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MDMA and impulsivity: A review

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Abstract: The illicit drug 3,4-methylenedioxymethamphetamine (MDMA; Ecstasy) has been shown to cause long-term serotonin (5-HT) deficits in rodents and non-human primates, and based on the results of brain imaging studies in frequent Ecstasy users, it appears that MDMA has the potential to affect the human brain in much the same way. Because the 5-HT system is known to take part in the regulation of impulsivity, it has been hypothesized that increased impulsivity may be one of the consequences of MDMA exposure seen in Ecstasy users. The purpose of this review is to evaluate the evidence for a relationship between Ecstasy use and higher levels of impulsivity. Cross-sectional studies that used measures of impulsivity to compare abstinent Ecstasy users to non-users will be summarized, and longitudinal studies that attempted to find changes in impulsivity in Ecstasy users will be examined. In closing, the overall evidence for an association between Ecstasy use and higher levels of impulsivity will be evaluated, and potential explanations for this association will be discussed.

Keywords: MDMA, Ecstasy, serotonin, impulsivity, inhibition, disinhibition.

INTRODUCTION

The illicit drug 3,4-methylenedioxymethamphetamine (MDMA; Ecstasy) has been shown to cause long-term serotonin (5-HT) deficits in several species of rodents and non-human primates [1-6]. Consistent with the hypothesis that MDMA may also cause persistent serotonergic alterations in humans, cross-sectional studies using positron emission tomography or single photon emission computed tomography have revealed less serotonin transporter binding in the brains of frequent Ecstasy users[1] in comparison to Ecstasy-naïve control participants [7-14]. Both preclinical and clinical studies have indicated that the 5-HT system plays an important part in the regulation of a number of emotional and behavioral processes, including mood, anxiety, impulsivity, and aggression [15]. Therefore, if MDMA causes persistent 5-HT deficits in humans, then elevated impulsivity may be observed in Ecstasy users.

A number of quasi-experimental studies have measured impulsivity in Ecstasy users. The purpose of this review is to evaluate the evidence for a relationship between Ecstasy use and higher levels of impulsivity. First, cross-sectional studies that used measures of impulsivity to compare abstinent Ecstasy users to non-users will be summarized. Second, longitudinal studies that attempted to find changes in impulsivity in Ecstasy users will be reviewed. Lastly, the overall evidence for an association between Ecstasy use and higher levels of impulsivity will be evaluated, and potential explanations for this association will be discussed.

METHOD

A search for quasi-experimental studies related to Ecstasy use and impulsivity was conducted using the PsycINFO database and the MAPS Psychedelic Bibliography (www.maps.org/wwwpb). Due to lack of inhibition often being equated or associated with impulsivity[2], target articles included studies that used self-report or behavioral measures of

impulsivity or inhibition/disinhibition. Word combinations such as "MDMA and impulsivity" and "MDMA and inhibition" were used in the search. In addition, cross-sectional studies that were not found through the use of an electronic database but that were referenced by the studies found in the search were also included.

To be included in the review, cross-sectional studies had to compare abstinent Ecstasy users to at least one group of Ecstasy-naïve or mostly Ecstasy-naïve individuals, and longitudinal studies had to use a follow-up period of at least 1 year after baseline measurements. If two different cross-sectional studies presented results from the same or nearly the same overall sample of Ecstasy users and control participants using identical measures, then the study that provided more descriptive information (e.g., provided more information regarding Ecstasy use, used additional measures of impulsivity or inhibition/disinhibition) was included in the review, whereas the other less descriptive study was excluded. Finally, one study was excluded due to not providing adequate information about sample sizes and drug use variables.

CROSS-SECTIONAL STUDIES THAT USED THE BARRATT IMPULSIVENESS SCALE (BIS) TO MEASURE SELF-REPORTED IMPULSIVITY

Daumann *et al.* [16] recruited 28 Ecstasy users with minimal exposure to other illicit drugs besides cannabis, 28 cannabis controls[3], and 28 drug-naïve controls[4]. Participants with a current or past Axis I psychiatric disorder were excluded except for drug abuse in the two drug user groups. Urine testing was used to disconfirm recent drug use. Ecstasy users reported an average lifetime use of 93 tablets of Ecstasy. Daumann *et al.* found that Ecstasy users scored significantly higher than drug-naïve controls on the non-planning impulsivity subscale of the BIS. However, Ecstasy users did not have significantly higher non-planning impulsivity subscale scores than cannabis controls. In addition, the group difference in non-planning impulsivity was

no longer significant after treating duration of cannabis use and age at onset of regular cannabis use as covariates.

Verkes *et al.* [17] recruited three groups of male volunteers: 21 heavy Ecstasy users, 21 moderate Ecstasy users, and 20 mostly drug-naïve controls[5]. All participants reported that they had attended rave parties regularly in the past year. Exclusion criteria for all three groups included regular use of illicit drugs besides cannabis, a history of alcohol or substance dependence, and the presence of a major psychiatric disorder within the past year. Notably, the *DSM-IV* diagnostic criteria for Attention-Deficit/Hyperactivity Disorder (ADHD) were scored retrospectively for each participant, and the number of reported ADHD criteria prior to 15 years old did not differ significantly between the groups. Urine testing was used to disconfirm recent drug use. Moderate and heavy Ecstasy users reported an average lifetime use of 169 and 741 tablets of Ecstasy, respectively. Verkes *et al.* failed to find any significant group differences in BIS scores or subscores.

