**Murphy, PN, Bruno, R, Ryland, I, Wareing, M, Fisk, JE, Montgomery, C and Hilton, J**

**The effects of ecstasy' (MDMA) on visuospatial memory performance: findings from a systematic review with meta-analyses**

# The effects of 'ecstasy' (MDMA) on visuospatial memory performance: findings from a systematic review with meta-analysis

(Running head: Ecstasy and visuospatial memory: meta-analyses)

Philip N. Murphy[1], Raimondo Bruno[2], Ida Ryland[3], Michele Wareing[4], John E. Fisk[5], Catharine Montgomery[6], Joanne Hilton[7]

[1] Evidence-based Practice Research Centre and Department of Social & Psychological Science, Edge Hill University, UK.

[2] School of Psychology, University of Tasmania, Australia.

[3] Evidence-based Practice Research Centre, Edge Hill University, UK.

[4] Department of Social & Psychological Science, Edge Hill University, UK.

[5] School of Psychology, University of Central Lancashire, UK.

[6] School of Psychology, Liverpool John Moores University, UK.

[7] Alder Hey NHS Trust, UK, and Department of Social & Psychological Science, Edge Hill University, UK.

Corresponding author

Dr. Philip Murphy, Department of Social & Psychological Sciences, Edge Hill University, St. Helens Road, Ormskirk, Lancashire, L39 4QP, United Kingdom.

Tel: +44(0)1695-584600 / 584508

Fax: +44(0)1695-579997

Email: murphyp@edgehill.ac.uk

Key words

Ecstasy (MDMA), visuospatial, memory, meta-analyses.

Abstract

*Objective*. To review performance differences, with meta-analyses, between ecstasy (MDMA) users and non-users on a wider range of tasks requiring processing of visual/spatial information than in our previous narrative review of tasks requiring working memory executive resources. *Method*. Abstracting databases were searched using the United Kingdom NHS Evidence Health Information Resource. Inclusion criteria were publication in English language peer-reviewed journals, and to be reporting new findings regarding human ecstasy users' performance on visual/spatial tasks. Data extracted included specific task demands, to provide a basis for meta-analyses for categories of tasks making similar demands. *Results*. Fifty-two studies were identified for review, although not all were suitable for meta-analysis. Significant weighted mean effect sizes indicating poorer performance by ecstasy users compared to matched controls were found for tasks requiring recall of spatial stimulus elements, recognition of figures, and production/reproduction of figures. There was no evidence of a linear relationship between estimated ecstasy consumption and effect sizes. *Conclusions.* Given the networked nature of processing for spatial and non-spatial visual information, future scanning and imaging studies should focus on brain activation differences between ecstasy users and non-users in the context of specific tasks for the identification of loci of potentially compromised activity in users.

## Introduction

The black market drug ‘ecstasy’ has been an important feature of illegal drug use since the late 1980s in many countries, with recent estimates of lifetime ‘ever use’ such as 2.6 million for 16 to 50 year olds in England Wales (Hoare & Moon, 2010), 14.2 million for those aged 12 years or older in the United States (Substance Abuse and Mental Health Services Administration, 2010), and 1.5 million for those aged 14 and older in Australia (Australian Institute of Health and Welfare, 2008). The dominant chemical constituent of ecstasy (3,4-methylenedioxymethamphetamine, or MDMA) is known to be neurotoxic with regard to serotonergic neurons in the brains of rats and primates (Puerta et al., 2009), and although the nature and duration of its effects on human brains has been hotly debated (Cowan, 2007), it is evident from scanning and imaging studies that the functioning of serotonergic neurons in a number of brain areas in ecstasy users can be altered in comparison to non-users. For example, using fMRI recordings of the blood-oxygen level dependent (BOLD) signal, Cowan et al. (2006) showed different activation patterns in the visual occipital areas of users in comparison to non-users in response to photic stimulation, whilst the use of SPECT has identified serotonergic axonal damage in thalamic and frontoparietal brain regions of users (de Win et al., 2008a, 2008b). McCann et al. (1998, 2005, 2008) examined the availability for binding of the presynaptic membrane serotonin transporter (SERT) using PET scanning, and reported significant global reductions in SERT binding activity in users compared to non-users in brain areas which included the dorsolateral prefrontal cortex (DLFPC), parietal cortex, temporal cortex, and occipital cortex. However, only the latest of these three studies investigated, and was therefore able to confirm, impaired cognitive performance and global SERT binding reductions in the same sample of ecstasy

users compared to non-users. However, SERT binding in fronto-striatal regions has been shown to be related to cognitive performance in healthy participants (Madsen et al., 2011). Whilst changes in SERT binding may be subject to different interpretations with regard to nature of the underlying neuronal damage (Reneman et al., 2006a), there is evidence that such changes may be reversible in humans with abstinence from ecstasy (Buchert et al., 2004; Selvaraj et al., 2009), although this may not be always be accompanied by equivalent levels of cognitive performance compared to non-users (Gouzoulis-Mayfrank & Daumann, 2009; Thomasius et al, 2006).

One of the cognitive functions potentially vulnerable to the disruption of serotonergic functioning is visuospatial memory. This has been demonstrated in humans by performance decrements related to administration of the 5-$HT_{2A}$ receptor anatagonist ketanserin (Wingen et al., 2007). Research into the effects of ecstasy use on visuospatial memory performance has produced contrasting results. We have previously reviewed findings from 18 studies which compared the performance of ecstasy users to that of non-users on tasks requiring the recall or recognition of specific spatial elements of a stimulus array (Murphy et al., 2009), and noted that where inter-group performance differences on computerised grids and block tapping tasks had been absent for simple versions of the task, increasing the performance of the task would sometimes lead to the emergence of significant differences. For example, this occurred where a spatial sequence had be recalled backwards rather than forwards (Halpern et al., 2004), or where additional spatial information processing demands were made of participants (Wareing et al., 2004, 2005). Latent variable analysis has shown visuospatial memory performance to draw heavily upon

the executive resources of working memory (Miyake et al., 2001), and that this is the case whether the task in question requires only basic retention and retrieval, constituting simple visuospatial memory, or additional goal orientated processing of the stimulus array, constituting visuospatial working memory. Our previous review tentatively concluded that the level of executive processing demands made by a visuospatial task might have a role in mediating differences in performance levels between ecstasy users and non-users, and recommended that this be further investigated.

With regard to neural structures, visuospatial memory has been shown to draw upon a network of structures involved with different aspects of the information processing required (see review by Zimmer, 2009) For example, the DLPFC appears to be concerned with processing spatial information, and also with the monitoring of information flow generally, as would be consistent with frontal lobe executive functioning more broadly. Parietal cortex has also been shown to contribute to the processing of spatial information, whilst temporal and occipital areas contribute to the processing of other stimulus features. Despite evidence for differentiation in brain areas processing spatial and other visual information, there is also evidence that both spatial and non-spatial visual stimuli draw upon common brain areas, including the DLPFC (Owen et al., 1998; Rypma, 2006), and primary visual occipital areas will process all visual stimuli from tasks. The widespread effects on brain functioning associated with ecstasy consumption discussed above, therefore have the potential to impair performance on visuospatial tasks in a combination of ways involving a range of neural locations. Consequently, task performance may conceivably suffer

due to impaired processing of spatial information, impaired monitoring of the flow of information, or impaired processing of nonspatial stimulus features.

