

## Harmful Effects of Recreational Ecstasy Use on Memory Functioning

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### Abstract

MDMA (3,4-methylenedioxyamphetamine), often referred to as 'ecstasy', has been shown to selectively and persistently impair central serotonergic neurotransmission in laboratory animals. As of recent, evidence in human studies has suggested a link between recreational ecstasy use and a disruption of the brain's serotonergic system. However, human neurocognitive and neuroimaging studies have yielded inconsistent findings regarding the functional impact of these neuro-adaptations, possibly due to methodological difficulties. Although the literature on the effects of recreational ecstasy use on neurocognitive function remains inconclusive, studies have most consistently shown negative effects on memory. Here, we provide a review of accumulating evidence supporting a link between recreational ecstasy use and impaired memory.

**Keywords:** Ecstasy; Neurocognitive; Recreational; Neuroimaging

### Introduction

Ecstasy (3,4-methylenedioxyamphetamine, MDMA) is a popular recreational drug. During the last two decades the recreational use of ecstasy has become a worldwide phenomenon. According to the United Nations survey on global drug use the overall prevalence of ecstasy use is estimated to be 0.4% of the world population and it is estimated that between 9 million and 28 million people have used ecstasy at least once in 2012 [1]. The current European Drug Report estimates that 10.6 million Europeans between the ages 15-64 years have used ecstasy at least once in their lifetime with 1.6 million people reporting ecstasy use in 2015 [2]. Ecstasy is particularly popular among young adults and is predominately used in recreational settings and subcultures associated with the rave and dance club scene. Addictive patterns of use are fairly rare and the addictive potential of ecstasy is rather low compared to other illicit drugs, such as cocaine. Most ecstasy users stop ecstasy use after a short experimental period. However, a minority develop problematic patterns of use, including regular intake and escalating doses [3]. Yet recent evidence suggests that even low cumulative doses of ecstasy may have harmful effects on brain function. This implicates a high relevance for examining adverse effects of ecstasy exposure. In particular, neuropsychological and neuroimaging studies have consistently shown an association between recreational ecstasy use and memory deficits. The aim of the present review is to provide a critical overview of the current literature, focusing on the chronic effects of recreational ecstasy use on memory in humans. Furthermore, this article discusses methodological issues that may have contributed to inconsistent findings in human ecstasy users.

### Ecstasy and the serotonergic system

Numerous studies conducted either in vitro or in laboratory animals have demonstrated the acute effects of MDMA. MDMA has a

particular high affinity for the serotonin (5-HT) transporter, where it blocks 5-HT reuptake and stimulates 5-HT release, thereby increasing the concentration of serotonin in the synaptic cleft [4,5]. Although MDMA also modulates other monoaminergic neurotransmission, such as dopamine and norepinephrine, its primary site of action appears to be the serotonergic system. Serotonergic neurons are abundantly present in the central nervous system and densely innervate the limbic system, known to be involved in a broad range of cognitive and emotional functions [6]. Across species, MDMA-induced alterations of the central serotonergic system have consistently been observed after the application of higher doses or repeated lower doses of MDMA [7]. These alterations appear to be selective for markers of serotonergic functioning in most species. Despite the widespread serotonergic damage throughout the neocortex, long-term effects of repeated MDMA exposure in animals seem largely limited to the hippocampal formation [8].

Human positron emission tomography (PET) studies have reported that global decreases of central 5-HT transporter binding potential is associated with chronic ecstasy use, suggesting that similar alterations of the serotonergic system in human ecstasy users are conceivable [9-12]. The functional implications of these alterations in humans remain under investigation. Given that serotonin is involved in several physiological and neuropsychological processes, including cognitive functions, sleep and psychomotor activity, damage to the serotonergic system may lead to a range of functional impairments [13]. However, no human studies have firmly established whether observed deficits in human ecstasy users represent neurotoxic effects of ecstasy or precede the onset of ecstasy use, possibly reflecting a predisposition promoting the development of regular use.

