Meta-analysis of executive functioning in ecstasy/polydrug users.

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Word Count: 4480

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Abstract

Ecstasy/MDMA use is proposed to cause damage to 5-HT axons in humans. Therefore, users should show deficits in cognitive processes that rely on, serotonin rich, prefrontal areas of the brain. However, there is inconsistency in findings to support this hypothesis. The aim of the current study was to examine deficits in executive functioning in ecstasy users compared to controls using meta-analysis. We identified k=39 studies, contributing 89 effect sizes, investigating executive functioning in ecstasy users and polydrug using controls. We compared function specific task performance in 1221 current ecstasy users and 1242 drug using controls, from tasks tapping the executive functions; updating, switching, inhibition and access to long term memory. The significant main effect demonstrated overall executive dysfunction in ecstasy users (SMD = -0.18, 95% CIs [-0.26, -0.11]; Z=5.05, $p < .001$, $I^2 = 82\%$), with a significant subgroup effect ($X^2 = 22.06$, df = 3, $p < .001$, $I^2 = 86.4\%$) demonstrating differential effects across executive functions. Ecstasy users showed significant performance deficits in access (SMD = -0.33, 95% CIs [-0.46, -0.19]; $Z = 4.72$, $p < .001$; $I^2 = 74\%$), switching (SMD = -0.19, 95% CIs [-0.36, -0.02]; $Z = 2.16$, $p < .05$; $I^2 = 85\%$) and updating (SMD = -0.26, 95% CIs [-0.37, -0.15]; $Z = 4.49$, $p < .001$; $I^2 = 82\%$). No differences were observed in inhibitory control. We conclude that this is the most comprehensive analysis of executive function in ecstasy users to date and provides a behavioural correlate of potential serotonergic neurotoxicity.

Introduction

Ecstasy (3,4-methylenedioxymethamphetamine: MDMA) remains popular despite reports of potential long-term negative consequences associated with repeated use (see Parrott, 2013). Furthermore, ecstasy poses a major public health concern due to an increase in recent MDMA related deaths (Anderson, 2014) as well as reported increases in tablet strength, with some sources suggesting tablets may contain upwards of 200mg of MDMA (Global Drugs Survey, 2015). Animal literature suggests that ecstasy causes damage to serotonin axons (Ricaurte, 1988: Molliver, 1990). There is also evidence of ecstasy-related alterations in mood (Curran et al., 2004) and long term changes in neuroendocrine function (Wetherell & Montgomery, 2014). However, perhaps public health warnings are not being taken seriously due to mixed messages in the media and scientific literature about relative harms of drugs (see, Nutt et al., 2010 for assessment of drug related harms, which poorly correlates with UK drug classification).

A recent review by Murphy et al. (2009) suggests that ecstasy related cognitive dysfunction is not consistently reported in the literature, thus monitoring of research is necessary to gain a coherent understanding of drug effects. Executive functions (EFs) have been defined as a set of general-purpose control processes, required for regulating thought and action (Miyake & Friedman, 2012). Moreover, the central executive (CE) is an integral component of working memory (Baddeley, 2000) and is required for coordinating and processing information. Some of the apparent inconsistency in the literature may be attributable to several of the classic working memory/"executive" tasks requiring use of multiple EFs: a problem of task impurity (Miyake & Friedman, 2012). An influential EF framework suggested that the CE is not a unified construct; rather it is comprised of several correlated but distinctly separable functions (Miyake et al, 2000). Three discrete EFs were originally identified; *mental set shifting/switching* ("switching"), *information updating and*

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monitoring ("updating") and *inhibition of prepotent responses* ("inhibition"). A fourth component, "access" to semantic memory, was later added by Fisk and Sharp (2004). These are the 4 classic EFs that have been assessed in the literature. However it is interesting to note that more recent developments in the *unity/diversity framework* (Miyake & Freidman, 2012) suggest that inhibitory control no longer exists as an EF, as it is subsumed under the concept of working memory and EF in general.

Montgomery et al. (2005a) suggested that there may be a differential pattern of executive impairment based on previous drug use and type of function, whereby ecstasy-related deficits were apparent in updating and access, but not in switching or inhibition. These conclusions were arrived at by administering tasks that are understood to assess one function only. As such, it may be that ecstasy users are impaired on some EFs and not others, supporting the unity and diversity framework (Miyake, et al 2000; 2012). There are nuances in the neuroanatomy underpinning each function, which may explain why impairment is potentially function specific. For example, the dorsolateral prefrontal cortex (DLPFC), is understood to be important for memory updating (Goldman-Rakic, 1996), whereas lesion studies suggest the left DLPFC in particular is important for letter based word fluency (Stuss et al., 1998). Ability to switch mental set is impaired following damage to the PFC and basal ganglia (Ravizza & Ciranni, 2002), and finally response inhibition performance has long been localised to the PFC, however of particular importance is the right inferior frontal gyrus (Chambers et al., 2009). The conclusions reached by Montgomery et al. (2005a) and the review by Murphy at al. (2009) are that ecstasy use has a stronger detrimental effect on updating and access, and that inhibitory control and mental set switching are unaffected by use. However, there are instances of ecstasy users showing no apparent deficit in function specific tasks that tap updating (Hanson & Luciana, 2004; Hoshi et al., 2007) and access (Gouzoulis-Mayfrank, 2000; Bedi & Redman, 2008) as well as instances of ecstasy-related

impairments in switching (von Geusau et al., 2004; Dafters 2006a) and inhibition (Yip & Lee, 2005).

