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The Effect of Catecholamine Depletion by Alpha-Methyl-Para-Tyrosine on Measures of Cognitive Performance and Sleep in Abstinent MDMA Users

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(±) 3, 4-Methylenedioxymethamphetamine (MDMA) is a popular recreational drug of abuse and a brain serotonin (5-HT) neurotoxin in animals. Growing evidence suggests that humans who use MDMA recreationally can also develop 5-HT neurotoxic injury, although functional consequences have been difficult to identify. Twenty-five abstinent MDMA users and 23 non-MDMA using controls were studied to determine whether pharmacologic depletion of brain catecholamines by alpha-methyl-para-tyrosine (AMPT) would differentially effect MDMA users on measures of cognition and sleep, two processes dually modulated by brain serotonergic and catecholaminergic neurons. During a 5-day in-patient study, all subjects underwent formal neuropsychiatric testing, repeated computerized cognitive testing, and all-night sleep studies. At baseline, MDMA users had performance deficits on tasks of verbal and visuospatial working memory and displayed increased behavioral impulsivity on several computerized tasks, reflecting a tendency to perform quickly at the expense of accuracy. Baseline sleep architecture was also altered in abstinent MDMA users compared to controls. AMPT produced differential effects in MDMA users compared to controls on several cognitive and sleep measures. Differences in cognitive performance, impulsivity, and sleep were significantly correlated with MDMA use. These data extend findings from earlier studies demonstrating cognitive deficits, behavioral impulsivity, and sleep alterations in abstinent MDMA users, and suggest that lasting effects of MDMA lead to alterations in the ability to modulate behaviors reciprocally influenced by 5-HT and catecholamines. More research is needed to determine potential relationships between sleep abnormalities, cognitive deficits and impulsive behavior in abstinent MDMA users.

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INTRODUCTION

Evidence that (±) 3, 4-methylenedioxymethamphetamine (MDMA) can produce a lasting loss of brain serotonin (5-HT) axonal markers in animals first appeared two decades ago (Schmidt *et al*, 1986; Stone *et al*, 1986). Since that time, numerous laboratories have confirmed and extended these initial findings (see Steele *et al*, 1994; Gudelsky and Yamamoto, 2003). Taken together, the available data support the view that MDMA has the potential to damage brain 5-HT axon terminals.

There are also data suggesting that MDMA has the potential to damage 5-HT neurons in humans. Early studies demonstrated that MDMA users, like MDMA-treated monkeys with documented serotonergic injury (Ricaurte *et al*, 1988), have selective deficits in cerebrospinal fluid measures of 5-hydroxyindoleacetic acid (McCann *et al*, 1994), the major metabolite of 5-HT. Subsequent studies using positron emission tomography (PET) and single photon emission computed tomography with radioligands that bind to the 5-HT transporter revealed that MDMA users, compared to non-MDMA-using controls, have reductions in 5-HT transporter density (McCann *et al*, 1998, 2005; Semple *et al*, 1999; Reneman *et al*, 2001; Buchert *et al*, 2003, 2004; Thomasius *et al*, 2006). There is also PET evidence suggesting that, as has been shown in non-human primates (Scheffel *et al*, 1998; Hatzidimitriou *et al*, 1999), some brain regions of MDMA users recover with prolonged abstinence (Buchert *et al*, 2003, 2004; McCann *et al*, 2005). It is not yet known whether regions that are less likely to recover from neurotoxic insult in animals (eg hippocampus, dorsal neocortex) are also less likely to recover in humans.

Despite strong evidence that MDMA is a 5-HT neurotoxin, it has been exceedingly difficult to identify functional consequences directly linked to serotonergic neural injury.

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The most consistently observed clinical deficit that has been reported in human MDMA users has been cognitive dysfunction, particularly in the areas of short-term memory (Krystal *et al*, 1992; Bolla *et al*, 1998; McCann *et al*, 1999; Rodgers, 2000; Morgan, 2000; Parrott, 2000; Zakzanis and Young, 2001; Verkes *et al*, 2001) and, possibly, certain tasks of executive functioning (Heffernan *et al*, 2001; von Geusau *et al*, 2004; Dafters, 2006). However, findings have not always been consistent (Croft *et al*, 2001; Gouzoulis-Mayfrank *et al*, 2000; Simon and Mattick, 2002; Thomasius *et al*, 2003). A major challenge in research addressing potential cognitive effects of MDMA users is the fact that these individuals commonly use other recreational drugs that may negatively impact cognitive function, particularly marijuana (Bolla *et al*, 2002, 2005). Unfortunately, much of the cognitive data collected in MDMA users has not included testing for presence of illicit drugs at the time of testing, and has not required subjects to remain abstinent for more than several days before testing. These methodological shortcomings limit the strength of conclusions that can be drawn regarding lasting effects of MDMA on cognitive function.

Other clinical and physiological abnormalities that have been reported in MDMA users include impulsivity (Morgan *et al*, 2006; Quednow *et al*, 2007), neuroendocrine dysfunction (Gerra *et al*, 1998, 2000, 2003; McCann *et al*, 2000; Verkes *et al*, 2001), alterations in pain modulation (O'Regan and Clow, 2004), sleep architecture (Allen *et al*, 1993; Ricaurte and McCann, 2001), visual-evoked potentials (Casco *et al*, 2005), and event-related potentials (Mejias *et al*, 2005). Like cognitive function, all of these behavioral spheres are known to be influenced, in part, by brain 5-HT systems. However, the role of 5-HT in these behavioral differences in MDMA users has not been established.

In addition to widespread polysubstance use in MDMA users, a major challenge in interpreting data collected in MDMA users is the fact that lesions produced by MDMA are not likely to be static, given preclinical data demonstrating recovery of 5-HT axon terminals in some brain regions. Thus, depending upon the duration of MDMA use, abstinence from drug, and nature of MDMA exposure, subjects are likely to vary with regard to compensatory mechanisms for various brain functions and/or degree of recovery. Although it could be argued that the development of compensatory mechanisms diminishes the clinical importance of MDMA-induced neurotoxicity, an alternative view is that MDMA-induced lesions produce a brain milieu of diminished functional reserve that may become clinically apparent under various forms of stress. One method that has proved useful for unmasking such 'subclinical' deficits in animals treated with neurotoxic doses of MDMA has been the use of pharmacological challenge (Poland *et al*, 1997; Virden and Baker, 1999; Shankaran and Gudelsky, 1999; Gardani *et al*, 2005). The foregoing studies demonstrate that animals with MDMA-induced lesions that exhibit normal behaviors or physiology at baseline have abnormal thermal, behavioral and circadian responses to pharmacological challenges with drugs that influence these 5-HT-mediated functional domains.

