

Executive Working Memory Deficits in Abstinent Ecstasy/MDMA Users: A Critical Review

(Running Head: Executive Deficits in ecstasy users)

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1 Abstract

2
3 *Aims.* This review examined studies of executive functioning in abstinent ecstasy
4 (MDMA) users on tasks which had been empirically mapped onto updating,
5 shifting, inhibition and accessing long term memory executive processes. Studies
6 of some aspects of visuospatial memory performance were also included
7 because of the investment of executive resources in such tasks.

8
9 *Methods.* Thirty three studies were identified for the review following searches of
10 the Psychinfo and Medline databases. Inclusion criteria included the reporting of
11 new empirical findings from participants drug free at the time of testing, in peer
12 reviewed journals in the English language.

13
14 *Results.* Evidence for ecstasy related performance deficits was strongest for the
15 updating of verbal material, and for visuospatial memory tasks requiring
16 additional processing beyond storage and retrieval. Such processing suggested
17 that overall level of executive demand was an important consideration. Executive
18 shifting showed little evidence of ecstasy related impairment, whilst examination
19 of inhibition and long-term memory access presented an unclear picture.

20
21 *Conclusions.* All but one of the studies had a cross-sectional design. Although
22 this is a potential weakness with regard to confounds, the necessity of such
23 designs was acknowledged. Studies were generally aware of the need to control
24 for potential confounds, especially the effects of other drugs, through a mixture of
25 group designs and statistical techniques. It was recommended that future studies
26 of executive functioning in ecstasy users should detail the relationship of the
27 tasks and dependent variables reported to specific executive processes, and
28 consider the level of executive demand imposed by such tasks.

29

30 Introduction

31

32 This review examined research reporting the presence or absence of deficits
33 associated with the use of the drug 'ecstasy' (MDMA) in executive working
34 memory processes in abstinent users. This is an important area to review for a
35 number of reasons. United Kingdom evidence indicates that ecstasy ranks fourth
36 in the list of Class A illegal drugs with regard to having been consumed at some
37 time, with over 2.3 million people reporting some exposure to it [1]. Furthermore,
38 as previous reviews have reported, ecstasy related performance deficits do not
39 appear on all cognitive tasks or in all published studies [2, 3], so that it is
40 important to monitor the patterns of findings in this field in order to establish a
41 coherent understanding of such effects. One particularly important issue
42 regarding ecstasy related performance deficits concerns the difficulties
43 associated with eliminating the effects of potential confounds from reported
44 results, most notably the possibility of effects arising from the use of other drugs
45 [4]. Other potential confounds include differences in age and IQ between ecstasy
46 users and controls. Attempts to control for such confounds across studies also
47 require some examination in order for the quality of evidence concerning ecstasy
48 related deficits to be established. The term 'abstinent' in this review indicates that
49 ecstasy users were not under the influence of the drug at the time they were
50 tested, even though use of the drug may have been relatively recent.

51

52 The construct of working memory combines short-term storage processes with
53 other aspects of cognitive activity, such as learning and reasoning [5]. Models of
54 working memory commonly emphasise both the storage and retrieval of task
55 related material, and additional processing relevant to that task [6]. This
56 additional processing is seen as part of the executive functioning of working
57 memory, implying a directive role in the employment of cognitive resources to
58 manage the demands facing a person. Working memory, therefore, involves both
59 executive and non-executive processes, with the latter concerned with storage.
60 Specific executive processes of working memory have been identified by logical
61 deduction (e.g. mediating access to long-term memory [7]), and empirically by
62 latent variable analysis [8, 9], and exploratory factor analysis [10] on data from
63 tasks thought likely to utilise executive processes. In particular, latent variable
64 analysis of visuospatial performance data demonstrated that any distinction
65 between tasks requiring only storage and retrieval, and tasks requiring additional
66 goal orientated processing could be discarded, as both types of task drew upon
67 executive capacity [9]. Table 1 summarises details of other executive processes
68 identified empirically and the tasks associated with them.

69

70

Insert Table 1 about here.

71

72 This review examined ecstasy related effects concerning the four executive
73 processes shown in Table 1 by examining studies using the tasks listed with an
74 empirically demonstrated link to them, or close variants of these tasks. In order to
75 maximise understanding of reported ecstasy related effects, or of their absence,

76 particular attention was paid to the dependent measures reported, and
77 researchers' attempts to control potential confounds. Visuospatial memory is a
78 broad area of functioning, and it is apparent that any form of visual stimulus is
79 likely to have a spatial dimension to it. In order to sharpen the focus of this review
80 it was decided to focus upon visuospatial findings from tasks requiring recall or
81 recognition targeted specifically upon the spatial distribution of individual
82 elements of a display, rather than the recall, reproduction, or recognition of
83 overall patterns or figures.

84 Method

85 Identification of Studies

86
87
88
89 Each task listed in Table 1 was paired with the terms 'ecstasy' and 'MDMA',
90 respectively, to form forty different search terms in the Psycinfo and Medline
91 databases. Additionally, the terms 'visuospatial', 'word fluency' and 'verbal
92 fluency' were also paired with 'ecstasy' and 'MDMA', respectively, to form six
93 more search terms. Searches were carried out between July and September
94 2008, and no date limitations on publication were specified. The broad term
95 'visuospatial' was chosen in order to include as many studies as possible at this
96 stage which had included coverage of this aspect of functioning in their
97 investigation. The terms 'word fluency' and 'verbal fluency' were included so as to
98 identify studies using close variants of the Chicago word fluency task identified in
99 Table 1 as being associated with access to long-term memory (LTM). As all such
100 fluency tasks require participants to produce as many words as possible within a
101 given time starting with a designated letter, it was decided that the review would
102 be enhanced by including all studies sharing this procedural similarity. The only
103 task subsequently to be included in this way is referred to in this review as the
104 FAS task (sometimes referred to elsewhere as the Controlled Oral Word
105 Association Task or COWAT), which employs oral word production in contrast to
106 the written production required by the Chicago word fluency task.

107
108 The initial searches produced references to 59 studies which were then
109 examined with regard to the inclusion and exclusion criteria for this review. The
110 fundamental inclusion criteria were that studies had to report new empirical
111 findings, or attempted replications, concerning the relationship between ecstasy
112 use and performance on either a task listed in Table 1, or a test of visuospatial
113 memory which required the recall or recognition of the spatial distribution of
114 individual elements of a display, rather than the recall, reproduction, or
115 recognition of patterns or figures. Studies also had to be published in peer
116 reviewed journals. Review articles, conference abstracts, and theses abstracts
117 were, therefore, excluded. By implication of these inclusion criteria, studies were
118 reporting findings concerning human rather than animal participants. Additionally,
119 for inclusion in the review it was necessary for studies to have employed some
120 criterion regarding a minimum period since ecstasy had last been used, so that
121 studies of task performance under the drug's intoxication were excluded. Studies

122 were excluded if they were not published in the English language, or if the
123 findings concerning the relevant tasks were reported in a composite form (i.e. as
124 a combined measure with other tasks). Application of the inclusion and exclusion
125 criteria yielded a total of 33 studies for inclusion in this review.

126 Data extraction

127
128
129 The national origin of each of the 33 included studies was recorded with regard to
130 where data collection had been conducted. The label 'community sample' was
131 applied where recruitment had employed advertisements or outreach work at
132 social events. Where recruitment had focussed primarily upon students, but with
133 additional snowball sampling which might have brought in non-students, these
134 studies were recorded as having a 'predominantly student sample', as none of
135 them provided a precise occupational breakdown for the sample. The status of
136 control groups was recorded according to whether they had been defined by
137 matching the ecstasy user group(s) on the use of more than one illicit drug
138 (recorded as 'polydrug controls'); defined as matching ecstasy users primarily on
139 the use of cannabis, with or without additional matching on other drug use
140 (recorded as 'cannabis using controls'); or defined as nonusers of illicit drugs
141 (labelled as 'drug naïve controls'). On occasions where researchers had allowed
142 minor infringements of group selection criteria, such as allowing participants with
143 very small levels of cannabis use into an otherwise drug naïve control group,
144 note of this was included in the coding (e.g. near drug naïve controls).
145 Descriptors such as 'light' or 'moderate' in relation to ecstasy user groups were
146 applied in the ways used by the authors of the studies in question.

147
148 Measures of time since last ecstasy use and estimates of lifetime use were
149 recorded in the form they were reported, with regards to means, standard
150 deviations, and ranges. Where statistics on time since last ecstasy use were not
151 reported, the study's minimal time since last use for inclusion in the sample was
152 recorded. Where estimates of lifetime use were not reported an implied estimate
153 was recorded based on the data available. For each study the executive task(s)
154 used from those listed in Table 1, or which tested visuospatial memory in a way
155 matching the inclusion criteria for this review, were recorded.

