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REVIEW

MDMA use and neurocognition: a meta-analytic review

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Abstract
Rationale To determine the association between MDMA misuse and neurocognition using meta-analysis.
Objective Separate analyses were conducted based on two sets of inclusion/exclusion criteria. A relatively stringent set required that the subjects be matched on important moderator variables, whereas the other did not. The study participants' performance in the following neurocognitive domains was reviewed: attention/concentration, verbal and nonverbal learning and memory, psychomotor speed and executive systems functioning.
Results In the 11 studies meeting the relatively stringent inclusion/exclusion criteria for this review, MDMA use was associated with neurocognitive deficits in each domain. Similarly, in the 23 studies meeting the relatively lenient inclusion/exclusion criteria for this review, MDMA use was associated with neurocognitive deficits in each domain. Small to medium effect sizes were generally observed. A comparison of the effect sizes across the two sets of analyses did not reveal significant differences.
Conclusions The findings from this review reveal that MDMA use is associated with neurocognitive deficits. The implications of these findings are discussed.

Keywords Cognition · Neuropsychology · Ecstasy · Drug abuse · Drug dependence

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Introduction

MDMA (3,4-methylenedioxymethamphetamine) is a synthetic, psychoactive drug that influences neurobiological functioning primarily, but not exclusively, via the serotonergic system (Nichols 1986; Rudnick and Wall 1992). Preclinical studies showed that chronic or acute, high dose MDMA administration adversely affects neurochemistry and brain morphology. In animals exposed to chronic MDMA, serotonin (5-HT) immunocytochemistry reveals pronounced denervation throughout the neocortex, striatum and thalamus, while lesser damage was observed in the hippocampus, hypothalamus and basal forebrain in rats (Molliver et al. 1990). The impact of acute MDMA exposure in rats includes transient inhibition of tryptophan hydroxylase activity and depletion of 5-HT and its principal metabolite 5-hydroxyindole acetic acid (5-HIAA); effects that gradually return to baseline within approximately 2 weeks (Gibb et al. 1990).

Human studies of MDMA exposure have yielded similar findings. For example, a number of investigators using ^{11}C (+)McN5652 PET (Buchert et al. 2004; McCann et al. 1998) or ^{123}I β-CIT SPECT (Reneman et al. 2001;

Semple et al. 1999) have reported global or regional reductions in 5-HT transporter binding in MDMA users as compared to controls. Moreover, an examination of resting brain metabolism using ^{18F}Flourodeoxyglucose PET, revealed marked reductions in the caudate and putamen (bilaterally) and the left amygdala in MDMA users as compared to controls (Obrocki et al. 2002).

Based on the findings from preclinical studies, it would be reasonable to infer that MDMA exposure is a risk factor for neurocognitive impairment; however, studies of neurocognitive deficits that accompany MDMA use in humans have yielded mixed results. In particular, whereas a subset of studies reported that MDMA users demonstrated neurocognitive deficits relative to matched controls (e.g., Bolla et al. 1998; Hanson and Luciana 2004; McCardle et al. 2004), others have not (Back-Madruga et al. 2003). In those studies in which positive findings were reported, MDMA users showed poorer performance on measures of attention/information processing speed, episodic memory (e.g., supraspan list learning task) and executive systems functioning (i.e., frontal lobe functioning).

It is noteworthy that the variability in the findings across studies might be related to the methodology utilized to study the association (Back-Madruga et al. 2003). Back-Madruga et al. 2003 commented that these variations included, but were not limited to, the lack of a control group and the failure to control for differences in age, education and/or IQ. The latter issue is particularly important as these factors typically moderate performance on neurocognitive tests.

To synthesize the findings from studies that have examined the association between neurocognition performance and MDMA exposure, we conducted a meta-analytic review. This approach provides an objective review of the association between neurocognitive profile and real-world vocational functioning and has a number of advantages over qualitative reviews. A primary advantage of meta-analytic techniques is that they provide the capacity to combine the results of studies utilizing different methodologies and statistical models (e.g., *t* test, chi-square) to calculate a single effect size that quantifies the magnitude of the association between two variables. This technique substantially increases the power of the statistical test of the association between deficits in specific neurocognitive domains and MDMA use. Furthermore, this approach allows us to determine whether the study design moderated the results of the studies.