Moeller *et al.* [18] recruited 8 heavy Ecstasy users, 8 infrequent Ecstasy users, and 20 drug-naïve controls. Ecstasy users had no current or past Axis I disorders except for substance abuse, and drug-naïve controls were free of current or past Axis I and Axis II disorders. Urine testing revealed that only two Ecstasy users had a negative drug screen, whereas all of the control participants had a negative drug screen. Heavy and infrequent Ecstasy users reported an average lifetime use of 180 and 30 doses of Ecstasy, respectively. Moeller *et al.* found that heavy Ecstasy users had significantly higher BIS total scores than drug-naïve controls, whereas infrequent Ecstasy users and drug-naïve controls had similar BIS total scores.

Bond *et al.* [19] recruited three groups of men: 32 current Ecstasy users, 32 former Ecstasy users, and 32 cannabis controls. Participants with a positive psychiatric history were

excluded. Current and former Ecstasy users reported an average lifetime use of 528 and 1106 tablets of Ecstasy, respectively. Ecstasy users also reported the occasional use of cocaine, amphetamines, and LSD, whereas none of the cannabis controls reported using other illicit drugs. Bond *et al.* found that current Ecstasy users had significantly higher BIS total scores than cannabis controls. In addition, both Ecstasy user groups scored higher on the motor impulsivity subscale in comparison to cannabis controls.

Daumann *et al.* [20] recruited 60 Ecstasy users and 30 mostly drug-naïve controls. Participants were excluded if they had a current or past Axis I disorder except for substance abuse in the Ecstasy user group. Urine testing was used to disconfirm recent drug use. Ecstasy users reported an average lifetime use of 271 pills of Ecstasy. Daumann *et al.* found that Ecstasy users scored significantly higher on the BIS non-planning impulsivity subscale than mostly drug-naïve controls.

Fingeret *et al.* [21] recruited 83 Ecstasy users and 91 mostly drug-naïve controls. Participants were excluded if they had a current or past Axis I disorder other than substance abuse or dependence in the Ecstasy user group. Urine testing was used to disconfirm recent alcohol use. Fingeret *et al.* found that Ecstasy users had significantly higher BIS total scores than mostly drug-naïve controls.

In the first Ecstasy study conducted in Brazil, de Almeida and Silva [22] recruited 52 Ecstasy users and 52 polydrug controls[6]. Ecstasy users were excluded if they had not used Ecstasy at least 10 times. The researchers failed to find a significant difference in BIS scores between the two groups.

Dafters [23] recruited 18 Ecstasy users, 18 cannabis users with minimal exposure to Ecstasy and other illicit drugs, and 18 mostly drug-naïve controls. Participants were excluded if

they reported a history of neurological disorder or brain injury. Ecstasy users reported an average lifetime use of 522 pills of Ecstasy, and cannabis users reported an average lifetime use of 4 pills of Ecstasy. Due to group differences in drug consumption, lifetime use of alcohol, cocaine, amphetamines, and tobacco were included as covariates in statistical analyses. Dafters found that both Ecstasy and cannabis users had significantly higher BIS total scores than mostly drug-naïve controls. However, the two drug user groups had similar BIS total scores.

Hanson *et al.* [24] recruited 22 Ecstasy users and 30 polydrug users with minimal or no exposure to Ecstasy[7]. Ecstasy users reported an average lifetime use of approximately 72 pills of Ecstasy, and polydrug users reported an average lifetime use of approximately 2 pills of Ecstasy (calculated from the Ecstasy use information provided by Hanson *et al.* in Table 2 of their article). Hanson *et al.* found that Ecstasy users and polydrug users had similar BIS scores and subscores.

Hoshi *et al.* [25] recruited four groups of male participants: 25 current Ecstasy users, 26 former Ecstasy users, 29 polydrug controls, and 25 drug-naïve controls. Participants were excluded if they reported receiving psychological treatment, having a history of drug dependence, or having a serious head injury in the past. Urine testing was used to disconfirm recent drug use. Current and former Ecstasy users reported an average lifetime use of 288 and 253 tablets of Ecstasy, respectively. Current Ecstasy users had used cocaine and LSD more recently than polydrug controls. Hoshi *et al.* found that current Ecstasy users had significantly higher BIS total scores than control participants, whereas former Ecstasy users and control participants had similar BIS total scores.

Ten cross-sectional studies that used the BIS to measure self-reported impulsivity in Ecstasy users have been reviewed. One study failed to find greater impulsivity in Ecstasy users

in comparison to mostly drug-naïve controls [17]; two studies failed to find greater impulsivity in Ecstasy users in comparison to polydrug users [22, 24]; three studies found greater impulsivity in Ecstasy users in comparison to drug-naïve or mostly drug-naïve controls but failed to include a cannabis or polydrug control group [18, 20-21]; and two studies found greater impulsivity in Ecstasy users in comparison to drug naïve or mostly drug-naïve controls but failed to find greater impulsivity in Ecstasy users in comparison to cannabis or polydrug users [16, 23]. Of the remaining two studies, one study [19] found greater impulsivity in current Ecstasy users in comparison to cannabis controls, and the other study [25] found greater impulsivity in current Ecstasy users in comparison to drug-naïve and polydrug controls. However, both of these studies reported drug use differences between Ecstasy users and drug-using control participants. To summarize, cross-sectional studies that used the BIS have not provided solid evidence for an association specifically between Ecstasy use and higher levels of self-reported impulsivity.

CROSS-SECTIONAL STUDIES THAT USED THE IMPULSIVENESS, VENTURESOMENESS AND EMPATHY SCALE (IVE) TO MEASURE SELF-REPORTED IMPULSIVITY

Morgan [26] recruited 41 Ecstasy users, 32 polydrug controls, and 35 drug-naïve controls. Exclusion criteria for all participants included current major depression, a history of psychosis, alcohol or opiate dependence, and current or past major medical illness. Ecstasy users reported an average lifetime use of 44 tablets of Ecstasy (calculated from the Ecstasy use information provided by Morgan in Table 3 of his article). Morgan found that Ecstasy users scored significantly higher than drug-naïve controls on the impulsiveness subscale of the IVE, whereas Ecstasy users and polydrug controls had similar impulsiveness scores.