156
157 Details of each study's attempts to control potential confounds were recorded,
158 with particular note being made of matching group designs (see above) and the
159 use of statistical techniques, respectively. The findings of each study were
160 recorded with regard to the particular dependent variables generated by tasks
161 upon which ecstasy related performance deficits were reported as either present
162 or absent.

163 Results

164 Overview

168 Table 2 summarises the data extracted from the 33 studies identified for inclusion
169 in this review. Given that ecstasy use is the focus of this review, and to avoid
170 verbal redundancy, the term ‘users’ is used in Table 2 to identify participant
171 groups who have used this drug. It was decided that the stated objectives for this
172 review, with regard to examining ecstasy related performance deficits in relation
173 to dependent measures reported and controls employed, would not be enhanced
174 by the application of statistical analysis at this point. Furthermore, the review was
175 concerned with differences in the appearance of such deficits across different
176 areas of executive functioning, rather than the establishment of an overall mean
177 effect size. Further details of results are presented below with regard to
178 previously identified areas of executive functioning [8, 9, 10].

179

180

Insert Table 2 about here

181

182 Ecstasy and executive updating

183

184 Nine studies listed in Table 2 report findings concerning the performance of
185 ecstasy users on tasks shown to load upon executive updating [11 - 19]. All but
186 one of these have been produced by some combination of the current authors,
187 with some additional colleagues contributing. Performance deficits in ecstasy
188 users on the computation span task were reported in seven of these studies [11 -
189 16, 19], with 27 of the 44 ecstasy users in Fisk et al. [13] also being included in
190 the user group of Montgomery et al. [14]. The computation span task requires
191 participants to perform a series of simple arithmetic calculations whilst
192 remembering the second digit from each calculation for subsequent serial recall.
193 The item for storage and retrieval is, therefore, verbal in nature. Of the five
194 studies where span scores are reported the largest mean difference is 2.48 span
195 items between former users who had abstained from ecstasy for at least 6
196 months and polydrug controls (scores of 2.75 and 5.23, respectively [19]). The
197 remaining two studies reported percentage scores as a dependent variable,
198 based upon the difference between computation and digit span scores [11, 15].

199

200 Where Analysis of Covariance (ANCOVA) was used to control for cannabis,
201 alcohol, and nicotine use [12, 13, 15], ecstasy related performance deficits
202 remained statistically significant, as they also did for amphetamine and cocaine
203 use [13]. As with all ANCOVA results concerning other drug use in this section on
204 updating, the validity of the obtained result was examined by testing the
205 homogeneity of regression with regard to the interaction of the independent
206 variable (participant group) and the covariate (e.g. cannabis use: see Discussion
207 and also [20]). Where ANCOVA was not possible due to too few users of a
208 particular drug, or where homogeneity of regression was not achieved, either
209 initial ANOVAs were repeated with the exclusion of participants with exposure to
210 the covariate drug in question, or bivariate correlations between computation
211 span performance and the covariate were reported. Performance deficits in
212 ecstasy users remained significant with the removal of participants with exposure
213 to amphetamine, cocaine, or poppers (amyl nitrate) [12]. However, the

214 correlational strategy did produce a slightly confused picture with task
215 performance showing a significant negative relationship with ecstasy but not
216 cannabis consumption [15], with cannabis but not ecstasy consumption [14], and
217 with the consumption of both drugs [11].

218

219 In addition to the use of other drugs, ANCOVA has also been used to control for
220 other potential confounds which could be responsible for ecstasy users'
221 performance deficits on computation span. The nocturnal lifestyle associated with
222 the drug's use has led to suggestions that cognitive deficits generally which have
223 been associated with its use may actually be the result of sleep disturbance [21].
224 However, ecstasy related computation span deficits remained significant when
225 sleep quality measures were controlled by ANCOVA [11], although homogeneity
226 of regression results were not reported. It has also been suggested that ecstasy
227 users may develop an increased vulnerability to age related cognitive deficits due
228 to ecstasy exacerbating the normal decline of serotonergic functioning with age
229 [22]. As age related cognitive deficits are characterised at a psychological level
230 by a decline in information processing speed, Wareing et al. [16] controlled this
231 variable with ANCOVA and found that ecstasy related computation span deficits
232 remained, with homogeneity of regression being achieved. This suggests that the
233 psychological mechanism underlying ecstasy related cognitive deficits is different
234 from that underlying age related deficits. It would be difficult to map such a
235 difference in psychological mechanisms onto neurobiological processes as
236 changes in serotonergic functioning have been reported in numerous brain
237 regions in relation to both ecstasy use [23] and ageing [24, 25].

238

239 Ecstasy users have been reported to perform worse than controls on the
240 consonant updating task [11, 14, 15, 17]. This task requires participants to recall
241 a given number of the most recent consonants in their correct order from
242 sequences of varying lengths. Performance may be scored in relation to correct
243 recall, either across all serial positions or for respective serial positions.
244 Correlational analysis has once again presented a slightly confusing picture with
245 performance on this task being negatively related to the consumption of cocaine
246 but not ecstasy and cannabis [11], to the consumption of ecstasy but not
247 cannabis or cocaine [15, 17], and unrelated to the consumption of ecstasy,
248 cannabis, cocaine, and amphetamine [14]. Performance deficits in ecstasy users
249 have been reported with ANCOVA controlling for age, and the consumption of
250 alcohol, tobacco, and cannabis, with homogeneity of regression being achieved
251 [15]. Given that working memory includes both passive non-executive storage
252 processes as well as active executive processes [6], one study [17] explored the
253 contribution of serial position and passive memory span to the performance
254 deficits observed in ecstasy users on this task. Users actually had significantly
255 higher letter span scores than polydrug controls, indicating that users' depressed
256 performance on the updating task did not arise from passive storage deficits.

257

258 Regarding other updating tasks, an initial performance deficit in ecstasy users in
259 reading span became nonsignificant when cannabis consumption was controlled

260 by ANCOVA [12], whilst ecstasy users showed no deficit in performance on the
261 keep track task [18] where cannabis use was controlled by a matched group
262 design. The reading span task presents participants with a series of sentences,
263 requiring them to answer a question about each sentence, respectively, whilst
264 remembering the last word of each sentence for subsequent serial recall. The
265 keep track task requires participants to recall the last word presented from each
266 of n categories, where presentation order has been randomised.

267

268 In summary, the studies cited report fairly robust effects with regard to
269 performance deficits for ecstasy users compared to controls on the computation
270 span and consonant updating tasks. Furthermore, the presence of computation
271 span deficits in users who had been abstinent for at least 6 months after
272 consuming an average in excess of 400 tablets may be considered noteworthy
273 [19: see also Table 2). However, correlational data between performance on both
274 tasks and the use of ecstasy and other drugs did not present the entirely
275 consistent picture which would be expected if such deficits were entirely linked to
276 ecstasy use. Furthermore, controlling for cannabis use has led to no ecstasy
277 related deficits being reported for two other updating tasks. Such inconsistent
278 results across tasks could be seen to raise questions of the specific brain areas
279 and non-executive processes recruited by respective tasks. However, it is also
280 important to consider the details of task administration and measurement
281 employed. For example, in their latent variable study Miyake et al. [8] employed
282 six categories in the keep track task whilst Dafters [18] employed only four with
283 ecstasy users and controls. This presumably reduced the demand on the
284 executive resources of participants. Further investigation here could vary this
285 level of demand. With regard to reading span [12], further investigation could, for
286 example, examine the correct number of serial positions recalled as a dependent
287 variable potentially more sensitive to executive workload than span scores.

288

289 Ecstasy and executive shifting

290

291 Six studies listed in Table 2 report results concerning the performance of ecstasy
292 users on tasks reported in Table 1 to load upon executive shifting [14, 26 – 30].
293 No ecstasy related differences were reported on either the plus/minus task or the
294 number/letter task [14]. The most commonly reported shifting task with ecstasy
295 users is the Wisconsin card sorting task (WCST) which requires participants to
296 sort cards according to one of three criteria, colour, shape or number. The
297 criterion for sorting is changed without warning when a designated number of
298 cards have been correctly sorted [8, 10]. The number of cards presented can be
299 varied, as can the number of correctly sorted cards required for a criterion
300 change. However, these details are not reported in all studies with ecstasy users
301 and studies also differ regarding the dependent variables they examine.

