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ORIGINAL ARTICLE

Laboratory Measures of Aggression in Methadone Patients Pre- and Postdose

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Abstract
Purpose Studies with humans have shown that acute opioid administration increases aggressive behavior, but no laboratory study has yet investigated whether opioid withdrawal produces comparable effects.
Methods This study investigated whether mild opioid deprivation affected aggression in 6 males and 6 females ($N = 12$) undergoing methadone maintenance therapy. Aggressive behavior was measured using the point subtraction aggression paradigm (PSAP). Trait aggression was assessed using the Buss–Perry Aggression Questionnaire. Behavior on the PSAP and mood ratings on the Profile of Mood States questionnaire (POMS) were measured on two separate days; once before and once following the participant's daily methadone dose, with order counterbalanced across participants.
Results There were no effects of opioid withdrawal on aggressive responding, control response rates, monetary reinforced responding, or self-reports of mood. Rates of responding on the monetary-reinforced option increased across sessions regardless of condition, suggesting an exposure effect.
Conclusion These data suggest that mild opioid deprivation occurring 24 hours following methadone administration in individuals undergoing methadone maintenance therapy does not increase aggression, at least in individuals showing low levels of aggressive behavior and low measures of trait aggression. Because participants reported no mood changes and there were no direct measures of withdrawal, it is possible that 24 hours of methadone deprivation produced no withdrawal in these participants. It remains to be determined whether more prolonged deprivation might generate more significant changes in mood and/or changes in aggressive behavior.

Keywords Aggression · POMS · PSAP · Methadone · Withdrawal

Opioid addiction is associated with a variety of harmful and maladaptive behavior patterns. For example, heroin addiction has been linked to antisocial behaviors and social deviance (Fieldman, Woolfolk, & Allen, 1995), anger and hostility (Steer & Schut, 1981), illegal and reckless behaviors (Darke, Hall, & Swift, 1994), violent crime (Darke, Torok, Kaye, Ross, & McKetin, 2010), and aggression (Gerra et al., 2001, 2004, 2007). The mechanism responsible for the association between opioid addiction and aggression is unclear. One possibility is that individuals with heightened aggressive tendencies may be more likely to abuse opioids (see discussion in Hoaken & Stewart, 2003). Opioid administration also may directly increase aggressive responses. Evidence for this hypothesis has been mixed, however. Many studies with nonhumans have shown that acute opioid administration decreased aggressive responding (for a review, see Hoaken & Stewart, 2003), but studies with humans have shown that acute administration of morphine (Berman, Taylor, & Marged, 1993) and codeine (Spiga, Cherek, Roache, & Cowan, 1990) increased aggressive responses on laboratory aggression tasks.

Opioid withdrawal also may increase aggressive behavior. Several studies with mice have found that morphine withdrawal markedly increased the number and length of attacks to a conspecific (Felip, Rodríguez-Arias, Espejo, Miñarro, & Stinus, 2000; Tidey & Miczek, 1992). Studies with humans have reported that participants in opioid detoxification

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displayed increased aggression and irritability, as shown by subjective effects questionnaires and objective behavioral observations (e.g., Bickel, Stitzer, Liebson, & Bigelow, 1988; Gerra et al., 2000). No laboratory study, however, has yet investigated the effects of opioid withdrawal on aggressive behavior in humans.

One method for evaluating the relation between mild opioid withdrawal and aggression in humans without inducing withdrawal experimentally is to measure behavior in individuals undergoing methadone maintenance therapy (MMT) for opioid dependence. Individuals undergoing MMT typically take one dose of methadone every 24 hrs. Methadone has a half-life of about 22 hrs and blood levels peak 2–4 hrs after administration (Eap, Buclin, & Baumann, 2002). Although not all studies have found behavioral effects across the dosing cycle (McMillan & Gilmore-Thomas, 1996; Torrens et al., 1998), many individuals in MMT report experiencing mild withdrawal before taking their daily methadone dose (Dyer et al., 1999; Hiltunen et al., 1995, 1999). For example, studies have found that objective physical signs of withdrawal, subjective participant ratings of withdrawal (Dyer et al., 1999; Hiltunen et al., 1995, 1999), and sensitivity to stressors (Ilgen, Jain, Kim, & Trafton, 2008) are affected by the passage of time since the last dose. Opioid withdrawal has been shown to be associated with increased reports of negative mood. For example, Dyer et al. (2001) found associations between methadone deprivation and scores on the Profile of Mood States (POMS) questionnaire indicating increased anger, depression, tension, confusion, and fatigue.