### Methodological Limitations

Studies that aim to examine the effects of recreational ecstasy use on the human brain face several methodological challenges, such as commonly reported poly-drug use or the lack of baseline data. These issues often render the clear interpretation of findings in human

ecstasy users difficult. For instance, cross-sectional studies are unable to disentangle whether the observed functional differences between ecstasy users and ecstasy-naïve controls represent a predisposition or a neurotoxic consequence of the drug. It is conceivable that individuals with inherently low serotonergic functioning have an increased risk of developing regular patterns of use. Users could consume MDMA to compensate for functional deficits of serotonergic neurotransmission, as has been postulated by the self-medication hypothesis for substance use [14]. At the same time, it appears plausible that, as observed in animals, ecstasy causes damage to serotonergic neurons, leading to associated behavioural changes. However, only carefully controlled, prospective, longitudinal studies have the capacity to establish a direct link between ecstasy use and serotonergic damage in humans.

Furthermore, an inherent component of studying the effects of human exposure to ecstasy in naturalistic settings is the challenge of controlling a range of confounds and the lack of controlled experimental variation. Confounding differences in lifestyle, such as altered sleep-wake cycles, may blur the data thereby preventing the isolation of ecstasy-specific effects.

Ecstasy users commonly report co-use of other illicit psychoactive substances. In a large sample of 1206 college students in the US, 98% of ecstasy users reported co-use of cannabis [15]. Additionally, the use of licit drugs, particularly alcohol and nicotine, is often higher among recreational ecstasy users than in socio-demographically comparable individuals, potentially confounding results in cross-sectional studies. Together, these challenges and methodological limitations need careful consideration when reviewing the literature on harmful effects of recreational ecstasy on neurocognitive functioning.

Finally, when studying memory alterations related to drug use, a careful selection of the specific neuropsychological tests may be crucial for the outcome. Sensitivity of the tests used to detect ecstasy-associated impairments might vary depending on the test and the memory domain (e.g., verbal or visual learning). For instance, memory sensitivity has been shown to differ between a same-different memory task and a 2-alternative-forced choice task despite encoding similarities in the same population [16]. Accumulating evidence suggests domain-specific memory impairments in ecstasy users. In a meta-analysis of cross-sectional studies comparing recreational ecstasy users and drug-naïve controls, Laws and Kokkalis reported impaired performance in tests of verbal memory, but normal performance in tests of visual memory, indicating that some memory domains might be particularly vulnerable to the harmful effects of ecstasy [17]. Finally, the comparison of findings across different studies is often hampered by the use of study-specific neuropsychological test batteries and test application procedures.

In summary, important confounders, particularly poly-drug use and the prevailing retrospective study designs, as well as differences in neuropsychological memory assessment may have contributed to inconsistent findings regarding the harmful effects of ecstasy on memory in humans. However, in recent years elaborate study designs alongside clearly defined and strictly controlled study criteria have allowed the field of research in recreational ecstasy users to address some of these methodological issues and to further establish an association between ecstasy use and potential neurocognitive impairments in the domain of memory.

## Memory performance in recreational ecstasy users

Neurocognitive performance in recreational ecstasy users has been investigated comprehensively within the past two decades, yielding discrepant results. Authors of neuropsychological studies have largely implemented cross-sectional designs comparing recreational ecstasy users with drug-naïve control subjects. While several of these studies revealed lower cognitive performance in recreational ecstasy users, others reported no differences to healthy controls [18-22]. These inconsistent findings might be related to the abovementioned methodological differences between studies. The present review will focus on memory, for which the most consistent findings to date on neurocognitive dysfunctions in human ecstasy users have been reported. Reviews of the literature concerning ecstasy-related alterations in other neurocognitive domains are provided elsewhere [23-25]. A potential explanation for selective learning and memory impairments was initially provided by the authors of an extensive neurocognitive study. Gouzoulis-Mayfrank and colleagues hypothesized that the hippocampus, implicated in transmitting information from short-term to long-term memory, might be particularly vulnerable to the harmful effects of recreational ecstasy use [26,27]. In this study, a large sample of recreational ecstasy users underwent a comprehensive neurocognitive test battery to determine whether reported memory deficits related to ecstasy exposure were secondary to global cognitive impairments. To this end, the authors compared 30 moderate users with a lifetime use of fewer than 80 tablets, 30 heavy users with a lifetime use of more than 80 tablets and 30 drug-naïve controls. Chronic heavy ecstasy users showed selective memory impairment compared to both moderate users and drug-naïve controls. This finding was in line with an early cross-sectional study reporting ecstasy-associated deficits in immediate and delayed recall in novice and regular users [28].