Our previous review of visuospatial performance in ecstasy users (Murphy et al., 2009) had two important limitations, these being that it was entirely narrative with no quantitative analysis, and that only a limited range of visual tasks with a spatial dimension were examined. This present review aims to address both of these limitations. An exploration of a wider range of visual tasks is considered important because all visual stimuli inherently possess a spatial dimension. The ability to compare abstract visual figures requires cortical processing of their spatial characteristics, even though the task of identifying whether two figures are the same or different would not generally be considered as a visuospatial task in the same way as a task requiring the recall of a spatial sequence for highlighted grid squares. Examination of potential ecstasy related effects with regard to differences in processing demands across tasks for visual and spatial information may therefore add to our knowledge of the neuropsychological consequences of using this drug. Given the range of tasks to be examined, the term ‘visual/spatial’ rather than ‘visuospatial’ will be used in referring to tasks for the remainder of this review, in order to avoid any conflict with the traditional use of the latter term. In the light of criticisms of studies concerning ecstasy related cognitive performance effects generally in relation to not adequately controlling for potential confounds in their results (Rogers et al., 2009), attention will also be paid in this review to the methods used by studies to control for the potential effects of other drug use, intelligence, and demographic variables on their results.

## Method

### Identification of studies

A preliminary search of literature covering the period up to November 2009 was undertaken to identify publications relating to the effects of ecstacy (MDMA) on visual/spatial performance in humans. The Psychinfo, Pubmed, and Web of Science databases were initially searched using eight terms in which either ‘ecstasy’ or ‘MDMA’ was paired, respectively, with ‘spatial’, ‘visual’, ‘visuospatial’, or ‘visuo-spatial’. This preliminary search covered the period up to May 2010. In the second phase a further systematic search of the literature was undertaken to identify publications up to the end of 2010. Electronic databases Medline, Embase, and PsychInfo were searched via the United Kingdom NHS Evidence Health Information Resource. The ISI Web of knowledge was searched independently. All databases were cross-checked to avoid duplication. The following keywords, and their corresponding synonyms, were employed in the search: ecstasy, MDMA, visual, visuo-spatial or visuospatial, spatial and performance. In this second search it was possible to explode these terms utilising the relevant database thesaurus to ensure completeness of data.

The search was restricted to English language publications with human participants. Other inclusion criteria were that studies had to be in peer-reviewed journals, and to be reporting new findings (including attempted replications) regarding visual/spatial memory performance with regard to ecstasy use. It was necessary for participants to have been abstinent from ecstasy and other drugs of misuse at the time of testing. By implication, therefore, studies which tested participants under the influence of ecstasy or another drug, animal studies, and studies published in a language other

than English were excluded from the review. Studies were also excluded if they were in the form of dissertations, conference presentations, reviews or meta-analyses, or used 'concrete' objects (including faces), as opposed to abstract figures, as stimuli in such a way which would be likely to recruit brain areas not recruited in other visual/spatial tasks (Haxby et al., 2000). A similar problem arose with the use of verbal items as stimuli, including digits, as there was the possibility of language related areas being recruited into participants' stimulus processing and response selection, in a way distinct from other tasks (Gruber & von Crammon, 2003). In practice, studies were included if participants had been required to focus their response upon the spatial location of stimuli, such as in recalling a sequence of highlighted grid squares, but not if their response was focussed upon verbal aspects of the stimulus, such as naming a letter. Decisions involving inclusion in the review were based upon consensus between at least two reviewers. Inclusion in the review sample did not automatically imply inclusion in meta-analyses, as additional criteria regarding study design, tasks employed, and the reporting of data were relevant to these decisions and are discussed below (see Analytic Strategy).

Data extraction

For each study included in the review, details were recorded for each sub-group of participants regarding age, estimated lifetime ecstasy consumption, and time since last ecstasy use. These variables were recorded in the form in which they were reported, which generally involved mean values qualified by standard deviations. Where studies did not report data for abstinence duration from ecstasy prior to testing the minimum abstinence duration for participants' inclusion in the study was recorded, if reported. Where studies did not report an estimate for lifetime ecstasy

consumption an implied estimate was calculated, if possible, from the available data. The descriptors applied by studies to their various sub-groups were generally recorded in their original form (e.g. novice ecstasy users, polydrug controls), with additional information being added if these descriptors were insufficiently detailed. It was also noted if the authors had allowed minor infringements of inclusion criteria for sub-groups, such as allowing participants with a very low level of cannabis use into otherwise drug naïve control groups. The term 'community sample' was assigned to samples recruited from the general population through advertisements and/or outreach activities in the community at large, whilst the term 'student sample' was assigned to samples recruited entirely through educational institutions. Other appropriate descriptive labels were applied to the few studies where the sample's origins were not covered by these three terms. The national origin of each included study, with regard to where data was collected, was also recorded. Statistical procedures for the control of potentially confounding variables, such age, intelligence, and the effects of other drug use by each study were recorded. Details of all tasks requiring visual/spatial memory performance were recorded, together with the reported findings for these tasks with regard to ecstasy use.

Where studies were included in one or more meta-analysis, the mean and standard deviation for each dependent variable (*DV*) considered appropriate for that analysis (see analytic strategy) were recorded for ecstasy user groups and for appropriate control groups. The sample sizes for each of these groups were also recorded. The direction of difference in performance between groups for each *DV* included was coded as 'negative' if it was consistent with an interpretation of ecstasy use having affected performance on that task, regardless of the size of difference. For example,

if ecstasy users made more errors on a task than controls, this would generally be coded as negative. However, on measures of impulsivity the predicted ecstasy related effect would be for users to score more highly than controls. Where observed, this direction of difference was coded as negative.

Analytic Strategy

Given the range of information processing and performance demands of the tasks identified, analysis for both narrative and quantitative reviewing began with the development of a classification system for tasks on the basis of these demands. The agreement of a minimum of three reviewers was required for the initial categorisation of a task, with other reviewers asked to challenge any classifications they considered inappropriate. It should be noted however, that some tasks generated *DV*s relevant to more than one category, in which case the task was noted for both categories. In response to these differences in task characteristics, it was decided to conduct meta-analyses within task categories, rather than including all the studies in one analysis. This was done in order to avoid the 'apples and oranges' problem whereby data which is inherently different in its origins and/or meaning is combined to produce a summary main effect of questionable meaning (Lipsey & Wilson, 2001; Borenstein et al., 2009). For one task category it was decided that sufficient common ground in task demands did not exist for a meaningful meta-analysis to be performed, so that performance on tasks in that category is reviewed in narrative form only. In the interests of consistency within the meta-analyses, all comparisons of ecstasy users' performance were to the performance of drug using controls, with comparisons to drug naïve controls excluded except where the ecstasy users were also naïve to the misuse of other drugs. In this way, all inter-group comparisons included in meta-

analyses had some degree of matching for the use of other drugs. Additionally, although all participants had been abstinent from ecstasy and other illegal drugs at the time of testing, performance comparisons were not made with groups designated as former ecstasy users. Given the evidence that compromised brain functioning may return to levels consistent with that of controls in former users (Buchert et al., 2004; Selvaraj et al., 2009), the inclusion of comparisons of both current and former users to controls in the same analysis would potentially confound its interpretation.

