-Mayfrank et al, 2000). Matching – On gender, age, approximately matched on education level. Ecstasy users and cannabis users matched on cannabis use.
Criteria for Inclusion, Ecstasy Users – Having used ecstasy regularly for 6 months or more, with minimum frequency of use at twice per month within the last 2 years, or having used ecstasy on at least 25 occasions in the past 2 years. No regular use of other legal or illegal drugs except for cannabis, (regular use defined as once a month or more in last 6 months) and no heavy use of alcohol (defined as self-reported severe drunkenness at least twice a month). Abstinence from ecstasy for at least 7 days prior to study day, with compliance verified through drug screen (unspecified, probably urinary) on day of study. Cannabis users – No current or prior use of ecstasy, and matched with ecstasy users on extent of cannabis use (not all members of the "cannabis user" control group used cannabis because not all ecstasy users were cannabis users). No regular use of any other psychoactive drugs, with regular use defined above, and no heavy use of alcohol, as defined above. Non-users – No past or current use of ecstasy, cannabis or any other legal or illicit drug. All groups – Absence of any major psychiatric or medical illness and no organic brain disorder, as screened via medical history and psychiatric interview. Both ecstasy users and cannabis users required to abstain from cannabis use on day of study. While drug screen is performed on study day, people with positive screens for cannabis were not excluded from the study.
Drug Use Parameters – Ecstasy users reported an average lifetime use of 93.4 ± 119.9 ecstasy tablets (20-500), and they used an average dose of 1.4 ± .9 tablets per occasion (.5 – 3.5 tablets per occasion). Average frequency of use was 2.4 ± 1.6 times per month (.75 – 8 times), and average duration of use in

months was 27 ± 18 months (6-60). Self-reported length of drug-free period before study day, in days was 41 ± 71 days (7-365 days, median 23 days). On average, people first took ecstasy at age 19.4 ± 3.8 years (14-27). 26 / 28 ecstasy users were regular ecstasy users and 2 / 28 were sporadic ecstasy users. Cannabis use – 22 ecstasy users were regular cannabis users, 1 used cannabis sporadically and 5 did not use cannabis. In matched cannabis user group, 23 were regular cannabis users, 2 were sporadic cannabis users and 3 did not use cannabis. Cannabis was used on 20.7 ± 11.5) days a month by ecstasy users and 20.9 ± 10.2 days per month by cannabis users. Duration of cannabis use extended for 66.6 ± 37 months for ecstasy users and for 35.1 ±24 months for cannabis users. Ecstasy users had last used cannabis 4.3 ± 5.3 days (median 2 days) before the study day and cannabis users last used cannabis 4 ± 15.5 days (median 1 day) before the study day. Age at onset of cannabis user for ecstasy users was 16.6 ± 2.9 years, and for cannabis users 17.1 ± 2.4 years. 17 ecstasy users and 20 cannabis users tested positive for presence of THC in urine on study day, and 11 ecstasy users and 8 cannabis users tested negative for THC in urinary analysis.

Group Demographics and Matched Variables – Ecstasy users matched with both cannabis user and non-user controls on gender, age and education level. Gender, as M / F ratio – ecstasy users, 16/12: cannabis users, 15/13: non-users, 17 / 11. Age. Ecstasy users, 18-29, mean = 23.25, cannabis users, 18-31, mean = 22.9, non-users, 18-30, mean = 23.5. Education level. Little / no secondary school – 1 ecstasy user, 0 cannabis users, 0 non-users: "Basic" school-leaving exam – 2 ecstasy users, 2 cannabis users, 0 non-users: "intermediate" school-leaving exam – 8 ecstasy users, 5 cannabis users, 8 non-users: "highest" school-leaving exam – 16 ecstasy users, 20 cannabis users, 20 non-users: university degree – 1 ecstasy user, 1 cannabis user, 0 non-users. Average education, ecstasy users = 3.5 (approx. 11 years), cannabis users = 3.7 (approx. 12 years), non-users = 3.7 (approx. 12 years). Cannabis Use – Ecstasy users matched with cannabis-user controls on cannabis use.

Measures: Personality Traits – Impulsiveness and novelty seeking measured via Sensation Seeking Scale (SSS –V) and Barratt Impulsiveness Scale before evoked potential recordings performed.

Evoked Potential Recording – Subjects passively listened to tones without paying special attention to stimuli. 1 kHz tones presented binaurally, with each tone lasting 30 ms and randomized within sweep. 4 blocks of stimuli were presented, with tones varying in intensity (60. 70, 80 and 90 dB). Each block presented tone of greater intensity due to limitations of AEP recording equipment. Raw data transformed into appropriate format for dipole source analysis, and filtered with low pass and high past filters. A source model formed from grand mean data from non-user controls tested against data, and the goodness of fit (adequacy, appropriateness) of the model for all 3 groups tested. Since model explained data for members of all 3 groups, it was used in later analysis.

Analyses: Personality Traits – Scores on the SSS-V and the Barratt Impulsiveness Scale were compared across groups using an ANOVA (unspecified, presumably 1-way for each score) with drug use (ecstasy and cannabis use versus cannabis use and no drug use) as between-group factor. Post-hoc comparison's made via Scheffe's test.

Relationships between Personality Traits and Evoked Potentials – Scores on the SSS-V and the Barratt Impulsiveness Scale correlated with differences calculated for AEP for increasingly loud tone (i.e. 70 – 60 dB, 80 – 70 dB, etc), using the Pearson correlation coefficient.

Dipole Source Model and Evoked Potential Recording – Latencies and amplitudes for each of the 2 dipole sources for the N1 / P2 components were analyzed via 2-way repeated measures ANOVA. Drug use (ecstasy and cannabis use, cannabis use or no drug use) as a between-group factor and tone intensity (60, 70, 80 or 90 dB) as a within-subjects factor. Due to artifacts, ANOVA examining dipole source modeling used 23 ecstasy users, 25 cannabis users and 27 non-users.