Several neuroimaging studies have concluded that ecstasy related neuronal adaptations may occur *neurophysiologically* before they manifest *functionally*. Roberts and Montgomery (2015a) suggested that ecstasy users display increased blood flow to areas of the PFC during a verbal fluency task, despite no differences in task performance. This suggests ecstasy users work harder to achieve similar performance to controls, and that functional differences may be apparent with increased workload. Similar conclusions have been drawn from EEG studies whereby ecstasy users display evidence of recruiting additional resources in comparison to controls, whilst showing similar performance (Burgess et al., 2011; Roberts et al., 2013 a, b and c). Similarly, fMRI studies have shown alterations to neuronal activation consistent with ecstasy-related damage despite not showing any performance deficits (Moeller et al., 2004; Daumann et al., 2005; Jager et al., 2008; Roberts & Garavan, 2010). Such neuroimaging studies suggest that neurophysiological correlates of executive performance are present before a behavioural difference manifests itself. It remains plausible that many behavioural studies lack statistical power to observe subtle impairments over the entire spectrum of EFs. Therefore, the aim of this meta-analysis was to examine the evidence for overall dysfunction of executive control in ecstasy users compared to polydrug users, but also to examine any functional specific deficits.

Methods

Eligibility criteria

Participants

Included studies were those assessing EF in human ecstasy/MDMA users aged 18 years+, who did not have a history of major psychiatric or neurological problems. Ecstasy user groups were eligible if they were described as current ecstasy users, control groups were eligible if they reported some use of drugs, but no ecstasy use – with the exception of studies in which the ecstasy users were recruited with the specific criteria of limited exposure to other drugs. In each case, participants were not intoxicated at the time of testing. The majority of studies included, used a minimum abstinence period of 7 days, with the exception of Heffernan et al., (2001), de Sola et al., (2008a) and Fagundo et al., (2010), who report a minimum abstinence period of 24 hours, 72 hours and 72 hours respectively. The mean age for ecstasy user group across studies was 23.39, with an average of 47.72% females. Mean lifetime dose across studies was 346.03 tablets. The mean age of the control group was 23.11, with an average of 54.67% females.

Studies

Studies comparing ecstasy users and controls in performance on behavioural tasks that are function-specific were eligible for inclusion. The EFs included this analysis were; updating, inhibitory control, switching and access. Tasks eligible for inclusion can be observed in Table 1. There were no date limitations on publication.

Outcome measures

As each EF can be assessed using several tasks, there are a number of outcome measures. The outcome measure from each task that most clearly taps its putative EF was selected for

inclusion in analysis. As such each task contributes one outcome measure to the analysis only. Tasks included as well as the outcome measure selected can be observed in Table 1.

Data search and extraction

Information sources and search strategy

The formal search strategy involved searching, 3 electronic databases during July 2015; PsychINFO, Scopus and Web of Science. Systematic searches used the key terms 'Ecstasy' OR 'MDMA' AND, 'executive function'. Supplementary searches were also conducted using the terms 'Ecstasy' and 'MDMA' combined with the name of each task in Table 1. Manual searches of reference sections of initially identified studies were conducted to supplement the formal electronic search, furthermore articles that were not identified in the initial searches that the authors knew to be eligible for inclusion were assessed for inclusion. These additional searches yielded a further 5 studies eligible for inclusion.

<<Insert Table 1 Here>>

Article selection and extraction of data

Initial searches were carried out by one author (CR). However supplementary searches and manual searches were carried out by two authors (CR and CM). Both authors were responsible for the assessment of articles for inclusion, and decisions over article inclusion were made through discussion. One author (CR) extracted the relevant data and a second author (CM) cross checked this. Several studies met inclusion criteria, but did not report sufficient information in the manuscripts to compute the effect size, in each case data was requested from the corresponding author of the manuscript. Data requests were not met for 5 articles; Semple et al., 1999; Thomasius et al., 2003; McCann et al., 2007; McCann et al., 2008 and Fagundo et al., 2010.

Additional Handling of data

Composite performance scores for letter updating, spatial updating and Random Letter Generation (RLG) were calculated from the available data, if the composite score itself was not reported in the paper. On occasions where reported values of behavioural performance were split by gender, a weighted mean by number in each sample was calculated. A weighted SD was also calculated by multiplying squared SDs by number in each group, adding these together, then dividing by total n. The square root of this total was then used as the SD in analysis. Data for the FAS task were provided by Morgan (2002), with means and SDs given for each letter. Therefore means for performance on each letter were added up to give a total score and the SDs were summed and divided by 3.

There were a number of cases where an article had used more than one task to assess an EF (Fox et al., 2001; Gouzoulis-Mayfrank et al., 2003; Montgomery et al., 2005a; Wareing et al., 2005; Lamers et al., 2006; Montgomery et al., 2007; Montgomery & Fisk, 2008; Fisk & Montgomery, 2009; Halpern et al., 2011). In these cases, means and SDs were entered for each task, however the number of participants in each group was divided by the number of tasks included for that function from that paper.