Meta-analyses were performed using the means, standard deviations, and group sizes (*n*) for all *DV*s from studies reporting results from tasks in the respective categories. Within each meta-analysis, each study was represented by mean effect sizes for all appropriate sub-group comparisons, which in turn represented all of the *DV*s compared for these sub-groups. In this way, our meta-analyses avoided the distorting effects of using multiple effect sizes where outcomes are not independent due to the same sub-samples of participants having been used in multiple comparisons. Studies were excluded from the quantitative aspect of the review if they did not compare the performance of ecstasy users to drug using controls (e.g. reporting within-participant changes over time), or reported task results in a composite form so as to combine *DV*s of interest with data from other tasks. In cases where task results had not been reported with sufficient clarity for inclusion, attempts were made to contact authors for clarification where possible. The effect size statistic chosen was Hedges' *g*, as this controls for distortions arsing from small samples in the more commonly used Cohen's *d* statistic (Borenstein et al., 2009). For each meta-analysis Rosental's *Fail-safe N* is reported, indicating the minimum number of studies which would be required to render the result nonsignificant. As

only studies in peer reviewed journals were included in this review, this statistic is important in the interpretation of meta-analytic results, given the possibility that studies reporting significant performance differences between ecstasy users and controls may be more likely to be published. Where studies had reported results for appropriate inter-group performance comparisons on relevant tasks, but had been excluded from the meta-analysis for some reason, a summary effect size was reported for the study so that its results may be seen in the same metric as the meta-analytic results for that category.

Given the variety of visual tasks employed, and the heterogeneous nature of the participant samples with regard to their drug use, it was decided that the assumptions for fixed effects models could not be made, and an *a priori* decision was made to only examine results for random effects models. The choice of random effects models in this way, rather than upon the results for heterogeneity in a fixed effects model, is currently recommended practice in meta-analysis (Borenstein et al., 2009). In addition to these performance comparisons between ecstasy users and controls, meta-regression (method of moments) was performed using estimated lifetime ecstasy consumption (in tablets) as a predictor of effect sizes, where estimates were available in this form. As effect sizes consistent with an ecstasy related effect were coded as negative, a relationship between these and increasing ecstasy consumption would yield a negative coefficient (*B*). Borenstein et al. recommend at least ten studies (or independent sub-groups within studies) per predictor in a meta-regression for adequate statistical power. Meta-analyses were conducted using Comprehensive Meta-Analysis (CMA 2.0™) software.

## Results

### Studies and task categories identified

A total of 325 studies, excluding duplication, were identified by the database searches. After checking against the inclusion and exclusion criteria, 52 studies were identified for inclusion in the review overall. Whilst 273 may at first seem a large number of papers to exclude, it should be noted that the search terms ‘ecstasy’ and ‘spatial’ led respectively to the identification of some papers from the realms of the creative arts and engineering. Other papers were excluded because they reported results from animal studies, or were reviews, meta-analyses, or dissertations.

Details of the 52 studies included in the review are summarised in Table 1. From these studies a total of 60 separate visual/spatial tasks were identified, although it should be noted that some of these tasks were very similar to each other regarding the demands they made of participants. These tasks were grouped into four categories as shown in Figure 1, with two examples from each category given. It should be noted that some studies used tasks from more than one category, so that the sum total of studies across categories in Figure 1 exceeds 52. Furthermore, the Aggie figures learning test (see Yip & Lee, 2005) and the Rey-Osterreith complex figures task (see Bedi & Redman, 2008) yielding dependent variables in both Categories 2 and 3. Table 1 records each task included from each study, including the category to which it was assigned, so that the tasks contributing to the effect sizes in subsequent forest plots for each analysis may be seen.

Insert Table 1 and Figure 1 about here

### Task Category 1

The 16 tasks assigned to this category required participants to recall or recognise the spatial distribution of individual stimulus elements presented, such as which cells in a computerised grid matrix had been highlighted or the order in which individual blocks in an array were to be tapped. Whilst 25 studies employed tasks within this category, data for meta-analytic comparisons between ecstasy users and drug using controls was only obtainable from 12 studies for a variety of reasons. Four of the 13 remaining studies had a significant proportion of participants in common with a study which was included in the meta-analysis. In the case of Fisk et al. (2006) the visual/spatial findings presented were based upon the same sample as for Wareing et al. (2005). The three other studies concerned were de Sola et al. (2008; overlapping with de Sola Llopiss et al, 2008), Montgomery and Fisk (2008; overlapping with Fisk & Montgomery, 2009), and Wareing et al. (2005; overlapping with Wareing et al., 2004). These four studies did report results from comparisons between ecstasy users and drug using controls, and further details are given below.

A further five studies did not report results from such comparisons, reporting instead either within-participant comparisons for users or regression analyses (Gouzoulis-Mayfrank et al., 2005; Indelkofer et al., 2009; Zakzanis & Campbell, 2006; Zakzanis & Young, 2001), or comparisons to apparently drug naïve controls (Hanson & Luciana, 2004). Four other studies did not report task results in sufficient detail for inclusion, due to a combination of no significant effects having emerged and the main focus of the study lying elsewhere (Hoshi et al., 2007; Semple et al., 1999; Ward et al., 2006; Wareing et al., 2000). Institutional practices on data disposal emerged as one problem in attempts to obtain clarification.

The 12 studies included in the meta-analysis yielded 18 a mean weighted effect size which was relatively small but highly significant (Hedges *g* = -0.394; 95% CI -0.608 (lower) to-0.180 (upper); *z* = -3.613, *p* < .000, two-tailed, Rosenthal's *Fail-safe N* = 75 studies), with ecstasy users performing worse than drug using controls. The results of this meta-analysis are illustrated in the forest plot in Figure 2. Using 15 sub-group estimates of lifetime ecstasy tablet consumption from 10 studies, meta-regression analysis showed a nonsignificant linear relationship between consumption and effects sizes (*B* = -.0004, *ns.*).

Insert Figure 2 about here

Three studies not included in the meta-analysis examined changes over time in ecstasy users' performance on tasks in this category. Performance on a route tracing task showed no significant change 1 year after baseline testing (Zakzanis & Young, 2001), whilst at 2 years from baseline current (i.e. continuing) users in the same sample showed performance deficits compared to their 1 year follow up (Zakzanis & Campbell, 2006). Former users who had been abstinent from ecstasy for at least 32 weeks at the 2 year follow up showed no performance decrements in comparison to their 1 year follow up performance. However, these findings are based on group sizes of eight former users and seven continuing users. With corresponding numbers of 17 interim abstainers and 21 continuing users, Gouzoulis-Mayfrank et al. (2005) reported no performance changes on a route tracing task over 18 months for the interim abstainers, whilst continuing users actually showed a significant improvement in immediate recall and no change in delayed recall performance. In another study not employing inter-group comparisons, Indlekofer et al. (2009) reported that lifetime frequency of ecstasy consumption was a highly significant predictor in linear

regression of omissions on a task which emphasised vigilance, whereas cannabis and alcohol consumption were not predictive.

The four studies excluded from the meta-analysis due to sample overlap did report results from comparisons between ecstasy users and controls matched for drug use. The respective effect size statistics for these studies were de Sola et al (2008: Hedges *g* = -0.105; 95% CI -0.909 (lower) to 0.699 (upper)); Fisk et al. (2006; Hedges *g* = -0.952; 95% CI -1.348 (lower) to -0.556 (upper)); Montgomery and Fisk (2008; Hedges *g* = -0.355; 95% CI -0.987 (lower) to -0.278 (upper)); and Wareing et al. (2005; Hedges *g* = -0.577; 95% CI -1.064 (lower) to -0.089 (upper)). Fisk et al. (2006) explored the potentially confounding effects of cannabis consumption for the assessment of ecstasy related effects, by examining whether or not visuospatial working memory span performance gave any indication that concomitant use of cannabis with ecstasy could be associated with either a potential neuroprotective, or neurotoxic effect, which would in turn have led to differences when performance was compared to that of ecstasy users with no concomitant cannabis use. However, no significant performance difference was found.