Parrott *et al.* [27] recruited 12 heavy Ecstasy users, 16 light Ecstasy users, and 22

polydrug controls. Both heavy and light Ecstasy users reported greater use of tobacco, cocaine, amphetamine, psilocybin mushrooms, and LSD in comparison to polydrug controls. Light and heavy Ecstasy users reported using Ecstasy on an average of 7 and 371 occasions, respectively. Parrott *et al.* found that heavy Ecstasy users scored significantly higher than polydrug controls on the impulsiveness subscale of the IVE, whereas light Ecstasy users and polydrug controls had similar impulsiveness scores.

Morgan *et al.* [28] recruited 18 current Ecstasy users, 15 former Ecstasy users, 16 polydrug controls, and 15 drug-naïve controls. Exclusion criteria for all participants included schizophrenia, major depressive disorder, and alcohol or opiate dependence. Current and former Ecstasy users reported an average lifetime use of approximately 303 and 512 tablets of Ecstasy, respectively (calculated from the Ecstasy use information provided by Morgan *et al.* in Table 1 of their article). Morgan *et al.* failed to find any significant group differences in IVE impulsiveness scores.

Butler and Montgomery [29] recruited 18 heavy Ecstasy users, 28 light Ecstasy users, 37 polydrug controls, 55 cannabis controls, and 116 drug-naïve controls. Light Ecstasy users reported having used Ecstasy on less than 20 occasions, and heavy Ecstasy users reported having used Ecstasy on more than 20 occasions. Butler and Montgomery found that both of the Ecstasy user groups and the polydrug control group scored significantly higher than drug-naïve participants on the impulsiveness subscale of the IVE. However, the four drug user groups had similar impulsiveness subscale scores.

Dafters *et al.* [30] recruited 16 heavy Ecstasy users, 19 light Ecstasy users, 15 cannabis controls, and 19 drug-naïve controls. Light and heavy Ecstasy users reported an average lifetime use of 20 and 364 tablets of Ecstasy, respectively. Dafters *et al.* failed to find any significant

group differences in IVE impulsiveness scores.

Roiser *et al.* [31] recruited 66 Ecstasy users, 30 cannabis controls, and 28 drug-naïve controls. Blood testing was used to disconfirm recent drug use. Ecstasy users reported having used Ecstasy on at least 30 occasions. Roiser *et al.* found that Ecstasy users scored significantly higher than cannabis and drug-naïve controls on the impulsiveness subscale of the IVE. However, amphetamine use correlated significantly with impulsiveness subscale scores in Ecstasy users, and after removing the Ecstasy users who had also used amphetamine frequently from the analysis, no significant group differences in impulsiveness subscale scores were found.

Dafters [23] recruited 18 Ecstasy users, 18 cannabis users with minimal exposure to Ecstasy and other illicit drugs, and 18 mostly drug-naïve controls. Ecstasy users reported an average lifetime use of 522 pills of Ecstasy, and cannabis users reported an average lifetime use of 4 pills of Ecstasy. Dafters found that both Ecstasy and cannabis users had significantly higher IVE impulsiveness subscale scores than mostly drug-naïve controls. However, the two drug user groups had similar impulsiveness subscale scores.

Roiser *et al.* [32] recruited 30 current Ecstasy users, 20 former Ecstasy users, 30 polydrug controls, and 30 drug-naïve controls. Participants with a current or past Axis I psychiatric diagnosis were excluded. Blood testing was used to disconfirm recent drug use. Current and former Ecstasy users reported an average lifetime use of 275 and 793 tablets of Ecstasy, respectively. Roiser *et al.* found that former Ecstasy users scored significantly higher than drug-naïve controls on the impulsiveness subscale of the IVE, but they failed to find any significant differences in impulsiveness subscale scores between the two Ecstasy user groups and polydrug controls.

Eight cross-sectional studies that used the IVE to measure self-reported impulsivity in

Ecstasy users have been reviewed. Two studies failed to find greater impulsivity in Ecstasy users in comparison to control participants [28, 30]. Four studies found greater impulsivity in Ecstasy users in comparison to drug-naïve or mostly drug-naïve controls but failed to find greater impulsivity in Ecstasy users in comparison to cannabis or polydrug controls [23, 26, 29, 32]. Of the remaining two studies, one study [27] found greater impulsivity in heavy Ecstasy users in comparison to polydrug controls, and the other study [31] found greater impulsivity in Ecstasy users in comparison to cannabis controls. However, the Ecstasy users in the first study had used several drugs significantly more than polydrug controls, and the Ecstasy users in the latter study no longer had greater impulsivity in comparison to cannabis controls after frequent amphetamine users were removed from the analysis. In summary, cross-sectional studies that used the IVE have not provided compelling evidence for an association specifically between Ecstasy use and higher levels of self-reported impulsivity.

CROSS-SECTIONAL STUDIES THAT USED OTHER MEASURES OF SELF-REPORTED IMPULSIVITY OR DISINHIBITION

McCann *et al.* [33] found that Ecstasy users scored significantly higher than polydrug controls on the Multidimensional Personality Questionnaire (MPQ) control scale (indicating less impulsivity in Ecstasy users), whereas Ecstasy users and polydrug controls had similar scores on the MPQ Constraint scale and impulsivity subscale of the Eysenck Personality Questionnaire. Daumann *et al.* [16] found that Ecstasy users, cannabis controls, and drug-naïve controls had similar scores on the disinhibition subscale of the Zuckerman Sensation Seeking Scale (SSS). In another study, Daumann *et al.* [20] found that Ecstasy users and mostly drug-naïve controls had similar scores on the disinhibition subscale of the SSS. Medina and Shear [34] found that Ecstasy users and cannabis controls had similar scores on the disinhibition subscale of the Frontal

Systems Behavioral Scale. Finally, Hanson *et al.* [24] found that Ecstasy users and polydrug users had similar scores on the MPQ Constraint scale and SSS disinhibition subscale. To summarize, cross-sectional studies that used other measures of self-reported impulsivity or disinhibition have consistently failed to provide evidence for an association between Ecstasy use and higher levels of impulsivity or disinhibition.