Since these early findings, the link between recreational ecstasy use and deficits in hippocampus-dependent memory functioning has been extensively studied. Authors of recent meta-analyses have combed the accumulating evidence to determine the magnitude of neurocognitive deficits. Importantly, meta-analytic methods allow to compensate for some methodological limitations of individual studies, such as small sample sizes and heterogeneous samples. An early meta-analysis from 2007 covering 27 neurocognitive studies aimed at exploring the impact of recreational ecstasy use on short- and long-term memory, as well as verbal and visual memory. The authors reported significant impairments in ecstasy users relative to ecstasy-naïve controls across all memory domains with moderate-to-large effect sizes, except for visual memory, suggesting a link between regular ecstasy exposure and widespread memory deficits [17]. A subsequent, more refined, systematic review of 100 neuropsychological studies aimed to determine ecstasy-specific impairments by employing subgroup analyses comparing ecstasy users with both drug-naïve and poly-drug using controls [29]. Despite differences in methodological quality between the studies, ecstasy users displayed deficits in immediate and delayed verbal memory of rather small effect size when compared to both drug-naïve controls and poly-drug users, indicating an association between ecstasy use and memory impairments. A quantitative meta-analysis specifically assessing visuospatial memory, verbal short-term memory and working memory concluded that recreational ecstasy users show significantly lower memory performances in all examined domains compared to drug-naïve and poly-drug using controls, suggesting that ecstasy use might additionally be associated with impairments in working memory [30]. Taken together, these meta-analyses highlight the potentially harmful

effects of recreational ecstasy use on memory function and provide evidence that the observed memory impairments across studies may be specific to ecstasy.

However, the reviewed literature employed retrospective cross-sectional designs, which do not allow evaluation of whether cognitive deficits precede the onset of ecstasy use or are a consequence of neurotoxic effects of ecstasy exposure. To bring more clarity into this matter, two elaborate, prospective longitudinal studies have examined baseline cognitive performance before the onset of regular ecstasy use while controlling for several known confounders. Individuals with an increased risk for future ecstasy use were included. Measures of drug-use and cognitive performances in the domains of attention, working memory and verbal and visual memory of 188 ecstasy-naïve subjects were investigated at baseline and after 18-36 months [31,32]. Fifty-eight subjects reported ecstasy use (average = 3.2 tablets) during the follow-up interval. Importantly, ecstasy-naïve participants and future ecstasy users showed comparable cognitive performance at baseline. Relative to persistent ecstasy-naïve subjects, subjects who continued ecstasy use during follow-up showed lower change scores of immediate and delayed verbal recall after the follow-up interval, indicating that even low cumulative doses may be linked to a decline in memory function. A study by Wagner and colleagues provided further prospective evidence regarding deficits in immediate and delayed recall [33]. In this study, a comprehensive neurocognitive test battery was employed to assess learning, memory and executive functioning in a cohort of 149 young adults. At study inclusion, subjects had recently initiated ecstasy use with a baseline lifetime exposure of fewer than 5 ecstasy tablets. After a 12-month interval, 23 subjects reported regular ecstasy use (more than 10 ecstasy tablets during the past 12 months) with an average cumulative dose of 33.6 ecstasy tablets. Specific impairments in immediate and delayed recall of a paired associates learning task were observed in regular ecstasy users. Based on the consistently observed pattern of specific impairments in hippocampus-dependent memory, these prospective studies provide supporting evidence that the hippocampus may be particularly vulnerable to the harmful effects of ecstasy use. Together with previous cross-sectional findings, these prospective findings strongly suggest that repeated ecstasy exposure adversely affects memory in humans. As of recent, another study investigating memory function in heavy ecstasy users compared to low-exposure ecstasy users and drug-naïve controls showed that both ecstasy using groups performed significantly worse in delayed recall [34]. Moreover, a regression analysis linked the extent of the memory impairments to the lifetime ecstasy exposure. These findings confirm that even low doses of ecstasy use may be harmful to hippocampal-dependent memory function. The neurobiological underpinnings of the observed neuropsychological deficits in ecstasy users have additionally been addressed by studies employing neuroimaging techniques.