Materials and methods

Sample The studies included in this review are listed in Table 1 and were retrieved using an online computer search of *PsycInfo* and *Medline*. The search terms utilized in the computer search, *MDMA*, *neurocognition*, *neuropsychology* and *cognition*, provided an initial bibliography of 61 papers. There were no restrictions with respect to the date of the study publication.

Table 1 Description of the studies included in the review

Study author(s)	Year published	Sample size[1]	
		Controls	MDMA users
Back-Madruga et al.	2003	23m/5f	14m/8f
Bhattachary and Powell	2001	11m/9f	10m/6f
Daumann et al.	2003	8m/3f	8m/3f
Fox et al.	2001	6m/14f	12m/8f
Fox et al.	2003	6m/14f	12m/8f
Gouzoulis-Mayfrank et al.	2000	17m/11f	16m/12f
Gouzoulis-Mayfrank et al.	2003	21m/9f	21m/9f
Halpern et al.	2004	9m/7f	8m/15f
Hanson and Luciana	2004	14m/12f	14m/12f
Heffernan et al.	2001	10m/27f	17m/13f
McCardle et al.	2004	13m/2f	13m/4f
Morgan	1999	19m/f	25m/f
Morgan et al.	2002	6m/9f	9m/9f
Parrott et al	1998	4m/6f	8m/2f
Reneman et al.	2000	4m/5f	4m/1f
Rogers	2000	6m/9f	7m/8f
Simon and Mattick	2002	37m/f	47m/f
Verkes et al.	2001	20m	21m
von Geusau et al.	2004	12m/21f	17m/9f
Wareing et al.	2000	5m/5f	5m/5f

[1] m=male/f=female

Based on our review of the studies, there was great variability in terms of the methodology used for the inclusion/exclusion of study participants and for the control of demographic variables. To address this point, we created two sets of inclusion/exclusion criteria for the studies. One set, which was relatively lenient, required studies to meet the following criteria:

1. The study included measures of neurocognition.
2. The study included matched controls.

Based on these criteria, 23 studies were included in the "lenient" analyses (Back-Madruga et al. 2003; Bhattachary and Powell 2001; Daumann et al. 2003; Fisk et al. 2004; Fox et al. 2001; Gouzoulis-Mayfrank et al. 2000, 2003; Halpern et al. 2004; Hanson and Luciana 2004; Heffernan et al. 2001; McCann et al. 1999; McCardle et al. 2004; Montgomery et al. 2005; Morgan 1999; Morgan et al. 2002; Parrott et al. 1998; Reneman et al. 2000; Rodgers 2000; Simon and Mattick 2002; Verkes et al. 2001; Vollenweider et al. 2005; von Geusau et al. 2004; Wareing et al. 2000).

An alternative set of criteria was relatively stringent. For a study to be included in the analyses, it needed to meet the following criteria:

1. The study included measures of neurocognition.
2. The study included matched controls.
3. The matched controls were similar to the MDMA users in terms of age and education or estimated level of premorbid intellectual functioning.
4. The MDMA users were non-treatment seeking and abstinent at the time of the assessment.

Based on these criteria, 11 studies were included in the meta-analysis (Back-Madruga et al. 2003; Bhattachary and Powell 2001; Daumann et al. 2003; Gouzoulis-Mayfrank et al. 2000, 2003; Hanson and Luciana 2004; McCardle et al. 2004; Morgan et al. 2002; Parrott et al. 1998; Thomasius et al. 2003; Verkes et al. 2001).

Effect size To determine the magnitude of the differences between the means of the comparison groups, effect size estimates were calculated using standard techniques (Rosenthal 1991). Estimates of the magnitude of the association between functional outcomes and neurocognition were operationally defined as Pearson's r and Cohen's d.