CROSS-SECTIONAL STUDIES THAT USED THE MATCHING FAMILIAR FIGURES TEST (MFFT) TO MEASURE BEHAVIORAL IMPULSIVITY

Morgan [26] recruited 41 Ecstasy users, 32 polydrug controls, and 35 drug-naïve controls. Ecstasy users reported an average lifetime use of 44 tablets of Ecstasy (calculated from the Ecstasy use information provided by Morgan in Table 3 of his article). Morgan found that Ecstasy users made significantly more errors and had significantly higher composite I scores than control participants on the MFFT (indicating greater behavioral impulsivity in Ecstasy users).

Morgan *et al.* [28] recruited 18 current Ecstasy users, 15 former Ecstasy users, 16 polydrug controls, and 15 drug-naïve controls. Current and former Ecstasy users reported an average lifetime use of approximately 303 and 512 tablets of Ecstasy, respectively (calculated from the Ecstasy use information provided by Morgan *et al.* in Table 1 of their article). Morgan *et al.* found that both current and former Ecstasy users had significantly briefer latencies to first response, made significantly more errors, and had significantly higher composite I scores than control participants on the MFFT.

Dafters *et al.* [30] recruited 16 heavy Ecstasy users, 19 light Ecstasy users, 15 cannabis controls, and 19 drug-naïve controls. Light and heavy Ecstasy users reported an average lifetime use of 20 and 364 tablets of Ecstasy, respectively. Dafters found that MFFT performance was

similar for all four groups.

Morgan *et al.* [35] recruited 20 Ecstasy users, 20 polydrug controls, and 19 drug-naïve controls. Participants were excluded if they reported serious medical problems or a history of severe mental illness. Ecstasy users reported an average lifetime use of 151 tablets of Ecstasy. Morgan *et al.* found that Ecstasy users made significantly more errors and had significantly higher composite I scores than control participants on the MFFT.

Quednow *et al.* [36] recruited 19 Ecstasy users, 19 cannabis users with minimal or no previous exposure to Ecstasy, and 19 drug-naïve controls. Participants were excluded if they had a current Axis I disorder or a family history of severe mental illness. Urine testing was used to disconfirm recent drug use only in the drug-naïve control group. Ecstasy users reported an average lifetime use of 458 tablets of Ecstasy. Most Ecstasy users reported amphetamine and hallucinogen use, whereas few cannabis users reported other illicit drug use. Quednow *et al.* found that Ecstasy users had significantly higher composite I scores than drug-naïve controls, but they failed to find a significant difference in I scores between the two drug user groups.

Five cross-sectional studies that used the MFFT to measure behavioral impulsivity in Ecstasy users have been reviewed. One study failed to find greater impulsivity in Ecstasy users in comparison to cannabis and drug-naïve controls [30]; another study found greater impulsivity in Ecstasy users in comparison to drug-naïve controls but failed to find greater impulsivity in Ecstasy users in comparison to cannabis users [36]; and three studies found greater impulsivity in Ecstasy users in comparison to polydrug and drug-naïve controls [26, 28, 35]. In summary, cross-sectional studies that used the MFFT have consistently provided evidence of greater impulsivity in Ecstasy users in comparison to polydrug and drug-naïve controls. Strangely, however, cross-sectional studies that used the MFFT have failed to provide evidence of greater

impulsivity in Ecstasy users in comparison to cannabis users.

CROSS-SECTIONAL STUDIES THAT USED A GO/NO-GO TASK TO MEASURE BEHAVIORAL INHIBITION OR IMPULSIVITY

Gouzoulis-Mayfrank *et al.* [37] recruited 28 Ecstasy users with minimal exposure to other illicit drugs besides cannabis, 28 cannabis controls, and 28 drug-naïve controls. Participants with a current or past Axis I psychiatric disorder were excluded except for drug abuse in the two drug user groups. Urine testing was used to disconfirm recent drug use. Ecstasy users reported an average lifetime use of 93 tablets of Ecstasy. Gouzoulis-Mayfrank *et al.* found that Ecstasy users and control participants had similar rates of premature reactions on the Go/No-Go task.

Fox *et al.* [38] recruited 20 Ecstasy users and 20 polydrug controls. Participants were excluded if they reported a history of psychiatric disorder, neurological problems, or alcohol dependence. Ecstasy users reported an average lifetime use of 172 pills of Ecstasy. Ecstasy users reported greater lifetime use of amphetamine, cocaine, and LSD than polydrug controls. Fox *et al.* found that Ecstasy users and polydrug controls made a similar number of distractor errors on the Go/No-Go task.

Gouzoulis-Mayfrank *et al.* [39] recruited 30 heavy Ecstasy users, 30 moderate Ecstasy users, and 30 mostly drug-naïve controls. Participants were excluded if they had a current or past Axis I disorder except for substance abuse in the Ecstasy user group. Urine testing was used to disconfirm recent drug use. Moderate and heavy Ecstasy users reported an average lifetime use of 503 and 40 pills of Ecstasy, respectively. Gouzoulis-Mayfrank *et al.* failed to find any significant group differences on the Go/No-Go task.

