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ORIGINAL INVESTIGATION

Altered pain responses in abstinent (±)3,4-methylenedioxy-methamphetamine (MDMA, "ecstasy") users

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Abstract
Rationale (±)3,4-Methylenedioxymethamphetamine (MDMA) is a popular recreational drug that has potential to damage brain serotonin (5-HT) neurons in humans. Brain 5-HT neurons play a role in pain modulation, yet little is known about long-term effects of MDMA on pain function. Notably, MDMA users have been shown to have altered sleep, a phenomenon that can lead to altered pain modulation.
Objectives This study sought to assess pain processing in MDMA users using objective methods, and explore potential relationships between pain processing and sleep indices.
Methods Forty-two abstinent MDMA users and 43 age-matched controls participated in a 5-day inpatient study. Outcome measures included standardized measures of pain, sleep polysomnograms, and power spectral measures of the sleep EEG. When differences in psychophysiological measures of pain were found, the relationship between pain and sleep measures was explored.
Results MDMA users demonstrated lower pressure pain thresholds, increased cold pain ratings, increased pain ratings during testing of diffuse noxious inhibitory control, and decreased Stage 2 sleep. Numerous significant relationships between sleep and pain measures were identified, but differences in sleep between the two groups were not found to mediate altered pain perception in MDMA users.
Conclusions Abstinent MDMA users have altered pain perception and sleep architecture. Although pain and sleep outcomes were related, differences in sleep architecture in MDMA users did not mediate altered pain responses. It remains to be determined whether alterations in pain perception in MDMA users are secondary to neurotoxicity of 5-HT-mediated pain pathways or alterations in other brain processes that modulate pain perception.

Keywords Pain · Sleep · Serotonin · Neurotoxicity · MDMA · Power spectra

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Introduction

3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") is a synthetic amphetamine analog and a popular drug of abuse. MDMA is also a selective brain serotonin (5-HT) neurotoxin that leads to lasting deficits in a variety of brain serotonin axonal markers (Gudelsky and Yamamoto 2008). Neuroanatomical studies in MDMA-treated animals indicate that regional brain losses of serotonin axonal markers are secondary to a distal axotomy of serotonin neurons (O'Hearn et al. 1988; Fischer et al. 1995; Hatzidimitriou et al. 1999). Imaging studies in humans provide strong evidence that some MDMA users also incur brain serotonin neurotoxicity (McCann et al. 1998, 2005, 2008; Semple et

al. 1999; Reneman et al. 2001; Buchert et al. 2003, 2004; Thomasius et al. 2006). Functional consequences of MDMA neurotoxicity in humans are not well defined, although persistent changes in cognitive function, sleep, and endocrine function have been found in abstinent MDMA users (Morgan 2000; Parrott 2000; El-Mallakh and Abraham 2007; Zakzanis et al. 2007; Kalechstein et al. 2007; Allen et al. 1993; McCann et al. 1999, 2007; McCann and Ricaurte 2007; Gerra et al. 2000; Verkes et al. 2001).

A relatively unexplored potential functional consequence of MDMA-induced 5-HT neurotoxicity is that of altered pain perception. This functional alteration might be anticipated since 5-HT is strongly implicated in the modulation of pain (Yoshimura and Furue 2006; Lopez-Garcia 2006). To date, there are only two published studies that have tested the possibility that MDMA users may have alterations in pain modulation (McCann et al. 1994; O'Regan and Clow 2004). The first study, conducted in MDMA users who, on average, had been abstinent for approximately 5 months prior to testing, noted no differences in MDMA users' response to an ischemic pain task (McCann et al. 1994) when compared to control subjects. A second study found reduced cold pain tolerance in MDMA users who had recently (i.e., 3–4 days prior to testing) used MDMA (O'Regan and Clow 2004).

Sleep disruption can influence pain perception (Edwards et al. 2008; Tiede et al. 2010), and experimentally induced pain or idiopathic pain syndromes frequently lead to sleep disruption (Smith et al. 2007). The mechanisms underlying the relationship between sleep and pain are complex, and can be related to altered attentional processes that are associated with sleep loss, as well as overlap in the brain systems that modulate both sleep and pain. Because the brain 5-HT system modulates both pain and sleep (Murillo-Rodriguez et al. 2009; Malemud 2009), MDMA users might be expected to have altered pain processes, either directly, by virtue of 5-HT injury or indirectly, as a result of altered sleep.