Drug Use Parameters and Dipole Source Evoked Potential Recording – Pearson's correlation coefficient used to examine the relationship between parameters of ecstasy and cannabis use and the intensity-dependence (alteration according to loudness of sound) of the NI / P2 evoked potential. Correlations performed on arithmetic differences in amplitude of each tone presented (70 – 60 dB, 80 – 70 dB, etc).

Results – Significant Differences: Personality Traits – Ecstasy users scored higher on experience seeking sub-scale of the SSS-V and non-planning impulsivity sub-scale of the Barratt Impulsiveness Scale.
Dipole Source Model of Evoked Potential Recording – N1 / P2 component varied by intensity and only marginally by drug use across all intensities (ecstasy users, cannabis users and non-users). There was a significant interaction between stimulus intensity and drug use. N1 / P2 differed between ecstasy users and cannabis users at 80 dB, and ecstasy users N1 / P2 in ecstasy users differed from cannabis users and non-user controls at 90 dB, though members of all 3 groups had similar AEPs with a 70 dB tone. Only ecstasy users showed increasing amplitude of tangential dipolar activity with increasing tone intensity, while amplitude of dipolar activity was not dependent on tone intensity in cannabis users or in non-user controls.
Results – No Differences Found: Personality Traits – Ecstasy users, cannabis users and non-users did not score differently on these Barratt Impulsiveness Scale scale scores: Global, motor, or cognitive impulsivity. Ecstasy users, cannabis users and non-user controls did not score differently on these SSS-V scales: Global, disinhibition, boredom susceptibility or thrill and adventure seeking.
Relationships between Personality Traits and Evoked Potentials – There were no correlations between scores on either psychometric scale (SSS-V or Barratt Impulsiveness Scale) and dependency of tangential dipoles on stimulus intensity (loudness.
Dipole Source Model of Evoked Potential Recording – There were no differences in latency for N1 / P2 across groups (ecstasy users, cannabis users and non-users), though there was a marginal tendency for shorter latency with increasing intensity appearing across all groups. There were no differences between ecstasy users, cannabis users and non-users in radial source of N1 / P2 component. AEP did not differ by hemisphere, so responses of hemispheres combined. Ecstasy users, cannabis users and non-user controls had similar N1 / P2 components when tone was 70 dB, but N1 / P2 differed in ecstasy users at higher tone intensities.
Relationships between Drug Use Parameters and Dipole Source Evoked Potential Recording – There were no significant correlations between frequency, duration or intensity of ecstasy use and extent of dependence of tangential dipole activity on ascending stimulus intensity. Frequency, duration or intensity of cannabis use was also not correlated with the extent of dependence of tangential dipole activity on stimulus intensity in ecstasy users.
Overall Effects: Auditory evoked potentials (AEPs) were compared across ecstasy users, cannabis users and non-user controls, with AEPs studied through dipole source analysis. In ecstasy users, tangential dipole source activity varied with loudness (intensity) of the tone presented. Intensity of tone did not change tangential dipole source activity in cannabis users or in non-users. All 3 groups had similar global scores on measures of sensation seeking and impulsivity, 2 traits associated in past research with reduced serotonergic activity. However, ecstasy users had higher scores than members of the other 2 groups on specific sub-scales of both measures of sensation seeking and impulsivity. Ecstasy users had higher scores on scales that assessed non-planning impulsivity and experience-seeking (but not thrill-seeking or prone-ness to boredom). There were no correlations between impulsivity and sensation-seeking scores and differences in the extent of dependence of dipole source activity on stimulus intensity. None of the drug use parameters tested were associated with the dependence of dipole source activity on stimulus intensity for ecstasy users, with frequency, duration and intensity of use all examined. The authors' specific hypothesis is confirmed; regular ecstasy use is related to changes in the NI / P2 component of auditory evoked potentials, producing changes that are associated with reduced serotonergic activity. These changes are also separable from the effects of cannabis use, as cannabis use did not produce the same changes in dipole source activity.
Comments: This paper is a companion paper to that of Gouzoulis-Mayfrank et al, 2000, since both papers rely on the same sample of ecstasy users, cannabis users, and non-user controls. That paper found ecstasy users performing worse on tests of memory and general intelligence, and on some tests of executive function, while this paper found differences in AEP. The authors state that measures of the tangential dipole allow for the separation the primary sensory cortex, which receives dense serotonergic innervation,

from the secondary sensory cortex, which receives less serotonergic innervation. However, unlike differences in performance on tests of cognitive function, the authors did not find a relationship between any parameter of drug use and across-group differences in AEP component. This is either an indication that changes in AEP are highly sensitive to ecstasy use (at 25 occasions of use or above) or that that these changes arise from another unmeasured drug use parameter. It is surprising to find that in this study, the two drug using groups did not differ from non-user controls on measures of sensation-seeking, and that ecstasy users only differ from members of the other 2 groups on sub-scales of these measures. This finding is especially notable considering that impulsivity and sensation-seeking, like changes in AEP, are associated with reduced serotonergic function. While ecstasy users did have slightly fewer years of education than cannabis users or non-user controls, this difference was not statistically significant.

Verkes et al. (2000). Cognitive performance and serotonergic function in users of Ecstasy.

Verkes, R. J., Gijsman, H. J., Pieters, M. S. M., Schoemaker, R. C., De Visser, S., Kuijerps, M., Pennings, E. J. M., de Bruin, D., van de Wijngaart, G., Van Gerven, J. M. A. & Cohen, A. (2000). Cognitive performance and serotonergic function in users of ecstasy. Psychopharmacology, 153, 196-202.