Hanson *et al.* [24] recruited 22 Ecstasy users and 30 polydrug users with minimal or no

exposure to Ecstasy. Ecstasy users reported an average lifetime use of approximately 72 pills of Ecstasy, and polydrug users reported an average lifetime use of approximately 2 pills of Ecstasy (calculated from the Ecstasy use information provided by Hanson *et al.* in Table 3 of their article). Hanson *et al.* found that Ecstasy users and polydrug users had a similar false alarm rate on the Go/No-Go task.

Quednow *et al.* [36] recruited 19 Ecstasy users, 19 cannabis users with minimal or no previous exposure to Ecstasy, and 19 drug-naïve controls. Urine testing was used to disconfirm recent drug use only in the drug-naïve control group. Ecstasy users reported an average lifetime use of 458 tablets of Ecstasy. Most Ecstasy users reported amphetamine and hallucinogen use, whereas few cannabis users reported other illicit drug use. Quednow *et al.* found that Ecstasy users made significantly more commission errors than cannabis users on the Go/No-Go task (indicating a lower level of behavioral inhibition or greater impulsivity in Ecstasy users). However, Ecstasy users and drug-naïve controls made a similar number of commission errors.

Five cross-sectional studies that used a Go/No-Go task to measure behavioral inhibition or impulsivity in Ecstasy users have been reviewed. Four studies failed to find evidence of greater impulsivity in Ecstasy users in comparison to control participants [24, 37-39], and one study found evidence of greater impulsivity in Ecstasy users in comparison to cannabis users but not in comparison to drug-naïve controls [36]. To summarize, cross-sectional studies that used a Go/No-Go task have consistently failed to find evidence of greater impulsivity in Ecstasy users in comparison to control participants.

STUDIES THAT USED THE CONTINUOUS PERFORMANCE TEST (CPT) TO MEASURE RESPONSE INHIBITION OR IMPULSIVITY

Moeller *et al.* [18] tested 8 heavy Ecstasy users, 8 infrequent Ecstasy users, and 20 drug-

naïve controls with a modified version of the CPT. Urine testing revealed that only two Ecstasy users had a negative drug screen, whereas all of the control participants had a negative drug screen. Heavy and infrequent Ecstasy users reported an average lifetime use of 180 and 30 doses of Ecstasy, respectively. Moeller *et al.* found that heavy Ecstasy users made a significantly higher proportion of commission errors to correct responses than drug-naïve controls on the CPT (indicating a lower level of response inhibition or greater impulsivity in heavy Ecstasy users), whereas infrequent Ecstasy users and drug-naïve controls had similar proportions of commission errors to correct responses.

Gamma *et al.* [40] recruited 16 Ecstasy users and 17 polydrug controls. Exclusion criteria included current Axis I diagnosis, past or present alcohol abuse or dependence, and past or present treatment for a psychiatric disorder. Ecstasy users reported an average lifetime use of 270 tablets of Ecstasy. Ecstasy users reported greater lifetime use of cannabis and LSD than polydrug controls. Gamma *et al.* failed to find any group differences in CPT performance.

Two cross-sectional studies that used the CPT to measure response inhibition or impulsivity in Ecstasy users have been reviewed. One study found evidence of greater impulsivity in Ecstasy users [18], and the other did not [40]. To summarize, cross-sectional studies that used the CPT to measure behavioral inhibition or impulsivity in Ecstasy users thus far have produced mixed results.

CROSS-SECTIONAL STUDIES THAT USED THE STROOP COLOR-WORD TEST TO MEASURE INHIBITION

Semple *et al.* [8] recruited two groups of male volunteers: 10 Ecstasy users and 10 polydrug controls. Exclusion criteria included having a psychiatric history, previous head injury, or neurological problems. Ecstasy users reported an average lifetime use of 672 tablets of

Ecstasy. Semple *et al.* found that the Stroop test performance of Ecstasy users and polydrug controls was similar.

Gouzoulis-Mayfrank *et al.* [37] recruited 28 Ecstasy users with minimal exposure to other illicit drugs besides cannabis, 28 cannabis controls, and 28 drug-naïve controls. Urine testing was used to disconfirm recent drug use. Ecstasy users reported an average lifetime use of 93 tablets of Ecstasy. Gouzoulis-Mayfrank *et al.* found that Ecstasy users and control participants performed similarly on the Stroop test.

Croft *et al.* [41] recruited 11 Ecstasy users and 18 cannabis users[8]. Participants were excluded if they had a psychiatric or neurological history. Ecstasy users reported an average lifetime use of 42 tablets of Ecstasy. Croft *et al.* found that Ecstasy users and cannabis users had comparable performance on the Stroop test.

Morgan *et al.* [28] recruited 18 current Ecstasy users, 15 former Ecstasy users, 16 polydrug controls, and 15 drug-naïve controls. Current and former Ecstasy users reported an average lifetime use of approximately 303 and 512 tablets of Ecstasy, respectively (calculated from the Ecstasy use information provided by Morgan *et al.* in Table 1 of their article). Morgan *et al.* failed to find any group differences in Stroop test performance.

Halpern *et al.* [42] recruited two groups of rave party attendees: 23 Ecstasy users with minimal exposure to other drugs and 16 mostly drug-naïve controls. Participants were excluded if they reported a medical illness that may influence executive functioning. Ecstasy users and mostly drug-naïve controls reported similar symptom levels of ADHD, depression, anxiety, and other psychopathology, and none of the participants met *DSM-IV* criteria for childhood conduct disorder. Halpern *et al.* employed a median split to separate Ecstasy users into 12 moderate Ecstasy users (median lifetime use = 31 occasions) and 11 heavy Ecstasy users (median lifetime

use = 100 occasions) and found that heavy Ecstasy users performed significantly worse than drug-naïve controls and moderate Ecstasy users on Stroop interference time (indicating a lower level of inhibition in heavy Ecstasy users). After adjusting for age, sex, and family-of-origin variables (e.g., family psychiatric history), heavy Ecstasy users no longer differed on Stroop test performance in comparison to drug-naïve controls, but Stroop interference time remained significantly worse in heavy Ecstasy users in comparison to moderate Ecstasy users.

