Deterioration of Executive Functioning in Chronic Ecstasy Users: Evidence for Multiple Drugs Effects

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Abstract: A quantitative meta-analysis was carried out on the chronic effects of ecstasy use on working memory (WM), assumed to consist of a central executive (CE) and four executive subcomponents: Updating, Attention shifting, Inhibition and Access to long term memory. Publications dating from January 1998 to January 2008 were only included when they fulfilled the criteria for a meta-analysis (number of subjects, means and standard deviations) and when polydrug users were used as controls. In addition, we also determined effect sizes for lifetime consumption differences between the groups of other psycho-active substances than ecstasy. Both Lifetime Total Ecstasy Consumption (LTEC) and the effect sizes for alcohol, nicotine, amphetamine, cocaine and lysergic acid diethylamide (LSD) were regressed on the mean effect sizes (mES)[1] of the WM subcomponents in order to study dose-response relationships.

Ecstasy users appeared to score significantly lower on the subcomponents Updating, Attention shifting and Access to long term memory, but not on Inhibition. We did not find significant regressions of LTEC on any of the executive functioning subcomponents mES values. Ecstasy users also consumed significantly more amphetamine, cocaine, alcohol, nicotine and LSD, but less alcohol than polydrug controls. However, also for these drugs no indications were found for a dose-response relationship with executive functioning.

Keywords: Ecstasy, working memory, meta-analysis, dose-response effects.

INTRODUCTION

In two recent reviews the conclusion was reached that chronic ecstasy users performed less well than non-users on verbal declarative short-term memory (STM) tests [1, 2]. The later authors [2] found no indication for a performance decrease in spatial and visual STM performance. In another review [3] the authors aimed at a wider spectrum of cognitive functioning and reported that chronic ecstasy users scored less well on some cognitive functions like learning, memory, verbal comprehension, attention, concentration, processing speed and executive function, But in still another review the authors found, besides lesser performance in some cognitive areas, also areas of performance in which ecstasy users did not do worse than controls (e.g. perceptual organization and motor skill). So, chronic ecstasy users seem to score lower on some psychological functions, but to do equally well on others. The latter is in contrast to the chronic effects of alcohol consumption that have a much more general negative effect on cognitive functioning [4].

But all four reviews seem to agree on the fact that working memory or short-term memory, as it is often also coined, is deteriorated by chronic ecstasy use. WM is assumed to exist of a non-domain specific information central executive (CE) with two domain specific-information slave systems, one for verbal-phonological information (the phonological loop) and one for visuo-spatial information (the visuo-spatial sketchpad) [5]. In this view the CE is a central control structure which regulates and controls the information in the two slave systems. Although sometimes the terms short-term memory and working memory are used interchangeably, that is probably not right: it has been suggested that verbal short-term memory (STM) should sooner be equated to the verbal-phonological slave system and visual short-term memory to the visuo-spatial sketchpad [6].

Recently the concept of WM has been further fractionated [7]. A Confirmatory Factor Analysis (CFA) on the scores of 9 different so-called executive functioning tests showed that the scores could best be explained by assuming that WM consists, besides the CE, of three different more basic underlying psychological functions which they coined Attention shifting, Updating and Inhibition. They demonstrated that these three functions could at the same time be differentiated, but were also correlated ('differentiated but also united'). These results supplied quantitative support for the WM theory, because they confirmed that performance in executive tests could be at the same time be dependent on both the CE and the functionality specific subsystems: one cannot go without the other.

The latter theory was confirmed and expanded [8]; a factor analysis on the scores of a whole range of tests aimed at various aspects of executive functioning identified four factors, which explained 67.6% of the total variance. In addition to the three factors proposed earlier [7], an additional factor was found, which was coined 'Access to long term memory (LTM)'. The factors Updating, Inhibition, Access to LTM and Attention shifting appeared to explain

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We use the abbreviation mES for the mean of specific WM sub-component ES values per study and the term mean ES for the mean ES of all studies per WM sub-component.

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32.2%, 13.5%, 12.1% and 9.8% of the total variance, respectively. It is important to note that the latter authors showed that the tasks never uniquely loaded on one executive function [7].

The purpose of the present meta-analysis is to determine on the basis of the existing literature whether or not, and if yes, to which extent these four WM subcomponents are affected by chronic ecstasy consumption. Does chronic ecstasy consumption only affect the non-domain specific CE, expressing itself in a general deterioration of all tests aimed at executive functioning, or does it have a more differential effect, expressing itself in deterioration of some and not of other WM subcomponents? To investigate this question we performed a meta-analysis on the four identified WM subcomponents [8]. We either accepted the classifications of the authors, or, in the absence of a classification of the tests in terms of Updating, Inhibition, Access to LTM and Attention shifting we decided on the basis of the existing literature.