The purpose of the present study was to test abstinent MDMA users and matched controls using standardized noxious thermal and mechanical stimuli in a controlled research setting. The working hypothesis was that MDMA-induced brain 5-HT neurotoxicity would lead to alterations in pain sensitivity and tolerance. In an effort to avoid the possibility of a false-negative finding, an enhanced battery of pain measurements was employed, including a test of diffuse noxious inhibitory control. This is a test of descending pain inhibitory processes (whereby the response to a painful stimulus is inhibited by another, often spatially distant, painful stimulus) that is believed to involve brain 5-HT neuronal systems, in part (Chitour et al. 1982). It was further hypothesized the MDMA users would have altered sleep architecture as well as altered sleep power spectra during the first two NREM cycles, and that alterations in sleep architecture and sleep power spectra would be related to alterations in pain modulation. Recent reviews have indicated that responses to pain in the laboratory are important predictors of the later experience of clinical pain (Edwards 2005; Edwards et al. 2005), findings that have been reported in epidemiological studies of headache (Buchgreitz et al. 2006), in patients with fibromyalgia (Staud et al. 2003), in generally healthy adults (Edwards and Fillingim 2001), and in numerous other samples. Any potential alterations in pain sensitivity and pain processing as a consequence of MDMA use, therefore, may have long-term consequences for individuals' future risk for experiencing a variety of clinical pain conditions.

Materials and methods

This research was approved by an Institutional Review Board and a General Clinical Research Unit review committee.

Subjects

Subjects were medically healthy adults who responded to advertisements placed in newspapers or posted fliers. Potential subjects first underwent a telephone screen involving questions about medical, psychiatric, and drug use histories, and if deemed suitable for participation were invited for a face-to-face screen. After providing verbal and written informed consent, subjects were further screened using blood tests for routine blood chemistries and urine samples for screening of illicit drugs including amphetamines, cannabinoids, cocaine metabolites, and opiates. Subjects were also assessed for current and past Axis I psychiatric diagnoses using the Structured Clinical Interview for DSM-I Diagnoses (SCID-I) (First et al. 2002). No subjects had a diagnosed or suspected sleep disorder, and no subjects had a pain condition or injury that required medical attention within the 6 months prior to study participation.

To be included in the study, all subjects agreed to remain drug-free for 2 weeks prior to study participation (including licit and illicit analgesics and benzodiazepines). Additional inclusion criteria included normal results from blood chemistries, negative drug screens (with the exception of marijuana, which can be detected in urine screens for three or more weeks after the last use) and, for female subjects, negative pregnancy tests. Inclusion criteria for the MDMA group included self-reported use of MDMA on at least 25 separate occasions. Several methods were employed to determine MDMA use histories: (1) a preliminary telephone

interview; (2) an MDMA questionnaire that asked about MDMA use patterns, duration, and frequency; (3) a standardized drug history questionnaire; and (4) the Scheduled Interview for DSM-III-R. Exclusion criteria included regular use of psychotropic medications, major medical illness, history of significant head injury, lifetime history of an Axis I psychiatric condition in which brain 5-HT has been implicated (i.e., major depression, bipolar affective disorder, psychosis, panic disorder, generalized social phobia, obsessive compulsive disorder) or lifetime diagnosis of a sleep disorder. Subjects in the control group were excluded if they had ever used MDMA.

Data for the current manuscript were pooled from two studies that were part of a three-study project to assess potential functional consequences of MDMA use. All three studies involved 5-day inpatient stays on a clinical research unit, and had common features (i.e., baseline demographic and neuropsychiatric assessments, sleep studies, pain testing, cognitive testing). Each of the three studies involved a pharmacological challenge [with either alpha-methyl-para-tyrosine (AMPT) or scopolamine] or a physiological challenge with total sleep deprivation. Some findings from the project have been published (McCann et al. 2007; McCann et al. 2009a, b). Only data from subjects who participated in the scopolamine and sleep deprivation challenges are included in the current report. There is no overlap of sleep and pain data in the current report with previously published reports.