Dafters [23] used a modified version of the Stroop test to measure conscious and unconscious inhibition in 18 Ecstasy users, 18 cannabis users with minimal exposure to Ecstasy and other illicit drugs, and 18 mostly drug-naïve controls. Ecstasy users reported an average lifetime use of 522 pills of Ecstasy, and cannabis users reported an average lifetime use of 4 pills of Ecstasy. Due to group differences in drug consumption, lifetime use of alcohol, cocaine, amphetamines, and tobacco were included as covariates in statistical analyses. Dafters found that interference was similar among the three groups (indicating comparable levels of conscious inhibition), whereas negative priming was significantly worse in Ecstasy users in comparison to the other two groups (indicating a lower level of unconscious inhibition in Ecstasy users).

McCann *et al.* [43] recruited 25 Ecstasy users and 23 mostly drug-naïve controls. Participants were excluded if they met diagnostic criteria for major depression, obsessive-compulsive disorder, or psychotic disorder, or if they had a history of head injury or neurological problems. Urine testing was used to disconfirm recent drug use. Ecstasy users reported an average lifetime use of approximately 287 tablets of Ecstasy (calculated from the Ecstasy use information provided by McCann *et al.* in Table 1 of their article). Most Ecstasy users also reported using cannabis, hallucinogens, cocaine, and ketamine. McCann *et al.* failed to find a group difference in Stroop test performance.

Seven cross-sectional studies that used the Stroop color-word test to measure inhibition in Ecstasy users have been reviewed. Five of these studies failed to find lower levels of inhibition in Ecstasy users in comparison to control participants [8, 28, 37, 41, 43]. Halpern *et al.* [42] initially found a lower level of inhibition in heavy Ecstasy users in comparison to moderate Ecstasy users and drug-naïve controls, but after adjusting for age, sex, and family-of-origin variables, only the difference between heavy and moderate Ecstasy users remained significant. Furthermore, Lyvers and Hasking [44] have criticized the Halpern *et al.* study for not using a corrected alpha level in making multiple comparisons between groups, which may have led to several significant findings due to chance. Finally, Dafters [23] found a similar level of conscious inhibition but a lower level of unconscious inhibition in Ecstasy users relative to cannabis users and mostly drug-naïve controls. In summary, cross-sectional studies that used the Stroop test have consistently failed to find evidence of lower levels of inhibition in Ecstasy users, although one study has suggested that differentiating between conscious and unconscious inhibition may prove worthwhile in this endeavor.

CROSS-SECTIONAL STUDIES THAT USED THE RANDOM LETTER GENERATION TASK TO MEASURE INHIBITION

Wareing *et al.* [45] recruited 10 current Ecstasy users, 10 former Ecstasy users, and 10 drug-naïve controls. Both current and former Ecstasy users reported an average lifetime use of approximately 1300 tablets of Ecstasy (calculated from the Ecstasy use information provided by Wareing *et al.* in Table 1 of their article). Wareing *et al.* found that current and former Ecstasy users made more vowel intrusions than drug-naïve controls on the random letter generation task (indicating lower levels of inhibition in the two Ecstasy user groups).

Fisk *et al.* [46] recruited 44 Ecstasy users and 59 mostly drug-naïve controls. Ecstasy

users reported an average lifetime use of 343 pills of Ecstasy. Fisk *et al.* found that Ecstasy users and mostly drug-naïve controls did not differ on random letter generation task performance.

Montgomery *et al.* [47] recruited 51 Ecstasy users and 42 mostly drug-naïve controls. Ecstasy users reported an average lifetime us of 374 tablets of Ecstasy. Montgomery *et al.* found that Ecstasy users and mostly drug-naïve controls had similar scores on the alphabetic and repeat sequences of the random letter generation task.

Three cross-sectional studies that used the random letter generation task to measure inhibition in Ecstasy users have been reviewed. Although one study found lower levels of inhibition in current and former Ecstasy users in comparison to mostly drug-naïve controls, it failed to include a polydrug control group [45]. Furthermore, two subsequent studies using larger sample sizes failed to find lower levels of inhibition in Ecstasy users in comparison to mostly drug-naïve controls [46-47]. In summary, cross-sectional studies that used the random letter generation task have failed to provide evidence for lower levels of inhibition in Ecstasy users.

CROSS-SECTIONAL STUDIES THAT USED OTHER BEHAVIORAL MEASURES OF IMPULSIVITY OR INHIBITION

Using two different behavioral tasks (i.e., the Stop Signal and Eriksen Flankers tasks), von Geusau *et al.* [48] found that male Ecstasy users and mostly drug-naïve controls had similar levels of inhibition. Reay *et al.* [49] found that Ecstasy users and mostly drug-naïve controls displayed similar performance on the Inhibition of Return task. McCann *et al.* [43] found that Ecstasy users (who also used cannabis, hallucinogens, cocaine, and ketamine) responded more quickly and less accurately than mostly drug-naïve controls on the Walter Reed Army Institute of Research Performance Assessment Battery (indicating greater impulsivity in Ecstasy users). To summarize, cross-sectional studies that used other behavioral measures of impulsivity or

inhibition have failed to provide evidence for an association specifically between Ecstasy use and higher levels of impulsivity or inhibition.