A continuing problem in the search for possible behavioural neurotoxic effects of ecstasy in humans is the fact that ecstasy consumers are almost by definition polydrug users, which means that there is the possibility that other drugs than ecstasy may influence the test results. There is evidence that chronic consumption of e.g. cannabis [9], cocaine [10], and amphetamine [11] have negative effects on executive functioning, probably by damaging frontal lobe areas [12]. This problem has up till now not been adequately approached in earlier meta-analyses. In the present study we approach this issue by performing a meta-analysis on the effect-sizes of such drug consumption differences between ecstasy users and polydrug controls in order to see whether there were besides differences in ecstasy consumption also differences in consumption of other drugs known to have negative effects on executive functioning.

Also in the case of a significant mean ES between ecstasy and polydrug control groups for a given WM subcomponent the question remains which working mechanism is involved. The strongest support would be a significant dose-response relationship, like the significant relationship that has been found between lifetime alcohol consumption and cognitive performance (4). Up till now in three different meta-analyses such dose-response relationships for ecstasy and cognitive functioning were investigated, but in only one instance a positive result has been reported [3]. The latter authors found that scores on attention and concentration tests, learning and memory tests and processing speed tests showed a significant regression on LTEC. In two other meta-analyses [1, 2] no such a significant relationship between LTEC and cognitive functions was found. In order to investigate dose-response relationships between LTEC and WM subcomponents we performed for each CE component a regression analysis between component scores and LTEC.

METHOD

In this study publications from January 1998 to January 2008 in Pubmed and PSYCLIT were searched using the search terms chronic ecstasy use, central executive, short-term memory, working memory, inhibition, attention and long term memory in various combinations. Studies which had in been included in Table **1a** in Verbaten [1], which pertained to STM analysis in the latter study, were not included in the present study in order to avoid overlap and thus guarantee independent conclusions in the present meta-analysis.

Studies were included if data were available on number of subjects, means and standard deviations. Subjects also had to be free for at least 3 days of MDMA and/or other illicit drugs at the time of the experiment. Exclusion criteria were a) a history of DSM-IV axis-I diseases b) neurological diseases and c) traumas involving the brain. Because ecstasy users are frequently polydrug users, in addition data were collected on alcohol, cannabis, cocaine, LSD, nicotine and amphetamine (see Table **2a-d**).

In ecstasy studies two types of control groups are used. First, drug-naïve controls, which had almost always used alcohol, nicotine and caffeine, but never illicit drugs like cannabis, ecstasy, cocaine, amphetamine, heroine or other psychoactive substances. Second, polydrug controls, which had consumed all kinds of psychoactive substances but ecstasy. In the present study we only compare ecstasy consumers with polydrug controls, which means that we excluded all studies in which an ecstasy group was only compared with drug-naïve controls.

Following earlier decomposition nomenclatures [7, 8] we report studies aimed at determining the effects of chronic ecstasy use on the four different central executive components mentioned in the Introduction, namely Updating, Inhibition, Attention shifting and Access to LTM. To that end we determined for each of the components the mean weighted effect-sizes and their significances [13]. In the case of a significant mean ES we estimated the failsafe N: the number of non-significant studies to render the mean ES in the present study to a non-significant level (we set the two-sided non-significant z-value at 1.96) [14]. We also determined the weighted regression coefficients between LTEC and the effect sizes of the individual studies for each CE component.

In case of more dependent variables per task per WM subcomponent per subject sample (=study) we first determined the ES for each of the variables separately and then determined the mean of all such ES values (mES) per study [13].

In the case of Access to Long Term Memory and Updating negative ES values indicate that ecstasy users performed less well than controls: with respect to Access to Long Term Memory e.g. lower scores on the Word Fluency test and in the case of Updating lower scores on e.g. recognition tests and digit span tests. The opposite is the case for Attention shifting; here positive ES values indicate that ecstasy users performed less well than polydrug controls; e.g. more perseveration errors.

Characterising Inhibition in terms of ES-values is more complicated. In some tests lack of inhibition is characterized by higher values (e.g. more False Alarms and/or more commission errors) and in other tests by lower values (e.g. shorter RTs in the Stroop Word-Colour test) leading to positive and negative ES values, respectively. Therefore we decided to adapt the sign of the ES values in such a way that

lack of inhibition was characterized by positive ES values and better inhibition by negative ES values.

RESULTS

Cognitive Measures (see Also Table 1A-D)

Access to Long Term Memory

Ecstasy Consumers *vs* Polydrug Controls

The mean ES appeared to be significant (mean ES=-0.68, z=-5.23, p<1%, two-tailed). The homogeneity index was not significant (Q=7.39, df= 4, p>5%, two-tailed).

The failsafe N was 8.

Mean Weighted Regression (Beta) Between LTEC and ES Access to Long Term Memory

Beta was not significant (standardized beta= 0.46, t=0.74, p> 5%, two-tailed).

Attention Shifting

Ecstasy Consumers *vs* Polydrug Controls

The meta-analysis showed that the mean ES was significant (mean ES= 0.44, z=4.89, p<1%, two-tailed). Q was not significant (Q=16.06, df=10, p>5% two-tailed). The failsafe N was 13.

Mean Weighted Regression (Beta) Between LTEC and ES Attention Shifting

Beta was not significant (standardized beta = 0.29, t=0.79, p> 5% two-tailed).