In the present study, we sought to determine whether transient disruption of brain catecholaminergic neurotransmission with the catecholamine synthesis inhibitor alpha-methyl-para-tyrosine (AMPT) would differentially influence cognitive function and sleep architecture of MDMA users. The rationale for this approach is based on the fact that there are known reciprocal serotonergic, dopaminergic, and noradrenergic interactions (Millan *et al*, 2000; Esposito, 2006), and these play an essential role in working memory and executive function as well as arousal and alertness (Robbins, 2005). Although the precise nature of catecholaminergic/serotonergic interactions with regard to cognitive function and sleep are not fully understood, recent studies in healthy humans indicate that simultaneous acute depletion of brain catecholamines and 5-HT leads to deficits in sustained attention that are not observed following depletion of catecholamines or 5-HT alone (Harrison *et al*, 2004; Matrenza *et al*, 2004). Similarly, Although the exact mechanisms by which catecholamines and 5-HT modulate sleep are not fully understood, it has been hypothesized that a dynamic balance between the various monoaminergic systems underlies the normal sleep–wake cycle (Gottesman, 2004). Therefore, in the present study, we reasoned that transient disruption of brain catecholaminergic neurotransmission with AMPT might lead to more pronounced changes in cognitive function and sleep in individuals with a history of recreational MDMA use, in whom 5-HT deficits are suspected (McCann *et al*, 1994, 1998, 2005; Semple *et al*, 1999; Reneman *et al*, 2001; Verkes *et al*, 2001; Buchert *et al*, 2003, 2004; Thomasius *et al*, 2006).

SUBJECTS AND METHODS

Subjects

Subjects were recruited by advertisements posted in newspapers, fliers, and the worldwide web. Some subjects were referred by participants who had previously participated in the protocol. Interested potential subjects underwent a telephone screen, and those subjects who appeared to meet inclusion criteria were invited to come for a face-to-face screening. Screening tools included assessment for Axis I psychiatric diagnoses using the Structured Interview for DSM-IV Axis I disorders (First *et al*, 1997), a physical examination and routine blood and urine chemistries. All subjects underwent urine drug screens for illicit drugs, and female subjects underwent urine pregnancy tests. To be included in the MDMA subject group, individuals needed to report that they had used MDMA on at least 25 separate occasions (on each 'occasion' subjects often took more than one dose, over several hours). MDMA use in these subjects outweighed all other illicit drug use. Indeed, aside from MDMA and marijuana, other drugs use did not meet DSM-IV criteria for abuse. Control subjects reported that they had never previously used MDMA, but were not excluded if they had used other recreational drugs. All subjects were in good general health. Exclusionary criteria included presence of an Axis I diagnosis in which brain 5-HT has been implicated (eg major depression, obsessive compulsive disorder, schizophrenia), psychosis, history of head injury, use of psychotropic medications (aside from illicit drugs), and any neuropsychiatric condition that is known to lead to cognitive impairment. All subjects agreed to refrain from drug and alcohol use for at least 1 week before study

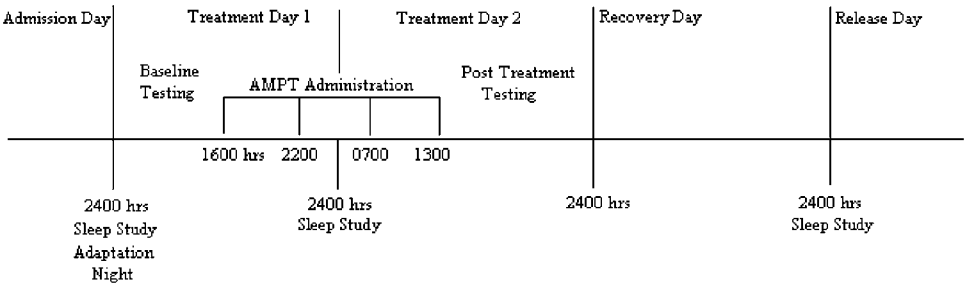

Figure 1 Schematic diagram of study timeline.

participation (with the exception of nicotine-containing cigarettes and caffeine). The study was approved by the Johns Hopkins Medicine Institutional Review Board and the Johns Hopkins Bayview Medical Center General Clinical Research Center Advisory Board. All subjects provided written informed consent.

Subjects who passed their initial screens and who provided informed consent were admitted to the Johns Hopkins Bayview Medical Center General Clinical Research Center (GCRC) for a 5-day/4-night in-patient admission. During this period, subjects underwent baseline and repeated cognitive assessments and all-night sleep polysomnographic testing. Testing took place before and after pharmacological challenge with AMPT. A schematic diagram of procedures is provided in Figure 1.

AMPT Regimen

Subjects received four, oral 1 g doses of AMPT, beginning at 1600 hours on the second day of admission, and ending at 1300 hours on the third day of admission. Serum prolactin concentrations were used as an indicator of AMPT's efficacy in reducing brain dopamine levels. In particular, because dopamine is a tonic inhibitor of prolactin, depletion of brain dopamine levels should result in increased plasma prolactin concentrations. Three blood samples were collected over 1 h on day 1 of admission, and an additional three blood samples were collected during the afternoon of day 3 of admission, during the anticipated time of peak dopamine depletion. Blood samples were immediately placed on ice, were centrifuged at 3600 r.p.m. for separation of plasma from cells, and plasma samples were stored at -70°C until analysis by radioimmunoassay. Concentrations of the three plasma prolactin values at each of these two times were averaged to obtain 'baseline' and 'post-AMPT' measures of serum prolactin.

Neurocognitive Testing

At baseline, subjects underwent formal neurocognitive testing using a standard neuropsychiatric battery containing the following tests: the Wisconsin Card Sorting Test (Berg, 1948) a test of executive function requiring abstraction and mental flexibility, the Stroop Color-Word Test (Stroop, 1935), another test of executive function that requires attention and response inhibition; the Trail Making Test (A and B) (Reitan and Wolfson, 1993), a test of visuoconceptual and visuomotor tracking; the Wechsler Memory Scale-III (Wechsler, 1987) a battery of memory tasks; the Wechsler Adult Intelligence Scales-III Vocabulary subtest, and the New Adult Reading Test-Revised (Wechsler, 1981), two tests that provide estimates of verbal intelligence and that are relatively insensitive to the effects of neurotoxicants (such as lead) and of aging, and are better predictors of neurobehavioral performance than level of education (Bolla *et al*, 1998); the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964; Taylor, 1959), a measure of both short-term and longer-term retention following interpolated activity; and the Rey Osterrieth Complex Figure Test, a measure of immediate and delayed visual memory. As a measure of gross motor activity, subjects wore wrist-mounted activity monitors (Actitrac, IM Systems, Baltimore) during their entire stay at the GCRC.

Computerized Cognitive Performance Assessment Battery

Subjects also underwent repeated cognitive testing during their 5-day admission using the Walter Reed Army Institute of Research Performance Assessment Battery (WRAIR PAB; Thorne *et al*, 1985). The WRAIR PAB is a computerized psychological test battery designed to examine the effects of assorted state-variables on a representative sample of psychomotor, perceptual and cognitive tasks. The battery, in various versions, has been used to study the effects of sleep deprivation (Thorne *et al*, 1985), stimulants (Newhouse *et al*, 1989) catecholamine depletion (McCann *et al*, 1992) sustained performance, jet lag, heat stress, physical fatigue, physical conditioning, atropine, hypoxia, and sickle cell disease on cognitive performance (Thorne *et al*, 1985). We have previously found abstinent MDMA users to differ from controls on several WRAIR PAB tasks when tested over a 5-day period (ie in the absence of pharmacological challenge). As the WRAIR PAB is specifically designed to be repeatedly administered, and has been found to be sensitive to the effects of AMPT (McCann *et al*, 1992), it seemed well suited for the current study.