Number of comparisons To determine the "sample size" for calculating the fail-safe N (see below), the total number of statistical comparisons examining the association between functional outcomes and neurocognition for each neurocognitive domain was calculated (Rosenthal 1991).

Coding scheme For the purpose of this review, the following neurocognitive domains were evaluated: attention/concentration, verbal learning and memory, nonverbal learning and memory, motor/psychomotor speed, and executive systems functioning. This coding scheme was based on taxonomies included in authoritative neuropsychology textbooks (Lezak 1995; Spreen and Strauss 1998).

Combined probabilities To compute combined probabilities for the various subgroups of studies, we employed the method described by Rosenthal (Rosenthal 1991). Specifically, we derived the meta-analytic Z (Z_{ma}) by converting the Pearson's r for each test of vocational functioning and neurocognitive functioning to a Z score, summing the Z scores for each subgroup of investigations, and dividing this sum by the square root of the number of studies included for each subgroup. The p value associated with the Z_{ma} indicates the level of statistical significance for associations between neurocognitive performance and vocational functioning.

Fail-safe N If Z_{ma} was significant, we computed the fail-safe N (N_{fs}) to determine the number of studies with null findings that would be needed to invalidate the conclusion that a significant association existed between vocational status and neurocognitive functioning in a particular domain (Rosenthal 1991). N_{fs} was obtained by summing the Z scores for the particular subgroup, dividing this sum by the Z score associated with a particular probability value, squaring this new number, and finally, subtracting the number of studies in that subgroup. A larger N_{fs} indicates a more reliable association between real-world vocational outcomes and neurocognitive impairment.

Estimating the magnitude of the effect size According to Pedhazur and Schmelkin (1991), Cohen constructed the most frequently used guidelines for the estimation of the magnitude of effect size using Cohen's d (Cohen 1988). Cohen proposed that a difference between the means of 0.2 of a SD be characterized as small, 0.5 as medium and 0.8 as large.

Results

The analyses for studies that met the relatively lenient criteria revealed that MDMA exposure was associated with poorer performance in each of the neurocognitive domains (Table 2). A medium effect size was observed for the associations between MDMA exposure and verbal and nonverbal learning and memory and executive systems functioning. Effect sizes approaching a medium level of magnitude were observed in the domains of attention/concentration and motor/psychomotor speed.

The analyses for studies that met the relatively stringent criteria revealed that MDMA exposure were associated with poorer performance in each of the neurocognitive domains (Table 3). A medium effect size was observed for the associations between MDMA exposure and motor/psychomotor speed. Effect sizes approaching a medium level of magnitude were observed in the domains of attention/concentration, verbal learning and memory, nonverbal learning and memory and executive systems functioning.

A comparison of the effect sizes listed in Tables 2 and 3 revealed that the stringency of the inclusion/exclusion criteria for the studies did not influence the effect sizes for any of the domains studied. Moreover, with regard to the studies that met the more stringent inclusion/exclusion criteria, two of the seven studies included in the latter set examined the association between patterns of MDMA and neuropsychological functioning, though neither examined the association in the subset of the MDMA users who were abstinent (Bhattachary and Powell 2001; Hanson and Luciana 2004). Self-reported level of depressive symptomatology, assessed using the Beck Depression Inventory

Table 2 Effect sizes (Pearson's *r* and Cohen's *d*) for the association between neurocognitive profile and MDMA exposure using relatively lenient inclusion/exclusion criteria for studies

Neurocognitive domain	Pearson's *r* [M (SD)]	Cohen's *d* [M (SD)]	Number of comparisons	Meta-analytic *Z* scores	*p* value	Fail-safe *N* (N_{fs})
Attention/ concentration	0.19 (0.12)	0.40 (0.27)	15	4.52	0.001	64
Verbal learning and memory	0.30 (0.23)	0.73 (0.69)	25	9.39	0.001	569
Nonverbal learning and memory	0.25 (0.23)	0.58 (0.64)	17	5.80	0.001	141
Motor/psychomotor speed	0.26 (0.14)	0.55 (0.32)	14	6.30	0.001	128
Executive systems functioning	0.24 (0.15)	0.52 (0.38)	60	12.24	0.001	2,292

(BDI), was not associated with cognitive functioning in the one study that tested this association (Hanson and Luciana 2004).