LONGITUDINAL STUDIES THAT MEASURED SELF-REPORTED IMPULSIVITY OR DISINHIBITION

Daumann *et al.* [20] initially recruited 60 Ecstasy users as part of a cross-sectional investigation. Participants were excluded if they had a current or past Axis I disorder except for substance abuse. Urine testing was used to disconfirm recent drug use. Baseline measures included the BIS and SSS. Eighteen months after the initial study, 38 of the original 60 Ecstasy users participated in a follow-up examination: 19 participants reported that they had continued to use Ecstasy over the 18-month period, and 19 participants reported that they had not continued to use Ecstasy. Participants who had continued to use Ecstasy reported an average interim use of 21 pills of Ecstasy. Daumann *et al.* compared the two groups and found no significant differences in BIS or SSS disinhibition scores.

In another longitudinal study, de Win *et al.* [50] recruited 188 Ecstasy-naïve participants who intended to use Ecstasy in the near future. Urine testing was used to disconfirm recent drug use. Baseline measures included the BIS and the Spannings Behoefte Lijst (SBL), a Dutch adaptation of the SSS. One to two years after baseline examination, 158 of the original 188 participants were administered the BIS and SBL: 64 incident Ecstasy users and 94 persistent Ecstasy-naïve participants. Incident Ecstasy users reported an average interim use of 6 tablets of Ecstasy. After correcting for baseline scores and potential confounders, de Win *et al.* found that incident Ecstasy users scored significantly higher than persistent Ecstasy-naïve participants on the disinhibition subscale of the SBL at follow-up, whereas incident Ecstasy users and persistent Ecstasy-naïve participants had similar BIS total and subscale scores.

Two longitudinal studies that measured self-reported impulsivity or disinhibition have been reviewed. One study failed to find evidence of increased impulsivity or disinhibition in Ecstasy users who continued to use Ecstasy relative to abstinent Ecstasy users [20], and the other study found evidence of increased disinhibition in incident Ecstasy users relative to persistent Ecstasy-naïve participants but failed to find evidence of increased impulsivity [50]. In summary, longitudinal studies that measured self-reported impulsivity or disinhibition in Ecstasy users thus far have failed to provide evidence of increased impulsivity and have produced equivocal results in regard to increased disinhibition.

CONCLUSION

Most cross-sectional studies that used measures of inhibition or disinhibition (associated with impulsivity) have failed to provide evidence for a relationship between Ecstasy use and lower levels of inhibition. In regard to longitudinal studies, both studies conducted thus far have failed to provide evidence of increased impulsivity in Ecstasy users, and only one study found evidence of increased disinhibition in Ecstasy users relative to Ecstasy-naïve participants. On the other hand, most cross-sectional studies that used the BIS, IVE, or MFFT have provided evidence of greater impulsivity in Ecstasy users in comparison to control participants. However, a sizeable proportion of these significant findings resulted from comparing Ecstasy users to drug-naïve or mostly drug-naïve controls. When only the cross-sectional studies that compared Ecstasy users to cannabis or polydrug controls are included, the evidence for a relationship between Ecstasy use and higher levels of impulsivity becomes much less favorable. In fact, of all the instruments that have been used to measure impulsivity in Ecstasy users, only a majority of the studies that used the MFFT have provided evidence for a relationship between Ecstasy use and greater impulsivity when held to this standard. In short, the overall evidence for an

association specifically between Ecstasy use and greater impulsivity (as opposed to a relationship between Ecstasy/polydrug use and greater impulsivity) is currently unconvincing.

Further complicating the issue is the fact that Ecstasy use studies have often suffered from methodological and interpretive weaknesses. Although some studies have used urine or blood testing to disconfirm recent drug use, many have not used objective measures of recent drug use and have instead relied solely on self-report, which may be inaccurate due to dishonesty or imperfect memory. In addition, the use of small sample sizes, usually ranging from 15 to 20 participants, has been a fairly common practice, and this practice decreases the probability of obtaining representative samples. Also, most studies have interpreted results strictly in terms of statistical significance without giving proper consideration to clinical or practical significance; for example, a 2-point difference in impulsivity scores may be statistically significant, but what are the real world implications (if any) of this 2-point difference? Future Ecstasy use studies should do a better job in general of addressing the above mentioned weaknesses because such weaknesses make it even more difficult to draw solid conclusions regarding the relationship between Ecstasy use and impulsivity.

Yet, some researchers have concluded that MDMA has likely caused elevated impulsivity in Ecstasy users. For example, Morgan [26] remarked that "it seems implausible that only individuals with high levels of behavioral impulsivity [as measured by the MFFT] would be especially predisposed to taking ecstasy…" (p. 263). Also, after finding an association between behavioral impulsivity and most tablets of Ecstasy taken on a single occasion, Quednow *et al.* [36] stated that such an association suggests that "elevated impulsivity…[is] a consequence of the MDMA intake" (p. 524). However, Lyvers and Hasking [44] have mentioned two other possibilities that seem just as likely to explain these results: the short-term residual effects of