The version of the WRAIR PAB used in this study contained seven tasks, including: the Time Wall Task, a time estimation task; the Serial Add and Subtract Test, a machine-paced mental arithmetic task requiring sustained attention; the Logical Reasoning Task, a self-paced task of semantic recognition and transformational grammar; the Manikin Task, a visuospatial rotation task that tests the ability to mentally manipulate objects and determine the orientation of a specific stimulus; a Code Substitution task, a subject-paced complex attention and incidental learning task similar to the Digit Symbol Task on the Wechsler

Intelligence Scale (Wechsler, 1981); a Matching to Sample Task, a machine-paced visual discrimination and working memory task: and a Delayed Recall Test, a test of recent memory.

Subjects performed WRAIR PABs three times each of the first 4 days of admission, and twice on the final day of admission. Based upon previous experience with the WRAIR PAB (McCann *et al*, 1992), the first three PABs were interactive sessions that were used to ensure that subjects adequately understood each of the seven tasks, and were not used in statistical analyses.

Sleep Recordings

Routine sleep EEG recordings were obtained on Nights 1 (pre-AMPT), 3 (post-AMPT), and 4 (recovery from AMPT) using two channels for eye movements, four EEG channels, (C4–A1, C3–A2, O1–A2, O2–A1) and one submental EMG channel. Recordings were visually scored by two independent raters for all sleep stages following the standard Rechtschaffen and Kales procedures (Rechstaffen and Kales, 1968). Technicians responsible for scoring polysomnograms were blinded to whether subjects were MDMA users or controls.

Statistical Analyses

Neuropsychiatric testing measures. Baseline neuropsychiatric test scores were compared by ANCOVA with MDMA status as the between-groups factor and gender as the covariate. Significance was set at $p \leqslant 0.05$. When significant differences between groups were observed, exploratory correlational analyses were conducted to examine potential relationships between MDMA and/or marijuana use on test performance were explored by Pearson's product moment correlation. In particular, potential relationships between test scores and MDMA use (total estimated dose, frequency of use, time since last use) and marijuana use (frequency of use, duration of use, time since last use) were performed to determine the potential relationship between drug use and test performance. Because correlational analyses were exploratory, significance was set at a level of $p \leqslant 0.05$, with no correction for multiple comparisons. These analyses were conducted using SPSS for Windows, Release 14 (Chicago, IL).

WRAIR PAB measures. Accuracy, Speed, and Impulsivity Factor (defined below) measures on the WRAIR PAB were compared by a ProcMix repeated measures ANCOVA, with gender as covariate, and MDMA status as the between group variable and time as within subject variables. For each subject an 'impulsivity factor' for each task over time was determined using a modification of a method originally established by Salkind and Wright (1977) for use in a Matching to Familiar Figures Task. In the current version, the impulsivity factor was defined as: 1−(mean percent accuracy−mean speed per question). This factor results in high scores when an individual performs quickly and inaccurately, and a low score when they perform slowly and accurately. When significant effects of Group, Phase or Time, or significant Group × Time interactions were observed, *post hoc*-independent sample *T*-tests (two-way) were conducted to determine if there were significant differences at individual time points. Significance was set at $p \leqslant 0.05$. These analyses were conducted using SAS (Cary, NC).

Sleep architecture. Sleep variables in MDMA users and controls were compared with a ProcMix repeated measures ANCOVA, with MDMA status as the between groups variable, gender as covariate, and time as the within subjects variable. Significance was set at $p \leqslant 0.05$. These analyses were conducted using SAS (Cary, NC). When a significant or near-significant main effect of Group or Group × Time and/or Phase interaction was found, *post hoc*-independent *T*-tests (two-way) were conducted on individual nights to further explore the nature of the effect. In addition, when a significant group difference in a baseline sleep architecture parameter was found, exploratory correlational analyses between MDMA and marijuana use patterns and sleep architecture parameters were conducted. In particular, potential relationships between sleep parameters and MDMA use (total estimated dose, frequency of use, time since last use, typical dose) and marijuana use (frequency of use, duration of use, time since last use) were performed to determine the potential relationship between drug use and changes in sleep architecture. As above, these exploratory analyses were not corrected for multiple comparisons. Correlational analyses were conducted using SPSS (Chicago, IL).

Prolactin

Baseline and Post-AMPT plasma prolactin concentrations were compared by one-way ANOVA. Significance was set at $p \leqslant 0.05$. Analyses were conducted using SPSS (Chicago, IL).

RESULTS

Demographics

Twenty-five MDMA subjects (17 males; eight females) and 23 controls (nine males; 14 females) completed the 5-day inpatient study. Demographics and drug use histories are shown in Table 1. Subjects were well matched with regard to age and level of education. There were no differences between the two groups in measures of estimated baseline intelligence, as reflected by scores on the Wechsler Adult Intelligence Scales-III Vocabulary subtest (MDMA = 44.44 ± 8.27; Control = 40.39 ± 10.45), and the New Adult Reading Test-Revised (Wechsler, 1981) (MDMA = 102.74 ± 8.81; Control = 99.38 ± 7.52). MDMA users, as a group, had previously used more types of recreational drugs than control subjects. However, except for marijuana, no other drug used by MDMA subjects met criteria for abuse. No subject had positive drug screens at the time of admission to the study, with the exception of a few subjects in whom the marijuana screen was positive because marijuana can persist in the urine for more than 3 weeks after last use (subjects were asked to refrain from illicit drug use for 7 days before admission). In particular, five of the 25 MDMA users and no controls had positive marijuana screens on admission; each of these five MDMA subjects reported smoking marijuana within the past 3 weeks but not within the past 7 days.

Baseline Neuropsychiatric Testing

Baseline neuropsychiatric testing revealed that MDMA users, compared to controls, had decreased performance on six subtests in Wechsler Memory Scale-III (Table 2), all related to verbal recall. In particular, MDMA users had poorer recall of specific items included in stories that had been read to them, as well as poorer recall of themes in the same stories. Interestingly, the second time that MDMA users heard a story and were asked to recall items in the story, they improved to the level of controls, as reflected in a significantly higher 'learning slope'. Memory impairments in MDMA users were seen both for specific items of information in the story, as well as themes in the story. No other significant differences were seen on baseline neuropsychiatric performance.

Table 1 Subject Demographics

	MDMA ($N=25$)	Control ($N=23$)
Gender	8 female, 17 male	14 female, 9 male
Average age	22.08	25.69
Average years of education	12.54	13.69
MDMA exposure		
Number of exposures	112.3 (range 30–324)	NA
Duration of use (in years)	2.72 years ± 2.14 months (range 5 months–11 years)	NA
Frequency of use (exposures per month)	3.99 ± 2.78 (range 1–14.28)	NA
Usual dose (in pills)	2.56 ± 2.12 (range 1–12)	NA
Maximum dose (in pills)	7.88 ± 7.47 (range 1–36)	NA
Time since last use (in months)	3.09 ± 6.92 (range 0.75–36)	NA
Lifetime 'other drug' exposure; number (%)		
Marijuana	24 (96)	8 (34)
Hallucinogens	20 (80)	1 (0.4)
Cocaine	13 (52)	2 (0.8)
Opioids	11 (44)	0
Sedatives	5 (20)	1 (0.4)
Ketamine	13 (52)	0
Inhalants	8 (32)	0

Exploratory correlational analyses revealed significant relationships between total estimated lifetime MDMA use, frequency of MDMA use and all of the verbal memory deficits found (Table 3). No relationship between MDMA use and learning slope, described above, was noted. Duration of abstinence was found to be significantly related to only one task (and, ironically, suggested that performance is worse with increased duration of abstinence).