Purpose: Neuropsychological, including mood, personality, cognitive function: to investigate the effects of ecstasy use on cognitive and serotonergic function and to control for a wide array of confounding variables by selecting all participants from the same sub-culture and by using analyses of covariance to control the effects of one or more confounding factor.
Design: Non-experimental (retrospective) 3-group between subjects (across groups) design comparing heavy ecstasy users and moderate ecstasy users with matched non-user controls. Drug use (ecstasy use or no ecstasy use) and extent of use (moderate ecstasy use or heavy ecstasy use) served as between-subjects factors.
D-Fenfluramine Challenge – Double-blind cross-over design, with all subjects receiving 1 placebo infusion and 1 d-fenfluramine infusion occurring at least 5 days apart, and with drug use and extent of use serving as between-subjects factors. All subjects completed measures of psychopathology and tests of cognitive function and all underwent d-fenfluramine challenge.
Subjects: 21 heavy ecstasy users, 21 moderate ecstasy users and 20 non-ecstasy users residing in the Netherlands, with subjects recruited from amongst the dance event community by advertisements.
Matching – On gender and age; moderate and heavy ecstasy users matched on use of other drugs.
Criteria for Inclusion, Heavy Ecstasy Users – Having used ecstasy on 48 or more occasions in last 2 years prior to study. Moderate Ecstasy Users – Having used ecstasy on 12-48 occasions in the last 2 years prior to study. Non-users – No past or current use of ecstasy. All Groups – Being male, aged 18-28, absence of current daily alcohol use > 3 units, current regular use of cocaine (> once a month) or amphetamine (> once a week or more often than ecstasy). No current use of opiates or prescription drugs. No history of major psychiatric disorder in last year, including history of alcohol or substance abuse. Abstinence from any psychoactive drugs, including all illicit drugs, for 1 week prior to last study day, with compliance verified through urinary drug screen performed on both study days.
Drug Use Parameters – Moderate ecstasy users took an average of 169 ± 252 tablets over a lifetime on an average of 73 ± 68 occasions; heavy users took an average of 741 ± 678 tablets over a lifetime on an average of 230 ± 170 occasions. (Ranges not provided in either case). Average dose per use was 2 ± 1.1 tablets for moderate users and 3.1 ± 1.1 tablets for heavy users (ranges not provided). Average duration of use, in months, for moderate ecstasy users = 52.8 ± 28.8 months, and for heavy ecstasy users = 54 ± 21.6 months (ranges not provided). Frequency information is not provided, but using other drug use parameters, frequency of use can be estimated at .5 – 3 occasions per month for moderate ecstasy users and at 3 – 5 times per month for heavy ecstasy users. Time from last use of ecstasy to psychometric study day, in days was 15.7 ± 9.5 days for moderate ecstasy users and 9.0 ± 7.5 days for heavy ecstasy users,

and time from last use to d-fenfluramine challenge was 28.1 ± 8.8 days for moderate users and 19 ± 8.6 days for heavy users. Other Drugs – Cannabis, average lifetime consumption in number of joints, moderate users = 1890 ± 2620 joints, heavy users = 1850 ± 2700, non-users – 379 ± 1190. Cannabis use in 3 months before study, moderate ecstasy users: 3 / 21 never used, 8 / 21 used 1 per wk, 10 used > 1 per wk. Heavy ecstasy users, 7 / 21 never used, 7 / 21 used 1 per wk and 7 / 21 used > 1 per wk. Non-users, 14 / 20 never used, 2 / 20 1 per wk and 4 / 20 used > 1 per week. Amphetamine, in last year – Moderate users, 10 / 21 never used, 8 / 21 used once per month or less, 3 used few times per month, 0 used more often. Heavy users, 0 never used, 8 / 21 used once per month or less, 8 used few times per month, 5 / 21 used 1 per wk. Non-users, 19 / 20 never used, 1 / 20 used once per month or less, and none used more often. Cocaine, 1 per month or less: moderate users, 14 / 21, heavy users, 14/ 21, non-users, 0 / 20.
Group Demographics and Matched Variables – Heavy ecstasy users, moderate ecstasy users and non-users were matched on gender and age, and both ecstasy using groups approximately matched on drug use. Gender, as M / F ratio: Heavy ecstasy users, 21 / 0: moderate ecstasy users, 21 / 0: non-users, 20 / 0. Age. Average age for moderate ecstasy users = 22.1 ± 2.3 (range not provided): average age for heavy ecstasy users = 21.7 ± 2.8: average age for non-users = 20.6 ± 2.2. Other variables – Education level, as coded and in approximate years, where 1 = lower general or vocational, 2 = intermediate, 3 = at least pre-university. For moderate users, 3 / 21 at level 1 (approx. 10 years), 7 / 21 at level 2 (approx. 12 years) and 11 / 21 at Level 3 (approx. 14 years). Heavy ecstasy users, 7 / 21 = Level 1 (approx. 10 years), 5 / 21 = Level 2 (approx. 12 years) and 9 / 21 = Level 3 (approx. 14 years). Non users, 1 / 20 = Level 1 (approx. 10 years), 6 / 20 = Level 2 (approx. 12 years) and 13 / 20 = Level 3 (approx. 14 years). On average, heavy ecstasy users had 11.5 years education (2.1), moderate users had 13 years education (2.4) and non-users had 13.5 years (2.6). Weight, in kg – Moderate users, 74.9 ± 8.4 kg, heavy users = 71.5 ± 10.7 kg, non-users = 73.8 ± 11.1 kg. Average Number of Raves Attended – Moderate users = 33.5 ± 25.2, heavy users = 47 ± 31.8, non-users = 32.5 ± 24.9. ADHD Diagnosis Before Age 15 – Average number of criteria for attention deficit disorder and for hyperactivity, moderate users = 2.5 ± 2.4 (AD), 3 ± 2.5 (HD), heavy ecstasy users = 2.9 ± 2.8 (AD), 3.3 ± 2.2 (HD), non-users, 1.7 ± 1.9 (AD), 3 ± 2.5 (HD).
Measures: Psychopathology, Mood – Psychiatric diagnoses, including ADHD, assessed via psychiatric interview. Depressed mood and symptoms of depression measured via BDI, and state and trait anxiety measured via STAI. All measures administered 1 week before d-fenfluramine challenge.
Impulsivity and Hostility – Impulsivity was measured via Barratt Impulsiveness Scale. Sensation seeking measured via Temperament and Character Inventory (TCI), similar to the TPQ in containing harm avoidance and novelty seeking. Aggression and hostility measured via BDHI. Subjects completed all measures on study day 1 week before d-fenfluramine challenge.
Tests of Cognitive Function – All tasks selected from a computerized battery of neuropsychological measures (FePsy). Tests of RT – Auditory and visual. Tests of Information Processing – Visual search involving matching to sample with grid patterns and adapted form of WCS, learn sorting rules through trial and error. Memory – Computerized Corsi Blocks (Watch sequence of flashing blocks and reproduce pattern, with increasingly complex patterns. Span and "supraspan" scored. Tests of Working Memory – View 6 words or figures, then view new list of 6 with one previously presented word, and select previously presented word, with serially presented and simultaneously presented words or figures (4 tests altogether, possibly form of "Sternberg task). Both correct responses and reaction time scored.
Neuroendocrine Response to d-Fenfluramine – Plasma prolactin and cortisol measured after infusion of 30 mg d-fenfluramine or placebo. Challenge performed after overnight fast and glucose drink, and hormones sampled in blood drawn hourly (1, 2, 3, 4, 5, 6, and 7 h post-infusion). No description of assays used for hormones, but concentration of d-fenfluramine and nor-dexfenfluramine measured via liquid-gas chromatography with mass selective detection.
Analysis: Psychopathology, Mood – Initial across-group comparisons made by performing Student's t-tests (for heavy ecstasy users, moderate ecstasy users and non-users). Subsequent analyses examining the impact of additional effects on each measure used ANCOVAs with the confounding variable serving as covariate. Potential confounding variables included: use of alcohol per day, cannabis use (lifelong and