Whilst a number of studies reported no difference in performance levels on measures of spatial span between ecstasy users and controls, some reported that the users went on to perform more poorly than the controls if the task was made more difficult in some way. This included the introduction of an additional concurrent tasks which drew upon executive resources (Fisk & Montgomery, 2009; Wareing et al., 2004, 2005), or under certain circumstances making the task more difficult by requiring the backwards recall of a sequence (de Sola Llopis et al., 2008; Halpern et

al., 2004). Given the dependence of all visuospatial memory performance upon executive resources (Miyake et al., 2001), there is an implication here based upon a small number of studies that the appearance of ecstasy related effects may be dependent upon the level of overall executive demand at the time of task performance. This is would be an important question for further research.

Task Category 2

The 20 tasks assigned to this category required participants to recognise visual displays which had previously been presented. Data for meta-analysis were obtained from 16 of the 22 studies in Table 1 identified as using such tasks. Of the remaining 6 studies not included in the meta-analysis, means and standard deviations for task performance were not available for 4 of them (Bolla et al., 1998; Dafters et al., 2004; McCann et al., 2009; Semple et al., 1999), due to a variety of reasons such as the presentation of results in the form of composite indices reflecting a range of tasks, and the presentation of results in graphical forms rather than the presentation of precise values. Roiser et al. (2006) appeared to have a significant sample overlap with Roiser et al. (2007), the latter study being included in the meta-analysis, whilst Gouzoulis-Mayfrank et al. (2005) reported within-participant comparisons for ecstasy users. It should be noted that whilst Yip and Lee (2005) used drug naïve controls, this matched the drug using profile of their ecstasy users, so that it was possible to include this study in the meta-analysis. Furthermore, it was possible to include results from McCann et al. (2007) for the matching to sample task from two testing sessions occurring prior to catecholamine depletion induced by alpha-methyl-para-tyrosine (AMPT). Data obtained following AMPT administration fell outside the scope of this review.

The 16 studies included in the meta-analysis yielded a weighted mean effect size which was relatively small but highly significant (Hedges *g* = -0.379; 95% CI -0.585 (lower) to -0.173 (upper); *z* = -3.607, *p* < .000, two-tailed, Rosenthal's *Fail-safe N* = 135 studies), with ecstasy users performing worse than controls matched for the use of other drugs. The results of this meta-analysis are illustrated in the forest plot in Figure 3. Using 14 sub-group estimates of lifetime ecstasy tablet consumption from 12 studies, meta-regression analysis showed a nonsignificant linear relationship between consumption and effect sizes (*B* = -0.0001, *ns.*).

Insert Figure 3 about here

Gouzoulis-Mayfrank et al. (2005) followed up some of the ecstasy users from their earlier sample (Gouzoulis-Mayfrank et al., 2003), and found that performance on the logos task (including in his meta-analysis) did not significantly differ from the baseline measures taken approximately 18 months earlier for either those who had continue to use, or those who had been abstinent since baseline. Roiser et al. (2006) examined users and controls with two forms of the serotonin transporter gene-linked polymorphism 5-HTTLPR, which had previously been found to be related to depression and abnormal emotional processing in users. Unlike tests of some other abilities, they reported that performance on neither the matching to sample task, nor a pattern recognition task, showed an interaction between participant group and genotype, indicating that there was no evidence of a genetic predisposition to ecstasy related effects in performance on these tasks. An effect size is not reported here for this study because drug using and drug naïve controls were pooled for comparisons to ecstasy users, so that an obtained value of Hedges *g* would not be interpretable in the same way as the summary main effect reported above. The

finding of Yip and Lee (2005) that ecstasy users showed significantly worse figure recognition than controls in their Hong Kong sample is particularly noteworthy because both groups were reported to have had no exposure to other illegal drugs, and minimal exposure to alcohol and tobacco. Such opportunities to test participants free of the potentially confounding effects of other drug use are rare in this research field.

Task Category 3

The 13 tasks assigned to this category required participants to either produce original abstract figures, or to reproduce (i.e. recall) figures previously seen. Data for meta-analysis were obtained from 12 of the 22 studies identified in Table 1 as using studies in this category. Of the remaining 10 studies, 2 had included control participants with minimal ecstasy exposure (Schilt et al., 2008, 2010). As minimal exposure to ecstasy has been associated with some effects on cognitive performance (Schilt et al., 2007), it was decided that it was safer to omit these two studies from the analysis. As with Category 1, de Sola et al. (2008) was omitted because of sample overlap with de Sola Llopiss et al. (2008), whilst as with category 2, Roiser et al. (2006) was omitted due to sample overlap with Roiser et al. (2007). The use of composite scores for *DV*s prevented the inclusion of Bolla et al. (1998) and McCann et al. (2007), whilst Indlekofer et al. (2009) reported regression analyses rather than inter-group comparisons. McCann et al. (2008) focussed upon the relationship between task performance and brain activity, rather than inter-group comparisons of performance. Two studies reported longitudinal within-participant comparisons for users on the WAIS-III Block Design Task (Zakzanis & Campbell, 2006; Zakzanis & Young, 2001). However, although Medina et al. (2005) did not

analyse inter-group performance differences, they did present data suitable for inclusion in the meta-analysis.

The 12 studies included in the meta-analysis yielded a mean weighted effect size which, once again, was relatively small but highly significant (Hedges *g* = -0.247; 95% CI -0.384 (lower) to -0.109 (upper); *z* = -3.518, *p* = .000, two-tailed, Rosenthal's *Fail-safe N* = 21 studies), with ecstasy users performing worse than controls matched for the use of other drugs. The results of this meta-analysis are illustrated in Figure 4. Using nine sub-group estimates of lifetime ecstasy tablet consumption from eight studies, meta-regression analysis showed a nonsignificant linear relationship between consumption and effect sizes (*B* = 0.0005, *ns.*).

One study excluded from the meta-analysis due to sample overlap did report inter-group comparison data for performance on the Rey-Osterreith complex figure task (de Sola et al., 2008; Hedges *g* = -0.657; 95% CI -1.476 (lower) to 0.162 (upper)). Two studies examined the relationship of performance on tasks in this category to different aspects of serotonergic brain functioning. Consistent with their findings for tasks assigned in this review to Category 2, Roiser et al. (2006) reported that there was no evidence of a genetic predisposition to ecstasy related effects in performance on the tile manipulation task associated with alternative forms of the serotonin transporter gene-linked polymorphism 5-HTTLPR. In the second study, McCann et al. (2008) reported no relationship between performance on the Rey Osterreith complex figure task and differences in SERT distribution across a range of brain areas between ecstasy users and controls. However, performance on this task was negatively correlated with estimated lifetime ecstasy consumption. Indelkofer et

al. (2009) also found lifetime ecstasy consumption to be negatively correlated with performance on this task. Contrary to predictions, however, Medina et al. (2005) found ecstasy consumption measures to be related to better performance on a design fluency task. Users' performance on the WAIS-III Block Design Task was found not to have changed over 1 year from baseline testing (Zakzanis & Young, 2001), nor between 1 year and 2 year follow ups for current (i.e. continuing) users in the same sample (Zakzanis & Campbell, 2006). However, between the two follow-up points the performance of former users who had abstained from ecstasy for at least 32 weeks had significantly improved. The limitation of very small numbers of both current and former users in this study was previously noted (see Category 1).