302

303 Where no ecstasy related WCST performance deficits were reported other drug
304 use was controlled through the use of one or more matched control group [26 -
305 29]. In one study results on the dependent variables analysed were not reported

306 in detail [26]. Where dependent variables were reported in detail no ecstasy
307 related deficits emerged on the number of categories completed, the number or
308 percentage of perseverative errors (i.e. failing to change the sorting principle
309 when the criterion had changed), the number or percentage of nonperseverative
310 errors [27, 29], as well as the number of trials taken to complete the first
311 category, and failure to maintain set [27]. In the remaining study [28] polydrug
312 using controls actually performed significantly worse than both current and former
313 ecstasy users on perseverative errors, whilst the other dependent variables
314 generated by this task which yielded no significant differences are not detailed.
315 As these studies had presumed abstinence from ecstasy and other illicit drugs for
316 at least 6 days prior to testing, no contradiction is posed by deficits reported in
317 ecstasy users who had consumed the drug 10 to 15 hours prior to testing [25: not
318 included in this review].

319

320 The only study to report ecstasy related deficits on the WCST in abstinent users
321 [30] recruited participants from a region of the United States where cultural and
322 religious norms minimised exposure to other drugs including alcohol. Only a
323 comparison between heavy users ($n = 11$, with more than 50 episodes of use)
324 and nonusers yielded a difference on total categories completed, with only simple
325 significance being achieved.

326

327 Although the Stroop task has been shown to be related to executive inhibition
328 rather than shifting (see Table 1), Dafters [18] manipulated the procedure for this
329 task by requiring participants to switch from naming the ink colour to naming the
330 word on certain trials. Ecstasy users showed longer reaction times than other
331 groups when doing this, which was interpreted as showing an impaired switching
332 or shifting process. However, such a measure has not been tested empirically
333 with regard to its relationship to other tasks loading on this process [8, 10].
334 Mapping the diverse requirements of individual tasks to specific executive
335 processes is not always straight forward (eg. random letter generation, see [10]),
336 and this manipulation could conceivably reflect a deficit in the regulation of
337 inhibition, rather than shifting.

338

339 In summary, there is little evidence to date to suggest that ecstasy use is related
340 to impairment of executive shifting.

341

342 Ecstasy and executive inhibition

343

344 Seventeen studies are identified in Table 2 as presenting results concerning
345 tasks shown in Table 1 as loading upon executive inhibition [13 - 15, 18, 22, 26,
346 27, 29, 32 - 40]. Eight of these report findings from the Stroop task. Conventional
347 Stroop measures reflect differences in the time taken to name a stimulus colour
348 when the stimulus is a conflicting colour word (such as 'red' written in blue ink),
349 compared to one or more conditions where either the word and the stimulus
350 colour match (such as 'red' written in red ink) or the stimulus is not a word (such
351 as a red asterisk). No ecstasy related deficits on standard measures from this

352 task were reported in six studies [18, 26, 33, 35, 39, 40]. Of the other two studies,
353 Croft et al [32] reported equivocal findings, in that an initial ANOVA showed no
354 significant main effect for processing speed across their three groups of
355 ecstasy/cannabis users, cannabis but not ecstasy users, and near drug naïve
356 controls. However, ANCOVA performed with both user groups combined, using
357 measures of cannabis and ecstasy use as respective covariates, indicated that
358 ecstasy use was more strongly related to performance deficits than cannabis
359 use. Homogeneity of regression results were not reported for these analyses.
360 Similarly equivocal were the findings from a Hong Kong sample [34] where
361 discriminant function analysis significantly classified ecstasy users with 99%
362 accuracy based on response times. However, after controlling for multiple
363 comparisons, users' task performance was not significantly worse than that of
364 controls who appear to have been drug naïve, although precise data is not
365 reported on their drug using history. Furthermore, estimated ecstasy
366 consumption did not correlate with task performance. This study is rare in the
367 literature on ecstasy related cognitive functioning as a whole, as the authors
368 report that the 100 ecstasy users tested had taken no other illicit drugs, with
369 regular use of alcohol and tobacco also being exclusion criteria.

370

371 Whilst reporting no ecstasy related deficits on standard Stroop measures, one
372 researcher manipulated the administration and measurement of performance on
373 this task in order to explore ecstasy related inhibitory effects further [35]. Dafters
374 claimed to have isolated negative priming inhibition as distinct from the conscious
375 inhibition of a prepotent response by, for example, presenting 'red' in blue ink on
376 one trial so that the response 'red' would be inhibited, and then making such an
377 inhibited response the target response on the next trial. In contrast to the
378 conventional measure, there were significant reaction time differences which
379 were interpreted as showing reduced negative priming inhibition in ecstasy users.
380 Whilst ANCOVA was used to control for the effects of other drug use,
381 homogeneity of regression results were not reported. A cannabis polydrug control
382 group was also used, but their use of cocaine and amphetamine was much less
383 than that of the ecstasy users.

384

385 The Tower of London (TOL) task is a close variant of the Tower of Hanoi (TOH)
386 task, and since the latter has been found to load on shifting [8], results from the
387 TOL task will be considered here. The TOL task requires participants to move
388 coloured balls between different locations in order to achieve a goal configuration
389 in the smallest number of moves. Three studies have reported no performance
390 deficits amongst ecstasy users on this task compared to controls, with two of
391 these studies comprising one publication [22]. In both of these studies no
392 intergroup effects were found for the dependent variables of excess moves per
393 problem, proportion of perfect solutions, and subsequent thinking time per move.
394 In Study 2 the dependent variable of initial thinking time showed a trend
395 approaching significance with post-hoc analyses showing that users and
396 polydrug controls took significantly less time than drug naïve controls, whilst no
397 effect was found on this variable in Study 1. In the third study no ecstasy related

398 effects were reported for the percentage correct, number of attempts required to
399 complete each set of moves, and latency to initial response variables [38]. Whilst
400 results for seven dependent variables are reported for these three studies, it is
401 likely that initial thinking time [22] and latency to initial response [38] constitute
402 the same measure. However, the relationship between proportion of perfect
403 solutions [22] and percentage correct [38] is not so clear. It is also apparent that
404 subsequent thinking time per move [22] and solution times [27: discussed below)
405 are not the same variable. Overall, there does appear to be a need in this field of
406 research for some standardisation of reporting the results from tasks generating
407 a range of dependent variables in order to facilitate the comparison of findings.
408

409 By contrast to these nonsignificant findings, ecstasy users reporting problems
410 with their use of the drug have shown significantly longer solution times
411 compared to controls with some level of polydrug use, whilst users not reporting
412 problems have shown significantly longer initial planning times than both this
413 control group and users with problems [27]. However, no performance deficits
414 were reported for the number of errors or number of trials completed.
415 Nonparametric ANOVA found no intergroup differences in other drug use. Finally,
416 although de Sola Llopis et al [36] report no intergroup differences for the total
417 number of movements or for initiation time, estimated lifetime ecstasy
418 consumption was significantly correlated with total number of movements.
419

420 Impaired performance on random letter (consonants only) generation has been
421 reported for ecstasy users compared to controls, with regard to the number of
422 vowel intrusions [37]. However, comparisons were not conducted on
423 performance differences between the current users, former users, and controls
424 on this dependent variable. Other drug use, information processing speed,
425 health, and mood measures were controlled by ANCOVA with homogeneity of
426 regression being reported. However, for some covariates there were no users in
427 at least one of the participant groups, thus compromising the procedure for
428 testing homogeneity of regression [20]. Furthermore, this specific dependent
429 variable was not tested for its relationship to executive processes [10], and two
430 further studies by the original research team failed to replicate group differences
431 on any measure from this task [13, 15]. It should be noted that, in so far as it can
432 be calculated from the data reported, the mean estimated lifetime ecstasy use in
433 the original study [37] was in excess of 1,000 tablets, which was much more than
434 in the subsequent studies. Whilst it remains possible that the initially reported
435 performance deficits could be related to excessive ecstasy intake compared to
436 subsequent studies, the small sample size of the initial study with only 10 current
437 and former users, respectively, also places a limit on the confidence which may
438 be placed in this finding.
439

440 In summary, there seems to be little evidence for ecstasy related impairments on
441 tasks of executive inhibition. However, the diversity of dependent variables
442 reported does not facilitate the development of a clear appraisal of this area. The
443 reporting of such an impairment for negative priming inhibition, but not for

444 conscious inhibition [35], suggests that the concept of executive inhibition itself
445 may need to be developed further in order to provide a better picture of how
446 research into the ways in which ecstasy use may or may not affect it may best be
447 conducted.

448 449 Ecstasy and access to long term memory (LTM)

450
451 The previous discussion of random letter generation in the context of inhibition
452 may also be applied to access to LTM, as this is the only task in Table 1 to have
453 been found to load significantly upon two executive functions [10]. The failures to
454 replicate original findings of ecstasy related deficits on this task [13 15], taken
455 together with the small sample size for the original study [37], are not consistent
456 with the ecstasy related impairment of this executive function.