Inhibition

Ecstasy Consumers *vs* Polydrug Controls

The mean ES was not significant (mean ES=0.002, z=0.02, p>5%, two-tailed). The failsafe N was 3.

Mean Weighted Regression (Beta) Between LTEC and ES Inhibition

Beta was not significant (standardized beta=-0.16, t=-0.51, p>5% two-tailed).

Updating

Ecstasy Consumers *vs* Polydrug Controls

When we compared the ecstasy group with a polydrug control group the mean ES was significant (mean ES=-0.41 z=10.25, p<1% two-tailed). The homogeneity index for this meta-analysis was not significant (Q=27.0, df=18, p>5%, two-tailed). The failsafe N was 37.

Mean Weighted Regression (Beta) Between LTEC and ES

Beta was not significant (standardized beta= -0.44, t=1.46, p>5% two-tailed).

WM Component Effect Sizes and Other Drugs than Ecstasy (See Also Table 2A-D)

We performed a post-hoc analysis in which we first determined whether the mean effect size of the difference in consumption of a given drug other than ecstasy between ecstasy groups and polydrug groups for a specific CE component was significant. If that was the case we then determined the weighted regression coefficients between the mES values for that CE component and the drug ES concerned to determine if there was a relationship between the two.

Access to LTM and Other Drugs

Mean effects sizes of the differences in consumption between ecstasy groups and polydrug groups were significant for amphetamine (mean ES=0.60, z=3.75, p<1% two-tailed, n=4), cocaine (mean ES=0.46, z=2.42, p<1% two-tailed, n=3) and LSD (mean ES=0.83, z=4.37, p<1% two-tailed, n=3). None of the subsequently determined weighted regression coefficients was significant.

Attention Shifting and Other Drugs

The mean ES sizes for amphetamine (ES=0.59, z= 4.92, p<1% two-tailed, n=6), cannabis (ES=0.65, z=6.50, p<1% two-tailed, n=8), nicotine (ES=0.27, z=2.07, p<1% two-tailed, n=5), cocaine (ES=0.98, z=7.54, p<1% two-tailed, n=6) and LSD (ES=0.32, z=2.00, p<1% two-tailed, n=4) were significant; in all these cases ecstasy groups consumed more than polydrug control groups. The two groups did not differ in terms of alcohol consumption. Of the subsequently determined weighted regression coefficients, only the one for LSD was significant (standardized beta=0.99, t=10.89, p< 1% two-tailed).

Inhibition and Other Drugs

The ecstasy control groups consumed significantly less alcohol (mean ES=-0.24, z= -1.85, p<5%, two-tailed, n=7), but significantly more nicotine (ES=0.38, z=2.11, p<1% two-tailed, n=4), more cannabis (ES=0.34, z=3.40, p<1% two-tailed, n=11), more cocaine (ES=0.52, z=5.20, p<1% two-tailed, n=8), more amphetamine (ES=0.29, z=2.90, p<1% two-tailed, n=9) and more LSD (ES=0.46, z=3.29, p<1% two-tailed, n=5) than polydrug controls.

The subsequently determined weighted regression coefficients were significant for alcohol (standardized beta=0.90, t=4.65, p< 1% two-tailed), amphetamine (standardized beta=0.85, t=4.18, p< 1% two-tailed) and cocaine (standardized beta=0.68, t=2.30, p< 5% one-tailed). However, the significances were all due to one study (Hoshi *et al.*, 2007) with extreme values. Deletion of that study rendered all above mentioned significant regression values insignificant (beta values became 0.15, 0.07 and -0.76, respectively).

Updating and Other Drugs

The mean effect sizes for cannabis (ES=0.23, z=3.83, n=15, p<1%, two-tailed), amphetamine (ES=0.36, n=11, z=4.00, p<1%, two-tailed), cocaine (ES=0.41, n=13, z=5.13, p<1%, two-tailed) and LSD (ES=0.41, n=6, z=3,41, p<1%, two-tailed), were all significant, indicating that Ecstasy users consumed significantly more of these drugs than the polydrug control groups. Not significant were the mean effects sizes for alcohol (ES=-0.44, n=11, z=-0.48, p>5%, two-tailed) and nicotine (ES=0.12, n=9, z=1.33, p>5% two-tailed).

None of the weighted regression coefficients between the significant ES-values for those differences in consumption and the mean ES values was significant.