Psychophysical pain procedures

Pain testing took place on a clinical research unit as part of a 5-day inpatient research protocol designed to assess potential functional consequences of MDMA use. While on the unit, subjects who were regular tobacco smokers were allowed to leave the unit (accompanied by a staff member) to smoke, but not within 1 h of pain or sleep testing. Subjects were permitted to have caffeinated beverages (coffee or tea) at breakfast, but had no caffeine-containing substances in the afternoon or evening. Pain testing took place during the second day of the study, after participants had been familiarized with the pain testing equipment and task instructions, and a day after they practiced trials of the procedures. The pain testing battery included measures of heat pain sensitivity and tolerance, pressure pain sensitivity and tolerance, cold pain sensitivity and tolerance, and measures of diffuse noxious inhibitory controls (DNIC), as described below.

Heat pain threshold and tolerance Contact heat stimuli were delivered using a Medoc Thermal Sensory Analyzer (TSA-2001, Ramat Yishai, Israel). Thermal assessment included sampling of heat pain thresholds (HPTh), and heat pain tolerances (HPTo) on the ventral forearm using an ascending method of limits paradigm with a rate of rise of 0.5°C/s (Edwards et al. 2004). Three trials of HPTh were performed first, followed by three trials of HPTo, with the thermode repositioned between trials.

Pressure pain threshold A Somedic algometer was used to assess pressure pain threshold (PPTh) over multiple muscle groups, similar to previous studies (Kosek and Hansson 1997; Edwards and Fillingim 2001). The algometer's 1-cm^2 rubber probe was placed over the muscle belly, with the pressure increased steadily at a constant rate (30 kPA/s), until the subject indicated that he/she "first felt pain." PPTh was assessed two times each at the following three body sites, bilaterally, in a randomized order: trapezius muscle, masseter muscle, and the proximal third of the brachioradialis muscle (forearm). At least 30 s were maintained between successive stimuli. A previous analysis of the test–retest reliability of these algometric procedures yielded reliability coefficients exceeding 0.90 (Smith et al. 2007).

DNIC The DNIC test was conducted last, due to potentially prolonged pain sensations stimulated by the cold pressor task that is included in this test. DNIC is a noninvasive test of endogenous pain-inhibitory systems using a heterotopic noxious conditioning stimulation paradigm (Edwards et al. 2003). Baseline PPTh was reassessed on the right brachioradialis or right trapezius in a randomized order. Immediately afterward, participants underwent a series of (four) cold pressor tasks [similar to previous DNIC studies (Talbot et al. 1989; Edwards et al. 2003)]. During each, participants immersed their contralateral hand (left) up to the wrist, in a circulating ice water bath maintained at approximately 4°C. Twenty seconds after commencing hand immersion, participants provided a (0–100) cold pressor pain rating, while the hand was still submerged in the ice bath, and PPTh was then reassessed on either the right brachioradialis or right trapezius (same site as baseline assessment). Finally, DNIC pain ratings (0–100; where 0 represents no pain and 100 represents the most pain imaginable) were obtained for the pain experienced at the time of the second PPTh test (i.e., while the contralateral hand was still submerged in ice water). The DNIC index for each subject was calculated using the following equation (Edwards et al. 2009): [(mean PPTh during cold pressor) / (mean PPTh prior to cold pressor)] × 100. The mean DNIC index for each group provides a quantitative measure of percent change in PPTh during the cold pressor tasks relative to baseline PPTh, with an increase in PPTh during cold pressor expected in subjects with healthy pain inhibition responses (Edwards et al. 2009). DNIC indices of each group were compared to a DNIC Index of 100 (indicating no DNIC effect) via a one-sample *t* test to determine if each group

displayed a significant DNIC effect (i.e., an increase in PPTh during cold pressor relative to baseline PPTh).

Sleep measures

All subjects underwent overnight polysomnographic (PSG) recordings during the first (adaptation) and second (baseline) night of their 5-day inpatient stay. Studies were conducted in individual rooms on a clinical research unit. Sleep schedules were standardized for all subjects on both nights, beginning with a "lights out" time of 11:00 PM and "lights on" time of 7:00 AM. Subjects were not permitted to sleep prior to "lights out" time or subsequent to "lights on" time. The overnight PSG consisted of continuous recordings of right and left electro-oculographic leads, four electroencephalographic leads (C3-A2, C4-A1, O1-A2, O2-A1), and submental and bilateral anterior tibialis electromyograms. Subject respiration was monitored via a nasal pressure cannula, a thermistor/thermocouple at the nose and mouth, and thoracic and abdominal strain gauges. Subject oxyhemoglobin saturation was obtained via oximetry. Baseline PSGs were visually scored at the Johns Hopkins Sleep Disorders Clinic by certified polysomnographers blinded to subject status. Visual PSG scoring was completed according to standards of the American Academy of Sleep Medicine (Iber et al. 2007). All subjects found to meet criteria for moderate to severe sleep-disordered breathing (indicated by an Apnea Hypopnea Index (AHI)≥15) were excluded from data analysis.