In contrast to findings with MDMA, no relationships between marijuana use (frequency of marijuana use, duration of use, time since last use) and verbal memory test scores were found (Table 3).

Computerized Cognitive Testing

A number of differences between MDMA users and controls were seen on repeated cognitive testing with the WRAIR PAB battery. These are summarized below, according to each of the three aspects of performance that were assessed (ie accuracy, speed, and impulsivity):

Accuracy. A significant effect of Group was seen on the Matching to Sample task ($F(1,45)=7.07$, $p=0.01$), with MDMA users performing more poorly on this working visual memory task than controls (Figure 2, top panel). Group × Time interactions were seen on the Code Substitution Task, ($F(10,444)=1.99$, $p=0.03$) (Figure 3, top panel), the Delayed Recall Task ($F(10,436)=1.86$, $p=0.05$) (Figure 4, top panel), and the Manikin Task ($F(10,454)=2.67$, $p=0.03$) (not shown), again reflecting poorer performance in MDMA users, as well as a differential effect of AMPT in MDMA users leading to more pronounced deficits on all three tasks. A significant effect of Time was seen for the Matching to Sample Task ($F(10,443)=2.01$, $p=0.031$) (Figure 2, top panel) and the Logical Reasoning Task (data not shown), reflecting a combined effect of improvement with practice and decreased accuracy following AMPT in both groups.

Speed. A significant effect of Group was seen on the Matching to Sample Task (with MDMA users answering questions more quickly than controls; $F(1,45)=7.15$, $p=0.010$) (Figure 2, middle panel), and there were significant effects of Time on the Matching to Sample ($F(10,454)=3.35$ $p<0.000$) (Figure 2, middle panel), Code Substitution ($F(10,454)=1.91$, $p=0.042$) (Figure 3, middle panel), Delayed Recall ($F(10,454)=3.03$, $p=0.001$) (Figure 4, middle panel), and Logical Reasoning ($F(10,$

Table 2 Scores on Wechsler Memory Scale-III Subtests in MDMA Users and Controls

	MDMA ($N=25$) Mean ± SD	Control ($N=23$) Mean ± SD
WMS, Logical Memory 1, Story A Recall Unit Score	13.12 ± 4.35**	16.6 ± 2.84
WMS, Logical Memory 1, Story B 1st Recall Unit Score	10.32 ± 3.82**	13.3 ± 2.86
WMS, Logical Memory 1, 1st Recall Total Score (Stories A and B1)	23.44 ± 7.17**	29.19 ± 4.86
WMS, Logical Memory 1, Recall Total Score (Sum Recall Unit Scores Story A, B1, B2)	39.72 ± 10.52*	46.56 ± 6.84
WMS, Logical Memory 1, Learning Slope	5.92 ± 2.75*	4.3 ± 1.96
WMS, Logical Memory 2, Story A Recall Unit Score	10.24 ± 4.8*	13.74 ± 3.94

*Significant difference from comparison group at level $p<0.05$.
**Significant difference from comparison group at level $p<0.01$.

Table 3 Relationship between Wechsler Memory Scale-III Subtest Scores and MDMA and Marijuana Use Parameters

	Total dose MDMA	Frequency MDMA use	Duration MDMA abstinence	Frequency MJ use	Duration MJ use	Duration MJ abstinence
WMS, Logical Memory 1, Story A Recall Unit Score	$r=-0.34$; $p<0.05$	$r=-0.47$; $p<0.001$	$r=-0.22$; NS	$r=-0.11$; NS	$r=0.09$; NS	$r=0.21$; NS
WMS, Logical Memory 1, Story B 1st Recall Unit Score	$r=-0.33$; $p<0.05$	$r=-0.31$; $p<0.05$	$r=-0.22$; NS	$r=-0.14$; NS	$r=0.18$; NS	$r=0.07$; NS
WMS, Logical Memory 1, 1st Recall Total Score (Stories A and B1)	$r=-0.38$; $p<0.05$	$r=-0.44$; $p<0.005$	$r=-0.10$; NS	$r=-0.14$; NS	$r=0.15$; NS	$r=0.10$; NS
WMS, Logical Memory 1, Recall Total Score (Sum Recall Unit Scores Story A, B1, B2)	$r=-0.34$; $p<0.05$	$r=-0.36$; $p<0.05$	$r=-0.18$; NS	$r=-0.09$; NS	$r=0.16$; NS	$r=-0.06$; NS
WMS, Logical Memory 1, Learning Slope	$r=0.98$; NS	$r=.18$; NS	$r=0.10$; NS	$r=0.02$; NS	$r=-0.10$; NS	$r=-0.03$; NS
WMS, Logical Memory 2, Story A Recall Unit Score	$r=-0.32$; $p<0.05$	$r=-0.50$; $p<0.001$	$r=-0.31$; $p<0.05$	$r=0.08$; NS	$r=0.07$; NS	$r=0.13$; NS

NS = not significant.

454) = 1.97, $p = 0.035$) (not shown). The nature of these effects was complex and depended upon the phase of the study and subject group. Control subjects tended to increase speed with practice, maintain the same speed following AMPT, and have a rebound increase in speed following AMPT cessation. In contrast, MDMA users had a paradoxical increase in speed on some tasks following AMPT treatment (eg Matching to Sample), and a more pronounced rebound in speed following AMPT discontinuation on others (eg Code Substitution, Delayed Recall).

Impulsivity. As indicated above (see Subjects and Methods), impulsivity behavior was defined as: 1−(mean percent accuracy−mean speed per question). Main effects of Group were seen on the Matching to Sample ($F(1,45) = 6.66$, $p = 0.013$) (Figure 2, lower panel) Code Substitution ($F(1,45) = 7.59$, $p = 0.025$) (Figure 3, lower panel), and Delayed Recall ($F(1,45) = 9.95$, $p = 0.003$) (Figure 4, lower panel). Notably, in all cases, MDMA users tended to respond more quickly and less accurately than controls, resulting in a higher impulsivity factor. Main effects of time were seen on the Code Substitution ($F(10,444) = 2.78$, $p = 0.003$), Delayed Recall ($F(10,431) = 2.61$, $p = 0.004$), Logical Reasoning ($F(10,435) = 3.04$, $p = 0.001$), Matching to Sample ($F(10,443) = 3.92$, $p < 0.001$), and Serial Add and Subtract Tasks ($F(10,440) = 1.10$, $p = 0.046$). As noted above, on several tasks (ie Code Substitution, Delayed Recall, Matching to Sample) MDMA users had a paradoxical increase in speed following AMPT treatment and/or discontinuation. As previously noted, increases in speed were associated with decrements in accuracy on the same task.