Table 1. Effect Sizes for the Four WM Subcomponents

Study	M1	n1	sd1	M2	n2	sd2	ES	mES	Tests
A. Access to Long Term Memory									
Croft, 2001 [15]	44.4	11.0	9.4	48.0	18.0	11.1	-0.34	-0.40	Word fluency letter
Croft, 2001 [15]	21.7	11.0	5.2	24.4	18.0	6.0	-0.47		Word fluency animals
Heffernan, 2001 [16]	10.3	46.0	2.68	14.2	46.0	4.06	-1.13	-1.08	Verbal fluency
Heffernan, 2001 [16]	10.9	46.0	3.51	14.5	46.0	3.4	-1.04		Semantic fluency
Montgomery, 2005 [17]	40.2	27.0	10.86	46.85	34.0	10.07	-0.64	-0.71	Semantic fluency (s)
Montgomery, 2005 [17]	11.5	27.0	5.37	16.0	34.0	6.3	-0.77		Semantic fluency (c)
Reneman, 2006 [18]	45.1	22.0	7.4	44.3	13.0	7.5	0.11	-0.01	Category fluency
Reneman, 2006 [18]	41.6	22.0	12.6	44.4	13.0	9.3	-0.24		Letter fluency
De Sola, 2008 [19]	23.2	37.0	3.5	26.2	23.0	6.4	-0.62	-0.62	Semantic fluency
B. Attention Shifting									
Morgan, 1998 [20]	1561.0	12.0	1335.0	1541.0	16.0	1510.0	0.02	0.02	TOL% perfect solutions
Fox, 2001 [21]	14.4	20.0	2.87	12.6	20.0	7.3	0.32	0.32	WCST% persev. errors
Alting, 2004 [22]	16.0	26.0	2.6	12.85	33.0	2.3	1.31	1.10	WCST id.
Alting, 2004 [22]	16.5	26.0	1.6	12.3	33.0	1.75	0.89		TOL solution time
Montgomery, 2005 [17]	8.6	27.0	19.46	29.58	34.0	18.18	-0.05	-0.01	Plus/Minus switch time
Montgomery, 2005 [17]	39.3	27.0	18.14	38.52	34.0	18.98	0.04		Number/Letter switch time
Dafters, 2006 [23]	966.0	33.0	137.0	856.0	17.0	114.0	0.85	0.85	Stroop switching RT
Lamers, 2006 [24]	6.0	11.0	3.5	7.6	15.0	5.1	-0.36	0.16	WCST% persevat. errors
Lamers, 2006 [24]	26.8	11.0	9.7	22.3	15.0	13.3	0.38		Trail Making test A
Lamers, 2006 [24]	51.0	11.0	17.7	45.0	15.0	9.3	0.45		Trail Making test B
Reay, 2006 [25]	17.0	14.0	3.82	13.57	15.0	3.18	0.97	0.97	Brixton Ant. test shift. tim
Reneman, 2006 [18]	19.7	22.0	14.6	19.3	13.0	15.7	0.03	0.03	WCST% persev. errors
Smith, 2006 [26]	13.3	20.0	9.9	6.5	20.0	2.9	0.93	0.47	WCST id.
Smith, 2006 [26]	7.8	13.0	2.0	7.9	13.0	4.4	-0.03		Letter/Number task
De Sola, 2008 [19]	88.0	37.0	17.7	78.9	23.0	11.1	0.59	0.59	TOL tot.number of mov.
C. Inhibition[1]									
Croft, 2001 [15]	22.1	11.0	5.2	21.5	18.0	4.2	-0.13	-0.13	Stroop Word-Colour test
Alting, 2004 [22]	216.0	26.0	65.4	203.9	33.0	65.5	0.18	0.18	Stop Signal task
Gamma, 2005 [27]	0.3	16.0	0.4	0.15	17.0	0.2	0.57	0.57	CPT% errors
Montgomery, 2005 [17]	-4.9	51.0	63.4	6.2	42.0	95.9	-0.17	-0.09	RNG: redundancy
Montgomery, 2005 [17]	-0.5	51.0	64.5	-0.7	42.0	69.6	0.01		RNG: repeat seq.
Montgomery, 2005 [17]	5.68	51.0	77.2	-7.2	42.0	78.2	0.17		RNG: alphabet. seq.
Montgomery, 2005 [17]	20.0	51.0	42.0	-25.0	42.0	101.4	-0.36		RNG: number of letters
Dafters, 2006 [23]	834.0	33.0	85.0	829.0	18.0	150.0	0.05	-0.05	Stroop Word-Colour test
Dafters, 2006 [28]	833.0	18.0	170.0	895.0	18.0	147.0	0.54	0.54	Stroop negative priming
Lamers, 2006 [24]	40.5	11.0	9.0	39.5	15.0	9.1	-0.11	-0.11	Stroop Word-Colour test
Reay, 2006 [25]	-12.1	15.0	31.3	-16.2	15.0	35.1	0.12	0.12	Inhibition of return test
Reneman, 2006 [18]	82.0	22.0	15.5	82.6	13.0	14.4	-0.04	0.04	Stroop Word-Colour test
Hoshi, 2007 [29]	12.0	25.0	2.4	14.0	29.0	3.0	-0.74	-0.74	Go-NoGo. number of FAs
Quodnow, 2007 [30]	12.8	18.0	6.5	11.0	17.0	5.9	0.29	0.29	Go-NoGo, commission er.
Fisk, 2009 [31]	6.3	14.0	2.5	5.9	28.0	2.3	0.17	-0.08	RNG: redundancy
Fisk, 2009 [31]	15.1	14.0	4.9	13.8	28.0	4.5	-0.28		RNG: repeat seq.
Fisk, 2009 [31]	7.5	14.0	3.8	7.5	28.0	4.5	-0.00		RNG: alphabet. seq.
Fisk, 2009 [31]	96.9	14.0	3.8	95.9	28.0	4.4	-0.24		RNG: number of letters

[1]Inhibition: positive ES values indicate worse performance in accordance with the expectations that Ecstasy will deteriorate inhibition. Negative ES values indicate that ecstasy users performed better than polydrug controls (see also pg. 7).