457
458 The Chicago word fluency task requires participants to write down as many
459 words as possible beginning with the letter 'S' in 5 minutes, and to repeat this
460 procedure with the letter 'C' in 4 minutes, with the added requirement that only
461 four letter words could be produced. Task completion requires access to
462 semantic long term memory [10]. Three studies report ecstasy related deficits on
463 this task [11, 14, 41]. Twenty seven of the 104 ecstasy users in the sample for
464 Montgomery et al. [11] had comprised the sample for Study 1 of the earlier
465 publication [14], and significant negative correlations were found between
466 performance and measures of both ecstasy and cocaine use in both studies.
467 Ecstasy related deficits also remained when sleep quality measures were
468 controlled by ANCOVA, although homogeneity of regression was not reported
469 [11]. The third study employed only the 'C' condition of the task, and employed a
470 matched control group with regard to cannabis but not cocaine use. However,
471 alcohol, cannabis and cocaine were controlled through ANCOVA, but without
472 homogeneity of regression being reported [41].

473
474 Table 2 also shows that three studies [38, 42, 43] reported performance deficits
475 in ecstasy users on a task where participants were required to produce orally (as
476 opposed to writing) as many words as possible beginning with the letters 'F', 'A',
477 and 'S', in 1 minute respectively for each letter (referred to as the FAS task in
478 Table 2). Other drug use was controlled for in two of these studies by a
479 combination of *t*-tests, correlation and ANCOVA [38, 42], although homogeneity
480 of regression results were not reported. The third study [43] relied on its group
481 design to control for other drug use. However, three other studies have reported
482 ecstasy users to show no performance deficits on this task compared to controls
483 [30, 32, 33].

484
485 In summary, the two tasks with an empirical basis for the claim that they load on
486 access to LTM [10] point to different conclusions regarding the ecstasy related
487 impairment of this function. As an oral variant of the Chicago word fluency task,
488 the FAS task has produced contradictory results. It is apparent that any firm
489 conclusion regarding the possible ecstasy related impairment of this executive

490 function requires further investigation. A broader range of tasks shown
491 empirically to have some relationship to this function would also be helpful.

492

493 Ecstasy and visuospatial memory

494

495 Table 2 lists 18 studies reporting results on the performance of ecstasy users on
496 visuospatial memory tasks. Table 3 summarises the findings from 11 of these
497 studies regarding tasks where ecstasy related performance deficits, or significant
498 relationships between ecstasy consumption and performance, were reported for
499 at least one measure. It can be seen that two of these studies reported deficits in
500 the updating of visuospatial material [15, 17] which may be consistent with the
501 deficits in updating verbal material reported above. Table 4 summarises findings
502 from 12 of the 18 studies regarding tasks which did not demonstrate these
503 ecstasy related effects. Studies are included in both tables where different tasks
504 produced contrasting results.

505

506 Insert Tables 3 and 4 about here

507

508 The majority of studies listed in Table 3 used some form of statistical control with
509 regard to potential confounds such as IQ and other drug use. The exception to
510 this was [39] where statistical comparisons between users and nonusers on such
511 confounds were confined to sub-groups selected for additional SPECT
512 examination. In six studies where ANCOVA was used homogeneity of regression
513 results were reported in three [15, 19, 45], but not in three others [36, 38, 44]. In
514 two studies performance deficits were reported in former users who had not used
515 ecstasy for at least 6 months [19, 45] as well as current users. The latter of these
516 studies also indicated that both cannabis and ecstasy could be contributing to the
517 observed impairments. Deficits were also reported in participants described as
518 “light users” [15] and “moderate users” [44] with respective means (and SDs) of
519 149.69 (96.91) and 169 (252) for estimated lifetime tablet consumption.

520

521 Latent variable analysis with visuospatial tasks has shown that both those tasks
522 which require minimal additional processing beyond storage and retrieval, and
523 those requiring significant additional processing, draw upon executive capacity
524 [9]. It may be argued that all of the findings in Table 4 come from tasks requiring
525 only minimal additional processing. By contrast, eight of the findings in Table 3
526 would appear to be from tasks requiring significant additional processing, the
527 exceptions being [27, 43, 44]. It should be noted that whilst conventional Corsi
528 block and span measures require minimal additional processing, backwards
529 spatial sequence and span measures do require additional processing [30, 36],
530 whilst the box search task of Fox et al [38] required processing the reverse order
531 presentation of previously learned stimuli. Reported visuospatial performance
532 deficits may, therefore, reflect the extent of demand placed upon participants’
533 executive capacity by tasks of this type. This would beg the question as to why
534 three studies did show ecstasy related effects on tasks which do not seem to
535 require more than the minimal additional processing characteristic of those listed

536 in Table 4. Overall ecstasy consumption would seem to be an unlikely
537 explanation as Hanson and Luciana [43] report a relatively low level of
538 consumption compared to studies listed in Table 4. Table 2 shows that Verkes et
539 al [44], who did find visuospatial performance deficits on a basic block tapping
540 procedure, also report a much shorter period since last ecstasy use than studies
541 with similar tasks listed in Table 4 [29, 40, 49]. However, this can only be a
542 speculative explanation for differences in findings as differences in task demands
543 make similar comparisons between studies problematic, and there was no formal
544 analysis of the relationship between time since last ecstasy use and task
545 performance in these studies.

546
547 In summary, ecstasy related deficits have been reported on visuospatial tasks
548 where potential confounds have been appropriately controlled. It is possible that
549 such deficits may be related to the level of demand made upon executive
550 capacity by the task in question. As there is no established measure of demand
551 made by a task on executive resources, this is presumably an issue relevant to
552 the field of substance use related executive effects as a whole.

553 554 Discussion

555
556 The evidence reviewed suggests that performance deficits in abstinent ecstasy
557 users seem particularly evident in the updating of both verbal and visuospatial
558 material, as well as other visuospatial tasks, especially where the demands on
559 executive capacity are relatively high. However, shifting processes appear
560 relatively immune to such deficits, and the evidence for their presence on
561 inhibitory processes and access to LTM seems weak and ambiguous. From the
562 range of brain regions which have been found to be associated with both verbal
563 updating tasks and visuospatial memory tasks, respectively, both types of task
564 have been associated with the dorsolateral prefrontal cortex (DLPFC), with
565 increased activity being reported in the left hemisphere for verbal updating [50]
566 and bilaterally for visuospatial tasks [51]. Increasing the workload of such tasks
567 increased the activation of this and other implicated brain areas, rather than
568 leading to the recruitment of new areas. Ecstasy related reductions in serotonin
569 transporter (SERT) density have also been reported in the DLPFC [23], indicating
570 a mechanism which may potentially underlie the relationship between ecstasy
571 use and deficits in updating and visuospatial memory. However, the DLPFC has
572 also been implicated in executive shifting [50] where there is little evidence of
573 ecstasy related deficits, although parietal areas may be more important for this
574 function. Significantly lower SERT densities in ecstasy users compared to
575 controls, indicating impaired serotonergic functioning, were actually reported in
576 12 brain regions using the radioligand [¹¹C]McN5652 [23], including a number of
577 those regions associated with updating, shifting, and inhibition. Where inhibition
578 is concerned, the suggestion from this current review that the concept of
579 executive inhibition may require further refinement before ecstasy related
580 performance effects may be properly understood, reflects a similar conclusion by
581 Colette et al. [50] in their review of the neural substrates of executive functioning.

582 They argue that a lack of homogeneity in this concept makes it difficult to
583 interpret the role of brain regions reported to be associated with it.

584

585 If there is a relationship between ecstasy use and performance deficits on tasks
586 requiring verbal updating and visuospatial memory, respectively, why do not all
587 studies using these tasks report such deficits? Our reading of the visuospatial
588 studies which either did or did not report such deficits (see Tables 3 and 4
589 respectively) suggests that future research should consider the extent of the
590 executive workload posed by the tasks employed, in addition to the standard
591 concerns of extent of ecstasy use and time since its last use. Furthermore, where
592 verbal updating was concerned, it was noted that for the tasks which had failed to
593 show ecstasy related deficits (reading span [12] and the keep track task [18]),
594 variations to either the measures taken (e.g. recording the total correct responses
595 for respective serial positions rather than span scores) or the procedure (e.g.
596 keeping track of six categories rather than four), might have been more sensitive
597 to the extent of executive demand. The prevailing concern of the studies
598 reviewed was to establish whether or not ecstasy users performed worse on a
599 task than nonusers, rather than the level of executive demand at which
600 performance differences may appear. Greater use of the type of dual task
601 procedure with a single task control condition used by Wareing et al. [45] might
602 be one approach to this.