Sleep Measures

Comparisons of sleep architecture measures revealed significant differences between MDMA users and controls at baseline (Night 1), with MDMA users having less Stage 2 sleep ($p = 0.003$) and more Stage 1 sleep ($p = 0.05$) than controls (Table 4). There were also trends suggesting decreased Total Sleep ($p = 0.06$) and decreased REM latency ($p = 0.09$) in MDMA users (Table 4). Repeated measures ANCOVA covarying for gender revealed a significant group effect on measures of Stage 2 sleep ($F(1,46) = 7.13$, $p = 0.01$), with MDMA users having less Stage 2 sleep on Nights 1 and 3 of sleep (ie before and after cessation of AMPT administration; Figure 5). AMPT administration led to significant changes in all sleep measures except for Stage 1 and Slow Wave Sleep, as reflected by a significant effect of night on Total Sleep ($F(2,78) = 27.83$, $p < 0.0001$), Sleep Efficiency ($F(2,78) = 22.94$, $p < 0.0001$), Sleep Latency ($F(2,78) = 13.12$, $p < 0.0001$), REM Latency ($F(2,77) = 6.28$, $p < 0.003$), Waking After Sleep Onset ($F(2,78) = 23.64$, $p < 0.0001$), Stage 2 ($F(2,78) = 28.39$, $p < 0.0001$), and REM ($F(2,76) = 32.17$, $p < 0.0001$). In most cases, the effects of AMPT on sleep architecture were similar for the two groups. However, differential effects of AMPT were observed on measures of sleep latency (Figure 6) and REM latency (Figure 7) as reflected by Group × Night interactions ($F(2,78) = 3.44$, $p < 0.04$) and ($F(2,77) = 3.24$, $p < 0.05$), respectively. With regard to Sleep Latency, differences between the groups were most pronounced during recovery sleep, with greater increases in sleep latency in controls than in MDMA users (Figure 6). With regard to REM latency, AMPT treatment led to increased REM latency in MDMA users and decreased REM latency in controls relative to baseline, during recovery sleep (Figure 7).

Exploratory correlational analyses between Stages 1 and 2 sleep (ie the baseline sleep measures on which MDMA users and controls differed significantly) and MDMA use patterns were conducted. Significant relationships between MDMA use and sleep architecture changes were found. In particular, consistent with the hypothesis that exposure to MDMA is related to reductions in Stage 2 sleep, significant negative correlations were found between time spent in Stage 2 and total lifetime dose of MDMA ($r = -0.30$, $p = 0.04$), and duration of MDMA use ($r = -0.36$, $p = 0.01$). Conversely, as would be predicted if increases in Stage 1 are related to MDMA use, positive correlations were found between time spent in Stage 1 total lifetime dose of MDMA ($r = 0.33$, $p < 0.03$), and duration of MDMA use ($r = 0.39$, $p < 0.01$). A negative relationship between Stage 2 sleep and duration of abstinence was found ($r = -0.36$, $p < 0.02$),

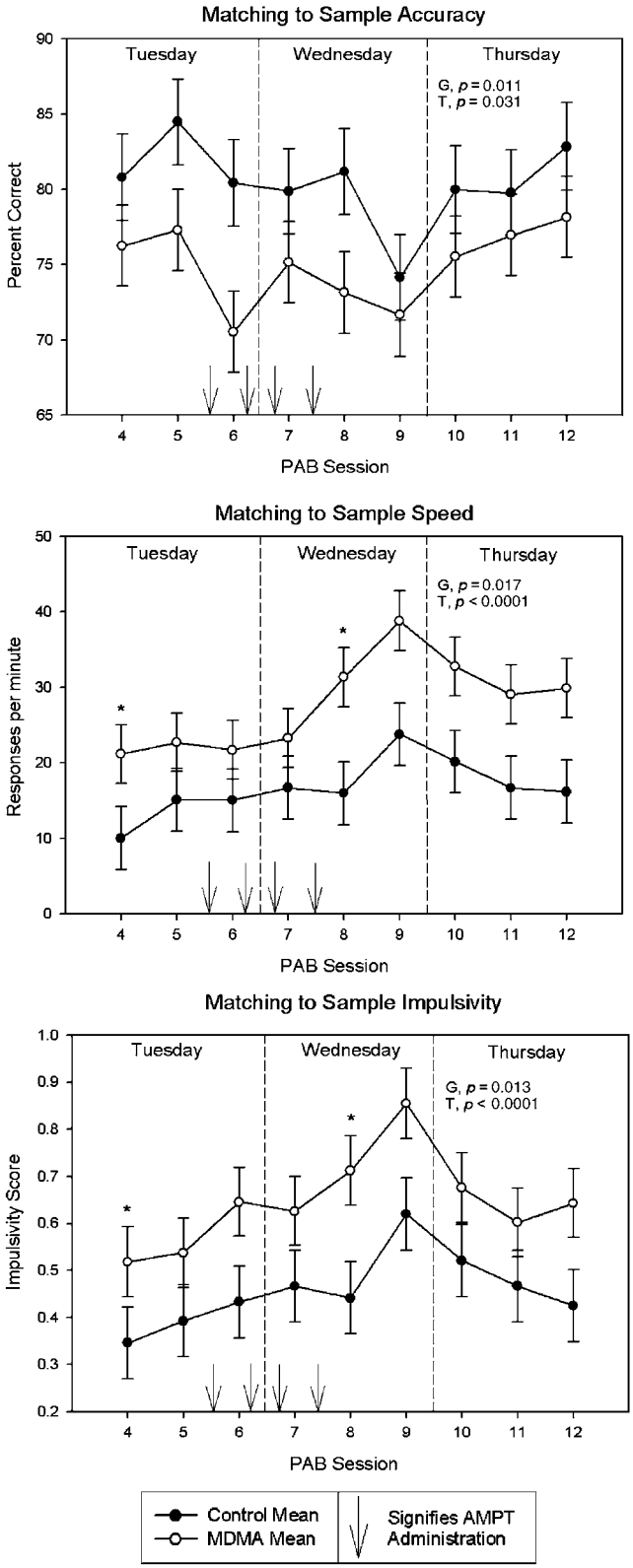

Figure 2 Accuracy, speed and impulsivity scores on a Matching to Sample Task in MDMA users and controls before, during, and after AMPT administration. Scores were compared using a repeated measure ANCOVA (covarying for gender). When significant main effects of Group, or Group × Time interactions were noted, *post hoc T*-tests (two-way) were conducted at individual time points to further evaluate the nature of the effect. Values shown represent mean (±SEM). *Signifies $p \leqslant 0.05$.