frequency of use in last 3 months), time since last use of ecstasy, BDI score (for measures other than BDI), STAI anxiety score, retrospective ADHD diagnosis and educational level.
Impulsivity and Hostility – Psychopathology, Mood – Initial across-group comparisons made by performing Student's t-tests (for heavy ecstasy users, moderate ecstasy users and non-users). Subsequent analyses examining the impact of additional effects used ANCOVAs with confounding variables serving as covariates. Potential confounding variables included: use of alcohol per day, cannabis use (lifelong and frequency of use in last 3 months), time since last use of ecstasy, BDI score, STAI anxiety score, retrospective ADHD diagnosis and educational level.
Tests of Cognitive Function – Initial across-group comparisons made by performing Student's t-tests (for heavy ecstasy users, moderate ecstasy users and non-users). Subsequent analyses examining the impact of additional effects used ANCOVAs with confounding variables serving as covariates. Potential confounding variables included: use of alcohol per day, cannabis use (lifelong and frequency of use in last 3 months), time since last use of ecstasy, BDI score, STAI anxiety score, retrospective ADHD diagnosis and educational level
Neuroendocrine Response to d-Fenfluramine Challenge – Difference scores calculated for plasma cortisol and plasma prolactin by subtracting time-corrected area under curve (AUEC) at placebo from AUEC after d-fenfluramine. Across-group comparisons made via 2-tailed Student's t-tests. Subsequent analyses examining the impact of additional effects used ANCOVAs with confounding variables serving as covariates. Potential confounding variables included: body weight, use of alcohol per day, cannabis use (lifelong and frequency of use in last 3 months), time since last use of ecstasy, AUC for dexfenfluramine, TCI scores on all 3 sub-scales (harm avoidance, reward dependence and novelty seeking), BDI score, STAI anxiety score, retrospective ADHD diagnosis and educational level.
Relationships between Neuroendocrine Response to d-Fenfluramine and Tests of Cognitive Function – Unspecified correlational or ANCOVA analyses performed to investigate any associations between neuroendocrine response to d-fenfluramine and scores on tests of cognitive function.
Results – Significant Differences: Psychopathology and Mood – Heavy ecstasy users had higher BDI and STAI scores than moderate ecstasy users and non-users, but significant differences disappear in analyses with other variables as covariates.
Tests of Cognitive Function – Reaction time, longest in heavy users, shortest in non-users (heavy ecstasy users > moderate ecstasy users > non-users). However, differences reduced after accounting for education level and BDI score. Span measured through computerized Corsi blocks test was shorter in ecstasy users when compared with non-users, with no significant differences in performance of heavy and moderate ecstasy users (heavy ecstasy users, moderate ecstasy users < non-users). Heavy and moderate ecstasy users both recognized fewer words on serially presented list than did non-users. Heavy ecstasy users recalled fewer words simultaneously presented than moderate ecstasy users or non-users; (heavy ecstasy users < moderate ecstasy users, non-users); moderate ecstasy users recognized fewer simultaneously presented words, but the difference was not significant. Heavy and moderate ecstasy users recalled fewer serially presented figures, heavy ecstasy users, moderate ecstasy users < non-users). (Heavy users did recall fewer figures than moderate users but the difference was not significant). Non-users also recalled more simultaneously presented figures than heavy ecstasy users or moderate ecstasy users; differences between recall of heavy and moderate users were not significant. (Heavy ecstasy users, moderate ecstasy users < non-users).
Neuroendocrine Response to d-Fenfluramine – Heavy ecstasy users had higher nor-dexfenfluramine AUCs than moderate ecstasy users, with moderate ecstasy users possessing lowest AUC and heavy users highest nor-dexfenfluramine AUC. (Differences between non-users and either group of ecstasy users not significant). Cortisol – Both heavy and moderate ecstasy users had lower plasma cortisol (difference score between fenfluramine and placebo AUEC), heavy ecstasy users, moderate ecstasy users < non-users), indicating blunted cortisol response after d-fenfluramine for both groups of ecstasy users. Analyses with other variables as covariates did not change differences in cortisol or prolactin response in ecstasy users and response in non-users.