In addition to standard sleep indices, sleep EEG signals were analyzed using power spectral methods. In particular, sequential distinct REM and NREM periods for each subject were isolated using the abovementioned staging procedures and methods described in Feinberg and Floyd (1979), except that no minimum duration was required to classify a period as REM. Spectral analysis of the C3-A2 EEG recording was accomplished using the discrete fast Fourier transform and a custom-made software program (Zhang et al. 2008), with frequency bands defined as follows: δ (0.8 to 4.0 Hz); θ (4.1 to 8.0 Hz); α (8.1 to 13.0 Hz); and β (13.1 to 20.0 Hz). Epoch-by-epoch spectral estimations were synchronized with the distinct NREM and REM periods, permitting power spectral analyses within sequential NREM and REM cycles. Wake epochs and sleep periods containing EEG artifacts were eliminated from analysis.

Data analyses

Comparisons between the two subject groups were made using multivariate regression, with age, gender, and race as a priori covariates. These covariates were included because they all have been previously found to influence pain or sleep. When significant differences were noted between groups on a particular pain outcome measure, Pearson's partial correlations were conducted to assess the potential relationship between pain ratings and sleep indices. In addition, correlation analyses were also conducted between pain indices and sleep EEG power spectra during the first two NREM periods, when δ power (a marker of sleep debt) is normally at its peak. Analyses of spectral measures were limited to the first two NREM cycles in an effort to decrease the number of comparisons, thereby increasing statistical power. Differences were considered significant when p values were <0.05.

Results

Eight subjects (six MDMA users and two controls) were removed from data analysis due to the discovery of sleep disordered breathing (AHI>15) (McCann et al. 2009a, b). None of these individuals had previously received the diagnosis of sleep apnea (which was an exclusion criteria). Demographics and MDMA use patterns in the two subject groups are shown in Table 1. The two groups were well matched with regard to age, BMI, and education. The MDMA group had a slightly greater proportion of male subjects than the control group (67% versus 53%), and the control group had a greater proportion of African American subjects (63% versus 33%). MDMA users reported a wide range of prior MDMA use (Table 1), but as dictated by inclusion criteria, had used MDMA on at least 25 separate occasions. No subject had used MDMA or any other drug of abuse within the 2 weeks of study participation (on average, abstinence for MDMA was greater than 4.5 months).

Sleep architecture MDMA users had significantly less Stage 2 sleep than controls (Table 2). No other significant differences in sleep architecture were found.

Pain responses As shown in Table 2, MDMA users had significantly decreased mechanical pain thresholds (PPThs) in the trapezius and masseter muscles compared to control subjects at baseline, with no significant differences between groups in PPThs of forearm muscles (Table 2). MDMA users also had lower PPThs in trapezius and forearm muscles during the cold pressor test, and reported greater levels of pain during the cold pressor test and during the DNIC trials (Table 2). MDMA users showed a nonsignificant trend toward lower heat pain thresholds than control subjects. No significant between-group differences were observed for heat pain tolerance (Table 2). A significant DNIC effect (increase in mean PPTh during cold pressor testing) was observed in both groups (one-sample t test,

Table 1 Subject demographics and drug use characteristics

	MDMA users (n=42)		Control (n=43)	
Age [years]	24.5±4.9		23.6±3.3	
Gender	28 M, 14 F		23 M, 20 F	
Race	23 Cauc, 14 Af.Am., 5 Other		15 Cauc, 27 Af.Am., 1 Other	
BMI	25.3±0.92		26.6±0.91	
Education	13.4±0.24		13.3±0.28	
MDMA exposure[a]				
Usual total dose [tabs/caps][b]	2.6±0.2 (0.5–7)		N/A	
Number of separate uses	209.7±38.3 (30–1,000)		N/A	
Duration of use [month]	55.6±6.0 (7–168)		N/A	
Frequency of use [uses/month]	4.1±0.6 (0.5–20.8)		N/A	
Max dose/24 h [tabs/caps][b]	5.9±0.5 (2.0–17.0)		N/A	
Time since last use [month]	4.8±1.2 (0.5–7.0)		N/A	
Other drug exposure	Lifetime	Past 6 months	Lifetime	Past 6 months
Alcohol [number (%)][c]	42 (100%)	40 (95%)	40 (95%)	35 (81%)
Tobacco [number (%)][c]	35 (83%)	29 (69%)	25 (58%)	18(42%)
Marijuana [number (%)][c]	41 (98%)	30 (71%)	31 (72%)	22 (51%)
Hallucinogens [number (%)][c]	30 (71%)	10 (24%)	8 (19%)	4 (9%)
Cocaine [number (%)][c]	27(64%)	19(45%)	1 (2%)	0
Opioids [number (%)][c]	18 (43%)	5 (12%)	1 (2%)	0