Discussion

The primary finding of this report is that MDMA exposure is associated with poorer neurocognitive functioning and the strength of the effect varied across domains. Moreover, the review revealed that the findings did not vary as a function of the study methodology employed. This manuscript offers a number of novel insights and conclusions. These include the pattern of deficits observed, the classification of abuse and dependence for MDMA users, the treatment for neurocognitive impairment in MDMA users, and the relationship between MDMA-associated neurocognitive deficits and functional outcomes.

Many of the reviewed studies included subjects with varying amounts of other drug use (e.g., Thomasius et al. 2003; Verkes et al. 2001). This approach potentially weakened the overall strength of the studies, given that co-occurring drug use might have also affected performance on the neurocognitive measures. Some studies attempted to correct the differences using statistical modeling (e.g., McCardle et al. 2004; Verkes et al. 2001). Others recruited controls whose use of other drugs was similar to that of the MDMA users (e.g., Verkes et al. 2001). A third group did not address the manner in which steps were taken to control for the use of other drugs (e.g., Parrott et al. 1998).

The issue of co-occurring drug use was a criticism of studies examining the neurocognitive consequences of MDMA exposure; however, one recently published study was included in this review that utilized a relatively sensitive sampling approach to address the issue of co-occurring drug use (Halpern et al. 2004). In this study, Halpern et al. 2004 employed a fine-grained screening approach and included only those individuals who engaged in minimal use of drugs other than MDMA. Moreover, they ensured that the association was not moderated by variables such as verbal IQ, self-reported level of depression, or recency of MDMA use. Thus, when they reported that relatively more severe MDMA use was associated with deficits on measures of information processing speed and executive systems functioning, they could rule out the likelihood that co-occurring drug use and other factors moderated the findings.

It is noteworthy that the recreational use of MDMA is associated with poorer performance on neurocognitive measures. To our knowledge, this finding was not observed

Table 3 Effect sizes (Pearson's *r* and Cohen's *d*) for the association between neurocognitive profile and MDMA exposure using relatively stringent inclusion/exclusion criteria for studies

Neurocognitive domain	Pearson's *r* [M (SD)]	Cohen's *d* [M (SD)]	Number of comparisons	Meta-analytic *Z* scores	*p* value	Fail-safe *N* (N_{fs})
Attention/concentration	0.18 (0.12)	0.38 (0.28)	11	3.71	0.001	28
Verbal learning and memory	0.33 (0.25)	0.85 (0.83)	12	7.29	0.001	143
Nonverbal learning and memory	0.25 (0.22)	0.57 (0.51)	11	4.73	0.001	53
Motor/psychomotor speed	0.25 (0.10)	0.53 (0.20)	9	5.11	0.001	52
Executive systems functioning	0.22 (0.16)	0.49 (0.40)	33	9.07	0.001	672

with respect to the recreational use of other drugs, such as methamphetamine, based on a literature search using the National Library of Medicine database. Moreover, and also to our knowledge, this issue was not addressed in other manuscripts on this topic. Future studies might focus on determining the mechanism that underlies the rapid onset of these neurocognitive deficits and whether these deficits are reversible.

It may be that the increased severity of MDMA exposure (i.e., abuse or dependence) or the intensity of MDMA exposure (e.g., number of times used in a month, years used) will be associated with poorer neurocognitive functioning relative to recreational exposure; however, in the one study that included individuals with a diagnosis of MDMA abuse or dependence, this was not observed (Hanson and Luciana 2004). A review of that paper revealed that individuals with an MDMA-related substance use diagnosis performed less well than recreational users on five of 25 indices reported (see Table 5 on p. 239 of Hanson and Luciana 2004). From our perspective, while their findings suggest the need for further research on this topic, these limited data do not support the assertion that the severity of use (i.e., abuse vs dependence) is associated with poorer neurocognition amongst MDMA users.