#### Alterations of brain structure in recreational ecstasy users

Few morphometric studies have investigated changes in brain structure related to recreational ecstasy use. Cowan and colleagues reported reduced grey matter density throughout the brain including cortical regions such as the occipital, left temporal and frontal cortex in recreational ecstasy users compared to ecstasy-naïve controls [35]. Subsequently, Daumann and colleagues compared grey matter volume of experienced ecstasy users to ecstasy-naïve controls and low-exposure ecstasy users with a lifetime use of fewer than 5 doses [36]. Experienced users showed significantly smaller volumes in medial frontal regions, particularly the orbital and medial frontal cortex,

compared to both control groups while low-exposure ecstasy users and ecstasy-naïve controls did not differ. Although these studies provide evidence that brain structure in regions implicated in memory function, such as prefrontal regions, may be subject to ecstasy-associated alterations, hippocampal structural integrity appears to remain unaffected [37].

#### Biochemical alterations in memory-associated brain regions

Imaging techniques have enabled researchers to examine the neurobiological basis of potentially harmful effects of recreational ecstasy use on the brain. PET binding studies have contributed to the knowledge on how serotonergic adaptations in humans are linked to ecstasy exposure thereby providing initial translational evidence for the hypothesis that the ecstasy-induced serotonergic damage observed in laboratory animals may be relevant to human ecstasy users. In addition, in a more recent PET study that compared 49 chronic ecstasy users with 50 non-using controls, Kish and colleagues reported an association between decreased serotonin transporter binding in the hippocampus and modest memory deficits in ecstasy users, suggesting a direct relationship between decreased serotonergic function in the hippocampus and memory deficits [38]. Moreover, PET can be used to assess brain glucose metabolism. Bosch and colleagues implemented this technique to compare regional cerebral metabolism at rest in recreational ecstasy users and drug-naïve controls [39]. Subsequently, they examined whether altered glucose metabolism associated with differences in memory performance. Results showed that ecstasy use was linked to deficits in verbal declarative memory performance. Furthermore, lower learning and recall scores correlated with decreased glucose metabolism in frontal and parietal cortical regions while worse recognition associated with hypometabolism in the mediotemporal and lateral temporal cortex. However, despite some evidence from cross-sectional PET studies for reduced serotonergic functioning and decreased cerebral glucose metabolism in ecstasy users, findings remain inconsistent regarding the specific brain regions affected. Furthermore, based on the available data, it cannot be excluded that reduced serotonergic functioning in ecstasy users precedes the initiation of use or might even render individuals vulnerable to regular ecstasy use.

#### Alterations of brain physiology in recreational ecstasy users

Functional magnetic resonance imaging (fMRI) studies addressed altered task-related neural activation patterns in recreational ecstasy users. Altered hippocampal activity was most consistently reported in a number of studies assessing memory-related brain functioning. In an early study, Jacobsen and colleagues assessed brain activation during a verbal working memory task in a small group of six novice ecstasy users compared to six non-using controls [40]. Even low-dose ecstasy exposure was linked to task-specific alterations in hippocampal activation. Although these initial findings were preliminary and covered only a small sample, altered hippocampal function in recreational ecstasy users has since been reported in a number of cross-sectional functional imaging studies employing hippocampus-dependent paradigms [41-43], however, ecstasy use associated patterns of brain activation have not been consistently linked to memory deficits. When comparing brain activation during retrieval in an associative learning task in 12 polyvalent ecstasy users and 12 non-using controls, Daumann and colleagues found normal episodic memory performance despite lower left hippocampal activity [41]. The authors hypothesized that alterations in hippocampal integrity as