MDMA and pre-existing impulsivity in heavy users of Ecstasy (and other drugs). In two of three MFFT studies that found evidence of greater behavioral impulsivity in Ecstasy users in comparison to polydrug controls, approximately 30-35% of Ecstasy users reported having used Ecstasy within the past week [26, 35]. Although studies using self-report measures have failed to provide evidence of increased impulsivity in Ecstasy users soon after their last use of Ecstasy [51-53], studies investigating the short-term residual effects of MDMA on behavioral impulsivity have not been conducted. Thus, it is possible that the elevated levels of behavioral impulsivity observed in these two studies were due in part to the short-term residual effects of MDMA. In support of this hypothesis, a recent double-blind placebo-controlled study [54] found that the oral administration of MDMA in humans (associated with increased serotonin flow) caused an acute decrease in behavioral impulsivity, which may indicate that the short-term residual effects of MDMA (associated with serotonin depletion) instead would result in an increase in behavioral impulsivity. Due to the current lack of knowledge concerning the potential short-term residual effects of MDMA on behavioral impulsivity (which hopefully will be addressed by future studies), researchers should require that Ecstasy users have been abstinent from Ecstasy for at least one week prior to testing. In the remaining MFFT study that found evidence of greater behavioral impulsivity in Ecstasy users in comparison to polydrug controls, current and former Ecstasy users reported an average lifetime use of approximately 303 and 512 tablets of Ecstasy, respectively [28]. As noted by Lyvers and Hasking [44], a large body of evidence has revealed that pre-drug impulsivity and deficits in executive functioning predispose individuals to the frequent use of alcohol and illicit drugs. Therefore, the reason for the association between heavy Ecstasy use and greater impulsivity in the remaining MFFT study may be that more impulsive individuals are more likely to use Ecstasy more frequently than less impulsive individuals. This

same possibility would do well to explain the findings of Quednow *et al.* [36]: More impulsive individuals may be more likely to extend a single occasion of Ecstasy use by continuing to take successive pills of Ecstasy, which may result in a higher number of Ecstasy tablets taken on a single occasion. Notably, ADHD symptoms, disruptive childhood behaviors, and Cluster B personality traits all have been associated with substance use problems [55-62], and an emerging body of evidence has suggested that genetically-linked behavioral disinhibition and impulsivity contribute to the development of childhood externalizing psychopathology, antisocial behaviors, and substance abuse [55, 59, 63-65]. Although some Ecstasy user studies have excluded participants with serious Axis I psychopathology (e.g., schizophrenia, psychosis, major depression), very few have controlled for childhood symptoms of ADHD, disruptive childhood behaviors, or Cluster B personality traits. Approximately 17% of heavy Ecstasy users in one study had a current diagnosis of ADHD [66], and 25.4% of Ecstasy users in a large community sample had a lifetime diagnosis of antisocial personality disorder (ASPD) [67]. In comparison, the estimated prevalence of current adult ADHD in the general population is 4.4% [68], and the estimated lifetime prevalence of ASPD in the general population is 3.6% [69]. In other words, based on the results of these studies, current ADHD appears to be about 4 times as prevalent in heavy Ecstasy users as in the general population, and lifetime ASPD appears to be about 7 times as prevalent in Ecstasy users as in the general population. In addition, two large-scale longitudinal studies conducted in two different countries both found a significant or nearly significant relationship between childhood delinquent behavior and later Ecstasy use [70-71]. Because childhood symptoms of ADHD, disruptive childhood behaviors, and Cluster B personality traits have been associated with impulsivity and are likely to precede Ecstasy use initiation, they routinely should be measured by researchers and included as part of an analysis of

covariance in order to reduce the effects of potential confounding variables.

With all that being said, why have some researchers so readily concluded that MDMA has likely caused elevated impulsivity in Ecstasy users? Undoubtedly, the well-evidenced ability of MDMA to cause persistent 5-HT deficits in rats and non-human primates and the known role of 5-HT neurotransmission in the regulation of impulsivity together create quite an intuitive appeal for the idea that Ecstasy use likely causes long-term increases in impulsivity. However, the experimental evidence for increased impulsivity in rats following MDMA administration has been mixed, with one study finding evidence of increased impulsivity [72], one study failing to find evidence of increased impulsivity [73], and one study finding evidence of both increased and decreased impulsivity [74]. Finally, the evidence for increased impulsivity in non-human primates following MDMA administration has been nonexistent.

In conclusion, it would be premature to speculate that Ecstasy use likely causes increased impulsivity. Furthermore, even if future cross-sectional studies provide stronger evidence for a relationship specifically between Ecstasy use and higher levels of impulsivity, this does not mean necessarily that MDMA has caused increased impulsivity. One alternative explanation for this phenomenon is that more impulsive individuals may use Ecstasy more frequently than less impulsive individuals. Perhaps future longitudinal studies spanning from childhood to adulthood will inform us on the relationship between childhood impulsivity and Ecstasy use. Also, future longitudinal studies spanning from pre- to post-Ecstasy use may further inform us on if changes in impulsivity typically occur subsequent to Ecstasy use initiation and as Ecstasy use continues. As it currently stands, however, the bulk of the evidence has not supported an association specifically between Ecstasy use and higher levels of impulsivity, although an association between heavy drug use and higher levels of impulsivity has been well-documented.

Notes

[1] Because Ecstasy users typically use other illicit drugs, it can be assumed that the phrase "Ecstasy users" refers to Ecstasy/polydrug users unless otherwise specified.

[2] Behavioral measures related to impulsivity have variously been described as measures of impulsivity, inhibition, behavioral impulsivity, behavioral inhibition, response inhibition, and cognitive impulsivity.

[3] The phrase "cannabis controls" refers to individuals who have had minimal or no exposure to illicit drugs besides cannabis.

[4] The phrase "drug-naïve controls" refers to individuals who have not used illicit drugs.

[5] The phrase "mostly drug-naïve controls" refers to an Ecstasy-naïve group in which the majority of individuals have not used illicit drugs.

[6] The phrase "polydrug controls" refers to Ecstasy-naïve polydrug users.

[7] Hanson *et al.* [24] also recruited drug-naïve controls but did not report individual comparisons between drug-naïve controls and the two drug user groups; drug–naïve controls were compared only to a combined drug user group. Therefore, information regarding drug-naïve controls is not included here.

[8] Croft *et al.* [41] also recruited drug-naïve controls but did not report individual comparisons between drug-naïve controls and the two drug user groups; drug-naïve controls were compared only to a combined drug user group. Therefore, information regarding drug-naïve controls is not included here.

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