[a] Exposure values represent the mean ± the standard error with the range in parenthesis

[b] Indicates the number of tablets and/or capsules typically used in a single "session"

[c] "Number" indicates the number of individuals who have ever been exposed to the drug; "%" indicates the percent of individuals with respect to the total number per group

$p<0.0001$ for each group; not shown in Table 2). DNIC indices [(mean PPTh during cold pressor testing / mean PPTh prior to cold pressor testing) × 100] in the two groups also reflect a similar increase in PPTH during cold pressor testing (Table 2).

Relationship between sleep and pain Numerous significant relationships were found between sleep measures and pain measures (Table 3). In general, the relationships support the notion that subjects with a higher sleep debt had lower cold pain thresholds and lower PPThs. In particular, sleep debt is characterized by increased δ power during the first two NREM sleep cycles, decreased Stages 1 and 2 sleep, increased Stage 3/4 sleep, increased sleep efficiency, decreased waking after sleep onset, and decreased sleep latency. As seen in Table 3, all of the significant correlations between pain and sleep measures are consistent with the notion that subjects with the greatest sleep debt (as demonstrated by sleep the night after pain testing) had lower PPThs (with and without cold pressor pain), as well as increased cold pain ratings (during the cold pressor test and during the DNIC test).

Testing of causality between sleep measures and pain To explore the possibility that significant differences in sleep architecture (i.e., reductions in Stage 2 sleep in MDMA users) mediate changes in pain measurements, Sobel's Interactive Mediation Tests were conducted. These revealed that even when accounting for differences in Stage 2 between groups, differences in pain perception persisted between groups, indicating that differences in Stage 2 did not mediate alterations in pain perception in MDMA users. The possibility that alterations in sleep power spectra in MDMA users mediated pain outcomes was not assessed because of the large number of tests that would be required, and the loss of power associated with multiple statistical comparisons.

Stepwise regression analysis to test for false positives In an effort to ensure that positive findings were not an artifact of the statistical analysis related to inclusion of age, gender, and race as fixed covariates in the statistical model, a stepwise regression analysis was also conducted (dropping covariates if their effect on the statistical outcome was not $p<0.05$). All of the initial positive results that had been obtained using the multivariate regression analysis remained positive (and most increased in significance) using this stepwise procedure. Furthermore, all of the covariates used in the multivariate analysis were significant on one or more pain outcome measures (gender and race were significant

Table 2 Sleep architecture and pain measures

	MDMA users[a] (n=42)	Controls[a] (n=43)	p value
PSG measure			
Stage 1 [%]	5.5±0.8	5.4±1.0	0.88
Stage 2 [%]	48.7±1.8	52.4±2.1	0.04
Stage 3/4 [%]	22.3±1.7	19.5±2.1	0.11
Stage REM [%]	23.6±1.2	22.9±1.4	0.52
Sleep latency [min]	14.6±5.5	16.7±6.6	0.70
Wake after sleep onset [min]	16.8±6.7	23.9±8.0	0.30
Total sleep time [min]	445.5±9.4	435.7±11.2	0.31
Time in bed [min]	476.8±2.7	476.3±3.2	0.86
Sleep efficiency[b] [%]	93.4±1.9	91.5±2.3	0.34
Pain measure			
HPTh[c]	44.0±1.1	42.0±1.3	0.06
HPTo[d]	48.4±0.4	48.5±0.5	0.89
PPTh-Trapezius[e]	9.7±0.7	11.4±0.8	0.02
PPTh-Forearm[e]	9.6±0.7	10.6±0.9	0.17
PPTh-Masseter[e]	4.9±0.4	5.8±0.5	0.03
Cold pressor pain rating[f]	67.0±5.0	55.2±6.0	0.02
PPTh-Trapezius with cold pressor[e]	11.2±0.7	12.8±0.8	0.03
PPTh-Forearm with cold pressor[e]	10.2±0.8	11.9±0.9	0.04
DNIC Index[g]	115.8±5.5	112.4±6.6	0.56
DNIC pain rating[h]	71.1±4.7	59.0±5.6	0.01