Insert Figure 4 about here

Task Category 4

The 13 tasks assigned to this category required a variety of visual/spatial judgements to be made which were not deemed to be consistent with the task demands characteristic of the other three categories. The heterogeneous nature of judgements required by these tasks led to meta-analysis being considered inappropriate for this category, as a meaningful interpretation of the result would be problematic. Two of the tasks (Raven's progressive matrices and the Test of Non-Verbal Intelligence (TONI-3)) are used fairly widely as tests of non-verbal intelligence, and did not yield any differences between ecstasy users and controls (e.g. Wareing et al., 2005; Yip & Lee, 2005). Furthermore, a reasoning task based upon spatial designs within a matrix, which forms part of both the Wechsler Adult Intelligence Scale (WAIS-III: Wechsler, 1997a) and the Wechsler Abbreviated Scale of Intelligence (WASI: Wechsler, 1997b) showed no differences between ecstasy users and controls (Medina et al., 2005; Zakzanis et al., 2002).

Only four of the tasks yielded significant performance differences between ecstasy users and controls. Using the manikin task, which requires the mental manipulation of an object's spatial orientation, McCann et al. (1999) reported no performance differences, whilst subsequently users were reported to show elevated impulsivity without impaired accuracy (McCann et al., 2009). Findings from a third study cannot be compared with these because the results reported for this task do not distinguish between performance before and after chemically induced catecholamine depletion (McCann et al., 2007). Two studies examined the tilt aftereffect associated with a Gabor, which is a visual stimulus described as "a sinusoidal variation of luminance level within a Gaussian window" (Brown et al., 2007 P.441). In effect, participants were presented with strips of light and dark areas at a specific angle of orientation to the vertical. A range of different angles were tested in these studies (see also Dickinson et al., 2009), and it was concluded that differences in tilt aftereffect between ecstasy users and controls indicated potential impairment of serotonergically mediated lateral inhibition in the occipital visual areas of users. There was also a suggestion that concomitant amphetamine use might have some protective effect from such changes in the visual systems of ecstasy users. However, concomitant cannabis showed no indication of a potential neuroprotective effect in relation to the ecstasy related effects observed. In the heading task (Rizzo et al., 2005) apparent observer motion over the ground was simulated by moving visual displays of white dots against a black background, with participants being required to indicate their direction of apparent travel in relation to a vertical bar appearing at the end of each trial. Users of both ecstasy and cannabis demonstrated poorer perception of their angle of travel at 1° and 2° to the vertical, but not at larger angles,

compared to regular users of cannabis with no ecstasy exposure and to controls with minimal cannabis exposure. Finally, Reay et al. (2006) reported that ecstasy users made more errors than controls with a similar profile of use for other substances, on the Brixton Spatial Anticipation Task, which tests executive shifting ability in discerning the rule governing the spatial location of highlighted visual stimuli. Such rules are subject to change without warning as trial progress.

In summary, the small number of tasks in this category showing significant effects related to ecstasy consumption, and differences in the nature of the tasks which do, limit the any general conclusions which may be drawn beyond the individual studies. However, impairments in a basic visual process such as lateral inhibition in occipital areas, and in perceived direction of motion may be seen as causes for concern with potential implications for everyday life, and as areas for further research.

Controlling potential confounds

All but a few studies in this review made use of inter-group performance comparisons between ecstasy users and non-ecstasy using controls. Given its prevalence of use, particular attention was paid to matching ecstasy using and non-using groups with regard to cannabis use, in order to facilitate conclusions regarding the relationship of ecstasy to any inter-group performance differences. However, it is very difficult to match groups exactly on a variable such as cannabis use, and it is not feasible to expect that all potential inter-group confounds, which will include a broad range of drug use and demographic variables, can be matched in a precise way. Table 1 records the use of statistical procedures in the studies reviewed, in

order to control for a wide range of potential confounds, in addition to study design as shown by the choice of control groups, and between-group matching.

## Discussion

The meta-analyses reported here have shown ecstasy users to have performed worse than non-users with comparable patterns of other drug use, on three categories of tasks which have different information processing and response demands with regard to visual/spatial information. The extent of lifetime ecstasy within the general population of various countries (e.g. Hoare & Moon, 2010) makes this an important finding. These results are consistent with the wide dispersal of the processing of such information from any visual stimulus (Zimmer, 2009) involving prefrontal, parietal, temporal, and occipital areas, and the similarly wide dispersal of ecstasy related effects on brain functioning. All of the visual stimuli presented will have been subject to thalamic and occipital processing where ecstasy users have been shown to have either compromised or altered functioning compared to non-users (Cowan et al., 2006; de Win et al., 2008a, 2008b). The processing of both spatial and non-spatial visual information in the DLPFC (Owen et al., 1998; Rypma, 2006; Zimmer, 2009) of users will have been potentially vulnerable to compromised serotonergic functioning due to reduced SERT binding compared to non-users (McCann et al., 1998, 2005, 2008). In summary, the present findings do not permit conclusions regarding which aspects of visual/spatial information processing may have been compromised in ecstasy users compared to non-users. One way forward for research, therefore, may be for future scanning and imaging studies to examine different characteristics of localised brain activity (e.g. the BOLD signal, SERT binding) in the context of performance on specific visual/spatial tasks by the same

participants. Despite the attention given to comparing scanning and imaging results from the brains of ecstasy users and non-users in the literature, McCann et al. (2008) point out that theirs was the first study to report a relationship between reduced SERT binding and impaired cognitive functioning in the same participant sample. Furthermore, the number of earlier attempts to relate validated markers of MDMA neurotoxicity (i.e. validated in laboratory settings using pharmaceutical MDMA) to cognitive performance in ecstasy users had been few in number. The pursuit of such a strategy for research would help in the precise identification of which aspects of visual/spatial information processing, with related neural structures, were compromised in ecstasy users, and which were not.

Inverse linear relationships between estimated lifetime ecstasy consumption and performance on the visual/spatial tasks in question were reported by a very small number of studies in the review, using correlation or regression analyses (e.g. Indelkofer et al., 2009; Montgomery & Fisk, 2008; Morgan et al., 2002). Many studies did not investigate this question, and others which did either reported no relationship between estimated ecstasy consumption and task performance (Bedi & Redman, 2008; Reneman et al., 2006), combined these task outcomes with data from other tasks so that relationships between consumption and individual tasks was not reported (Bolla et al., 1998), or in one case reported that estimated lifetime consumption was significantly related to better task performance (Medina et al., 2005). It is important to note that meta-regression using estimated lifetime ecstasy tablet consumption as the predictor failed to show a significant linear relationship to effect sizes in any of the three categories where quantitative analyses were deemed appropriate. Whilst it was not possible to obtain usable estimates from all of the

studies in each task category, only the analysis for Category 3 fell below the recommended minimum level of ten studies (or independent sub-groups within studies) for adequate power in meta-regression (Borenstein et al., 2009), with nine independent sub-groups providing consumption data.