Although changes in self-reported negative mood have been related to opioid deprivation, no laboratory or field study has measured aggressive behavior directly in methadone patients across the 24-hr dosing cycle. The results of the studies described above suggest, however, that at the end of the 24-hr dosing cycle, methadone-maintenance patients experience mild withdrawal, which may in turn increase negative mood attributes and may also possibly increase aggressive behavior. Thus, MMT may be a useful model for investigating the effects of opioid deprivation on aggression.

The main purpose of this study was to investigate whether there were changes in aggressive behavior in patients undergoing MMT across mildly opioid deprived and nondeprived states. Performance on a laboratory aggression task, the Point Subtraction Aggression Paradigm (PSAP; Cherek, 1981) was measured on two occasions, once immediately before and once soon after patients received their daily methadone dose. A second purpose of the study was to investigate whether there were differences in reports of mood under the mildly deprived and nondeprived states. Thus, using the POMS questionnaire, ratings of mood were also measured before and after the aggression task in deprived and nondeprived states to assess the effects of PSAP task completion and deprivation condition on mood ratings. The Buss–Perry Aggression Questionnaire (AQ) was administered to determine if there were relationships between trait aggression and aggressive responding on the PSAP during withdrawal. These manipulations therefore aimed to improve the understanding of the relation between opioid use and aggression and provide additional data on whether the mild deprivation occurring across the 24-hr methadone dosing regimen generates any undesirable behavioral or mood changes.

Method

Participants

All methods were approved by the Human Subjects Institutional Review Board. Twelve adults (six females and six males) ages 25 to 52 years (average 36 years) currently on methadone maintenance therapy with a history of opioid dependence participated. Participants were recruited with flyers advertising a study on decision making posted in several methadone clinics in the Mid-west. After completing the informed consent process, participants completed a brief screening survey. Inclusionary criteria required reporting the following: no visual impairments that may affect task completion, taking no psychiatric medications, drinking fewer than 14 alcoholic drinks per week, and the ability to read and understand the instructions. No participants were excluded because of these criteria. Overall, 17 participants completed informed consent. One participant reported being intoxicated and subsequently failed to reschedule sessions. One participant's data were excluded from the analysis after she disclosed that she had taken her methadone dose before experimental sessions on both test days. Three participants failed to complete the second day of testing. Thus, a total of 12 participants completed the study. Of these, nine were Caucasian (75 %), two were Hispanic (16.67 %), and one was American Indian (8.33 %). Length in methadone maintenance treatment ranged from 2 weeks to 9 years ($M = 3.08$ years, $SD = 2.8$). Drug use histories are shown in Table 1.

Apparatus

Sessions were conducted in conference rooms at the methadone clinics. Curtains were used to create a 0.37 square meter cubicle. The cubicle contained a small table with a PC laptop computer, a chair, and a computer mouse. The laptop computer recorded and controlled experimental sessions. Random (pink) noise was generated and played through an individual speaker in each cubicle space.

Procedure

The study required 3 days of participation. On the first 2 days, participants completed a recent drug-use questionnaire to

Table 1 Mean years of drug use (with standard deviation in parentheses) and percent of participants that reported prior use of each drug

Drug	Average	% of Participants
Prescription narcotics (including opioids)	14.58 (*SD* = 11.56) years	100 % (12/12)
Marijuana	12.7 (*SD* = 9.8) years	92 % (11/12)
Powder cocaine	8.85 (*SD* = 9.45) years	83 % (10/12)
Heroin	5.38 (*SD* = 5.32) years	67 % (8/12)
Illicit methadone	2.17 (*SD* = 2.94) years	58.33 % (7/12)
Morphine	5.2 (*SD* = 6.11) years	58.33 % (7/12)
Crack cocaine	4.63 (*SD* = 9.32) years	50 % (5/10)

determine time of last methadone dose and then the Profile of Mood States (POMS) questionnaire (McNair, Lorr, & Droppleman, 1971). Methadone clinic staff verified whether participants received their dose before or after participating in sessions each day. Participants next completed three experimental (PSAP) sessions (six sessions total across the study). Each PSAP session lasted 25 min, followed by a 5-min break. After completing all daily experimental sessions, participants completed a postexperiment questionnaire evaluating whether they actually believed they were working with a partner. The POMS questionnaire was then repeated. On the third day, participants were asked to complete the Buss–Perry Aggression Questionnaire (AQ), which measures trait aggression (Buss & Perry, 1992). Afterward, participants were paid their completion bonus and were partially debriefed. Full debriefing (i.e., information about the social deception) occurred when all participants had completed the study, using a debriefing phone script.