assessed by fMRI might reflect “a more sensitive or earlier index of MDMA-related neurotoxicity than neuropsychological performance”. A similar pattern of altered memory-related processing in the hippocampal formation in the context of normal memory performance was observed in recreational ecstasy users in a prospective fMRI study [42]. In this study, 40 ecstasy users were examined at two time points separated by a 12 month interval. At baseline, subjects had little experience with ecstasy (lifetime dosage <5 tablets). After 12 months, users who continued use displayed a decrease in memory encoding-related, left para-hippocampal activation, whereas users who had stopped using ecstasy after the baseline examination showed an increase. This prospective data suggests that altered activity in the hippocampal formation during memory processing might represent an effect of chronic ecstasy use rather than a predisposition. However, both studies examined poly-drug ecstasy users and therefore cannot exclude that other substances of abuse, such as cannabis and amphetamine, may have contributed to the observed effect. Previous studies have reported associations between cannabis and amphetamine use and altered memory-related hippocampal activity [43]. Therefore, the widespread co-use of amphetamine and cannabis in ecstasy users might have contributed to observed hippocampal alterations. To specifically address this limitation, cannabis-using subjects were included as an additional control group in a subsequent fMRI study that examined the association between recreational ecstasy use and altered memory-related hippocampal function [44]. Findings included changes in para-hippocampal activation in both cannabis and ecstasy users compared to non-using controls, suggesting that deficits in hippocampal function may not be specific to recreational ecstasy use. To further disentangle drug-specific effects on neurocognitive performance and associated neural activity patterns, Jager and colleagues examined subjects with varying previous exposure to commonly abused drugs, including ecstasy [45]. Results showed that amphetamine use, not ecstasy use, was linked to deficits in hippocampus-dependent associative memory performance. Ecstasy use, on the other hand, was associated with altered neural activation in dorsolateral prefrontal and middle occipital regions during memory processing.

In summary, to date, fMRI evidence regarding the harmful effects of ecstasy use on memory function remains inconclusive and warrants further investigations. Most of all, ecstasy-specific effects remain to be distinguished from the effects of other substances and further clarification regarding the causality is needed.

### The Impact of functional alterations related to recreational ecstasy use

Despite methodological limitations, accumulating evidence from neurocognitive and neuroimaging studies suggests an association between recreational ecstasy use and memory deficits. However, important questions need to be clarified. As individual studies and more recent meta-analytic reviews have mostly reported small to moderate effect sizes for the memory deficits in ecstasy users, it remains unclear whether the observed functional impairments in laboratory settings are relevant to everyday functioning [29]. Several studies have attempted to answer this question using a variety of assessment tools, including the Prospective Memory Questionnaire, self-reported Everyday Memory Questionnaire, virtual board games mimicking work-related activities and virtual-reality memory tasks simulating office tasks, and have compiled empirical evidence for impairments of prospective everyday memory function in ecstasy users

[46-49]. Although experimental settings cannot be overcome, these reports suggest that ecstasy-related retrospective memory deficits may be apparent in everyday settings.

An additional topic that has gained interest and warrants further research, is the role of individual differences that may mediate vulnerability to the harmful effects of recreational ecstasy use on brain function. Emerging empirical findings suggest that individual differences, including genetic variations, personality traits and baseline cognition, may mediate the harmful effects of ecstasy exposure on brain functioning. For instance, genetic studies have revealed that certain genotypes of candidate genes involved in the serotonergic system are associated with variations in cognitive performance of ecstasy users [50-52]. Recently, Fagundo and colleagues reported that recreational ecstasy users carrying the ss-allele of the 5-HTTLPR polymorphism on the SLC6A4 gene, which codes for the serotonin transporter, performed worse on a verbal fluency task than users carrying other alleles [51]. Overall, poorer outcomes were observed for all ecstasy users relative to control subjects. This indicates that baseline differences of the serotonergic system may be related to the extent of adverse effects linked to recreational ecstasy use. A neurocognitive study by Roiser and colleagues implicated trait impulsivity as a risk factor for ecstasy-related cognitive impairments [22]. In this study, higher scores of trait impulsivity were associated with greater impairments in memory performance. These individual vulnerabilities may influence whether and to which extent memory function is affected by recreational ecstasy use. Future studies should consider further exploring the role of individual differences in order to identify subgroups that are particularly vulnerable to the harmful effects of ecstasy use.

### Conclusion

In summary, research on ecstasy-related memory effects has come a long way. From initial early studies that suffered from methodological shortcomings to more advanced and refined designs, the literature has consistently suggested an association between recreational ecstasy use and neuropsychological deficits in the domains of learning and memory. In more recent years, neuroimaging studies have brought forth accumulating evidence concerning altered brain activation in memory-related regions, in particular implicating the hippocampal formation. However, evidence from fMRI studies remains inconclusive regarding the specific neural effects of ecstasy and the affected brain regions. Recent prospective studies have provided first evidence that the commonly observed memory deficits in recreational ecstasy users may be caused by harmful effects of ecstasy rather than by predispositions preceding the onset of ecstasy use. We still have a great deal to learn from future research, yet accumulating evidence suggests that recreational ecstasy users put themselves at risk for impaired hippocampus-dependent memory function.

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