In de Sola et al., (2008a and b), between group comparisons were given a year apart. For the meta-analysis, we used baseline measurements of lifetime drug use and task performance. In cases where ecstasy user groups were broken down into further subgroups e.g. 'heavy and 'light' users (as per Fisk & Montgomery, 2009), data from the heavy user group was included in the analysis. In Fox et al., (2001) the user groups were split into problem/non-problem users and low/medium/high intensity users. The group of high intensity users was included in the current analysis. Although the "heavy" and "high intensity" user group criteria were arbitrarily decided in the original papers, it seemed pertinent to include the user groups with

the heaviest background ecstasy use in the current analysis, as these would be the most likely to show ecstasy related cognitive impairment.

Data items extracted for individual studies

From each of the published manuscripts, the following information was extracted for each group: number of participants, gender split, age, estimated lifetime dose of ecstasy, time since last use, task used (Table 2), outcome measure (Table 1) and means and SDs for each outcome variable. In cases where mean ecstasy abstinence duration was not reported, the minimum abstinence period required for the study was recorded. If not reported in the manuscript, estimates of mean lifetime dose of ecstasy were calculated from the available data. Reported ecstasy user groups could generally be defined by two categories; current users and former users. There were several categories of control groups, including: cannabis only users, polydrug control groups (who have been recruited due to them having some degree of matching for other substances), non-users (this was a general catch all name given to controls who were ecstasy naïve but did have some other drug use) and drug naïve controls (no illicit substance use, but allowed for use of alcohol and nicotine).

Statistical and subgroup analysis

Standardised Mean Difference (SMD) and Standard Error (SE) of the SMD between experimental conditions were calculated for each executive task outcome separately in each study. SMDs were employed due to variation in outcome measures in the behavioural tasks included in the analysis. SMD estimates differences between 2 experimental conditions on an outcome variable (SMD = Mean1 − Mean2 / pooled SD). This allowed for a subgroup analysis to be conducted by executive function (inhibitory control, updating, access and switching). The meta-analysis used generic inverse variance methods to synthesise individual SMDs, in the software package RevMan 5.2 (The Nordic Cochrane Centre, Copenhagen).

The magnitude of SMDs can be interpreted thus: 0.2 = small, 0.5 = moderate, and 0.8 = a large effect (Higgins & Green, 2011).

Analytic Strategy: The meta-analysis was conducted by separating effect sizes from tasks employed in each study into distinct EFs. The main effect and formal sub-group analysis was examined, whereby each EF was considered a sub-group.

Outcome measures of the various tasks that were included in this meta-analysis had to be reviewed by the authors so that the direction of differences in task performance were consistent for interpretation of ecstasy related impairment. For example, if ecstasy users produced fewer words on the verbal fluency tasks relative to controls, this would be indicative of ecstasy related impairment in verbal fluency and would result in a negative SMD in the meta-analysis. However, a greater amount of perseveration errors on the WCST would be indicative of impairment yet would yield a positive SMD, should ecstasy users produce more errors here. As such outcome measures were negatively coded where appropriate.

The main analysis was conducted on the 39 studies that assessed one or more EF in a current ecstasy user group verses a control group that had some use of recreational drugs. Studies that employed a drug naïve control group and no drug user control group were not included in the analysis, with the exception of 3 studies (Halpern et al., 2004; Yip & Lee, 2005; Halpern et al., 2011). These studies were included, with a drug naïve control group, as their current ecstasy user groups had minimal exposure to other drugs. The remaining studies featured a drug using control group, as such, all between group comparisons in this meta-analysis have at least some degree of matching for other drug use. Random effects models were employed due to high heterogeneity in the data across studies.

Results

Study Selection

Initial literature searches yielded 99 papers using Web of Science, 79 using Scopus and 386 papers from PsychINFO. After removing 76 duplicated papers, 459 articles remained. A brief review of the remaining articles titles and abstracts led to exclusion of 370 irrelevant articles. Excluded papers at this stage included; review articles (23), acute administration studies (26), studies that were conducted using other substances/did not involve ecstasy users (75), studies that were not experimental/did not include behavioural data/assess cognition (232), case studies (8), studies conducted in non-human samples (4), a study not written in English (1) and reanalyses of data (2). This left a total of 88 articles for full review. Further studies were excluded at this stage if they did not employ a function specific task identified in Table 1 (35), did not employ a control group or current user group, or did not conduct between group analysis (10). Longitudinal studies using a within groups design and prospective studies on novice users were also excluded at this stage (4). Following these data exclusion procedures 39 studies remained. A further 5 studies eligible for inclusion were identified from supplementary searches. Of the 44 studies that met all the inclusion criteria, data was not available for 5, as such the final meta-analyses were conducted on data from 39 articles.

<<Insert Figure 1 about here>>

Overview

Participant characteristics

Individual study information including sample sizes and participant characteristics are given in Table 2.

<<Insert Table 2 Here>>

Meta-analysis on executive function in ecstasy polydrug users

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Data from 39 published studies, contributing 89 effect sizes, were included in analysis, including data from a total of 1221 current ecstasy users and 1242 controls. For descriptive information from each study see Table 2.