Design

The experiment used a repeated-measures design. Participants were randomly assigned to one of two sequences: deprivation/satiation or satiation/deprivation. Thus, on Day 1, half of the participants ($n = 6$) began the PSAP sessions just prior to receiving their daily methadone. This was approximately 24 hrs after having received their last methadone and was therefore a time at which the participant was expected to experience mild withdrawal. The other half of the participants ($n = 6$) began the PSAP sessions approximately 60 min after receiving their methadone. Because peak effects of methadone occur 120 min after administration on average (Eap et al., 2002), we expected peak effect of methadone to occur during the last (third) experimental session. On Day 2, the testing sequence was reversed, so that those who completed PSAP sessions before receiving methadone took it after, and vice versa. This counterbalancing of test condition (before or after methadone administration) was designed to control for effects of repeated exposure to the PSAP task.

Point Subtraction Aggression Paradigm (PSAP) The laboratory task was the PSAP (Cherek, 1981). In this task participants are provoked by money losses and can respond to subtract money from their partner's earnings. Aggression on this task is therefore defined as responding to present an aversive stimulus (money loss) to another individual. The validity of the PSAP as a measure of aggression has been supported in many studies (e.g., Cherek, Lane, Dougherty, Moeller, & White, 2000; Cherek, Moeller, Schnapp, & Dougherty, 1997; Moeller, Dougherty, Lane, Steinberg, & Cherek, 1998; New et al., 2009), and one prior study has shown that opioid (codeine) administration increased aggression on this task (Spiga et al., 1990).

The PSAP task required responding to stimuli on the screen using a computer mouse. An earnings counter located at the top of the screen began at $0.00 and showed total earnings. The earnings counter never went into the negative. Money subtractions occurred on a variable time schedule with intervals ranging from 6 to 120 s. These subtractions were attributed to the behavior of a fictitious partner who supposedly kept the money taken from the participant. The participant chose between three response options, which were designated on the computer screen with three letters, A, B, and C (left to right, approximately 50.8 mm in height). To choose an option, the participant had to move the mouse pointer over the letter and click. Clicking on a letter caused it to briefly flash and caused the other letters to disappear until the response requirement was completed on the selected option. Button A, the monetary-reinforced option, had a response requirement of 100 mouse clicks to earn money (15¢). Button B was the aggressive response option with a response requirement of 10 clicks. The participant was told that Option B would subtract 15¢ from the counter of their partner, but this money would not be added to their own counter. Option B also produced a time-out from the schedule of money subtractions for a variable time period averaging 125 s, although participants were not told about this contingency. Button C was an escape option with a response requirement of 10 mouse clicks. Option C also produced a time-out from the schedule of money subtractions equal to that of Option B and thus served as a control comparison. One money subtraction was required to occur before responses on Button C or B initiated the provocation-free period. Thus, the number of subtractions could be reduced but not completely avoided.

Before the first PSAP session, participants were given instructions identical to those published in Gerra et al. (2001), except that monetary gains and losses were 15¢ instead of £200. Briefly, the instructions described that the participant was paired with others on the computer task, that the partners could take earnings from the participant, and that participants could choose one of three response options: one for earning money, one for subtracting money from partners' earnings (although this money was not added to their own counter), and one for protecting their earnings against subtractions by partners. If the participant had any questions, the relevant portion of the instructions was re-read to them. On Day 2, all participants reported remembering the instructions and declined offers to have them read again. A written copy of the instructions was left in the cubicle with participants during all sessions.

Earnings

On Days 1 and 2, participants were paid the amount earned during each of the three daily sessions (session earnings averaged $6.64 per hr), plus $2 for every 15 minutes they spent completing questionnaires, listening to the instructions, and being partially debriefed (1 hr total across the study). On Day 3, seven participants were paid an additional amount so that their total earnings averaged at least $8 per hr of participation, and all participants were given a completion bonus of $10. All payments were made in the form of gift cards to large retail or grocery stores, depending on each participant's preference, and were rounded up to the nearest $5. Total earnings (including the completion bonus) ranged from $40 to $55 with a mean of $45.42.

Data Analysis

Data were analyzed using nonparametric statistics due to the presence of outliers and departures from normality. To compensate for the increased potential for Type I error associated with multiple comparisons, the significance level was set at .01.

Results

PSAP Responding

All 12 participants indicated that they believed they were paired with others each day. Thus, data from all participants were included in the analysis. Across participants, the mean self-reported time from methadone administration was 24.3 (±.9) hrs in the deprivation condition and 56.8 (±7.049) min in the satiation condition.