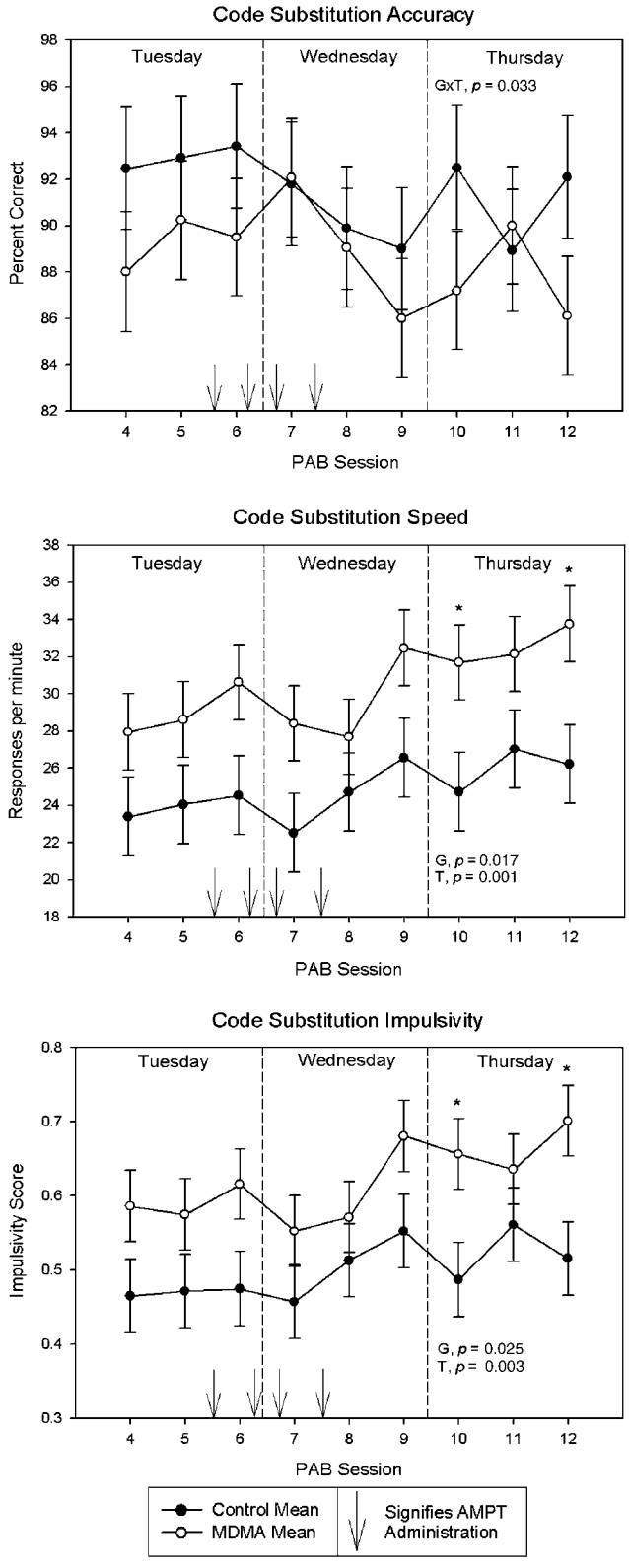

Figure 3 Accuracy, speed, and impulsivity scores on a Code Substitution Task in MDMA users and controls before, during and after AMPT administration. Scores were compared using a repeated measure ANCOVA (covarying for gender). When significant main effects of Group, or Group × Time interactions were noted, *post hoc T*-tests (two-way) were conducted at individual time points to further evaluate the nature of the effect. Values shown represent mean (±SEM). *Signifies $p \leqslant 0.05$.

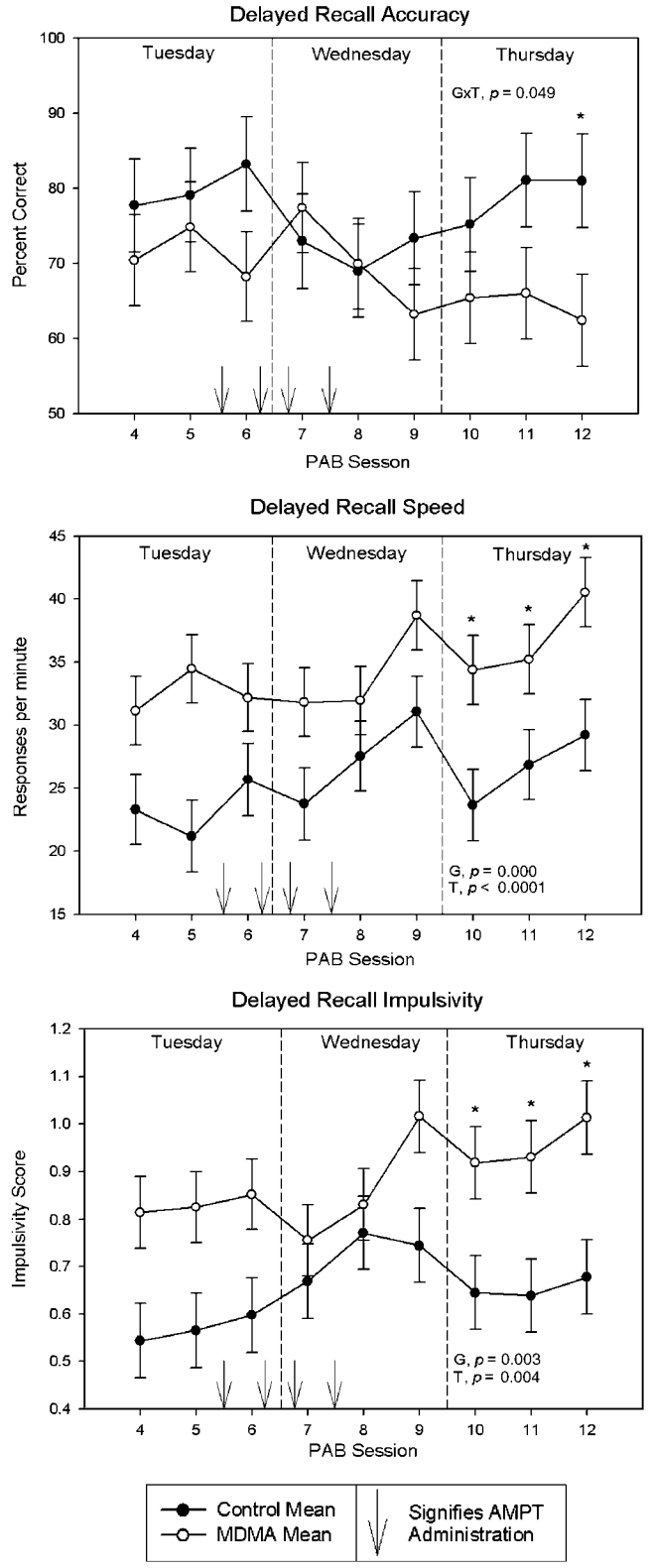

Figure 4 Accuracy, speed, and impulsivity scores on a Delayed Recall Task in MDMA users and controls before, during, and after AMPT administration. Scores were compared using a repeated measure ANCOVA (covarying for gender). When significant main effects of Group, or Group × Time interactions were noted, *post hoc T*-tests (two-way) were conducted at individual time points to further evaluate the nature of the effect. Values shown represent mean (±SEM). *Signifies $p \leqslant 0.05$.

Table 4 Baseline Sleep Measures in Abstinent MDMA Users and Controls

Sleep parameter	Control	MDMA
Total sleep	424.94 (17.07)	391.45 (15.66)[a]
Sleep efficiency	89.86 (3.53)	83.46 (3.24)
Sleep latency	14.32 (6.69)	29.23 (6.14)
REM latency	106.41 (10.78)	75.97 (9.90)[b]
WASO	32.14 (12.11)	24.25 (11.12)
Stage 1	24.80 (8.54)	44.26 (7.84)[c]
Stage 2	270.06 (12.97)	221.04 (11.9)[d]
Stage 3/4	58.39 (7.73)	54.62 (7.09)
Stage REM	73.70 (5.87)	90.87 (5.55)

Values represent time in minutes (SE). Sleep parameters were compared by two-way *T*-tests.
[a]Signifies trend towards a difference between groups at a level of $p = 0.06$.
[b]Signifies a trend towards a difference between groups at a level of $p = 0.09$.
[c]Signifies significant difference between groups at a level of $p = 0.05$.
[d]Signifies significant difference between groups at a level of $p = 0.003$.

