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

(Running Head: Executive Deficits in ecstasy users)

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Key Words

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Abstract

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

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

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

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

Introduction

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

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

Insert Table 1 about here.

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

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

Method

Identification of Studies

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

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

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

Data extraction

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

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

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

Results

Overview

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

Insert Table 2 about here

Ecstasy and executive updating

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

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

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

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

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

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

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

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

Ecstasy and executive shifting

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

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

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

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

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

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

<u>Ecstasy and executive inhibition</u>

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

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

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

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

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

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

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

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

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

Ecstasy and access to long term memory (LTM)

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

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

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

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

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

Ecstasy and visuospatial memory

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

Insert Tables 3 and 4 about here

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

With minor exceptions, this review was limited to a restricted group of tasks with a demonstrated empirical link to the executive processes of updating, shifting, inhibition, access to LTM, or which drew upon certain aspects of visuospatial memory. Studies reporting ecstasy related deficits on other tasks believed to draw upon executive functioning were, therefore, not included [eg. 54]. Further empirical developments in mainstream cognitive psychology concerning the relationships of tasks to executive structure will benefit this area of research. It is recommended that future reporting of executive performance in users of ecstasy or any other drug should outline the relationship of the task administered to executive functioning. Where tasks generate multiple dependent variables clarity is needed in reporting and discussing these. These steps will enhance the clarity of evidence in this field. With regard to visuospatial memory, this review was limited to tasks requiring either recall or recognition of the spatial distribution of individual elements of a stimulus display. As any visual stimulus will have some spatial dimension to it would seem appropriate for a more extensive review of 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 (*M*) with (*SD*s) 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, *M* = 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 *t*-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, *M* = 3.00 weeks (3.66) since last use: 17 former users, *M* = 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, *M* = 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 t-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 (*M*) with (*SD*s) 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, *M* = 4.97 weeks (7.27) since last use: 34 controls. Study 2: 51 users, *M* = 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: *t*–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, *M* = 22 weeks since last use: 39 light users, *M* = 27 weeks since last use (no *SD*s 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 *t*-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 (*SD*s not given)	Community sample: 25 users, *M* = 3.09 (± 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 (*M*) with (*SD*s) 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 ≥ 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 ≥ 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: *t*-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. (*SD*s 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 $\geq$ 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 *t*-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
Semple et al. (1999) [39] (UK) Users: 25.5 yrs. (4.4) Controls: 24.2 yrs (5.2)	Community sample: 40 users, *M* = 18.0 days (8.0) since last use: 31 controls with some polydrug use.	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.
Gouzoulis-Mayfrank et al. [40] (Germany) Users: 23.25 yrs. (range 18-29) Cannabis controls: 22.9 yrs. (range 18-31) Controls: 23.5 yrs (range 18-30)	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.	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 (*M*) with (*SD*s) 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, *M* = 8.56 days (6.44) since last use: 26 regular current users, *M* = 7.42 days (6.34) since last use: 16 abstinent users, *M* = 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
Wareing et al (2004) [45] (UK) Current users: 21.92 yrs. (2.80) Former users: 28.00 yrs. (5.64) Controls: 25.22 yrs. (8.00)	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.	Current users: 655.58 (805.50). Former users: 469.20 (414.96).	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).	ANCOVAs on visuospatial working memory performance using age, education, IQ, and other drug use as covariates.	Users showed deficits in visuospatial working memory span, but not in simple visuospatial span.
McCann et al (1999) [46] (USA) Users: 26.23 ± 1.99 yrs. Controls: 30.35 ± 1.98 yrs.	Community sample (users were self-referred inpatients): 22 users, 13.91 ± 6.54 weeks since last use: 23 polydrug controls.	215 ± 33 exposures	Matching to sample task (visuospatial memory).	Data for age, gender, education, & other drug use are reported but not analysed.	Users showed no impairments on 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
Schilt et al (2007) [47] (Holland) Baseline: Users: 21.8 yrs. (3.1) Controls: 21.5 yrs. (2.1)	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.	At follow-up: 3.2 (5.2)	Judgement of line orientation from memory (visuospatial memory)	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.	Users showed no impairments on visuospatial memory.
Schilt et al (2007) [48] (Holland) Whole sample: 23.5 yrs (3.9) Group statistics not given.	Community sample: 31 designated users with consumption > 10 tablets: 36 designated 'nonusers' with consumption $\leq$ 10 tablets. *M* = 8.7 weeks (9.9) since last use. Other drug use levels within groups not given.	Designated users: 327 (364)	Judgement of line orientation from memory (visuospatial memory)	Unspecified analysis of ages between the groups. Hierarchical regression to control for other drug use, age, & IQ on task performance.	Users showed no impairments on visuospatial memory.

Table 2 continued

Authors/study, (country), & participants' mean (*SD*) ages if given	Sample details: Means (*M*) with (*SD*s) 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 ≥ 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