The variability found in reporting practices regarding lifetime ecstasy consumption in the literature reviewed represents an area which could be addressed in future research. The issue of cumulative effects on cognitive performance related to estimated lifetime consumption of ecstasy will remain an important one for researchers, so that a greater degree of common practice would facilitate its exploration. Variability in tablet intake per session over time (Murphy et al., 2006; Topp et al., 1999) indicates that reporting lifetime sessions of use is likely to have a larger margin of error than estimates of tablet intake based on careful questioning, so that the latter would be the preferable measure for reporting. It should also be noted that a linear relationship between ecstasy intake and effects on cognitive performance of any sort should not be assumed automatically, with the possibility other forms of cumulative relationship being a potential area for possible further investigation. For example, might there be one or more levels of consumption beyond which the likelihood of impaired performance, increases, decreases, or remains unchanged for tasks in difference performance domains?

Of the 52 studies identified in this review, only 1 had a prospective cohort design (Schilt et al., 2007). Cross-sectional group designs heavily dominated the remaining studies, although some did include an element of longitudinal follow-up. It is clear that prospective cohort studies of the relationship between ecstasy use and

performance on visual/spatial tasks (and indeed performance on tasks in other cognitive domains) constitute a 'gold standard' of evidence with regard to maximising researchers' ability to control potential confounds in their analyses (Rogers et al., 2009). However, reliance on evidence from such studies alone would be problematic in itself, given the much smaller number of such studies it would be possible to run compared to those with other designs, the length of time required for data collection, the limited range of measures it would be possible to include in any one study, and the logistical and resource problems inherent in prospective designs. Cross-sectional studies are a response to the obvious ethical and legal barriers to administering MDMA or placebos to groups of drug naïve volunteers on a double blind basis, and measuring subsequent inter-group differences in brain and cognitive functioning. Despite their vulnerability to confounds arising from pre-existing inter-group differences intelligence, education, other drug use, and a range of other variables, they have provided a valuable evidence-base regarding effects on cognitive performance related to ecstasy use. Table 1 shows a high level of awareness of potential confounds in the majority of studies reviewed, with a range of statistical techniques employed to control for them in the results reported. In evaluating the contribution of cross-sectional studies to the evidence-base on ecstasy use, it should be noted that prospective studies do not recruit users of ecstasy and no other drug, so that statistical procedures are also required here to control for other drug use and other potential confounds (de Win et al., 2008a; Schilt et al., 2007). However, given their vulnerability to confounds, the pre-dominance of cross-sectional studies in the ecstasy literature does highlight the need for the replication of findings by different research groups, and for clarity in reporting practices to facilitate reviews and meta-analyses, so that confidence in reported findings may be maximised. The meta-

analysis reported here were facilitated by studies which reported data at the level of group results (means, *SD*s) for each dependent variable from a task, and hindered when only results from composite variables summarising results from a range of tasks were reported. In performing meta-analyses, it is recommended that researchers be mindful of differences task demands and the related areas of performance reported upon, and avoid the 'apples and oranges' mistake which can make the interpretation of meta-analytic findings problematic (Borenstein et al., 2009; Lipsey & Wilson, 2001).

In conclusion, this review found that ecstasy users performed worse than controls with comparable histories of other drug use on three categories of visual/spatial tasks. Whilst the weighted mean effect sizes for each category of these laboratory based tasks were relatively small, this does not necessarily mean that there are no implications of these findings for ecstasy users in everyday life. Bridging the gap between laboratory based findings and everyday life in this area is very difficult, not least because task performance in everyday settings is susceptible to many influences, and attempts to monitor ecstasy users performance on tasks requiring visual/spatial processing in such settings would not only be subject to these additional confounds, but would endanger the participant's right to confidentiality. In this context, the performance demands of the tasks reviewed here may be seen as proxies for task demands in everyday life, with the demonstrated impaired performance of ecstasy users being a cause for concern and further research.

## References


Australian Institute of Health and Welfare. 2008. *2007 National Drug Strategy Household Survey: Detailed Findings.* Drug statistics series No. 22. Cat. No. PHE 107. Canberra: AIHW

*Back-Madruga C, Boone KB, Chang L, Grob CS, Lee A, Nations H, Poland RE. 2003. Neuropsychological effects of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) in recreational users). *Clin Neuropsychol* **17**: 446-459.

*Bhattachary S, Powell JH. 2001. Recreational use of 3,4-methylenedioxymethamphetamine (MDMA) or ecstasy: Evidence for cognitive impairment. *Psychol Med* **31**: 647-658.

*Bedi G, Redman J. 2008. Ecstasy use and higher level cognitive functions: weak effects of ecstasy after control for potential confounds. *Psychol Med* **38**: 1319-1330.

*Bolla KI, McCann UD, Ricaurte GA. 1998. Memory impairment in abstinent MDMA ("Ecstasy") users. *Neurology* **51**: 1532-1537.

Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. 2009. *Introduction to Meta-Analysis*. Wiley: Chichester, UK.

*Brown J, Edwards M, McKone E, Ward J. 2007. A long-yerm ecstasy-related change in visual perception. *Psychopharmacology (Berl)* **193**: 437-446.

Buchert R, Thomasius R, Wilke F, Petersen K, Nebeling B, Obrocki J, Schilze O, Schmidt U, Clausen M. 2004. A voxel-based PET investigation of the long-term effects of "ecstasy" consumption on brain serotonin transporters. *Am J Psychiatry* **161**: 1181-1189.

Cowan RL. 2007. Neuroimaging research in human MDMA users: a review. *Psychopharmacology (Berl)* **189**: 539-556.

Cowan RL, Haga E, Frederick B deB, Dietrich MS, Vimal RLP, Lukas SE, Renshaw PF. 2006. MDMA use is associated with increased spatial BOLD fMRI visual cortex activation in human MDMA users. *Pharmacol Biochem Behav* **84**: 219-228.

*Dafters RI, Hoshi R, Talbot AC. 2004. Contribution of cannabis and MDMA ("ecstasy") to cognitive changes in long-term polydrug users. *Psychopharmacology (Berl)* **173**: 405-410.

*de Sola LLopis S, Miguelez-Pan M, Peña-casanova J, Poudevida S, Farré M, Pacifici R, Böhm P, Abanades S, Verdejo-García A, Langohr K, Zuccaro P, de la Torre R. 2008. Cognitive performance in recreational polydrug users: a two-year follow-up study. *J. Psychopharmacol* **22**: 498-510.

*de Sola S, Tarancón T, Peña-casanova J, Espadaler, JM, Langohr K, Poudevida S, Farré M, Verdejo-García A, de la Torre R. (2008). Auditory event-related potentials

(P3) and cognitive performance in recreational ecstasy polydrug users: evidence from a 12 month longitudinal study. *Psychopharmacology (Berl)* **200**: 425-437.

de win, MML, Jager G, Booij J, Reneman L, Schilt T, Lavini C, Olabarriaga SD, den Heeten GJ, van den Brink W. 2008a. Sustained effects of ecstasy on the human brain: a prospective neuroimaging study in novel users. *Brain* **131**: 2936-2945.

de win, MML, Jager G, Booij J, Reneman L, Schilt T, Lavini C, Olabarriaga SD, Ramsay NF, den Heeten GJ, van den Brink W. 2008b. Neurotoxic effects of ecstasy on the thalamus. *Br J Psychiatry* **193**: 289-296.