Meta-analyses:

The test for overall effects was significant (SMD = -0.18, 95% CIs [-0.26, -0.11]; Z=5.05, $p <$ .001, I^2 = 82%), suggesting an overall executive performance deficit in ecstasy users relative to controls, albeit a small effect. However there was also a significant subgroup effect (X^2 = 22.06, df = 3, $p < $ .001, I^2 = 86.4%) demonstrating differential effects across EFs. Individual analyses are reported below.

Access:

A total of 13 studies, contributing 13 effect sizes, assessed access to long term/semantic memory, with a total of 483 ecstasy users and 491 controls. A significant difference was observed between these two comparison groups (SMD = -0.33, 95% CIs [-0.46, -0.19]; $Z =$ 4.72, $p < $ .001; I^2 = 74%), demonstrating that ecstasy users perform poorly compared to controls in this EF.

Inhibition:

Twenty studies, contributing 20 effect sizes investigated performance difference in inhibitory control providing a comparison between 606 ecstasy users and 632 controls. No between group difference was observed in performance of this EF (SMD = 0.04, 95% CIs [-0.07, 0.15]; $Z = 0.77$, $p > $ .05).

Switching:

Switching was assessed in a total of 488 ecstasy users and 459 controls, in a total of 18 papers, contributing 23 effect sizes. There were significant between group differences in this function (SMD = -0.19, 95% CIs [-0.36, -0.02]; Z = 2.16, $p < .05$; $I^2 = 85\%$), demonstrating that ecstasy use leads to impairment in mental set switching.

Updating:

A total of 872 ecstasy users and 904 controls were compared for updating performance from a total of 24 articles, contributing 33 effect sizes. Again, there was a significant between group difference in performance of updating tasks (SMD = -0.26, 95% CIs [-0.37, -0.15]; Z = 4.49, $p < .001$; $I^2 = 82\%$). This demonstrates that there is an ecstasy related impairment with regards to updating performance.

<<Insert Figure 2 Here>>

Meta-regression

We conducted a method of moments (random-effect model) meta-regression across the 64 comparisons included in the main meta-analysis, with the available data for estimates of lifetime dose of ecstasy. This was conducted to observe whether there was a relationship between lifetime dose of ecstasy and SMD in executive performance. The overall meta-regression was non-significant (regression coefficient: -0.0001, 95% CIs [-0.0004, 0.0002], Z = -0.74, $p > .05$), suggesting that lifetime dose did not predict performance differences. Furthermore, individual meta-regressions performed separately for each specific EF were all non-significant ($p > .05$ in each case).

Evidence of publication bias

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Examination of a funnel plot revealed asymmetry, therefore an Egger's test of publication bias was conducted (Egger et al., 1997) on the 89 effect sizes included in this meta-analysis. Egger's test was significant ($t(88)= -1.96, p = .05$), suggesting evidence of publication bias. However, these results should be interpreted with caution due to the high heterogeneity between studies (Sterne et al., 2011).

Discussion

The results from this meta-analysis demonstrate EF deficits in current ecstasy users. However, the size of this overall effect was small. Subgroup analyses showed that effect sizes varied by the specific component of EFing. Individual analyses by function showed ecstasy related deficits in the EFs access, switching and updating, though there was no inhibition performance deficit.

Meta-regression using estimated lifetime dose of ecstasy to predict effect size of between group differences was non-significant. This suggests that lifetime dose is not the greatest predictor in magnitude of EF deficit. However there were 9 studies (providing 25 comparisons) that did not give lifetime estimates of use and so were not included in the analysis, which may have potentially given a different outcome. Nevertheless, there was high variability in effects and although estimates of lifetime use were not possible for all studies, there were 64 comparisons from 30 studies which did include estimated lifetime dose, which is far greater than the minimum of 10 required for adequate power in a meta-regression (Borenstein et al., 2009). Despite adequate power to detect an effect, it could be that the analysis is conceptually flawed, given that it is conducted on SMDs in performance between ecstasy users and controls rather than estimated lifetime dose and task performance (Murphy et al., 2012). Alternatively, it could be that there are other ecstasy using behaviours that have a stronger impact on behavioural measures, for example recency of use, frequency of use and

higher nightly doses. Recency of use has been identified as a predictor of haemodynamic response to a cognitive task in ecstasy users (Roberts & Montgomery, 2015b). Furthermore, higher nightly doses may impact cognition more than cumulative intake, indeed a single high dose of MDMA is enough to cause neurotoxicity in lab animals (Molliver et al., 1990). Unfortunately there is substantial variance in the reporting of drug use histories in the literature, limiting interpretation. Perhaps some unity on background drug use reporting would vastly improve research and our understanding of harmful behaviours. We propose a unified reporting criterion should be applied to future research. There are also a number of variables that may contribute to the impact of cumulative dose (Murphy et al., 2012) including earlier onset of use, use of other drugs, and increased bioenergetic stress (Parrott, 2009).