Correlation, Neuroendocrine Response to d-Fenfluramine and Tests of Cognitive Function – Amount of cortisol released after d-fenfluramine infusion correlated with memory span scores, apparently indicating that greater cortisol release after d-fenfluramine was related to greater memory span scores.
Results – No Differences Found: Psychopathology, Mood – When other (unspecified) variables used as covariates, heavy ecstasy users no longer had higher BDI or STAI scores than moderate users or non-users. Signs of ADHD were the same in all 3 groups.
Impulsivity and Hostility – Members of all 3 groups had similar scores on the TCL, the BDHI and the Barratt Impulsiveness Scale. Ecstasy users had higher novelty seeking scores than non-users, but the difference was not significant.
Tests of Cognitive Function – Heavy and moderate ecstasy users did not differ in span on computerized Corsi blocks, though both performed less well than did non-users. All 3 groups (heavy ecstasy users, moderate ecstasy users and non-users) scored similarly on the visual match to sample task (test of test of information processing). All 3 groups (heavy ecstasy users, moderate ecstasy users and non-users) scored similarly on the computerized WCS-like task.
Neuroendocrine Response to d-Fenfluramine – AUC for plasma d-fenfluramine did not differ across groups (heavy ecstasy users, moderate ecstasy users and non-users had similar d-fenfluramine AUC). While prolactin release after d-fenfluramine was highest in the non-user group and lowest in heavy ecstasy users, the differences between groups were not statistically significant.
Relationships between Neuroendocrine Response to d-Fenfluramine and Tests of Cognitive Function – Cortisol release after d-fenfluramine was not associated with RT, general information processing or classification (these analyses unreported, so perhaps not performed). No relationships reported between prolactin release after d-fenfluramine and any test of cognitive function.
Overall Effects: Heavy ecstasy users, moderate ecstasy users and non-users all drawn from the Dutch dance event scene scored similarly on tests of impulsivity and hostility. Ecstasy users had slightly higher scores on novelty seeking, but their scores were not significantly different from non-users. While heavy ecstasy users scored higher on the BDI and the STAI than moderate ecstasy users and non-users, differences in these measures disappeared when controlling for the effects of other variables. RT seemed to increase with ecstasy use, (compared across all 3 groups), but differences in RT were reduced when BDI scores and education level were controlled for. Both groups of ecstasy users did not perform as well on verbal and visual memory, including a test of spatial sequential memory (Corsi blocks). However, all 3 groups performed similarly on a test of information processing (visual search) and a classification task (executive function). While both heavy and moderate ecstasy users showed blunted cortisol release after d-fenfluramine, differences in prolactin release after d-fenfluramine (while present) were not significant. Controlling for the potentially confounding effects of other variables did not change across-group differences in prolactin and cortisol release. Cortisol release after d-fenfluramine was positively associated with memory span score, with greater release of cortisol usually indicating higher memory span score.
Comments: This paper is one of several papers that divides ecstasy users into a "heavy user" group and a "moderate user" group, and compares both to a non-user control group sampled from the same sub-culture. Extent of use in this paper is not defined by commutative exposure (either as number of occasions or tablets) but as number of tablets consumed within a specified period, so that the two groups are divided on frequency of use more than cumulative use. Hence this paper may not be strictly equivalent to other papers if differences in the impact of specific drug use parameters exist. While this study may benefit from using an all-male sample drawn from the same sub-culture, the multitude of comparisons performed by the authors may have introduced both Type I errors (false positives, from sheer number of comparisons) and Type II errors (false negatives, arising from number of analyses of covariance performed). It is notable that while extent of ecstasy use seems to be associated with performance in some areas (some tests of verbal and visual memory), simply using ecstasy seems to affect other areas of cognitive function measured (span on Corsi blocks, cortisol response to d-fenfluramine).

Wareing et al. (2000). Working memory deficits in current and previous useres of MDMA ("Ecstasy").

Wareing, M., Fisk, J. & Murphy, P. N. (2000). Working memory deficits in current and previous users of MDMA ("Ecstasy"). British Journal of Psychology, 91, 181-188.

Purpose: Mood, cognitive function: To investigate whether changes in mood (affect) or cognitive function seen after ecstasy use are no longer present after continued abstinence from ecstasy use, or whether they remain after continued abstinence. Specific hypotheses tested – That both current and previous ecstasy users would not perform as well on a test of executive function (letter generation task) than would non-users; that current ecstasy users, former ecstasy users and non-users would differ in arousal (direction unspecified) and that ecstasy users would exhibit higher levels of anxiety than non-users.
Design: Non-experimental (retrospective) 3-group between-subjects (across groups) design comparing current ecstasy users and previous ecstasy users with non-user controls on psychometric measures and tests of cognitive function, with drug use (ecstasy use versus non-use) and time of use (current versus previous ecstasy use) as between-subjects variables. All subjects completed measures of anxiety, arousal and tests of cognitive function.
Subjects: 10 current ecstasy users, 10 previous ecstasy users and 10 non-users residing in England and recruited via "snowball technique" (direct contact with researchers and word of mouth through friends). Matching – On gender, age and education.
Criteria for Inclusion, Ecstasy Users – Having regularly used ecstasy up 7 days prior to study day. Previous Ecstasy Users – Abstinence from ecstasy for at least six months prior to study date and having regularly used ecstasy before abstinence. Non-users – No past or current use of any illicit drug, including ecstasy. All Groups – No other inclusionary or exclusionary criteria reported. All ecstasy users reported abstention from ecstasy for at least 7 days prior to study day, but it is unclear whether this was a requirement for study participation.
Drug Use Parameters – No information reported for lifetime use of ecstasy, either in occasions or tablets. Calculating from figures provided, current ecstasy users had taken ecstasy on an average of approximately 414.92 ± 138.644 occasions over a lifetime, (approximately 1348.49 tablets) and previous users had taken ecstasy on an average of approximately 376.74 ± 87.395 occasions (approximately 1280.92 tablets). The average dose per use, in tablets, was 3.25 ± .86 for current users and 3.4 ± 1.6 tablets for previous users. Frequency of ecstasy use was, on average, approximately 8.43 ± 3.33 times per month (101 ± 40.05 days a year) for current users and 8.05 ± 6.07 times per month for previous ecstasy users (96.6 ± 72.83 days per year). Duration of use was, on average, 49.2 ± 16.44 months for current users and 46.8 ± 14.4 months for previous users. Time since last use, in days, was (on average) 8.2 ± 5.75 days for current users and 323.25 ± 130.05 days for previous users. Other Drugs – Percentage of current and previous ecstasy users who had taken each drug: amphetamines, 70% current users, 60% previous users, cocaine, 0% current users, 10% previous users, LSD, 30% current users, 60% previous users, marijuana, 70% current users, 60% previous users. Non-users did not report using any of these drugs.
Group Demographics and Matched Variables – Current ecstasy users, previous ecstasy users and non-ecstasy users matched on gender, age and education. Current and previous ecstasy users approximately matched on use of other drugs. Gender, Actual numbers not reported, but authors state "each group had equal numbers of males and females," meaning either that each group had a 5 / 5 gender ratio or that each group contained the same (but unequal) number of men to women (6 / 4, for example). Age. Average age of current ecstasy users = 22.2 ± 2.2: average age of previous ecstasy users = 22.6 ± 2.22: average age of non-users = 22.6 ± 2.12 (ranges not provided). Education Level, in years – Current users average education level = 12.2 ± 1.03: average education level of previous ecstasy users = 12.6 ± .84: average education of non-users = 12.3 ± .67. Other Variables – On average, current users rated own health (on