*Dickson C, Bruno R, Brown J. 2009. Investigating the role of serotonin in visual orientation processing using an 'ecstasy' (MDMA)-based research model. *Neuropsychobiology* **60**: 204-212.

*Fisk JE, Montgomery C. 2009. Evidence for selective executive function deficits in ecstasy/polydrug users. *J Psychopharmacol* **23**: 40-50.

*Fisk JE, Montgomery C, Wareing M, Murphy PN. 2006. The effects of concurrent cannabis use among ecstasy users: neuroprotective or neurotoxic. *Hum Psychopharmacol* **21**: 355-366.

*Fox HC, McLean A, Turner JJD, Parrott AC, Rogers R, & Sahakian BJ. 2002. Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users. *Psychopharmacology (Berl)* **162**: 203-214.

*Fox HC, Parrott AC, Turner JJD. 2001. Ecstasy use: cognitive deficits related to dosage rather than self-reported use of the drug. *J Psychopharmacol* **15**: 273-281.

*Golding JF, Groome DH, Rycroft N, Denton Z. 2007. Cognitive performance in light current users and ex-users of ecstasy (MDMA) and controls. *Am J Drug Alcohol Abuse* **33**: 301-307.

Gouzoulis-Mayfrank E. Daumann J. 2009. Neurotoxicity of drugs of abuse – the case of methylenedioxyamphetamines (MDMA, ecstasy), and amphetamines. *Dialogues Clin Neurosci* **11**: 305-317.

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

*Gouzoulis-Mayfrank E, Fischermann T, Rezk M, Thimm B, Hensen G, Daumann J. 2005. Memory performance in polyvalent MDMA (ecstasy) users who continue or discontinue MDMA use. *Drug Alcohol Depend* **78**: 317-323.

*Gouzoulis-Mayfrank E, Thimm B, Rezk M, Hensen G, Daumann J. 2003. Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users. *Prog Neuropsychopharmacol Biol Psychiatry* **27**: 819-827.

Gruber O, von Cramon DY. 2003. The functional neuroanatomy of human working memory revisited: evidence from 3-T fMRI stdies using classical domain-specific interference tasks. *Neuroimage* **19**: 797-809.

*Halpern JH, Pope HG, Sherwood AR, Barry S, Hudson JI, Yurgelun-Todd D. 2004. Residual neuropsychological effects of illicit 3,4-methylenedioxymethamphetamine (MDMA) in individuals with minimal exposure to other drugs. *Drug Alcohol Depend* **75**: 135-147.

*Hanson KL, Luciana M. 2004. Neurocognitive function in users of MDMA: the importance of clinically significant patterns of use. *Psychol Med* **34**: 229-246.

Haxby JV, Hoffman EA, Gobbini MI. 2000. The distributed human neural system for face perception. *Trends Cogn Sci* **4**: 223-233.

Hoare J, Moon D. .2010. *Drug Misuse Declared: Findings from the 2009/10 British Crime Survey: England and Wales*. Home Office Statistical Bulletin 13/10, London.

*Hoshi R, Mullins K, Boundy C, Brignell C, Piccini P, Curran HV. 2007. Neurocognitive function in current and ex-users of ecstasy in comparison to both matched polydrug-using controls and drug naïve controls. *Psychopharmacology (Berl)* **194**: 371-379.

*Indlekofer F, Pietchatzek M, Daamen M, Glasmacher C, Lieb R, Pfister H, Tucha O, Lange KW, Wittchen HU, Schütz CG. 2009. Reduced memory and attention performance in a population-based sample of young adults with a moderate lifetime use of cannabis, ecstasy and alcohol. *J. Psychopharmacol* **23**: 495-509.

*Lamers CTJ, Bechara A, Rizzo M, Ramaekers JG. 2006. Cognitive function and mood in MDMA/THC users, THC users and non-drug using controls. *J Psychopharmacol* **20**: 302-311.

Lipsey MW, Wilson DB. 2001. *Practical Meta-Analysis*. Sage: Thousand Oaks, California.

Madsen K, Erritzoe D, Mortensen EL, Gade A, Madsen J, Baarè W, Knudsen GM, Hasselbalch SG. 2011. *Psychopharmacology (Berl)* **213**: 573-581.

*McCann UD, Mertl M, Eligulashvili V, Ricaurte GA. 1999. Cognitive performance in (±) 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) users: a controlled study. *Psychopharmacology (Berl)* **143**: 417-425.

*McCann UD, Peterson SC, Ricaurte GA. 2007. The effect of catecholamine depletion by alpha-methyl-para-tyrosine on measures of cognitive performance and sleep in abstinent MDMA users. *Neuropsychopharmacology* **32**: 1695-1706.

McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. (1998). Positron emission tomographic evidence of toxic effect of MDMA (“ecstasy”) on brain serotonin neurons in human beings. *Lancet* **352**: 1433-1437.

McCann UD, Szabo Z, Seckin E, Rosenblatt P, Mathews WB, Ravert HT, Dannals RF, Ricaurte GA. 2005. Quantitative PET studies of the serotonin transporter in MDMA users and controls using [$^{11}$C] McN5652 and [$^{11}$C] DASB. *Neuropsychopharmacology* **30**: 1741-1750.

*McCann UD, Szabo Z, Vranesic M, Palermo M, Mathews WB, Ravert HT, Dannals RF, Ricaurte GA. 2008. Positron emission tomographic studies of brain dopamine and serotonin transporters in abstinent (±)3,4-methylenedioxymethamphetamine ("ecstasy") users: relationship to cognitive performance. *Psychopharmacology (Berl)* **200**: 439-450.

*McCann UD, Wilson MJ, Sgambati FP, Ricaurte GA. 2009. Sleep deprivation differentially impairs cognitive performance in abstinent methylenedioxymethamphetamine ("ecstasy") users. *J Neurosci* **29**: 14050-14056.

*Medina KL, Shear PK, Corcoran K. 2005. Ecstasy (MDMA) exposure and neuropsychological functioning: a polydrug perspective. *J Int Neuropsychol Soc* **11**: 753-765.

Miyake A, Friedman AP, Rettinger DA, Shah P, Hegarty M. 2001. How are visuospatial working memory, executive functioning, and spatial abilities related? A latent variable analysis. *J Exp Psychol Gen* **130**: 621-640.

*Montgomery C, Fisk JE. 2008. Ecstasy-related deficits in the updating component of executive processes. *Hum Psychopharmacol*: **23**: 495-511.

*Morgan M. 1998. Recreational use of "ecstasy" (MDMA) is associated with elevated impulsivity. *Neuropsychopharmacology* **19**: 252-264.

*Morgan M, Impallomeni LC, Pirona A, Rogers RD. 2006. Elevated impulsivity and impaired decision making in abstinent ecstasy (MDMA) users compared to polydrug and drug naïve controls. *Neuropsychopharmacology* **31**: 1562-1573.

*Morgan M, McFie L, Fleetwood LH, Robinson JA. 2002. Ecstasy (MDMA): are the psychological problems associated with its use reversed by prolonged abstinence? *Psychopharmacology (Berl)* **159**: 294-303.

Murphy PN, Wareing M, Fisk JE. 2006. Users' perceptions of the risks and effects of taking ecstasy (MDMA): a questionnaire study. *J Psychopharmacol* **20**: 447-455.

Murphy PN, Wareing M, Fisk JE, Montgomery C. 2009. Executive working memory deficits in abstinent ecstasy/MDMA users: a critical review. *Neuropsychobiology* **60**: 159-175.