603

604 One general limitation within this sample of reviewed studies was that only one
605 [47] had a genuinely prospective design involving the recruitment of ecstasy
606 naïve participants who were subsequently tested at a follow up point, by which
607 time it was possible to compare task performance for those who had used
608 ecstasy to those who had not. All of the other studies may be considered to have
609 had cross-sectional, or quasi-experimental designs, by which pre-existing groups
610 of ecstasy users and nonusers were recruited. Unfortunately, such designs make
611 it impossible to rule out pre-existing differences between groups as a potential
612 cause of performance differences. However, prospective studies in this field take
613 years to complete, with there being the risk of insufficient ecstasy use within the
614 sample by follow up for important research questions to be addressed. For
615 example, in the case of Schilt et al. [47] the mean estimated consumption for
616 users was 3.2 tablets after 3 years. True experimental studies would require the
617 systematic administration of ecstasy / MDMA to participants randomly allocated
618 to a user group, over a period running into years in order to mimic use in the
619 community. Impairments to brain functioning and task performance would then
620 be investigated in relation to randomly allocated control participants. Such a
621 study would clearly be entirely unethical and unacceptable. Cross-sectional
622 studies therefore become a necessary means of investigating ecstasy related
623 executive deficits. In turn, this emphasises the importance of the replicability of
624 findings and of the controls employed for potential confounds.

625

626 All studies reviewed showed an awareness that ecstasy users have generally
627 used other illegal drugs. Controlling for the potentially confounding effects of

628 cannabis is particularly important because of its potentially neurotoxic effects
629 [52], and its high prevalence in the population. For example, in the United
630 Kingdom it is estimated that over 9.5 million people have used cannabis at some
631 time in their life [1]. Population statistics do not record cannabis use amongst
632 ecstasy users, but within this review cannabis use was present in all ecstasy user
633 groups except for Yip and Lee [34], although it was relatively rare in Halpern et al
634 [30]. One statistical method used within the studies reviewed to control for the
635 effect of other drugs, and also other potential confounds such as age and IQ, was
636 ANCOVA. This method removes all the shared variability between a dependent
637 variable (e.g. computation span) and a covariate (e.g. cannabis use) [20]. This
638 has the conservative merit that any significant difference observed between
639 ecstasy users and nonusers may be regarded as being free from the covariate's
640 influence. However, any variability shared by the covariate and the independent
641 variable (e.g. between cannabis and ecstasy use) is also removed, so that the
642 effects of any interaction between these drugs cannot be studied. This
643 constitutes an important limitation of ANCOVA in this type of research. Its use,
644 therefore, is a matter of choice with both benefits and costs which need to be
645 understood. Where ANCOVA is used, its results should be qualified by reporting
646 whether or not homogeneity of regression, in the form of a nonsignificant
647 interaction between the covariate and the independent variable, was achieved
648 [20]. Failure to achieve homogeneity of regression renders ANCOVA results
649 invalid. Furthermore, testing for homogeneity of regression requires the covariate
650 to be adequately represented in all groups constituting the independent variable,
651 in order for the test itself to be meaningful.

652

653 Many of the studies listed in Table 2 controlled for the effects of cannabis through
654 group design. For example, participants were classified as users of both ecstasy
655 and cannabis, users of cannabis but not ecstasy, or controls with no exposure to
656 either drug [18, 32]. However, it would not be possible to design studies to control
657 for all commonly misused drugs in this way, and the matching of participant
658 groups on all potential confounds will always have a margin of error. A
659 combination of matched groups and ANCOVA may, therefore, offer the best
660 approach to control in future studies. One further technique for controlling for a
661 potential covariate drug was to repeat a primary analysis whilst omitting
662 participants with exposure to that drug. However, this is only possible if the
663 reduced sample size does not diminish statistical power unacceptably. Bivariate
664 correlation possibly offered the simplest means to highlight the relationship
665 between specific drugs and task performance, although multiple analyses will
666 require alpha levels to be adjusted appropriately [14].

667

668 Do ecstasy related deficits on laboratory tasks of executive functioning indicate
669 that ecstasy is significantly harmful to its users in a practical sense? The
670 laboratory based tasks employed by the studies reviewed here stand essentially
671 as proxies for everyday behaviours from which it would be difficult to obtain
672 precise measures in naturalistic settings, and which cannot easily be reproduced
673 in a laboratory. It may therefore be useful to consider the findings of studies

674 which report impaired cognitive functioning of ecstasy users in everyday life [41,
675 53] as providing an important additional perspective in evaluating the relevance
676 of laboratory findings to assessments of ecstasy related harm in society.
677 However, the self-report nature of data concerning ecstasy related cognitive
678 impairments in everyday life may itself be seen as a limitation on the usability of
679 such evidence, and confidentiality requirements would probably limit other forms
680 of investigating the cognitive performance of ecstasy users in community
681 settings.

682
683 With minor exceptions, this review was limited to a restricted group of tasks with
684 a demonstrated empirical link to the executive processes of updating, shifting,
685 inhibition, access to LTM, or which drew upon certain aspects of visuospatial
686 memory. Studies reporting ecstasy related deficits on other tasks believed to
687 draw upon executive functioning were, therefore, not included [eg. 54]. Further
688 empirical developments in mainstream cognitive psychology concerning the
689 relationships of tasks to executive structure will benefit this area of research. It is
690 recommended that future reporting of executive performance in users of ecstasy
691 or any other drug should outline the relationship of the task administered to
692 executive functioning. Where tasks generate multiple dependent variables clarity
693 is needed in reporting and discussing these. These steps will enhance the clarity
694 of evidence in this field. With regard to visuospatial memory, this review was
695 limited to tasks requiring either recall or recognition of the spatial distribution of
696 individual elements of a stimulus display. As any visual stimulus will have some
697 spatial dimension to it would seem appropriate for a more extensive review of
698 evidence concerning ecstasy use and visuospatial performance to be conducted.

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Table 1

Tasks empirically related to specific executive process [5, 7]

Updating
Letter memory Brooks spatial sequences Tone monitoring Computation span Reading span Consonant updating Operation span Keep track Random number generation
Shifting
Wisconsin card sorting Plus / minus Number / letter Local / global
Inhibition
Random letter generation Random number generation Stroop Tower of Hanoi / London Anti-saccade Stop signal
Access to long term memory
Chicago word fluency Random letter generation