(Table 1) contd…..

Study	M1	n1	sd1	M2	n2	sd2	ES	mES	Tests
D. Updating									
Croft, 2001 [15]	45.5	11.0	7.0	48.3	18.0	1.8	-0.62	-0.20	Recogn. test (words)
Croft, 2001 [15]	40.9	11.0	5.6	40.7	18.0	3.7	0.04		Recogn. test (faces)
Croft 2001 [15]	9.2	11.0	1.6	9.6	18.0	1.5	-0.26		Digit span forward
Crof, 2001 [15]	8.0	11.0	2.6	7.9	18.0	1.8	0.05		Digit span backward
Fox, 2002 [32] 85.8	20.0	6.5	84.0	20.0	8.2	0.24	-0.21		Spatial recognition% corr.
Fox, 2002 [32]	87.5	20.0	8.9	95.2	20.0	4.5	-1.09		Pattern recognition% corr
Fox, 2002 [32]	4.7	20.0	1.5	4.5	20.0	1.8	0.12		Memory score, 6-box tr.
Fox, 2002 [32]	4.6	20.0	2.2	5.0	20.0	1.6	-0.08		Idem, 8-box tr.
Morgan, 2002 [33]	7.7	18.0	0.8	8.6	16.0	0.7	-1.19	-1.26	Immediate recall
Morgan, 2002 [33]	1.7	18.0	0.5	1.1	16.0	0.4	-1.32		Subtr. Serial Seven's test
Thomasius, 2003 [34]	57.0	30.0	4.0	54.0	28.0	4.0	-0.75	-0.38	AVLT immediate recall
Thomasius, 2003 [34]	9.5	30.0	1.2	9.5	28.0	1.2	0.0		RBMT immediate recall
Wareing, 2004 [35]	2.6	42.0	0.94	3.1	31.0	1.16	-0.47	-0.56	Reading span
Wareing, 2004 [35]	3.1	42.0	1.85	5.2	31.0	2.1	-1.07		Computation span
Wareing, 2004 [35]	4.2	42.0	0.76	4.6	31.0	0.72	-0.53		Word span
Wareing, 2004 [35]	6.5	42.0	1.23	6.7	31.0	1.15	-0.16		Digit span
Wareing, 2004 [36]	2.9	25.0	1.27	4.0	18.0	1.24	-0.89	-0.66	Visual spatial span
Wareing, 2004 [36]	2.7	25.0	1.52	3.6	18.0	1.2	-0.65		Id. + alphabetic gener.
Wareing, 2004 [36]	2.2	25.0	1.46	2.8	18.0	1.17	-0.43		Id. + rand. lett. gen.
Montgomery, 2005 [17]	2.1	27.0	0.5	2.45	34.0	0.54	-0.59	-0.61	Updating
Montgomery, 2005 [17]	3.8	27.0	1.63	4.5	34.0	1.19	-0.46		Computation span
Dafters 2006 [23]	6.3	18.0	2.5	5.8	17.0	1.7	0.23	0.23	Keep Track test
Lamers, 2006 [24]	20.6	11.0	7.6	22.3	15.0	6.8	-0.24	-0.06	Rey O' figure
Lamers, 2006 [24]	51.5	11.0	4.09	52.3	15.0	7.1	0.13		RAVLT recall
Quednow, 2006 [37]	56.2	19.0	8.16	64.8	19.0	6.21	-1.18	-1.20	Learning performance
Quednow, 2006 [37]	86.6	19.0	8.61	94.8	19.0	3.94	-1.22		Recall consistency
Reay, 2006 [25]	5.6	15.0	1.19	7.0	15.0	1.4	-1.08	-1.08	Digit span backward
Reneman, 2006 [18]	17.9	22.0	3.8	17.9	13.0	6.1	0.00	-0.68	Rivermead imm.
Reneman, 2006 [18]	38.4	22.0	2.6	39.4	13.0	1.9	-0.42		WMS imm. (vis.)
Reneman, 2006 [18]	47.0	22.0	8.6	60.0	13.0	6.8	-1.63		RAVLT imm.
Golding, 2007 [38]	8.2	20.0	2.73	8.6	20.0	2.04	-0.15	-0.35	Verbal memory imm.
Golding, 2007 [38]	44.1	20.0	12.8	47.65	20.0	8.81	-0.32		Acodes number corr.
Golding, 2007 [38]	47.1	20.0	16.21	55.1	20.0	9.95	-0.59		Sternberg numb. corr.
Quednow, 2007 [30]	8.1	19.0	4.09	5.95	19.0	4.36	-0.52	-0.52	Matching Fam. Fig.
Rendell, 2007 [39]	62.3	27.0	11.85	68.9	34.0	10.77	-0.28	-0.28	Digit symbol test.
Rosier, 2007 [40]	88.9	30.0	15.1	91.4	30.0	10.7	-0.19	-0.02	Pattern recogn.% corr.
Rosier, 2007 [40]	88.7	30.0	14.6	86.7	30.0	13.2	0.14		Delayed Match% corr
Rosier, 2007 [40]	80.3	30.0	16.5	77.3	30.0	15.1	0.19		Pattern recogn. lat.
Rosier, 2007 [40]	1753.2	30.0	372.4	1672.5	30.0	383.3	-0.21		Delayed Match lat.
Wareing, 2007 [41]	4.0	29.0	1.9	5.1	46.0	1.8	-0.59	-0.59	Computation span
Schilt, 2007 [42]	59.6	58.0	6.5	61.7	60.0	5.9	-0.33	-0.09	RAVLT imm.
Schilt, 2007 [42]	94.4	58.0	7.8	96.8	60.0	6.6	-0.33		MFD imm.
Schilt, 2007 [42]	15.5	58.0	2.8	15.1	60.0	2.2	0.16		Digit span forward
Schilt, 2007 [42]	11.8	58.0	2.4	11.4	60.0	2.9	0.15		Digit span backward
De Sola, 2008 [19]	54.7	37.0	9.4	59.3	23.0	7.6	-0.53	-0.23	CVLT Total A1-A5
De Sola, 2008 [19]	12.2	37.0	2.7	11.7	23.0	1.8	0.2		Letter-Number seq.