Neuronal regions implicated in working memory and EF include the DLPFC and the hippocampus (depending on the nature of the task). These structures have dense innervation of 5-HT neurons (Pazos et al., 1987; Curtis & D'Esposito, 2003). Therefore ecstasy related degradation to the serotonin system, through neurotoxicity or down-regulation following chronic recent use, is understood to be a potential cause of cognitive impairment in the functions supported by these areas. If ecstasy is a serotonin-specific neurotoxin in humans as it is in animals (Green et al., 2003), one would expect functional alterations following repeated use. Several molecular imaging studies in human ecstasy users suggest a reduction in pre-synaptic SERT availability in areas including the frontal cortex (McCann et al., 1998; Kish et al., 2010) and the DLPFC (McCann et al., 2005). Increases in post-synaptic 5-HT$_{2A}$ receptors have also been observed in ecstasy users relative to controls in the DLPFC (Urban et al., 2012). Decreased pre-synaptic SERT and increased post-synaptic 5-HT$_{2A}$ receptor availability are consistent with serotonin axon damage. Moreover functional neuroimaging studies have observed ecstasy related adjustments to cerebral blood flow in frontal areas, with

fNIRS (Roberts & Montgomery, 2015a) and fMRI (Moeller et al., 2004; Jager et al., 2008; Roberts & Garavan, 2010). It is noteworthy that all of the functional imaging studies mentioned observe increased neuronal activity to achieve similar behavioural performance to controls. This suggests that molecular and functional neuroimaging detect changes in serotonin signalling which cause future deficits in EF. The current results support this by demonstrating behavioural correlates for the supposed neuronal degradation.

Ecstasy-related impairments in switching were unexpected, given that previous reviews in this area have concluded that this function is relatively stable (Murphy et al., 2009). However, some studies have observed significant switching differences between ecstasy users and controls (Halpern et al., 2004; Dafters, 2006a) and neuroimaging studies have suggested atypical processing during switching (Roberts, 2013c). This highlights the necessity for larger samples to elucidate this performance deficit. However, this difference was the weakest of the 3 significant differences and had a small effect size; thus it should be treated with caution. The reduced performance in updating and access in ecstasy users relative to controls is more consistent with previous reports (Montgomery et al., 2005a; Murphy et al., 2009). Nevertheless there have been previous reports of null findings in these functions. The ability to update ones memory is reflective of the concept of working memory as a whole, and Miyake and co-workers (Friedman et al., 2006; Miyake & Friedman, 2012) maintain that updating is the key over-arching EF which is important for daily function.

Although, not unexpected, it is interesting to consider why there were no apparent group differences in inhibitory control. One explanation could be that ecstasy users are high functioning impulsives and this increased impulsivity serves to mask performance deficits on the tasks employed here (Fritsche et al., 2011). Alternatively, perhaps inhibitory control impairment is associated with other psychostimulants that are primarily dopaminergic in nature, e.g. cocaine (Fillmore & & Rush, 2002) and methamphetamine (Monterosso et al.,

2005). Interestingly, in recent models of the unity and diversity of EFs, Miyake & Freidman (2012) confer that inhibitory control is not necessarily a unique EF. Instead, inhibitory control is subsumed by common EF ability. With this in mind, it could be suggested that ecstasy users, are therefore impaired at each level of EF.

There are a number of limitations of the current analysis. Concomitant use of other drugs is often posited to contribute to the cognitive deficits displayed by ecstasy users. To try and incorporate this in to the meta-analysis, comparisons were made between ecstasy users and controls that have at least some experience with drugs other than ecstasy. Nevertheless, it should be noted that in many of the studies in the analysis, the use of drugs other than ecstasy was, in fact, higher in the ecstasy user groups than the polydrug control groups (in terms of total lifetime dose, frequency of use and variety of drugs used). As such, we cannot rule out the possibility that alcohol and other drugs may also contribute to deficits in executive functioning. However despite the increased polydrug use among ecstasy user groups, there are several instances of drug use indices predicting unique variance in executive functions in regression analyses (for example Schilt et al., 2008), this suggests that various chronic drug effects do show independence from one another. Increased cohesion in reporting of drug use variables would help to remove some of this uncertainty in future. Similarly, it cannot be ruled out that the direction of causality is interpreted incorrectly. It could be that, individuals with EF deficits are more likely to have a stronger propensity for ecstasy use, though the authors think that this is unlikely. Future research should concentrate on longitudinal studies to obviate confusion over direction of causality. Furthermore, as the current analysis is conducted on current users and therefore cannot make any predictions about function recovery following abstention, longitudinal studies may also help to determine whether recovery is possible.   The current results suggest that ecstasy users may struggle with higher level executive functioning, and it has been suggested that such impairments would lead to

difficulty in performing the majority of occupational tasks (Parrott, 2013). Montgomery et al. (2010) observed ecstasy users to be impaired at a virtual reality office work task, with the suggestion that office work, as well as those occupations requiring greater executive resources will be adversely affected by ecstasy use. Taken together, these findings suggest that prolonged ecstasy use can lead to everyday functioning problems; therefore an understanding of the processes underpinning such impairments may prove valuable to clinicians

To conclude, the current meta-analysis demonstrated that EF performance in ecstasy users is significantly reduced overall compared to controls. The three functions that show significant impairment are updating, switching and access, whilst inhibitory control is unaffected by ecstasy use. This is the most comprehensive analysis of EF in ecstasy users to date and provides a behavioural correlate of potential serotonergic neurotoxicity.

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Table 1: Tasks included for assessment of each executive function.