Table 2

Summary of studies identified in this review

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (<i>M</i>) with (<i>SDs</i>) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Montgomery et al. (2007) [11] (UK) Users: 21.68 yrs. (1.96) Controls: 21.11 yrs. (1.66)	Predominantly student sample: 103 ecstasy users, <i>M</i> = 19.35 weeks (43.46) since last use: 103 controls with some polydrug use.	349.97 (464.41)	Computation span & consonant updating (updating). Chicago word fluency test (access to LTM)	Age, IQ, and other drug use compared by <i>t</i> -tests. ANCOVA to control for sleepiness with executive measures.	Deficits in users reported on all three executive tasks, which remained when sleepiness was controlled.
Wareing et al. (2004) [12] (UK) Current users: 21.69 yrs. (2.57) Former users: 26.06 yrs. (5.09) Controls: 23.39 yrs. (6.47)	Student sample: 42 current users, <i>M</i> = 3.00 weeks (3.66) since last use: 17 former users, <i>M</i> = 111.66 weeks (87.98) since last use: 31 controls with some polydrug use.	Current users 552.99 (681.49): former users 385.10 (362.02).	Reading span & computation span (updating).	ANOVA & post hoc comparisons for intergroup IQ & age differences. ANCOVA to control for other drug use, age, & passive memory storage differences with executive measures.	Both user groups showed deficits on both executive tasks which remained when age, other drug use, & passive memory storage differences were controlled.
Fisk et al. (2004) [13] (UK) Users: 21.52 yrs. (1.66) Controls: 21.37 yrs. (1.84)	Predominantly student sample: 44 users, <i>M</i> = 10.90 weeks (27.86) since last use: 59 controls with some polydrug use.	343.38 (376.94)	Random letter generation (inhibition & LTM access). Computation span (updating)	Age, education, IQ, & other drug use compared by <i>t</i> -tests. ANCOVA for other drug use with executive measures.	Deficits in users on computation span with other drug use controlled. No intergroup differences on random letter generation.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (<i>M</i>) with (<i>SDs</i>) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Montgomery et al. (2005) [14] (UK) Users: 21.70 yrs. (1.66) Controls: 21.59 yrs. (1.88)	Predominantly student samples. Study 1: 27 users, <i>M</i> = 4.97 weeks (7.27) since last use: 34 controls. Study 2: 51 users, <i>M</i> = 22.15 weeks (40.71) since last use: 42 controls. Both studies: controls had some polydrug use.	Study1: 345.96 (365.76) Study 2: 373.87 (542.91)	Study 1: consonant updating, computation span (updating). Chicago word fluency test (access to LTM). Study 2: Random letter generation (inhibition & LTM access). Plus / minus & number / letter (shifting)	Both studies: <i>t</i> -tests for age, IQ, education, & sleepiness. Correlations examined between performance & use of ecstasy & other drugs. Study 1: additional use of ANCOVA to control for IQ, sleepiness & gender.	Users showed deficits on both updating tasks, but not on the inhibition or shifting tasks. Cannabis use was negatively correlated with updating performance & cocaine use with LTM access.
Fisk & Montgomery (2009) [15] (UK) Heavy users: 22.86 yrs. (2.38) Light users: 21.41 yrs. (2.05) Controls: 20.71 yrs. (1.37)	Predominantly student sample: 14 heavy users, <i>M</i> = 22 weeks since last use: 39 light users, <i>M</i> = 27 weeks since last use (no <i>SDs</i> given): 28 controls with some cannabis use.	Heavy users 1,000.21 (786.41): light users 149.69 (96.91)	Computation span, consonant updating (updating). Random letter generation (inhibition & LTM access). Spatial span & spatial updating (visuospatial memory).	ANOVAs for age, education, IQ, passive memory storage differences, alcohol & tobacco use. ANCOVA to control for age, & alcohol, tobacco & cannabis use on performance.	Users showed deficits on computation span & spatial updating, but not on random letter generation or spatial span.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (M) with (SDs) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Wareing et al. (2007) [16] (UK) Current users: 21.72 yrs. (2.00) Former users: 25.30 yrs. (5.21) Controls: 22.58 yrs. (5.50)	Sample origins unspecified: 29 current users, $M = 1.86$ weeks (1.50) since last use : 10 former users, $M = 124.60$ weeks (94.05) since last use: 46 controls with some polydrug use.	Current users 536.00 (515.73): Former users 525.90 (410.02).	Computation span (updating)	ANOVAs for age education & IQ. ANCOVA controlled for information processing speed on computation span.	Users deficits on updating remained when information processing speed was controlled.
Montgomery & Fisk (2008) [17] (UK) Users: 21.77 yrs. (2.11) Controls: 20.73 yrs. (1.73)	Predominantly student sample: 73 users, $M = 32.15$ weeks (62.82) since last use: 73 controls with some polydrug use.	309.86 (486.25)	Consonant updating (updating). Spatial span, spatial updating (visuospatial memory).	Age, education, IQ, passive memory storage differences, alcohol, tobacco & cannabis use compared by <i>t</i> -tests. Correlations between performance, cannabis & cocaine use examined	Users showed deficits on consonant & spatial updating linked to serial presentation positions. No deficits shown on spatial span.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (M) with (SDs) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Dafters (2006) [18] (UK) Ecstasy/cannabis users: 23.24 yrs. (2.33) Cannabis controls: 23.19 yrs. (1.15) Drug naïve controls: 22.67 yrs. (2.56)	Predominantly student sample: 18 ecstasy / cannabis users: 17 cannabis using controls: 18 nearly drug naïve controls. All groups had some polydrug use. Time since last ecstasy use not reported.	522.33 (936.71)	Keep track task (updating). Stroop task (inhibition, but with an additional improvised shifting measure which had not been empirically tested for its relationship to this function).	Unspecified statistical analysis on measures of other drug use. Some of these measures were included as predictors in multiple regression.	Users showed no deficits on updating or traditional Stroop measures. Deficits found on the improvised Stroop shifting measure.
Wareing et al (2005) [19] (UK) Current users: 21.81 yrs. (2.52) Former users: 26.83 (5.80) Controls: 22.39 yrs. (6.47)	Predominantly student sample: 36 current users, M = 3.3 weeks since last use: 12 former users, M = 92.94 weeks (81.08) since last use: 31 controls. All groups had some polydrug use.	Current users: 591.33 (718.44). Former users: 433.36 (411.07).	Simple visuospatial span, & visuospatial working memory span [i.e. with a related concurrent task] (visuospatial memory). Computation span (updating).	ANOVAs for age, education, IQ, & other drug use. ANCOVAs on visuospatial working memory performance with age, simple spatial span, computation span, & other drug use as covariates.	Users showed deficits in visuospatial working memory span & updating. No deficits were found in simple visuospatial span.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (M) with (SDs) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Morgan (1998) [22] (UK) Study 1: Users: 20.94yrs. (1.88) Polydrug controls: 20.25 yrs. (1.48) Drug naïve controls: 21.87 yrs. (6.09) Study2: Users: 22.28 yrs. (2.48) Polydrug controls: 23.00 yrs. (4.71) Drug naïve controls: 21.74 (2.94)	Samples of students or graduates. Study 1: 16 users, $M = 20.4$ days (33.6) since last use: 12 polydrug controls & 16 drug naïve controls. Study 2: 25 users, $M = 65.1$ days (85.7) since last use: 20 polydrug controls & 19 drug naïve controls.	Study 1: 35.6 (17.5). Study 2: 49.6 (33.2)	Study 1: Tower of London (inhibition). Spatial span (visuospatial memory). Study 2: Tower of London (inhibition).	Both studies: Group design to control for polydrug use. MANOVA for age, gender ratio, education, height, weight, & pre-morbid IQ. Unspecified parametric analysis of other drug use.	Study 1: no deficits shown by users regarding inhibition or spatial span. Study 2: no deficits shown by users regarding inhibition, but nondrug controls showed a trend for longer initial thinking times than both other groups.
McCann et al (2007) [26] (USA) Users: 22.08 yrs Controls: 25.69 yrs (SDs not given)	Community sample: 25 users, $M = 3.09 (\pm 6.92)$ months since last use: 23 controls with some polydrug use.	112.3 exposures (range 30-324).	Wisconsin card sorting task (shifting). Stroop task (inhibition).	Age, education and IQ compared, but no details of statistical analysis given.	Users showed no performance deficits.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (M) with (SDs) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Fox et al (2001) [27] (UK) Problematic users: 27.4 ± 4.5 yrs Nonproblematic users: 26.2 ± 5.0 yrs Controls: 23.3 ± 6.5 yrs	Community sample: 20 users with self-reported ecstasy related problems, 7.8 ± 11.5 months since last use: 20 non-problematic users, 2.5 ± 5.4 months since last use: 20 controls with some polydrug use.	Self-reported problem users: 372.3 ± 663.3. Nonproblematic users: 356.9 ± 339.8.	Wisconsin card sorting task (shifting). Tower of London (inhibition). Spatial working memory (visuospatial memory).	Nonparametric ANOVAs on other drug use.	Both user groups showed impairments on inhibition and spatial working memory. No deficits were shown by users on shifting.
Thomasius et al. (2003) [28] (Germany) Current users: 24.50 ± 4.00 yrs Former users: 24.13 ± 4.21 yrs Polydrug controls: 24.41 ± 4.55 yrs Drug naïve controls: 23.13 ± 3.67 yrs	Community sample: 30 current users, 21.60 ± 16.38 days for males & 24.73 ± 16.32 days for females since last use: 31 former users, 485.40 ± 533.09 days for males & 545.13 ± 470.74 days for females since last use: 29 polydrug controls and 30 drug naïve controls.	Current users: males, 1,033.77 ± 1,702.44; females, 600.42 ± 565.28. Former users: males, 987.31 ± 824.50; females, 533.80 ± 317.22.	Wisconsin card sorting task (shifting).	Group design to control for polydrug use. ANOVAs for age, education, IQ, psychopathology, & for alcohol, tobacco, & other drug use.	Users showed no performance deficits, with both user groups making significantly fewer errors than polydrug controls.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (<i>M</i>) with (<i>SDs</i>) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Reneman et al (2006) [29] (Holland) Moderate users: males 25.6 ± 7.5 yrs., females 22.7 ± 2.8 yrs. Heavy users: males 27.1 ± 6.0 yrs., females 25.0 ± 4.1 yrs. Former users: males 26.4 ± 6.2 yrs., females 24.1 ± 4.7 yrs. Polydrug controls: males 29.3 ± 6.9 yrs., females 23.3 ± 1.3 yrs.	Community sample: 15 moderate users, 4.3 ± 7.5 months for males & 2.7 ± 2.1 months for females since last use: 23 heavy current users, 1.97 ± 2.67 months for males & 2.6 ± 2.1 months for females since last use: 16 former users, 37.1 ± 25.4 months for males & 21.0 ± 10.1 months for females since last use: 15 polydrug controls.	Moderate users: 29.5 ± 17.5 for males & 27.3 ± 19.7 for females. Heavy current users: 831.8 ± 733.0 for males & 200.9 ± 171.2 for females. Former users: 126.9 ± 91.4 for males & 409.3 ± 868.7 for females.	Stroop task (inhibition). Wisconsin card sorting task (shifting). Corsi block span tasks (visuospatial memory).	ANOVA for education and other drug use. Unspecified analyses for age, gender, and pre-morbid IQ.	Users showed no executive functioning deficits.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (M) with (SDs) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Halpern et al. (2004) [30] (USA) Users: median = 20 yrs., interquartile range 19, 20 yrs. Controls: median =22 yrs., interquartile range 19, 25 yrs.	Community sample: 23 users, asked to abstain from ecstasy for at least ≥ 10 days prior to testing: 16 drug naïve controls.	Subsamples: 11 heavy users, median 100 episodes (range 60-450), & 12 moderate users (range 22-50 episodes).	Wisconsin card sorting task (shifting). WMS III spatial span (visuospatial memory) [Also the FAS task (access to LTM)].	Regression analyses controlling for age, gender, parental education, parental household income, family substance abuse history, & family psychiatric history.	Heavy users showed shifting deficits when age, gender, & family of origin variables were controlled, & visuospatial memory deficits when age & gender were controlled. No deficits reported on access to LTM.