[a] Values represent least square means ± standard error, adjusting for age, gender, and race

[b] Sleep Efficiency = (Total Sleep Time/Time in Bed) × 100

[c] *HPTh* Heat Pain Threshold [°C]

[d] *HPTo* Heat Pain Tolerance [°C]

[e] *PPTh* Pressure Pain Threshold [lbs/cm^2]

[f] Pain rating scale=0–100

[g] Diffuse Noxious Inhibitory Controls Index = [mean PPTh with Cold pressor/mean PPTh prior to Cold Pressor] × 100

[h] Mean Pain Ratings of PPTh trials for both right trapezius and bronchioradialis with Cold Pressor, scale=0–100

on seven of ten pain measures; age was significant on two of ten pain measures), supporting the decision to include them in the statistical model.

Discussion

Results from the present study indicate that healthy abstinent MDMA users have alterations in pain perception. In particular, when compared to control subjects who have never used MDMA, abstinent MDMA users have decreased mechanical pain thresholds, increased cold pain sensitivity, and a trend toward decreased heat pain sensitivity. MDMA users also had altered sleep architecture, with significantly less Stage 2 sleep. Correlation analyses exploring the potential relationship between sleep measures and pain outcomes in both groups revealed numerous significant relationships that generally supported the notion that increased sleep debt is associated with decreased pain thresholds. However, differences in sleep architecture did not appear to underlie altered pain perception in MDMA users.

Alterations in pain function might be anticipated in individuals with MDMA-induced 5-HT neurotoxicity because 5-HT plays a key role in the modulation of pain (Yoshimura and Furue 2006; Lopez-Garcia 2006). The present results confirm and extend findings by O'Regan and Clow (2004) who found reduced cold pain tolerance in regular MDMA users who had used MDMA 3–4 days prior to testing. These investigators found decreased cold pain tolerance in MDMA users compared to polydrug users who had never used MDMA previously. Notably, MDMA is known to lead to midweek decreases in mood (Curran and Travill 1997), and in the study by O'Regan and Clow, mood and pain measures were related, with low mood associated with decreased cold pain tolerance. In contrast, in the current study, MDMA users, on average, had not used MDMA for nearly 5 months and, although daily mood ratings were not obtained, did not meet criteria for a mood disorder. Therefore, in the current study, findings were not related to subacute effects of MDMA but, rather, were related to more enduring effects of MDMA.

No previous studies have evaluated PPths, heat pain tolerance (HPTo), heat pain thresholds (HPThs), or DNIC in MDMA users. The finding of decreased PPThs in MDMA users indicates that altered pain perception in MDMA users is not limited to cold pain tolerance or sensitivity. Moreover, the trend toward an increase in HPThs in MDMA users, as compared to controls, suggests that results are not merely secondary to overreporting of pain in the MDMA cohort.

This finding of decreased Stage 2 sleep in MDMA users is consistent with two previous studies (Allen et al. 1993; McCann et al. 2007) and similar to findings from a study where nonsignificant decreases in Stage 2 sleep were observed (McCann and Ricaurte 2007). Other studies have documented additional or different changes in sleep architecture in abstinent MDMA users, including decreased total sleep time (Allen et al. 1993; Randall et al. 2009), increases in Stage 1 sleep (McCann et al. 2007), and decreases in Stage 3/4 sleep (Randall et al. 2009). A variety of factors could underlie the differences among studies, including differences in MDMA exposure histories, durations of abstinence in the various cohort, and lack of an adaptation night in the sleep laboratory. Nevertheless, the most consistent polysomnographic finding in abstinent MDMA users has been a reduction in Stage 2 sleep.