M1: mean score ecstasy users, n1: number of ecstasy users, sd1: standard deviation ecstasy users, M2: mean score polydrug controls, n2: number of polydrug controls, sd2: standard deviation polydrug controls, ES: effect size, mES: mean effect size per study.

*All means and sd values in Montgomery, 2005 [17] have been multiplied by 100 for textual reasons.

Table 2. Study, n1, n2, ES, LTEC and Effect Sizes of the Differences in Life Time Consumption Between Ecstasy Users and Polydrug Controls of Alcohol, Nicotine, Cannabis, Amphetamine, Cocaïne and LSD

Study	LTEC	ES alc	ES nic	ES can	ES amph	ES coc	ES LSD
A. Access to Long Term Memory							
Croft *et al*., 2001 [15]	41.9	-0.33		0.22	0.35	0.06	
Montgomery *et al*., 2005 [17]	345.9			0.61	0.03	0.79	
Reneman *et al*., 2006 [18]	516.3	0.31	-0.08	0.79	1.49	1.69	
De Sola *et al*., 2008 [19]	206.0	0.01	0.78		0.69		
B. Attention Shifting							
Morgan *et al*., 1998 [20]	35.6	-0.43	-0.10	1.40	-0.08		-0.47
Alting *et al*., 2004 [22]	46.3			1.04	0.78	1.35	0.91
Montgomery *et al*., 2005 [17]	345.9			0.61	0.03	0.79	
Dafters, 2006 [23]	522.3	-0.06	0.87	-0.06	0.47	0.56	0.42
Lamers *et al*., 2006 [24]	37.6	0.20		-0.56	0.47	0.62	-0.26
Reay *et al*., 2006 [25]	459.7	0.40	-0.19	1.32		0.35	
Reneman *et al*., 2006 [18]	516.3	0.31	-0.08	0.79	1.49	1.69	
Smith *et al*., 2006 [26]	42.8						
De Sola *et al*., 2008 [19]	206.0	0.01	0.70	0.68			
C. Inhibition							
Croft *et al*., 2001 [15]	41.9	-0.33		0.22	0.35	0.06	
Alting *et al*., 2004 [22]	46.3			1.04	0.78	1.35	0.91
Gamma *et al*., 2005 [27]	270.2						
Montgomery *et al*., 2005 [17]	345.9			0.61	0.03	0.79	
Dafters, 2006 [23]	522.3	-0.06	0.87	-0.06	0.47	0.56	0.42
Dafters, 2006 [28]	522.3	-0.06	0.87	-0.06	0.47		0.42
Lamers *et al*., 2006 [24]	37.6	0.20		-0.55	0.47	0.62	-0.26
Reay *et al*., 2006 [25]	459.7	0.40	-0.19	1.32			
Reneman *et al*., 2006 [18]	516.3	0.30	-0.08	0.79	1.49	1.69	
Hoshi *et al*., 2007 [29]	670.1	-1.90		-0.82	-1.53	-1.01	0.42
Quodnow *et al*., 2007 [30]	457.9			-0.48	0.96	0.22	
Fisk *et al*., 2009 [31]	1000.2			1.83			
D. Updating							
Croft *et al*., 2001 [15]	41.9	-0.33		0.22	0.35	0.06	
Fox *et al*.,, 2002 [32]	172.0	-0.16	0.19	0.51		1.03	0.53
Morgan *et al*., 2002 [33]	303.0	-0.25	0.66	-0.06	0.66	-0.09	0.61
Thomasius *et al*., 2003 [34]	817.0	-0.71	-1.04	-0.27	0.57	-0.17	0.31
Wareing *et al*., 2004 [35]	552.9						
Wareing *et al*., 2004 [36]	655.5						
Montgomery *et al*., 2005 [17]	345.9			0.61	0.03	0.79	
Dafters, 2006 [23]	522.3	-0.06	0.87	-0.06	0.47	0.56	0.42
Lamers *et al*., 2006 [24]	37.6	0.20		-0.55	0.47	0.62	-0.26
Quednov *et al*., 2006 [37]	457.9			-0.48	0.96	0.22	
Reay *et al*., 2006 [25]	459.7	0.40	-0.19	1.32		0.35	

(Table 2) contd…..