Owen AM, Stern CE, Look RB, Tracey I, Rosen BR, Petrides M. 1998. Functional organisation of spatial and nonspatial working memory within the human lateral frontal cortex. *Proc Natl Acad Sci* **95**: 7721-7726.

Puerta E, Hervais I, Aguirre N. 2009. On the mechanisms underlying 3,4-methylenedioxymethamphetamine toxicity: the dilemma of the chicken and the egg. *Neuropsychobiology* **60**: 119-129.

*Reay JL, Hamilton C, Kennedy DO, Scholey AB. 2006. MDMA polydrug users show process-specific central executive impairments coupled with impaired social and emotional judgement processes. *J Psychopharmacol* **20**: 385-388.

Reneman L, De Win MML, Van Den Brink W, Booij J, Den Heeten G.J. 2006a. Neuroimaging findings with MDMA/ecstasy: technical aspects, conceptual issues and future prospects. *J Psychopharm* **20:** 164-175.

*Reneman L, Schilt T, de Win MM, Booij J, Schmand B, van den Brink W, Bakker O. 2006b. Memory function and serotonin transporter promoter gene polymorphism in ecstasy (MDMA) users. *J Psychopharmacol* **20**: 389-399.

*Rizzo M, Lamers CTJ, Sauer CG, Ramaekers JG, Bechara A, Andersen GJ. 2005. Impaired perception of self-motion (heading) in abstinent ecstasy and marijuana users. *Psychopharmacology (Berl)* **179**: 559-566.

Rodgers J. 2000. Cognitive performance amongst recreational users of “ecstasy”. *Psychopharmacology (Berl)* **151**: 19-24.

Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P, Zawada A, Somerville M. 2009. The harmful health effects of recreational ecstasy: a systematic review of observational evidence. *Health Technology Assessment* **13**: Part 6.

*Roiser JP, Rogers RD, Cook LJ, Sahakian BJ. 2006. The effect of polymorphism at the serotonin transporter gene on decision-making, memory and executive function in ecstasy users and controls. *Psychopharmacology (Berl)* **188**: 213-227.

*Roiser JP, Rogers RD, Sahakian BJ. 2007. Neuropsychological function in cstasy users: a study controlling for polydrug use. *Psychopharmacolgy (Berl)* **189**: 505-516.

Rypma B. 2006. Factors controlling neural activity during delayed-response task performance: testing a memory organisation hypothesis of prefrontal functioning. *Neuroscience* **139**: 223-235.

*Schilt T, de Win MML, Jager G, Koeter MW, Ramsey NF, Schmand B, van den Brink W. 2008. Specific effects of ecstasy and other illicit drugs on cognition in poly-substance users. *Psychol Med* **38**: 1309-1317.

*Schilt T, de win MML, Koeter M, Jager G., Korf DJ, van den Brink W, Schmand B. 2007. Cognition in novice ecstasy users with minimal exposure to other drugs: A prospective cohort study. *Arch Gen Psychiatry* **64**: 728-736.

*Schilt T, Koeter MWJ, Smal JP, Gouwetor MN, van den Brink W, Schmand B. 2010. Long-term neuropsychological effects of ecstasy in middle-aged ecstasy/polydrug users. *Psychopharmacology (Berl)* **207**: 583-591.

Selvaraj S, Hoshi R, Bhagwager Z, Murthy NV, Hinz R, Cowen P, Curran HV, Grasby P. 2009. Brain serotonin transporter binding in former users of MDMA ('ecstasy'). *Br J Psychiatry* **194**: 355-359.

* Semple DM, Ebmeier KP, Glabus MF, O'Carroll RE, Johnstone EC. 1999. Reduced *in vivo* binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. *Br J Psychiatry* **175**: 63-69.

Substance Abuse and Mental Health Services Administration. 2010. *Results from the 2009 National Survey on Drug Use and Health: Volume II. Technical Appendices and Selected Prevalence Tables* (Office of Applied Studies, NSDUH Series H-38B, HHS Publication No.SMA 10-4586Appendices). Rockville, MD.

Thomasius R, Zapletalova P, Petersen K, Buchert R, Andresen B, Wartberg L, Nebeling B, Schmoldt A. 2006. Mood, cognition, and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective. *J Psychopharmacol* **20**: 211-225.

Topp L, Hando J, Dillon P, Roche A, Solowij N. 1999. Ecstasy use in Australia: patterns of use and associated harm. *Drug Alcohol Depend* **55**: 105-115.

*Verdejo-García AJ, López-Torrecillas F, Aguilar de Arcos, F, Pérez-García M. 2005. Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: a multiple regression analysis. *Addict Behav* **30**: 89-101.

*Verkes RJ, Gijsman HJ, Pieters MSM, Schoemaker RC, de Visser S, Kuijpers M, Pennings EJM, de Bruin D, Van de Wijngaart G, Van Gerven JMA, Cohen AF. 2001. Cognitive performance and serotonergic function in users of ecstasy. *Psychopharmacology (Berl)* **153**: 196-202.

*Ward J, Hall K, Haslam C. 2006. Patterns of memory dysfunction in current and 2-year abstinent MDMA users. *J Clin Exp Neuropsychol* **28**: 306-324.

*Wareing M, Fisk JE, Montgomery C, Murphy PN, Chandler MD. 2007. Information processing speed in ecstasy (MDMA) users. *Hum Psychopharmacol* **22**: 81-88.

*Wareing M, Fisk JE, Murphy PN. 2000 Working memory deficits in current and previous users of MDMA ("Ecstasy"). *Br J Psychol* **91**, 181-188.

*Wareing M, Fisk JE, Murphy PN, Montgomery C. 2005. Visuospatial working memory impairments in users of MDMA (ecstasy). *Hum Psychopharmacol* **20**: 115-123.

*Wareing M, Murphy PN, Fisk JE. 2004 Visuospatial memory impairments in users of MDMA ('ecstasy'). *Psychopharmacology (Berl)* **173**: 391-397.

Wechsler D. 1997a. Wechsler Adult Intelligence Scale-III. Psychological Corporation: San Antonio, Texas.

Wechsler D. 1997b. Wechsler Abbreviated scale of Intelligence. Psychological Corporation: San Antonio, Texas.

Wingen M, Kuypers KPC, Ramaekers JG. 2007. Selective verbal and spatial memory impairment after 5-$HT_{1A}$ and 5-$HT_{2A}$ receptor blockade in healthy volunteers pre-treated with an SSRI. *J Psychopharmacol* **21**: 477-485.

*Yip JTH, Lee TMC. 2005 Effects of ecstasy use on neuropsychological function: A study in Hong Kong. *Psychopharmacology (Berl)* **179**: 620-628.

*Zakzanis KK, Campbell Z. 2006. Memory impairment in now abstinent MDMA users and continued users: a longitudinal follow-up. *Neurology* **66**: 740-741.

*Zakzanis KK, Young DA. 2001. Memory impairment in abstinent MDMA ("Ecstasy") users: a longitudinal investigation. *Neurology* **56**: 966-969.

*Zakzanis KK, Young DA, Radkhooshnoud NF. 2002. Attentional processes in methylenedioxymethamphetamine (ecstasy) users. *Appl Neuropsycho*: **9**: 84-91.

Zimmer HD. 2009. Visual and spatial working memory. *Neurosci Biobehav Rev* **32**: 1373-1395.