Table 3 Relationship between pain and sleep measures

Pain measure	Sleep measure	MDMA r[a]	MDMA *p* value	Control r[a]	Control *p* value	MDMA and control r[a]	MDMA and control *p* value
Cold Pressor[b]	Stage 1 [min]	−0.40	0.02	−0.38	0.02	−0.34	0.003
Cold Pressor[b]	Stage 1 [%]	−0.38	0.02	−0.39	0.02	−0.33	0.003
Cold Pressor[b]	Stage 2 [%]	−0.06	0.74	−0.30	0.07	−0.25	0.03
Cold Pressor[b]	Stage 3/4 [min]	0.02	0.92	0.32	0.05	0.24	0.04
Cold Pressor[b]	Stage 3/4 [%]	0.04	0.84	0.33	0.05	0.25	0.03
Cold Pressor[b]	Stage REM [min]	0.20	0.23	0.29	0.09	0.23	0.05
Cold Pressor[b]	Stage REM [%]	0.28	0.09	0.28	0.10	0.25	0.03
PPTh-Trap[c]	Non-REM Pd. 2 (α)[e]	0.05	0.78	0.29	0.09	−0.22	0.05
Cold Pressor[b]	Non-REM Pd. 1 (δ)[e]	−0.13	0.45	−0.25	0.14	0.23	0.04
Cold Pressor[b]	Non-REM Pd. 1 (α)[e]	−0.01	0.93	−0.25	0.13	−0.24	0.03
Cold Pressor[b]	Non-REM Pd. 1 (β)[e]	−0.36	0.03	−0.43	0.01	−0.23	0.04
PPTh-Fore CP[c]	WASO [min][f]	−0.34	0.04	−0.42	0.01	−0.27	0.02
PPTh-Fore CP[c]	Stage REM [min]	−0.09	0.60	−0.31	0.07	0.24	0.04
PPTh-Fore CP[c]	TST [min][g]	0.05	0.77	0.31	0.07	0.27	0.02
PPTh-Fore CP[c]	Sleep Efficiency [%]	0.06	0.70	0.32	0.06	0.25	0.03
PPTh-Fore CP[c]	WASO [min][f]	0.20	0.24	0.37	0.03	−0.29	0.02
DNIC Pain[d]	Stage 1 [min]	0.27	0.11	0.38	0.02	−0.35	0.002
DNIC Pain[d]	Stage 1 [%]	−0.10	0.56	−0.30	0.08	−0.34	0.002
DNIC Pain[d]	Stage 2 [%]	0.36	0.03	0.14	0.44	−0.26	0.02
DNIC Pain[d]	Stage 3/4 [min]	−0.22	0.18	−0.22	0.20	0.24	0.03
DNIC Pain[d]	Stage 3/4 [%]	−0.01	0.96	−0.36	0.03	0.26	0.02
DNIC Pain[d]	Stage REM [min]	0.19	0.27	0.29	0.09	0.25	0.03
DNIC Pain[d]	Stage REM [%]	−0.03	0.88	0.41	0.02	0.28	0.02
DNIC Pain[d]	Non-REM Pd. 1 (α)[e]	−0.08	0.67	0.39	0.02	−0.26	0.02
DNIC Pain[d]	Non-REM Pd. 2 (δ)[e]	−0.01	0.96	−0.37	0.03	0.23	0.05
DNIC Pain[d]	Non-REM Pd. 2 (β)[e]	−0.37	0.02	−0.12	0.46	−0.24	0.04

[a] Pearson's Partial Correlation Coefficient, adjusting for age, gender, and race. Only significant findings are reported

[b] Cold Pressor Pain Rating, scale=0–100

[c] *PPTh* pressure pain threshold [lbs/cm^2], *Trap* trapezius, *Fore* forearm, *CP* with Cold Pressor

[d] Mean Pain Ratings of PPTh trials for both right trapezius and bronchioradialis with Cold Pressor, scale=0–100

[e] Non-REM Pd. (period) with: δ=0.8–4.0 Hz; θ=4.1–8.0 Hz; α=8.1–13.0 Hz; β=13.1–20.0 Hz

[f] *WASO* Wake After Sleep Onset

[g] *TST* Total Sleep Time

Delta power during the first two sleep cycles is a surrogate marker for sleep debt (Borbely 2009). In particular, the greater the sleep debt, the greater the percent of delta power (and the lower the percent of alpha and beta power) in the sleep EEG at sleep onset and, roughly, during the first third of the night. Other markers of sleep debt include decreased Stages 1 and 2 sleep, increased Stage 3/4 sleep, increased sleep efficiency, decreased waking after sleep onset, and decreased sleep latency. The present results in both MDMA users and controls revealed strong positive relationships between sleep debt and cold pain sensitivity, with a strong inverse relationship between sleep debt and mechanical pain thresholds. The basis for these relationships is not known, but could be a result of the effects of sleep deprivation on arousal and attention, or because of overlap in the brain substrates that modulate sleep and pain, including brain 5-HT neurons.