scale of 1 = very good to 5 = very poor), 2.8 ± .92, previous ecstasy users rated own health as 2.5 ± .85 and non-users rated own health as 1.7 ± .48.
Measures: State Anxiety and Arousal – Author-devised measures (previously used with normal healthy humans), specifically tailored to measure anxiety and arousal in experimental setting.
Central Executive Function – Measured via consonant-generating task (Generate random string of consonants, without repeating sequence or alphabetic sequence, at set rate of 4, 2 or 1 seconds per letter. Scores were redundancy (frequency of each letter produced), number of letters produced per set and number of vowel intrusions.
Information Processing Speed – Measured via visual search / match to sample task (indicate whether 2 rows of letters are "same" or "different," with rows growing increasingly longer), with scores for total number of rows classified and number classified correctly.
Measures of Memory – Measured via visual memory task (not described) and word span.
Measures of Cognitive Function, Other – Brook's spatial matrix task (not described, either visual search or match to sample) and verbal fluency (not described, either estimated verbal IQ or crystallized intelligence (if vocabulary) or executive function (if word generation-FAS).
Analyses: State Anxiety and Arousal – Analysis not specifically stated: highly likely that either each measure was examined via 1-way ANOVA, with drug use (current ecstasy user, previous ecstasy user or non-user) as between-subjects factor or both were analyzed together via MANOVA, with drug use as a between-subjects factor and each score as dependent variable. Post-hoc comparisons were made via Tukey's test (stated in paper).
Tests of Cognitive Function – Analysis specified only for test of central executive function and information processing speed, but probably used to analyze other measures as well. Tests of executive function measured via MANOVA with drug use (current ecstasy user, previous ecstasy user and non-user) as between-group variable and scale scores as dependent variables.
Additional Analyses – The effects of other variables on performance on tests of central executive function and information processing speed were examined via ANCOVA. Covariates included were: health self-rating, anxiety score, arousal score and use of LSD, marijuana and amphetamines (dummy coded, 1 if used, 0 if did not use), with each covariate entered separately. ANCOVAs applied to both information processing speed scores (number of rows classified, percentage correct) and to all 3 consonant production scores (number of letters generated, percentage redundant and vowel intrusions).
Results – Significant Differences: State Anxiety and Arousal – Current ecstasy users were more anxious than non-users; previous ecstasy users were more anxious than non-users and less anxious than current ecstasy users, but the difference between all 3 groups significant. Previous ecstasy users experienced greater arousal than current ecstasy users (non-users experienced an intermediate level of arousal, differences not significant).
Test of central executive function – Non-users had fewer vowel intrusions than either current or previous ecstasy users at all levels of production (4 s, 2 s and 1 s) (current ecstasy users > = previous ecstasy users > non-users). Non-users had a lower percentage of redundant letters and produced a greater number of words during the 1 s condition, with non-users < current ecstasy users < = previous ecstasy users).
Tests of Information Processing Speed – Non-users had a greater percentage of correct responses than either current or previous ecstasy users, but only at highest level of difficulty (longest rows).
Additional Analyses – Differences between ecstasy users and non-users on information processing speed scores and for letter production and percent redundant in consonant generation task regained after controlling for self-reported health rating, anxiety, arousal and use of LSD, marijuana and amphetamine. Group differences in arousal were still significant after controlling for the factors listed above.
Results – No Differences Found: Test of central executive function – While non-users had a lower percentage of redundant letters and produced more letters than either group of ecstasy users in the 4 s and 2 s conditions, these differences were not significant. Previous ecstasy users had a lower percentage of redundant letters than did current ecstasy users, but these differences were not statistically significant.