Executive Function	Task	Outcome measure
Inhibitory control	Stroop	Stroop interference RT
	RLG	Composite task score (reverse scored)
	Go NoGo	NoGo errors
		Or NoGo correct responses (reverse scored)
	Eriksen Flankers task	Interference cost
	Stop signal	Stop signal reaction time
Switching	Stroop switch	Switch RT
	ToL	Total movements / solution time / proportion of perfect solutions
		Or solution time
	3D ID-ED	Simple reversal (switch cost)
	WCST	Perseverative errors
	Trail Making Test B	Time
	Stockings of Cambridge	
	Number-Letter Task	Switch cost
	Plus-Minus Task	Switch cost
	Dots-Triangles Task	Switch cost
	Local-Global Task	Switch cost
	Rule Shift Cards Test	Task score
Updating	Keep Track	Words
	Computation Span	Task Score
	Consonant/letter Updating	Composite score
	Spatial Updating	Composite score
	Digit Span Backwards	Task Score
	2-Back Letters	Correct responses
	2-Back Figures	Correct responses
	Spatial Span Backwards	Task score
	Subtracting Serial Sevens	errors
	Mental Counters	Correct responses
Access	COWA/FAS/Word fluency	Total words
	CWFT – C letter words	Total words
	CWFT – standardised score	Composite score
	Semantic Retrieval Task	Low association errors

Table 2: Summary of studies included in meta-analysis on executive function in current ecstasy users and drug using controls

Authors and Study	Participants and Design	Task(s) used	Result
Bedi & Redman (2008)	45 ecstasy polydrug users (47% F, mean age: 22.8±3.0, MLD = 170.6±362.8, MTSLU = 79.2±108.5 days). 48 Cannabis polydrug users (46% F, mean age = 21.7±3.5)	COWA FAS	No between group differences in original analysis
Croft et al. (2001)	11 MDMA and cannabis users (55% F, mean age: 27.5±4.7, MLD = 41.9 (49.3), no ecstasy abstinence data given). 18 cannabis users (22% F, mean age: 26.6±8.1)	COWA FAS Stroop Digit span backwards	No differences in performance between MDMA users and cannabis users
Dafters (2006a)	33 ecstasy and cannabis users (36% F, mean age: 23.09±2.34, MLD = 499.1±671.56, min abstinence = 5 days). 18 non-users (44% F, mean age: 22.67)	Stroop Stroop switch) Keep track	Ecstasy users, significantly impaired on task-switching Stroop, but not in Stroop interference or Keep Track Task.
Dafters (2006b)	18 ecstasy and cannabis users (33% F, mean age: 23.24±2.33, MLD = 522.33±936.71, min abstinence = 5 days). 18 non-users (44% F, mean age: 22.67±2.56)	Stroop	No significant between group differences
de Sola et al. (2008a)	37 ecstasy polydrug users (49% F, mean age: 23.6±3.5, MLD = 206±228.3, min abstinence = 72h). 23 cannabis users (65% F, mean age: 22.0±1.9)	ToL	No significant between group differences at baseline
de Sola et al. (2008b)	14 ecstasy polydrug users (57% F, mean age = 25.2±3.3, MLD = 207.4±151.0, no abstinence data given). 13 cannabis users (61% F, mean age: 25.1±2.9)	ToL	No significant between group differences at baseline
Fisk & Montgomery (2009)	14 heavy ecstasy users (36% F, mean age: 22.86, MLD = 1000.21±786.41, MTSLU = 22 weeks). 28 non-users (75% F, mean age: 20.71)	RLG Computation span Consonant updating Spatial updating	Heavy user not impaired at RLG . All updating measures show ecstasy related deficits, and these were significant in 2 out of 3 measures.
Fisk et al. (2004)	44 ecstasy users (mean age: 21.52±1.66, MLD = 343.38±376.94, MTSLU = 10.90±27.86 weeks). 59 non-users (mean age: 21.37±1.84)	RLG Computation span	No group differences on RLG performance. Ecstasy users significantly impaired on computation span
Fox et al. (2001)	11 high intensity ecstasy users (45% F, mean age: 28.0±5.3, MTSLU = 2.8±5.9 months). 20 polydrug controls (70% F, mean age: 23.3±6.5)	WCST ToL	No between group differences in WCST perseverative errors or ToL solution time
Fox et al. (2002)	20 ecstasy polydrug users (50% F, mean age: 27.3±6.7, MLD = 172.0±227.36, MTSLU = 51.9±25.9 months). 20 polydrug controls (60% F, mean age: 27.5±7.6)	3D IDED	No between group differences
Gouzoulis-Mayfrank et al. (2000)	28 ecstasy users (43% F, mean age: 23.25, MDL = 93.4±119.9, MTSLU = 41±71.1 days). 28 polydrug controls (46% F, mean age: 22.9)	Stroop Digit span backwards Phonological word fluency	Ecstasy users performed worse than non-users in digit span backwards. No performance differences observed in Stroop interference or word fluency