The present study did not involve collection of validated measures of MDMA-induced 5-HT neurotoxicity such as positron emission tomography of the 5-HT transporter or cerebrospinal fluid measures of 5-hydroxyindoleacetic acid. Therefore, it is not possible to relate measures of brain 5-HT neuronal integrity with objective pain measurements. However, a number of previous studies in MDMA users with similar or lower MDMA exposure histories found evidence of significant brain 5-HT injury (McCann et al.

1998, 2005; McCann et al. 2008; Semple et al. 1999; Reneman et al. 2001; Buchert et al. 2003, 2004; Thomasius et al. 2006). As such, it is likely that the current cohort of MDMA, like previous similar cohorts, had sustained brain 5-HT injury. Nevertheless, even if MDMA-induced neurotoxicity is conceded to have occurred, it is not possible to conclude that 5-HT injury is the basis for the observed alterations in pain processing observed in MDMA users. It should also be noted that a large number of statistical comparisons were made, and results were not corrected for multiple comparisons. However, the broad and consistent nature of the findings suggests that results are not spurious. A number of factors can influence self-reported pain, including mood and anxiety, gender, race, menstrual status, and age (Bair et al. 2008; Woodrow et al. 1972). The current data analysis took into account gender, race, and age, and as such, these factors do not account for the observed differences in MDMA users. However, although the cohort of MDMA users who participated in this research did not meet criteria for any Axis I disorder, subclinical changes in mood or anxiety, or differences in the menstrual status of female subjects could potentially have influenced the findings.

As has been found in numerous previous studies and epidemiological surveys, MDMA users in the present study tended to experiment with other drugs (Wu et al. 2009). Although the control subjects in this study had also been exposed to recreational drugs other than MDMA, the MDMA group had higher levels of exposure than controls. However, all subjects had been abstinent from recreational drugs as well as licit analgesics and psychotropic medications for at least 2 weeks and, in general, hadn't used recreational drugs for months. Further, none of the other drugs that either group had used in the past have been found to lead to lasting changes in pain processing. Therefore, it is unlikely that "other drug" exposure played a role in altered pain processing observed in MDMA users.

5-HT is known to modulate pain by both central and peripheral mechanisms (Yoshimura and Furue 2006; Lopez-Garcia 2006; Aira et al. 2010; Malemud 2009). Since the neurotoxic effects of MDMA are diffuse and involve 5-HT neurons in both cortical and subcortical brain regions, it is not possible to precisely identify a mechanism by which brain 5-HT neurotoxicity might lead to the current findings. 5-HT also modulates sleep processes (Murillo-Rodriguez et al. 2009), and sleep disruption is known to lead to changes in pain processing (Smith et al. 2007; Edwards et al. 2008; Tiede et al. 2010). The current MDMA cohort had altered sleep architecture (i.e., decreased Stage 2 sleep) and pain measures in all subjects were significantly related to numerous sleep indices. However, statistical analyses assessing the role of differences in sleep (i.e., Stage 2) in altered pain processing in MDMA users were negative, indicating that factors other than altered sleep architecture are responsible for the current findings. Additional research, possibly involving PET of the SERT and fMRI during objective pain measures, before and after sleep deprivation, would be useful to better understand the relationship between MDMA-induced 5-HT injury, sleep disruption and pain processing in MDMA users.

In conclusion, the present findings are the first to document lasting altered pain perception in abstinent MDMA users. MDMA users had decreased mechanical pain thresholds, increased cold pain sensitivity, and a trend toward decreased heat pain sensitivity. Increases in cold pain sensitivity and reductions in pressure pain thresholds were positively correlated with increased sleep debt, but differences in sleep architecture in the two groups were not found to be responsible for differences in pain perception. Alterations in pain processes in MDMA users could be secondary to the direct effects of MDMA-induced 5-HT neurotoxicity on brain pain pathways, or be a secondary phenomenon related to 5-HT-mediated cognitive or emotional processing. Additional research will be required to fully understand the relationship between MDMA-induced 5-HT neurotoxicity and pain processing in MDMA users.

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Conflicts of interest None of the authors has a conflict of interest.

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