Study	LTEC	ES alc	ES nic	ES can	ES amph	ES coc	ES LSD
D. Updating							
Reneman *et al*., 2006 [18]	516.3	0.31	-0.08	0.79	1.49	1.69	
Golding *et al*., 2007 [38]	55.0						
Quednow *et al*., 2007 [30]	457.9			-0.48	0.96	0.22	
Rendell *et al*., 2007 [39]				0.54			
Rosier *et al*., 2007 [40]	274.6	0.60	0.11	-0.13	-0.60	0.45	0.58
Schilt *et al*., 2007 [42]	3.2	-0.14	0.15	0.44	0.18	0.29	
Wareing *et al*., 2007 [41]	536.0						
De Sola *et al*., 2008 [19]	206.0	0.01	0.70	0.68			

n1: number of ecstasy users, n2: number of polydrug controls, mES: mean effect size central executive component scores per study, LTEC: lifetime ecstasy consumption, ES alc: effect size alcohol consumption difference between n1 and n2, ES nic: effect size nicotine consumption difference between n1 and n2, ES can: effect size cannabis consumption difference between n1 and n2, ES amph: effect size amphetamine consumption difference between n1 and n2, ES coc: effect size cocaine consumption difference between n1 and n2, ES LSD: effect size LSD consumption difference between n1 and n2.

DISCUSSION

We found that ecstasy users performed significantly worse on the Updating, Attention shifting and Access to LTM components of executive functioning than polydrug controls, but not on the Inhibition sub-component. The mean effect sizes were moderate, however: much lower than in an earlier ecstasy meta-analysis published by the present author [1]. But in the latter meta-analysis study mean ES values were mainly determined on the basis of comparisons between groups of ecstasy users and drug-naïve control groups. Since then more studies were published in which polydrug controls were used as controls, which enabled us to determine ES values solely based on ecstasy *vs* polydrug users comparisons in the present study.

To illustrate this point we post-hoc determined mean ES-values based on ecstasy *vs* drug-naïve subjects and mean ES-values based on ecstasy *vs* polydrug controls for 20 studies in which both types of control groups were used and in which the updating component of executive functioning was investigated. The mean ES for the first comparison was –0.30 and for the second comparison –0.68. Although both mean ES values were significant, the difference is substantial and illustrates that drug-naïve subjects are not the proper controls for the exact determination of the chronic effects of ecstasy consumption on cognitive functions; using such controls produces inflated ES values.

But in the present meta-analysis also these non-inflated ES values showed that ecstasy users performed less well than polydrug controls in three aspects of executive functioning. The pattern of the negative effects of ecstasy consumption on WM sub functions appeared to be not general in nature, with clear effects on the sub functions Updating (mean ES=-0.41), Attention shifting (mean ES=0.44) and Access to long term memory (mean ES= -0.68), but no effect on Inhibition (mean ES=0.24). Although in the latter case the mean ES was not significant, it was, because the failsafe N for Inhibition was only 3, not very robust.

If ecstasy would have deteriorated only the functionality of the CE, the 'uniting' factor [7], then we would have expected that all subcomponents would be negatively affected by chronic ecstasy use to the same extent. As mentioned above, that was not the case here. However, that does not necessarily lead to the conclusion that ecstasy consumption did not influence the CE: another possible explanation for the different effects of ecstasy on the WM subcomponents might be that tests utilized for the measurement of the separate WM subcomponents might have differed in terms of sensitivity and/or validity. It is therefore not possible to come to conclusions about the specificity of the alleged neurotoxic effects of ecstasy on the CE or the WM subcomponents, although it could be that Inhibition is less vulnerable than for the neurotoxic effects of ecstasy than the other three WM subcomponents. Elsewhere, significant negative relationships between TLEC and some aspects of cognitive functioning (learning and memory, attention and concentration and processing speed) have been reported [3], but not for other cognitive domains (verbal comprehension, executive functioning and perceptual organization), although no explanation is available for such possible differences in vulnerability to ecstasy.

Although the WM subcomponents mean ES values for the differences between ecstasy users and polydrug controls were significant and in some cases substantial (see above), that does not necessarily lead to the conclusion that ecstasy consumption is the responsible factor for this lower performance. Such a conclusion would have been supported if we could have identified a working mechanism responsible for such effects. E.g. if we could have demonstrated significant dose-relationships between LTEC and mES values [1, 3]. However, in the present meta-analysis for none of the tested WM subcomponents a significant dose relationship between mean ES and LTEC could be shown, confirming earlier findings in meta-studies on ecstasy and neurocognition [1, 2, 43].