Gouzoulis-Mayfrank et al. (2003)	30 heavy ecstasy users (30% F, mean age: 25.1±4.65, MDL = 503.2±555.5, MTSLU = 194.8±351.8 days). 30 non-users (30% F, mean age: 25.37±2.72)	Go NoGo Digit span backwards 2back letters 2back figures	No differences between ecstasy users and controls in central executive function.
Halpern et al. (2004)	23 ecstasy users with minimal exposure to other drugs (65% F, mean age: 20, MDL = 60 episodes). 16 controls equally involved in rave culture (44% F, mean age: 22)	COWA FAS Stroop WCST Digit span backwards	No between group differences in FAS, WCST, Stroop or digit span backwards. However ecstasy related impairment on digit span backwards when adjusted for age and sex
Halpern et al. (2011)	52 ecstasy users (46% F, mean age: 22, MDL = 43.5 episodes, MTSLU = 121 days). 59 non-users (36% F, mean age: 24)	Spatial span backwards Digit span backwards Stroop WCST TMT-B	No significant between group differences on any of the executive measures.
Hanson & Luciana (2004)	26 ecstasy users (46% F, mean age: 21.3±3.6, MLD = 123.31, MTSLU = 10.9±10.5 weeks). 26 non-users (46% F, mean age: 20.7±3.4)	COWA FAS Digit span backwards	No between group differences in COWA total words, or digit span backwards performance
Heffernan et al. (2001)	30 regular ecstasy users (43% F, mean age: 23.9±4.47, min TSLU = 24h). 37 ecstasy free controls (73% F, mean age: 25.5±8.76)	Word fluency, C letter words	Ecstasy users performed significantly worse than controls in verbal fluency measure.
Hoshi et al. (2007)	25 ecstasy users (mean age: 28.64±4.59, MLD = 1111.68, MTSLU = 14.2 days). 29 polydrug users (mean age: 31.93±8.41)	Subtracting serial sevens Verbal fluency TMT-B Go Nogo	No significant group differences were found in Serial Sevens, verbal fluency, the TMT.
Lamers et al. (2006)	11 MDMA/THC users (mean age: 22.9±2.4, MTSLU = 228.1±140.3 days) 15 cannabis users (mean age: 24.3±5.3)	TMT-B WCST	No between group effects on TMT-B or WCST
McCardle et al. (2004)	17 ecstasy users (24% F, mean age: 21.06±1.56), MTSLU = 130 days). 15 controls (13% F, mean age: 21.91±1.62)	Digit span backwards TMT-B	No between group effects observed in digit span backwards or TMT-B
Montgomery & Fisk (2008)	73 ecstasy polydrug (47% F, mean age: 21.77±2.11, MLD = 309.86±486.25, MTSLU = 32.15±62.82 weeks). 73 non-ecstasy users (73% F, mean age: 20.73±1.73)	Letter updating Spatial updating	Ecstasy users impaired in four out of six sub-sample analyses.
Montgomery et al. (2005a)	Study 1: 27 ecstasy users (48% F, mean age: 21.70±1.66, MLD = 345.96±365.76, MTSLU = 4.97±7.27 weeks). 34 non-users (71% F, mean age: 21.59±1.88) Study 2: 51 ecstasy users (47% F, mean age: 21.96±2.11, MLD = 373.87±542.91, MTSLU = 22.15 weeks). 42 non-users (79% F, mean age: 20.83±1.45)	CWFT C letter words Computation span) Letter updating Number-letter task Plus-minus task RLG	Ecstasy users performed worse on both updating tasks and access to long-term memory tasks. Ecstasy users performed significantly better on the inhibition task. No group differences were observed in switching.
Montgomery et al. (2005b)	22 MDMA users (50% F, mean age: 21.36±1.67, MLD = 303.3±374.04, MTSLU = 4.61±6.82 weeks). 26 non-MDMA users (62% F, mean age: 21.31±1.69)	RLG – task score (inhibition) Computation span – task score (updating)	Ecstasy users performed significantly worse than non-users in the computation span task. There were