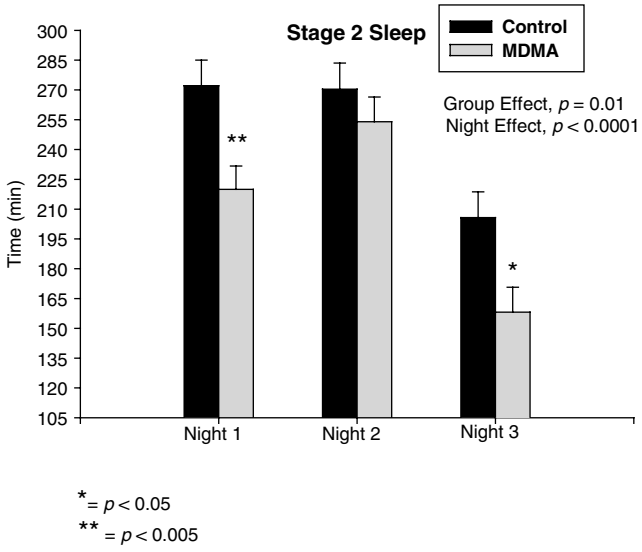

Figure 5 Stage 2 sleep in MDMA users and controls before, during, and after AMPT administration. Sleep measures were compared using a repeated measure ANCOVA, covarying for gender. When significant effects of Group or Group × Night interactions were noted, *post hoc T*-tests (two-way) were conducted on individual nights to further evaluate the nature of the effect. Values shown represent mean (±SEM). *Signifies $p \leqslant 0.05$.

suggesting increased change with increased abstinence. No relationship between duration of abstinence and Stage 1 sleep was found ($r = 0.22$, $p < 0.14$).

In contrast to significant correlations between MDMA use patterns and sleep changes, no relationships between marijuana use and time spent in Stage 2 sleep or Stage 1 sleep were found (Stage 2: duration of marijuana use: $r = 0.15$, NS; frequency of marijuana use: $r = -0.12$, NS; duration of abstinence: $r = 0.16$, NS; Stage 1: duration of marijuana use: $r = 0.03$, NS; frequency of marijuana use: $r = -0.03$, NS; duration of abstinence: $r = -0.18$, NS).

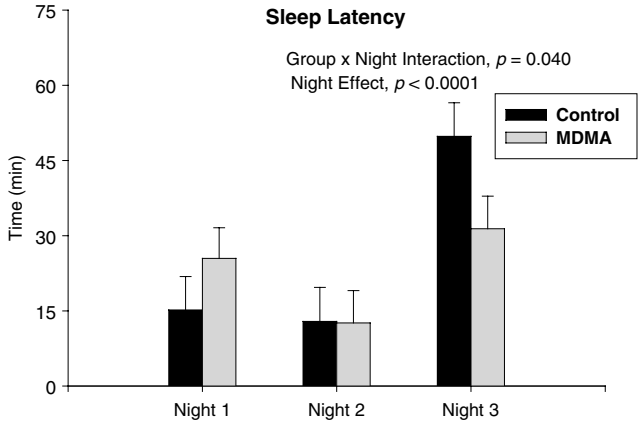

Figure 6 Sleep latency (mean values ± SE) in MDMA users and controls before, during, and after AMPT administration. Sleep measures were compared using a repeated measure ANCOVA, covarying for gender. When significant effects of Group or Group × Night interactions were noted, *post hoc T*-tests (two-way) were conducted on individual nights to further evaluate the nature of the effect. Values shown represent mean (± SEM).

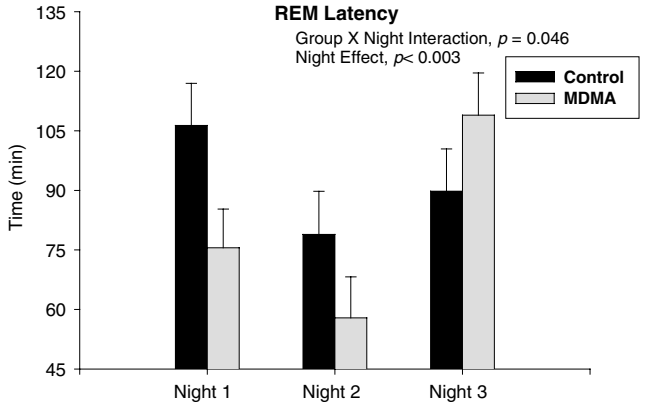

Figure 7 REM latency in MDMA users and controls before, during, and after AMPT administration. Sleep measures were compared using a repeated measure ANCOVA, covarying for gender. When significant effects of Group or Group × Night interactions were noted, *post hoc T*-tests (two-way) were conducted on individual nights to further evaluate the nature of the effect. Values shown represent mean (± SEM).

Prolactin Measures

One-way ANOVA revealed a significant effect of AMPT on plasma prolactin in both groups ($F(1,42) = 69.85$, $p < 0.001$), with no significant differences between groups ($F(1,42) = 2.80$, $p < 0.101$) (mean pre-AMPT plasma prolactin concentrations in controls and MDMA subjects = 11.9 ± 4.5 and 11.5 ± 9.5, respectively; post-AMPT plasma prolactin concentrations in controls and MDMA subjects = 31.2 ± 19.2 and 22.7 ± 11.2, respectively).

DISCUSSION

To our knowledge, this is the first clinical study to assess directly the possibility that prior MDMA exposure can lead to alterations in behaviors dually modulated by brain 5-HT and catecholaminergic systems. Findings from the present study confirm and extend previous studies demonstrating alterations in cognitive function and sleep architecture in MDMA users, and demonstrate that abstinent MDMA users have differential responses to catecholaminergic depletion by AMPT in both behavioral domains.

The present cognitive data are consistent with earlier findings (see Introduction) demonstrating short-term verbal memory deficits in MDMA users, with apparent normal performance in a wide range of other cognitive domains. Exploratory correlational analyses demonstrate that working and short-term verbal memory deficits are significantly correlated with estimated lifetime MDMA exposure and frequency of MDMA use, but not duration of abstinence. Notably, there was no relationship between marijuana use and memory deficits observed in the present cohort of abstinent MDMA subjects.

Results from repeated computerized cognitive testing also revealed differences between MDMA users and controls on measures of accuracy, speed, and impulsivity on several working memory tasks. MDMA users performed less accurately (and more quickly) on a visual working memory task, and had differential responses to AMPT on two 'verbal' working memory tasks (a Code Substitution task and Delayed Recall of the same code). On all three of these memory tasks, MDMA users displayed increased behavioral impulsivity relative to controls. In particular, despite equal levels of intelligence in the two groups, MDMA users tended to perform less accurately and more quickly, with accuracy of performance inversely related to speed of performance. The inverse relationship between speed and accuracy in MDMA users on tasks of working memory suggests that their inaccuracy is not related to lack of ability but, rather, to impulsive responding. The observation that MDMA users respond to questions quickly, at the expense of answering them accurately, raises the possibility that previously noted working memory deficits in MDMA users may, at least in part, be related to deficits in impulse control. This possibility is in keeping with the fact that brain 5-HT is strongly implicated in impulse control and response inhibition (Volmm *et al*, 2006), and the fact that MDMA is known to have the potential to produce lasting brain 5-HT deficits. Additional research is needed to better understand the nature of this phenomenon in MDMA users.