Although each of the studies included groups of MDMA users, the intensity of use varied across studies. For example, in one study, regular use was defined as ingestion of MDMA on at least ten occasions (Parrott and Lasky 1998). Moreover, in other studies, abstinent MDMA users had taken MDMA on at least 75–80 occasions, but were not characterized as meeting the diagnostic criteria for MDMA abuse (e.g., Thomasius et al. 2003); however, in another study, MDMA users who had taken the drug approximately 95 times, on average, were diagnosed with MDMA abuse or dependence (Hanson and Luciana 2004). In that study, relatively "heavy" MDMA users demonstrated deficits on measures of information processing speed and executive functioning.

The difficulty with respect to the classification of MDMA use highlight one of the unique challenges of research with MDMA users and, to our knowledge, remains an issue that was not adequately addressed. Individuals who abuse or are dependent on other drugs, such as methamphetamine, tend to use the drug on a daily basis or in a particular pattern (e.g., binging); in contrast, the pattern of MDMA use tends to occur on a social and intermittent basis. One potential solution may be to clarify the differences between recreational use and abuse of MDMA. Another may be to reconceptualize abuse of MDMA as it is applied in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (First et al. 1995). This approach was used successfully to characterize the symptom profile of other disorders in the DSM, such as dementia.

The mechanisms by which MDMA impairs cognition may involve serotonergic neurotoxicity. For example, a growing body of literature has demonstrated that tryptophan depletion is associated with decrements in cognition in samples of healthy controls (Evers et al. 2005; Klaassen et al. 1999; Murphy et al. 2002). One study showed that manipulation of tryptophan levels in abstinent MDMA users is associated with altered performance on a memory test (Curran and Verheyden 2003). If tryptophan depletion is associated with cognitive decrements, it would be interesting to determine if a tryptophan-rich diet could reverse the neurocognitive deficits observed in recreational MDMA users and whether this approach would be more effective than abstinence (Cowan 2006). However, to our knowledge, such a study was not conducted in humans.

A review of literature regarding MDMA exposure and neurocognition revealed that a number of important issues were not adequately addressed. An issue of primary importance is whether these deficits recover after the initiation of abstinence. A review of research from imaging studies has preliminarily shown that 5-HT transporter binding recovers during abstinence (Cowan 2006), whereas the single study that utilized measures of neurocognition suggested that the neurocognitive deficits are less likely to resolve (Thomasius et al. 2006). Given the prevalence of MDMA use and the potential consequences of using the drug, this would seem to be an important area of study. Secondarily, the studies did not determine whether gender moderated the effects of recreational MDMA exposure. In particular, given that baseline levels of 5-HT tend to be much lower in women (Nishizawa et al. 1997), it would be helpful to know if this translates into a risk for demonstrating neurocognitive deficits. Furthermore, to our knowledge, none of the available studies has sought to characterize the pattern of neurocognitive deficits associated with MDMA exposure. Based on the results of this review, the pattern is most consistent with a "frontal-subcortical" typology (Cummings 1993). Namely, deficits were consistently observed in the following domains: attention/information processing speed, learning and memory and executive systems functioning. Conceptualizing the pattern of deficits in this manner may be useful with respect to the development of pharmacological interventions for MDMA users. In addition, an important limitation of this review is that we cannot conclude that MDMA caused the deficits observed. Nonetheless, as previously stated, the results of this review support the assertion that MDMA users exhibit poorer neurocognition.

To date, the neurocognitive deficits observed in MDMA users were not linked to functional deficits, such as employment status or treatment outcome. For example, a meta-analytic review in methamphetamine users showed that neurocognitive deficits across a variety of neuropsy-

chiatric disorders were associated with a greater likelihood to be unemployed (Kalechstein et al. 2003). Because it is likely that a subset of MDMA users demonstrated neurocognitive deficits, it would be useful to determine if this association is present in this cohort as well. It is also plausible that this neurocognitive dysfunction would impact treatment outcomes. For instance, it may be that a subset of MDMA users has difficulty remembering information that they learned in treatment sessions. If they are unable to learn and apply this information, then this impairment might be associated with an increased risk for relapse.

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