			no group differences in RLG performance
Montgomery et al. (2007)	104 ecstasy users (mean age: 21.68±1.96, MLD = 349.97±464.41, MTSLU = 19.35±43.46 weeks). 103 non-users (mean age: 21.11±1.66)	CWFT Computation span Letter updating	Ecstasy users performed worse than controls on all measures
Morgan (1998)	Study 1: 16 ecstasy users (50% F, mean age: 20.94±1.88, MLD = 35.5±17.5, MTSLU = 20.4±33.6 days). 12 polydrug controls (mean age: 20.25±1.48). Study 2: 25 ecstasy users (52% F, mean age: 22.28±2.48, MLD = 49.6±33.2, MTSLU = 65.1±85.7). 20 polydrug controls (mean age: 23±4.71)	ToL	No between group differences of ToL performance in either study
Morgan et al. (2002)	18 ecstasy users (50% F, mean age: 23.4±3.2, MLD = 303±267.5, MTSLU = 4.05±3.2 weeks). 16 polydrug users (50% F, mean age: 22.1±3.3)	TMT-B COWA FAS Stroop Subtracting serial sevens	Ecstasy users worse on SSS than all groups. However, no between group differences observed in verbal fluency, Stroop interference RT, or TMT-B completion time.
Murphy et al. (2011)	15 ecstasy and cannabis users (73% F, mean age: 24.5±3.4, MLD = 364.8±665.1, MTSLU = 365 days). 13 cannabis users (54% F, mean age: 21.9±4.6)	RLG	Ecstasy users had significantly higher redundancy on RLG than drug naïve controls but not cannabis controls
Nulsen et al. (2011)	11 ecstasy users (64% F, mean age: 22.9±2.6, MLD = 32.5±27.2). 13 polydrug controls (70% F, mean age: 23.2±3.3)	Digit span backwards	No significant between group differences in digit span backwards performance
Reay et al. (2006)	15 ecstasy polydrug users (40% F, mean age: 25±5.8, MLD = 593.4). 15 polydrug controls (53% F, mean age = 21.3±538)	Digit span backwards Brixton spatial anticipation task Inhibition of return	Ecstasy users performed significantly worse on digit span backwards and the Brixton spatial anticipation task. No between group differences observed in inhibition of return
Reneman et al. (2006)	23 heavy ecstasy (48% F, mean age: 26.05±5.05, MLD = 516.35±452.1, MTSLU = 2.29±2.39 months). 15 polydrug controls (53% F, mean age: 26.3±4.1)	COWA FAS Stroop WCST TMT-B	No between group differences overall on executive functioning
Roberts et al. (2013a)	20 ecstasy polydrug users (50% F, mean age: 23.95±2.50, MLD = 177.65±301.73, min abstinence = 7 days). 20 polydrug controls (55% F, mean age = 22.58±3.45)	Go NoGo	No between group differences in NoGo errors
Roberts et al. (2013b)	20 ecstasy polydrug users (50% F, mean age: 23.95±2.50, MLD = 177.65±301.73, min abstinence = 7 days). 20 polydrug controls (55% F, mean age = 22.58±3.45)	Semantic retrieval task	No behavioural between group differences
Roberts et al. (2013c)	20 ecstasy polydrug users (50% F, mean age: 23.95±2.50, MLD = 177.65±301.73, min abstinence = 7 days). 20 polydrug controls (55% F, mean age = 22.58±3.45)	Number-letter task	No behavioural between group differences
Rodgers (2000)	15 ecstasy users (53% F, mean age: 31 years 5 months, MLD = 20 occasions, min abstinence = 2 months).	Digit span	No performance difference in digit span

	15 cannabis users (53% F, mean age = 30 years 3 months)		
von Geusau et al. (2004)	26 ecstasy users (35% F, mean age: 21.55±1.3, min abstinenece = 2 weeks). 33 non-users (64% F, mean age: 21.7±2.1)	WCST ToL Stop signal task Mental counters	Male MDMA users performed worse on tasks that tap cognitive flexibility. No differences were observed on other cognitive tasks. Female users showed no impairments
Wareing et al. (2004)	42 ecstasy users (48% F, mean age: 21.69±2.57, MLD = 552.99±681.41, MTSLU = 3±3.66 weeks). 31 non-users (61% F, mean age: 23.39±6.47)	Computation span	MDMA users performed significantly worse than controls on computation span task
Wareing et al. (2005)	36 ecstasy users (mean age: 21.81, MLD = 591.33±718.44, MTSLU = 3.30±3.87). 31 non-users (mean age: 23.39±6.47)	Spatial working memory span Computation span	Ecstasy users (users and former users) show impaired spatial working memory compared to controls.
Wareing et al. (2007)	29 ecstasy users (mean age: 21.72±2.00, MLD = 536±515.73, MTSLU = 1.86±1.50 weeks). 46 non-users (mean age: 22.85±5.50)	Computation span	Both ecstasy user groups performed significantly worse than non-users on the computation span measure
Yip & Lee (2005)	100 ecstasy users (mean age: 28.48±5.71, MLD = 35.81±13.21, MTSLU = 2.23±0.51 months). 100 non-users (mean age: 28.82±5.78)	Stroop Digit span backwards	No between group differences on backwards digit span. However ecstasy users performed significantly worse at the Stroop task
Zakzanis & Young (2001)	30 ecstasy users (67% F, mean age: 22.96, MLD = 37.76, MTSLU = 19.96 weeks). 24 non-users (67% F, mean age: 19.54)	Rule shift cards test	No significant difference between groups in rule shift cards test performance

MLD = Mean lifetime dose, MTSLU = Mean time since last use. Information on previous exposure to other drugs and other groups not included in the meta-analysis can be viewed online (supplementary material)

Figure 1: Meta-analysis search results and flow chart.

564 articles identified from initial database searches

76 removed due to duplication

459 titles and abstracts screened

370 articles removed due to not being relevant to the current analysis.

Reviews, acute administration, other substances/did not involve ecstasy users, were not experimental/did not include behavioural data/assess cognition, case studies, non-human samples and reanalyses of data

88 articles eligible for full text review.

A further 49 articles removed after full text review

Reasons for exclusion: No function specific task, no control group or current user group. Longitudinal studies using a within groups design and prospective studies on novice users

39 articles Identified for inclusion from electronic searches.

5 articles excluded due to unobtainable data

5 additional articles identified for inclusion from additional searches

39 articles identified for meta-analysis

Std. Mean Difference | Std. Mean Difference

Study or Subgroup	Std. Mean Difference	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI

1.1.1 Access

1.1.2 Inhibition

1.1.3 Switching

1.1.4 Updating

Total (95% CI)