AMPT administration led to more prominent increases in speed and impulsivity in MDMA users than in controls on the Code Substitution and Delayed Recall Tasks, working and short-term memory tasks, respectively. In particular, following AMPT administration, MDMA users increased their speed of performance to a greater degree than that of controls, with significant differences between groups in speed and impulsivity at several time points on the day after drug discontinuation. This differential effect of AMPT on speed and accuracy could be related to an exaggerated catecholaminergic rebound in MDMA users secondary to a decrease in 5-HT inhibitory tone, or could be related to the finding that 5-HT/CA systems are both involved in response inhibition/behavioral impulsivity, as has been recently demonstrated in preclinical studies (Chamberlain *et al*, 2006).

The finding of increased behavioral impulsivity in MDMA users is consistent with previous studies that found impulsive responding in MDMA users performing a Matching Familiar Figures Task (Morgan, 1998; Morgan

et al, 2007; Quednow *et al*, 2007). As suggested in a recent study by Quednow *et al* (2007), MDMA users may be more likely to display impulsivity on tasks related to disinhibition/attention than on tasks related to punishment or extinction, two distinct, but related facets of impulsivity, as defined by Moeller *et al* (2001). This observation is notable because, as mentioned above, disinhibition is believed to be modulated by brain 5-HT systems.

Baseline sleep data demonstrating decreased Stage 2 and increased Stage 1 sleep in the present study are similar, although not identical, to the two previous studies in which sleep architecture has been evaluated in MDMA users (Allen *et al*, 1993; Ricaurte and McCann, 2001). Specifically, both previous studies found reductions in Stage 2 sleep in MDMA users, although this difference was statistically different in only one of these studies (Allen *et al*, 1993). The same study (Allen *et al*, 1993) found near-significant increases in Stage 1 sleep and significant decreases in total sleep, results that are consistent with findings of significantly increased Stage 1 and near-significantly decreased total sleep in the present study. Differences among the three studies could be related to a number of factors, including different MDMA exposures and durations of abstinence. Nevertheless, the observation that changes in Stage 1 and 2 sleep in the present study were significantly correlated with MDMA use (but not marijuana use), suggesting that sleep changes are related to MDMA exposure.

MDMA users were also found to have a differential sleep response to AMPT. In particular, on measures of REM latency and sleep latency, MDMA users differed from controls in the direction and/or extent of AMPT-induced sleep changes, particularly during the 'recovery' phase, more than 36 h after the last dose of AMPT. Previous studies have documented that healthy volunteers tend to exhibit improved mood, or even hypomania, during the day following AMPT discontinuation, as well as difficulty falling asleep (McCann *et al*, 1992). In the present study, difficulty in falling asleep during recovery was more pronounced in controls, who took more that 30 min longer to fall asleep than at they had at baseline, compared to a less than 5-min increase in MDMA subjects. In contrast, following AMPT discontinuation, MDMA users had large increases in REM latency (more than 30 min greater than at baseline), whereas control subject's REM latency values were slightly less than at baseline. Although the neurobiology underlying this differential response to AMPT is not known, the findings are consistent with our experimental hypothesis that reductions in brain catecholamine neurotransmission would differentially influence behaviors that are known to have dual 5-HT/catecholamine modulation in MDMA users.

Studies demonstrating that adolescents are particularly vulnerable to sleep loss, and that sleep deprivation increases the risk for learning difficulties, impulsive and risk-taking behavior, and mood instability (Carskadon *et al*, 2004; O'Brien and Mindell, 2005) raise the possibility that cognitive and behavioral differences seen in abstinent MDMA users might be related to alterations in sleep. The present study does not permit us to draw conclusions regarding potential links between sleep quality and cognitive and behavioral changes in MDMA users, or whether MDMA-induced 5-HT changes are responsible for either. Ongoing studies are aimed at addressing this important issue. Although the clinical significance of changes in memory and sleep in MDMA users is not clear, it is noteworthy that subjects with overt psychiatric or cognitive disorders were excluded from the study and, therefore, the pool of MDMA users with clinically significant symptoms would not have met inclusion criteria.

Limitations of this study should be recognized. First, as already mentioned, MDMA users in the study tended to have experimented with recreational drugs that control subjects had never tried. Therefore, the possibility remains open that 'other drug' exposure, alone or in interaction with MDMA, plays a role in memory deficits and sleep alterations seen in the present study. However, it should be emphasized that, aside from marijuana, MDMA subjects did not meet criteria for 'abuse' of any other drug. Also, marijuana users in studies that have found long-lasting cognitive changes (Bolla *et al*, 1998) used much more marijuana than MDMA users who participated in the present study, who, as a group, would be considered 'light' marijuana users in the marijuana research field. Further, cognitive changes in MDMA users correlated with MDMA use parameters but not marijuana use parameters. Second, with regard to sleep abnormalities, there is little known about the long-term effects of most recreational drugs of abuse on sleep architecture. However, given preclinical reports of lasting effects of MDMA on circadian regulation (Gardani *et al*, 2005; Biello and Dafters, 2001) and the known roles of 5-HT and catecholamines in sleep regulation, it is certainly plausible that sleep abnormalities in the present study could be related to lasting effects of MDMA on 5-HT systems as well as altered 5-HT/catecholamine interactions. Third, as with all studies involving retrospective accounts of drug use, drug use histories could be clouded by the passage of time, inaccuracy of recall (given memory deficits), or because drugs believed to be MDMA may have been contaminated with other drugs. Fourth, it is conceivable that all of the differences between MDMA users and controls found in the present study preexisted MDMA use, a possibility that can only be fully explored in prospective studies of currently MDMA-naïve individuals. In particular, it is possible that MDMA users (particularly heavy users) are more impulsive than controls before using MDMA.

In conclusion, results from the present study, the first study to evaluate the possibility that prior MDMA exposure leads to alterations in behavior dually modulated by brain 5-HT and catecholamines, confirm and extend earlier data on cognitive function, impulsivity and sleep in MDMA users. They also show that AMPT, which alters brain catecholaminergic neurotransmission (as evidenced by the increase in prolactin concentrations), produces differential effects in abstinent MDMA relative to controls. Differences in sleep architecture in MDMA users were observed both at baseline and after AMPT. As with cognitive deficits, sleep abnormalities in MDMA users correlated with MDMA (but not marijuana) use, and responded differentially to AMPT. The relationship between alterations in sleep, cognitive function and impulsive behavior in abstinent MDMA users is not clear, but deserves future study. Taken together, the present findings support the notion that MDMA can lead to subtle functional deficits in brain functions modulated by brain 5-HT, or involving reciprocal 5-HT/catecholamine interactions. In addition, these findings are the first to raise

the possibility that behavioral abnormalities in MDMA users may become manifest when they are exposed to drugs or other stimuli that interact with brain catecholamine systems, or with known losses of brain catecholamines that occur with age.

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