That raises the question which working mechanisms might be then responsible for the deterioration of executive functioning in ecstasy users, for we did find that they scored significantly lower on such tests than controls. There are a number of possibilities ranging from pre-drug use differences between ecstasy users and polydrug controls to

the possibility that already a once in a lifetime dose of ecstasy is responsible for the inferior performance of ecstasy users. Although there is evidence in animals that such a once in a lifetime dose of ecstasy may damage the brain [44] we concluded in an earlier study [1] that such evidence in humans was absent. The latter conclusion has recently been confirmed in a well-designed study in which novel ecstasy users (their first dose of ecstasy served as the once in a lifetime dose) were both compared with themselves (pre- *vs* post-drug) and a drug-naive control group [45]. The groups were tested repeatedly at the same moments in time. The authors did not find an effect of ecstasy on cognitive functioning. Neither did the latter authors find pre-drug differences in cognitive functioning between the (novel) ecstasy users and controls. So, there seems to be as yet no evidence for the once in a lifetime hypothesis in humans, nor for the pre-drug performance differences hypothesis.

Another possibility is that the concurrent use of other drugs than ecstasy might be the responsible factor. A continuing problem in the search for possible damaging effects of chronic ecstasy use on cognitive functioning is that ecstasy users are notorious polydrug users. In many studies researchers tried to control for polydrug use by testing whether ecstasy groups differed significantly from controls. Not infrequently, differences between ecstasy users and polydrug controls were noted not only for LTEC, but also for the life time consumption of other drugs like cocaine and cannabis [29], leading to the possibility that not ecstasy consumption but the consumption of these other drugs is responsible for the lower performance (or the interaction between them).

In the present meta-analysis this problem was for the first time investigated in a quantitative way by performing a meta-analysis on the effect-sizes of such drug differences between ecstasy users and polydrug controls. It appeared that in many cases these drug ES values were significant and substantial and pointed in the direction of more intensive consumption of drugs like cannabis, cocaine, amphetamine and LSD in ecstasy users, although we found that ecstasy users consumed less alcohol than their poly-drug controls. In order to see whether such differences in drug consumption might have influenced the test results we first tested for significant ES differences, and in the positive case, for significant relationships between performance on the four WM subcomponents and lifetime consumption doses of such drugs. However, as was the case with LTEC, also lifetime amphetamine, alcohol, amphetamine, LSD and cocaine consumption did not regress significantly on WM subcomponent mES values.

However, in contrast to what is the case with ecstasy, there is ample evidence that some of the latter drugs can damage the brain. Cocaine appears to damage dopaminergic cells in humans [46]. The fact that such cell damage did not concur with Parkinson symptoms suggested the damage pattern caused by cocaine is rather specific, most probably damaging more anterior neural structures [47]. Indeed, others [48] found gray volume decreases (MRI) in frontal brain areas of abstinent cocaine users. Also, in cocaine users deficiencies in executive function concurred with fMRI detected abnormalities in prefrontal areas [51]. Like cocaine, methamphetamine is toxic to dopaminergic cells, causing symptoms that resemble those of patients with damage to the frontal lobes [49], as well as abnormalities in frontal brain tissues of methamphetamine users [50]. Whether or not chronic LSD consumption leads to brain damage is less clear [52], although there are indications that hallucinogens induce persisting perception disorders [53], probably by interfering with or damaging serotonergic neurons.

The fact that we did not find significant relations between lifetime consumption of cocaine and methamphetamine and scores on executive tests in the present meta-analysis might therefore mean that the way lifetime use of the various drugs was defined in the studies included in the present meta-analysis was too inaccurate to indicate reliably the real effects of such drugs on the brain, and, consequently, on behaviour.

CONCLUSION

In the present meta-analysis we found convincing evidence that chronic ecstasy users score consistently lower on Access to long term memory tests, Attention shifting tests, and Updating tests. But, not on Inhibition tests. We did not find significant dose-response relationships between LTEC and executive functioning: LTEC did not regress significantly on ES values. One of the possible reasons for this might be that the way lifetime consumption of the drug was determined was too inaccurate. Such estimates depend on what users remember about their consumption and there are indications that also long term memory functions less well in ecstasy users [1].

In addition chronic ecstasy users consumed more cocaine, amphetamine and LSD than polydrug controls, but also in these cases lifetime consumption of these drugs did not show a significant relationship with performance on specific executive function tests. In contradiction with the fact that it has been repeatedly shown that methamphetamine and cocaine can damage the brain in humans.

Key Learning Objectives:

- Review research on the effects of chronic ecstasy use on executive functioning in humans.
- Identify the intensity of the concurrent use of other legal/illegal drugs in ecstasy users and relate that to executive functioning.
- Discuss the proper control groups in research on the effects of chronic ecstasy use on behaviour.

Future Research Questions:

- How can we discriminate between possible negative behavioural effects of ecstasy and other concurrently consumed drugs in chronic ecstasy users?
- How can we devise experiments to investigate dose-response relationships for ecstasy in humans?
- How can we gain further insight in the working mechanism(s) of ecstasy in humans?

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