Croft et al. (2001) [32] (UK) Ecstasy/cannabis users: 25.7 yrs (4.7) Cannabis controls: 26.6 yrs. (8.1) Controls: 23.5 yrs (6.8)	Community sample: 11 ecstasy/cannabis users: 18 cannabis using controls.. Abstinence ≥ 48 hours requested from both drugs. Some polydrug use in both groups: 31 near drug naïve controls.	Ecstasy / cannabis users: 41.9 (49.3). A mean of 0.6 (1.3) was reported for the cannabis group.	Stroop task (inhibition). [Also the FAS task (access to LTM)].	Group design to control for cannabis use between user groups. ANOVAs for age, IQ, education levels, & gender, which were also included in some ANCOVAs.	Equivocal findings reported regarding the relationship between ecstasy use and impaired inhibition indicated. No deficits reported on access to LTM.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (M) with (SDs) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Morgan et al (2002) [33] (UK) Current users: 23.4 ± 3.2 yrs. Former users: 24.7 ± 2.5 yrs. Polydrug controls: 22.1 ± 3.3 yrs Drug naïve controls: 22.4 ± 4.1 yrs	Community sample: 18 current users, 5.1 ± 3.9 weeks for males & 3.0 ± 2.5 weeks for females since last use: 15 former users, 110 ± 58 weeks for males & 113 ± 97 weeks for females since last use: 16 polydrug & 15 drug naïve controls.	Current users: males, 513 ± 470; females, 93 ± 65. Former users: males, 336 ± 248; females, 577 ± 884.	Stroop task (inhibition). [Also the FAS task (access to LTM)].	Group design to control for polydrug use. ANOVA for age, gender ratio, education, height, weight, pre-morbid IQ, alcohol, tobacco, & other drug use.	No deficits in users indicated for inhibition or access to LTM.
Yip & Lee (2005) [34] (Hong Kong) Users: 28.46 yrs. (5.71) Controls: 28.82 yrs. (5.78)	Community sample: 100 users, $M = 2.23$ months (0.51): 100 implied drug naïve controls to match users.	35.84 (13.21)	Stroop task (inhibition)	Strict exclusion criteria for alcohol, tobacco, & other drug use. ANOVA for age, education, non-verbal IQ & depression.	Equivocal findings reported regarding the relationship between ecstasy use and impaired inhibition.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (M) with (SDs) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Dafters (2006) [35] (UK) Users (≥ 50 tablets): 23.24 yrs (2.33) Users (< 50 tablets): 23.19 yrs. (1.15) Controls: 22.67 yrs (2.56)	Predominantly student sample: 18 users of ≥ 50 tablets & cannabis: 18 users of < 50 tablets who had \geq exposures to cannabis: requested abstinence periods: ecstasy 5 days, cannabis 2 days: 18 near drug naïve controls	Users of ≥ 50 tablets & cannabis: 522.33 (936.71). Users of < 50 tablets who had \geq exposures to cannabis: 4.00 (6.88).	Stroop task (inhibition)	Age differences reported but not tested. Group design controlled for cannabis. ANCOVA controlled for other drug use.	Users of ≥ 50 tablets & cannabis showed impaired inhibition related to negative priming, compared to the other groups.
de Sola Llopis (2008) [36] (Spain) Baseline: Users: 23.6 yrs. (3.5) Cannabis controls: 22.0 yrs. (1.9) Drug naïve controls: 22.0 yrs. (2.6)	Community sample with follow-ups at 6, 12 & 24 months. Baseline: 37 users with some polydrug use, 23 cannabis using controls with no polydrug use, & 34 drug naïve controls (72 hour abstinence from illicit drug use requested). Some participants re-classified at follow-up	Baseline: 206 (228.3).	Tower of London (inhibition). Corsi block tapping task: backward sequence span (visuospatial memory).	ANOVA or χ^2 for baseline age, gender, education, employment status, IQ. & drug use; repeated to compare the 24 months sample to drop outs: <i>t</i> -test for drug use changes between baseline & 24 months. ANCOVA for gender & pre-morbid IQ on executive tasks.	Baseline: Heavy users (> 100 tablets) showed deficits on visuospatial memory, and ecstasy use correlated with planning times on the inhibition task. At 24 months, the deficit in visuospatial performance persisted.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (M) with (SDs) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Wareing et al. (2000) [37] (UK) Current users: 22.20 yrs. (2.20) Former users: 22.60 yrs. (2.22) Controls: 22.60 yrs. (2.12)	Community sample: 10 current users $M = 8.20$ days (5.75) since last use: 10 former users, $M = 323.25$ days (130.05) since last use, (some polydrug use in both groups), 10 drug naïve controls.	Current users: implied estimate of 1,349. Former users: implied estimate of 1,281. (SDs not calculable.)	Random letter generation (inhibition & LTM access).	ANOVA for self rated health, age, & education. ANCOVA for health, anxiety, arousal, and other drug use.	Evidence of impaired inhibition for both users groups compared to controls.
Fox et al (2002) [38] (UK) Users: 27.3 ± 6.7 yrs. Controls: 27.5 ± 7.6 yrs.	Community sample: 20 users with polydrug use, abstinent from illicit drug use for ≥ 2 weeks: 20 polydrug controls.	172.0 ± 227.36 (range 10 – 1,000).	Spatial working memory, pattern & spatial recognition (visuospatial memory). Tower of London variant (inhibition). [Also the FAS task (access to LTM)].	Age, pre-morbid IQ, & other drug use compared by <i>t</i> -tests. ANCOVA for other drug use on task performance	Users showed deficits on visuospatial memory except for spatial recognition, & access to LTM. No deficits found for inhibition.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (M) with (SDs) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
<p>Semple et al. (1999) [39] (UK)</p> <p>Users: 25.5 yrs. (4.4) Controls: 24.2 yrs (5.2)</p>	<p>Community sample: 40 users, $M = 18.0$ days (8.0) since last use: 31 controls with some polydrug use.</p>	672 (647)	Stroop task (inhibition). Spatial working memory & matching to sample task (both visuospatial memory). [Also the FAS test (access to LTM)].	Data reported for body size, demographic characteristics, pre-morbid IQ, & other drug use, but not analysed for the full sample.	No deficits in users on visuospatial memory, inhibition, or LTM access. Ecstasy use correlated with spatial working memory errors.
<p>Gouzoulis-Mayfrank et al. [40] (Germany)</p> <p>Users: 23.25 yrs. (range 18-29) Cannabis controls: 22.9 yrs. (range 18-31) Controls: 23.5 yrs (range 18-30)</p>	<p>Community sample: 28 users, $M = 41$ days (71.1) since last use: 28 cannabis using controls: 28 controls with no use of either drug. Regular users of any other illicit drug were excluded from all three groups.</p>	93.4 (119.9)	Stroop task (inhibition). Corsi block tapping span test (visuospatial memory). [Also the FAS test (access to LTM)].	Gender, age and cannabis use reported, but only χ^2 analyses for education differences were reported. ANCOVAs on task performance with IQ as the covariate.	No deficits reported for block tapping, inhibition, or LTM access.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (<i>M</i>) with (<i>SDs</i>) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Heffernan et al (2001) [41] (UK) Users: 24.6 ± 5.89 yrs. Controls: 26.1 ± 6.53 yrs.	Community sample: 30 users with some cannabis & cocaine use: 37 cannabis using controls. Abstinence: cannabis ≥ 3days, ecstasy ≥ 1 day.	Not calculable	Variant of Chicago word fluency test (access to LTM).	ANOVAs for age. ANCOVAs for other drug use on task performance.	Users showed deficits on access to LTM.
Bhattachary & Powell (2001) [42] (UK) Novice users: 23.6 ± 3.0 yrs. Regular users: 23.8 ± 3.4 yrs. Abstinent users: 24.6 ± 3.4 yrs. Controls: 22.1 ± 2.8 yrs.	Student & community sample: 18 novice current users, <i>M</i> = 8.56 days (6.44) since last use: 26 regular current users, <i>M</i> = 7.42 days (6.34) since last use: 16 abstinent users, <i>M</i> = 46.25 days (25.15) since last use & 20 drug naïve controls. All user groups had some polydrug use.	Tablets/doses were rated on an ordinal frequency scale. Modal responses: novice current users, 1 – 5: regular current users, ≥ 51: former users, ≥ 51.	[FAS test (access to LTM)]	χ^2 for gender ratio. ANOVA for age & other drug use. Provision made for covariate analysis of other drug use if correlations with respective test performance were significant.	Users showed deficits on access to LTM. Performance was negatively correlated with lifetime ecstasy consumption.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (M) with (SDs) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Hanson & Luciana (2004) [43] (USA) Users: 21.3 yrs. (3.6) Controls: 20.7 yrs. (3.4)	Student & community sample: 26 users, $M = 10.9$ weeks (10.5) since last use: 26 drug naïve controls. Users had some polydrug use.	Episodes of use: $M = 64.9$ (122.9).	Spatial delayed response task (visuospatial memory). [Also the FAS task (access to LTM)].	χ^2 for gender ratio, handedness distribution, ANOVA for age, depression, & IQ. Correlations with some measures of other drug use.	Users performed better than controls on "no delay" spatial response trials, but were more impaired than controls in delay conditions. Users were also impaired on access to LTM.
Verkes et al. (2001) [44] (Holland) Heavy users: 21.7 yrs. (2.2) Moderate users: 22.1 yrs. (2.3) Controls: 20.6 yrs. (2.2)	Community sample: 21 heavy users, $M = 9.0$ days (7.5) since last use: 21 moderate users, $M = 15.7$ days (9.5) since last use: 20 controls with some cannabis & amphetamine use.	Heavy users: 741 (678). Moderate users: 169 (252).	Corsi block tapping span test (visuospatial memory). A variant of the Wisconsin card sorting task (called the classification task) was also used, but its results were not separately reported.	Age, body weight, number of rave visits, education, ecstasy use, other drug use, & psychopathology were analysed by t -tests, with significant results indicating covariates for ANCOVAs on task performance.	Users showed deficits in visuospatial memory.