Information Processing Speed – Current ecstasy users, previous ecstasy users and non-users classified similar numbers of rows at all levels of difficulty and had a similar percentage of correct responses for all but the highest level of difficulty.
Measures of Memory – There were no differences between the 3 groups (current ecstasy users, previous ecstasy users or non-users) on scores on the visual memory task or the word span task.
Measures of Cognitive Function, Other – Current ecstasy users, previous ecstasy users and non-users all had similar scores on Brook's spatial matrix task and in verbal fluency.
Additional Analyses – Group differences in vowel intrusions were no longer significant after controlling for all of the following factors: self-reported health score, anxiety, arousal, use of LSD, marijuana and amphetamines. Group differences in state anxiety were also reduced to below significance after controlling for all the factors listed above (excepting anxiety).
Overall Effects: Both previous and current ecstasy users did not perform as well as non-users on a consonant production task, described as a test of central executive function. However, differences between ecstasy users and non-users were only statistically significant when people were asked to generate 1 consonant per second. Current and previous ecstasy users had a higher rate of vowel intrusions across all rates of consonant generation (4 s, 2 s and 1 s rates). Non-users, current ecstasy users and previous ecstasy users had similar scores on a test of information processing speed. While all 3 groups were also equally accurate under conditions of low and intermediate difficulty, both current and previous ecstasy users were less accurate under condition of highest difficulty. Non-users, current ecstasy users and previous ecstasy users scored similarly on tests of verbal memory, visual memory, verbal fluency and visual search or matching to sample. Current ecstasy users reported the highest levels of state anxiety, previous ecstasy users an intermediate level of anxiety and non-users the lowest level of anxiety, though authors indicated that members of all 3 groups scored lower on anxiety than expected from previously established norms with healthy adults. Current ecstasy users reported the lowest level of arousal, non-users reported an intermediate level of arousal and previous users reported the highest level of arousal. Some of the group differences in vowel intrusion may have been due in part to differences in self-rated health, anxiety, arousal or extent of drug use (LSD, marijuana and amphetamine), since performing an analysis of covariance with these factors reduced group differences in vowel intrusion. Performing an analysis of covariance that includes self-reported health rating, arousal, LSD, marijuana and amphetamine use also reduced group differences in state anxiety. The authors' first hypothesis was partially confirmed: current and previous ecstasy users did not perform as well as non-users on a test of executive function, but this was only true for the fastest rate of letter generation and for vowel intrusions at all rates of generation. While the authors' second hypothesis was confirmed (current ecstasy users, previous ecstasy users and non-users differed on levels of state anxiety and arousal), the hypothesis was non-directional and hence easily confirmed by any form of group differences.
Comments: This paper is notable for its attempt to pinpoint the longevity of changes in affect and decrements in cognitive function seen after regular ecstasy use. The author also attempted to control for other potential confounding variables, such as use of other drugs, state arousal, and anxiety. The findings suggest that group differences in anxiety and increase in vowel intrusions in ecstasy users performing the letter generation task might both be due in part to factors other than ecstasy use. It is possible that the authors tried to perform too many analyses with a small number of subjects (10 per cell), especially in the series of ANCOVAs meant to detect the effects of potentially confounding variables. Though the authors do not highlight the point, it is surprising that they were unable to find group differences in visual or verbal memory. The sample size is small and caution should be used when generalizing from this study to the population at large.

Zakzanis & Young (2001). Memory impairment in abstinent MDMA ("Ecstasy") users: A longitudinal investigation.

Zakzanis, K. K. & Young, D. A. (2001). Memory impairment in abstinent MDMA ("ecstasy") users: A longitudinal investigation. Neurology, 56, 966-969

Purpose: Cognitive function (Memory): To investigate whether continued ecstasy (MDMA) use produces progressive memory impairment over time in recreational users.
Design: Non-experimental (prospective but uncontrolled) 1-group within-subject design comparing drug-free ecstasy users at baseline and 1 year after baseline. All subjects completed measures of intelligence (WAIS-III Vocabulary and Block Design) and memory (RBMT) at baseline and again 12 months after baseline.
Subjects: 15 ecstasy users residing in the Toronto (Ontario, Canada) area, recruited via word-of-mouth and self-referred. Matching – Within-subjects design, so no comparison groups were employed. Criteria for Inclusion – Selection criteria for ecstasy use unspecified, but statistics on number of times ecstasy used suggests all subjects had to have used ecstasy at least once. No past or current major medical or psychiatric illnesses as assessed through medical history and psychiatric interview, and no history of migraine, eating disorders or dyslexia. Fluent English-speaking individual. Absence of positive drug screen for illicit or prescription psychoactive drugs and absence of alcohol dependence. At least 7 nights of 7-9 hours sleep, and abstinence from ecstasy for at least 2 weeks prior to study day, with compliance verified via urinary drug screen conducted at unspecified date (presumably on study day). Drug Use Parameters – Ecstasy Use-At Baseline – Ecstasy users had taken ecstasy on an average of 19 occasions over a lifetime (1-55 occasions), taking an average of 1.2 tablets (117 mg) per occasion (.5-2.5 tablets). Average frequency of ecstasy use was 2.4 times per month (0-8 times per month), and duration of use was, on average, 18.4 months (1-60 months). Average time since last use, in days, was 42 days (14-168 days). Average monthly intake, in milligrams (calculated by multiplying usual dose by frequency of use) was reported at 280 mg (approximately 2.8 tablets) (50-2000 mg, or .5-20 tablets). Ecstasy Use-Follow Up (12 months later) – Ecstasy users had taken ecstasy on an average of 55 occasions over a lifetime (3-225 occasions), taking an average of 1.75 tablets (175 mg) per occasion (.5-3 tablets). Average frequency of ecstasy use was reported at 2.4 times per month (0-15 times per month), and duration of use was, on average, 30.4 months (13-72 months). Average time since last use, in days, was 28 days (14-252 days). Average monthly intake, in milligrams (calculated by multiplying usual dose by frequency of use) was reported at 420 mg (approximately 4.2 tablets) (50-4500 mg, or .5-45 tablets). Use of Other Drugs – 7/15 had used amphetamines at baseline, and 9 / 15 had used amphetamines at follow-up. 8 / 15 ecstasy users had used cocaine at baseline and 10 / 15 had used cocaine at follow-up. 1 / 15 had used a benzodiazepine at baseline, and 1 / 15 had used a benzodiazepine at follow-up. 5 / 15 had used a sedative hypnotic at baseline and 5 / 15 had used a sedative hypnotic at follow-up. 8 / 15 had used LSD or other hallucinogens at baseline and 10 / 15 had used LSD or other hallucinogens at follow-up. 14 / 15 had used cannabis at baseline and 15 / 15 (all subjects) had used cannabis at follow-up. 1 / 15 had used solvents or inhalants at baseline and 1 / 15 had used solvents / inhalants at follow-up. 6 / 15 had used opiates at baseline and 7 / 15 had used opiates at follow-up. 5 / 15 had used PCP or related drugs at baseline and 6 / 15 had used PCP or related drugs at follow-up. 14 / 15 had used alcohol at baseline and 14 / 15 had used alcohol at follow-up. 14 / 15 had used nicotine at baseline and 14 / 15 had used nicotine at follow-up.
Group Demographics and Matched Variables – No control groups participated in this study, so there are no matched variables. Gender, as M / F ratio – 12 / 3. Age – Ecstasy users were aged 17-31, and the modal age was 24.1. Education – On average, ecstasy users had received 14 years of education.
Measures: Measures of Intelligence – the Vocabulary and the Block Design tests from the WAIS-III. Vocabulary is a measure of verbal IQ, and block design is a measure of non-verbal (performance) IQ. Tests of Memory – The complete Rivermead Behavioral Memory Test battery. The RBMT contains tests of retrospective and prospective memory. Tests of Retrospective Memory – First and Second Name (Recall for name of person in photograph immediately after presentation and after delay), Pictures (Name objects in 10 pictures and select targets from set of 10 after filled delay), Story (Listen to and recall story immediately after presentation and again after delay) Faces (Select 5 target faces from set of 10, with filled delay between presentation and recall), Route (Retrace route within room immediately after presentation and again after delay). Tests of Prospective Memory – Belonging (Remember to ask for