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (M) with (SDs) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
<p>Wareing et al (2004) [45] (UK)</p> <p>Current users: 21.92 yrs. (2.80) Former users: 28.00 yrs. (5.64) Controls: 25.22 yrs. (8.00)</p>	<p>Predominantly student sample: 25 current users, M = 3.4 weeks (2.87) since last use: 10 former users, M = 107.93 weeks (80.80) since last use: 18 controls. All groups had some polydrug use.</p>	<p>Current users: 655.58 (805.50). Former users: 469.20 (414.96).</p>	<p>Simple visuospatial span, & visuospatial working memory span [i.e. with a related concurrent task], with additional random letter generation as a dual task (visuospatial memory & inhibition).</p>	<p>ANCOVAs on visuospatial working memory performance using age, education, IQ, and other drug use as covariates.</p>	<p>Users showed deficits in visuospatial working memory span, but not in simple visuospatial span.</p>
<p>McCann et al (1999) [46] (USA)</p> <p>Users: 26.23 ± 1.99 yrs. Controls: 30.35 ± 1.98 yrs.</p>	<p>Community sample (users were self-referred inpatients): 22 users, 13.91 ± 6.54 weeks since last use: 23 polydrug controls.</p>	<p>215 ± 33 exposures</p>	<p>Matching to sample task (visuospatial memory).</p>	<p>Data for age, gender, education, & other drug use are reported but not analysed.</p>	<p>Users showed no impairments on visuospatial memory.</p>

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (M) with (SDs) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
<p>Schilt et al (2007) [47] (Holland)</p> <p>Baseline: Users: 21.8 yrs. (3.1) Controls: 21.5 yrs. (2.1)</p>	<p>Prospective community sample with zero baseline ecstasy use ($N = 188$), and 3 year follow up. At follow up: 58 users, $M = 11.8$ weeks (12.0) since last use: 60 controls with some cannabis & cocaine use.</p>	<p>At follow-up: 3.2 (5.2)</p>	<p>Judgement of line orientation from memory (visuospatial memory)</p>	<p>Mann-Whitney tests for other drug use & level of education at baseline & follow up, & t-tests for age & verbal IQ. MANCOVA for ecstasy, other drug use, verbal IQ & age, on baseline to follow up performance comparisons.</p>	<p>Users showed no impairments on visuospatial memory.</p>
<p>Schilt et al (2007) [48] (Holland)</p> <p>Whole sample: 23.5 yrs (3.9) Group statistics not given.</p>	<p>Community sample: 31 designated users with consumption > 10 tablets: 36 designated 'nonusers' with consumption ≤ 10 tablets. $M = 8.7$ weeks (9.9) since last use. Other drug use levels within groups not given.</p>	<p>Designated users: 327 (364)</p>	<p>Judgement of line orientation from memory (visuospatial memory)</p>	<p>Unspecified analysis of ages between the groups. Hierarchical regression to control for other drug use, age, & IQ on task performance.</p>	<p>Users showed no impairments on visuospatial memory.</p>

Table 2 continued

Authors/study, (country), & participants' mean (SD) ages if given	Sample details: Means (<i>M</i>) with (<i>SDs</i>) in brackets in most cases	Mean (SD) estimated lifetime ecstasy use (Tablets unless stated)	Executive tasks used & related functions identified in Table 1	Statistical controls for potential intergroup confounds	Main findings for executive tasks identified in Table 1
Rodgers (2000) [49] (UK) Users: 31.42 yrs. (4.17) Cannabis controls: 30.25 yrs. (6.25) Drug naïve controls: 32.08 yrs (4.08)	Community sample: 15 users with some polydrug use, ecstasy free \geq 2 months prior to testing: 15 cannabis using controls with no polydrug use: 15 drug naïve controls.	20 exposures	Visual memory span (visuospatial memory)	Group design to control for cannabis use, but no statistical comparisons on demographic or drug related variables.	Users showed no impairments on visuospatial memory.

Table 3

Studies reporting either an ecstasy related performance deficit on or a relationship between ecstasy use and performance on visuospatial memory tasks

Study	Task details
Fisk & Montgomery [15]	Updating and recall of sequentially highlighted computerised grid cells
Montgomery & Fisk [17]	Updating and recall of sequentially highlighted computerized grids.
Wareing et al [19]	Single task procedure: Computerised grid processing for an auxiliary task, and grid recall
Fox et al [27]	Recall of sequentially illuminated windows in a computerised 'house' image
Halpern et al. [30]	Backward and total spatial span – Wechsler Memory Scale (WMS-III)
De Sola Llopis et al. [36]	Corsi block tapping: backwards spatial sequence recall.
Fox et al [38]	Computerised box search requiring the development of a search strategy
Semple et al. [39]	Computerised box search requiring the development of a search strategy
Hanson & Luciana [43]	Computerised spatial location recall
Verkes et al [44]	Corsi block tapping – spatial sequence recall
Wareing et al [45]	Dual task procedure: Computerised grid processing for an auxiliary task and grid recall, plus concurrent random letter generation

Table 4

Studies reporting no ecstasy related deficits on or relationships between ecstasy use and visuospatial memory task performance

Study	Task details
Fisk & Montgomery [15]	Computerised grid recall only
Wareing et al. [19, 45]	Computerised grid recall only
Morgan [22]	Computerised block tapping
Reneman et al. [29]	Corsi block tapping – spatial sequence recall
Fox et al. [39]	Computerised spatial location recognition
Semple et al. [39]	Computerised matrix matching
Gouzoulis-Mayfrank et al. [40]	Corsi block tapping – spatial sequence recall
McCann et al. [46]	Computerised matrix matching
Schilt et al. [47, 48]	Judgement of line orientation from memory
Rodgers [49]	Visual memory span: block tapping