borrowed possession and recall location of borrowed item at the end of test session), Appointment (Remember to ask question pertaining to near feature at sound of clock alarm) and Message (undescribed, apparently remember to give message).
Analyses: Tests of Intelligence and Tests of Memory – A paired Student's t-test was performed on the Vocabulary, Block Design and RBMT sub-test scores, with scores compared across administrations (at baseline and 12 months after baseline), with time of administration as a within-subjects factor, with t-tests compared using Cohen's d.
Relationships between Cognitive Function and Drug Use Parameters – Change scores were calculated for each measure (follow-up – baseline) and each change score was correlated with drug use parameters (number of times used, frequency of use, duration of use, average dose per use and time since last use).
Results-Significant Differences Found: Tests of Memory – Overall RBMT significantly declined from baseline to follow up. Performance on each of the RBMT sub-tests either remained stable or declined across administration. Performance on Story-Immediate and Story-Delayed significantly declined from baseline to follow-up.
Relationships between Cognitive Function and Drug Use Parameters – Performance on the WAIS-Vocabulary declined with increasing frequency of ecstasy use (significant negative correlation between Vocabulary change score and frequency of use). Performance on the First and Second name RBMT sub-test was inversely correlated with total number of times ecstasy used, with lower scores on the First and Second Name task associated with increased number of occasions where ecstasy was used. Poorer immediate recall of Route was associated with a longer duration of ecstasy use (significant negative correlation between Route score and duration of use).
Results-No Significant Differences: Tests of Intelligence – There were no differences between performance at baseline and performance at follow-up for WAIS-III Vocabulary or WAIS-Block Design tests.
Tests of Memory – Though overall RBMT score declined from baseline to follow-up, individual test scores for the following tests were not significantly lower at follow-up when compared to baseline: First-Second Name, Belonging, Appointment, Pictures, Faces, Route-Immediate, Route-Delayed, or Message.
Relationship between Cognitive Function and Drug Use Parameters – Time elapsed since last use of ecstasy was not correlated with changes in performance on any test. There were no correlations between change scores for Block Design, Belonging, Appointment, Pictures, Story-Immediate, Story-Delayed, Faces, Route-Delayed or Message and any of the drug-use parameters measured (lifetime use, frequency of use, duration of use, days since last use).
Overall Effects: While performance on 2 selected measures of intelligence did not change after a year of continued ecstasy self-administration, level of performance on a measure of memory at follow-up had declined from the level measured at baseline. Ecstasy users had a lower total score on the RBMT at follow-up and their scores on all sub-tests of the RBMT either remained stable or declined from baseline to follow-up. When compared with performance at baseline, immediate and delayed recall for a short story declined at follow-up. However, there were no significant changes in performance from baseline to follow-up in any of the tests of prospective memory (such as remembering to request a borrowed belonging) or for either immediate or delayed recall of faces or pictures. Frequency of ecstasy use was related to changes in performance on WAIS-Vocabulary, with more frequent ecstasy use associated with poorer Vocabulary scores. Performance on First and Second Name was related to number of times ecstasy was used in a lifetime, with a greater number of exposures associated with poorer performance on First and Second Name. Immediate, but not delayed, recall for a route presented by the experimenter was inversely related to duration of ecstasy use, with longer duration of use associated with poorer immediate recall of the route.
Comments: To date, this is the first longitudinal study of the effects of continued ecstasy use on any one cognitive function. While the authors did not enroll participants in a controlled schedule of ecstasy or MDMA administration, they did assess memory after a year of unrestricted self-administration of ecstasy. The authors attempted to reduce the effects of erratic sleep patterns on performance by testing subjects only after subjects reported getting 7 to 9 hours sleep a night for at least 7 nights in a row. The within-

subjects design also allowed for some control of the effects of other drugs on performance, since drug use patterns remained fairly similar from baseline to follow-up. However, little is known about drug use parameters for other drugs, so it is possible that volume or frequency of other drugs used increased over time. Since duration, frequency and degree of ecstasy use were still chosen by the subjects themselves, the relationship between these drug use parameters and subsequent changes in performance on tests of memory or intelligence might be related to one or more pre-existing factors that might control level of ecstasy consumption and changes in test performance. This paper may be the first step toward conducting more prospective studies on the effects of ecstasy on cognitive performance.