The primary dependent measures on the PSAP were aggressive, escape, and monetary-reinforced responses per session. Figure 1 shows mean responses summed across all three sessions on the PSAP on the three response options during methadone deprivation (predose) and satiation (postdose) conditions. There was no main effect of sequence within condition, so data from the three daily sessions were combined. Individual data are shown in the Appendix. Rates of responding on all measures were similar across conditions. Wilcoxon Matched-Pairs Signed Rank test confirmed no significant effect of deprivation condition on mean monetary-reinforced, aggressive, or escape responses. This analysis also showed no significant effect of deprivation condition on responses when response rates from only the last session of each day were compared.

Figure 2 shows monetary-reinforced, escape, and aggressive responses as a function of session across the six consecutive experimental sessions. A Friedman test revealed a significant increase in monetary-reinforced responses between the first session and the last session ($p = .003$), and a significant decrease in escape responses between the first session and the last session ($p = .006$). There were no significant changes in aggressive responding.

Profile of Mood State (POMS)

There were six missing values for POMS questionnaire data out of 3,835 items. For these analyses, missing questionnaire data were handled as follows: The mean of the scores for that participant in that mood category was used to replace the missing value. Measures on the POMS questionnaire were compared across deprivation and satiation states before completing the PSAP aggression task to assess effects of deprivation on mood independent of task completion, as shown in Fig. 3. Mood on the POMS questionnaire was not affected by deprivation condition. A Friedman test confirmed no significant differences between the composite mood scores when compared prior to task completion on both deprivation and satiation days.

Ratings on the POMS were also compared pre- and post-PSAP task on deprivation and satiation days to evaluate the effects of task completion on mood. Figures 4 and 5 show responses on the POMS questionnaire before and after the PSAP aggression task on both satiation and deprivation days, respectively. Mood on the POMS questionnaire was not affected by the PSAP task. A Friedman test confirmed no significant differences between the composite mood scores when compared prior to and after the computer task on both deprivation and satiation day.

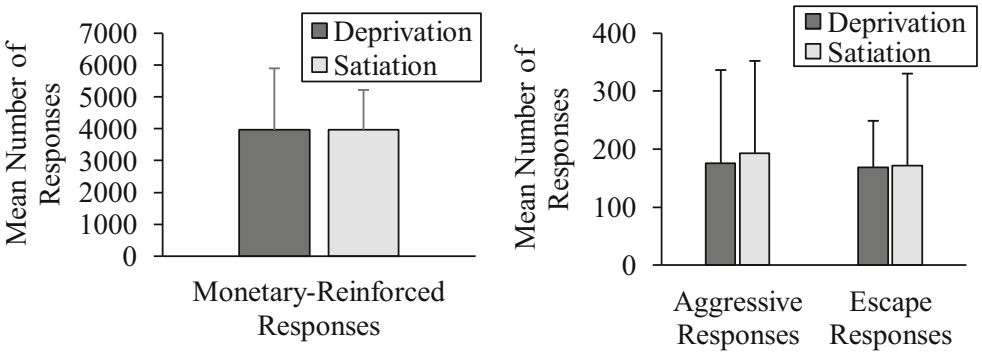

Fig. 1 Mean and standard deviation of aggressive, escape, and monetary-reinforced responses on the PSAP compared on deprivation day and satiation day

Buss–Perry Aggression Questionnaire (AQ)

Total aggression scores on the AQ averaged 83.17 ± 15.7. Mean scores for the subscales were as follows: Physical Aggression, 25.08 ± 8.51; Verbal Aggression, 14.33 ± 3.2; Anger, 18.5 ± 3.92; Hostility, 25.25 ± 3.25.

Correlations

Spearman's correlations found no significant correlations between length in treatment, aggressive responses on the PSAP (in either condition), reports of anger on the POMS, or measures of AQ trait aggression. Aggression responses on the first day of sessions were highly correlated with aggressive responding on the second day, regardless of condition ($p = .02$). There was no relationship between satiation-day aggression scores and change in aggression levels between deprivation day and satiation day. Point-biserial correlations showed no significant gender differences on measures of aggression on the PSAP, POMS, or total AQ scores, or any subscale scores.

Discussion and Conclusions

The goal of this study was to investigate the effects of mild opioid deprivation on aggressive responding during a laboratory aggression task in patients currently undergoing opioid (methadone) replacement therapy. Specifically, performance on the Point Subtraction Aggression Paradigm (PSAP) was

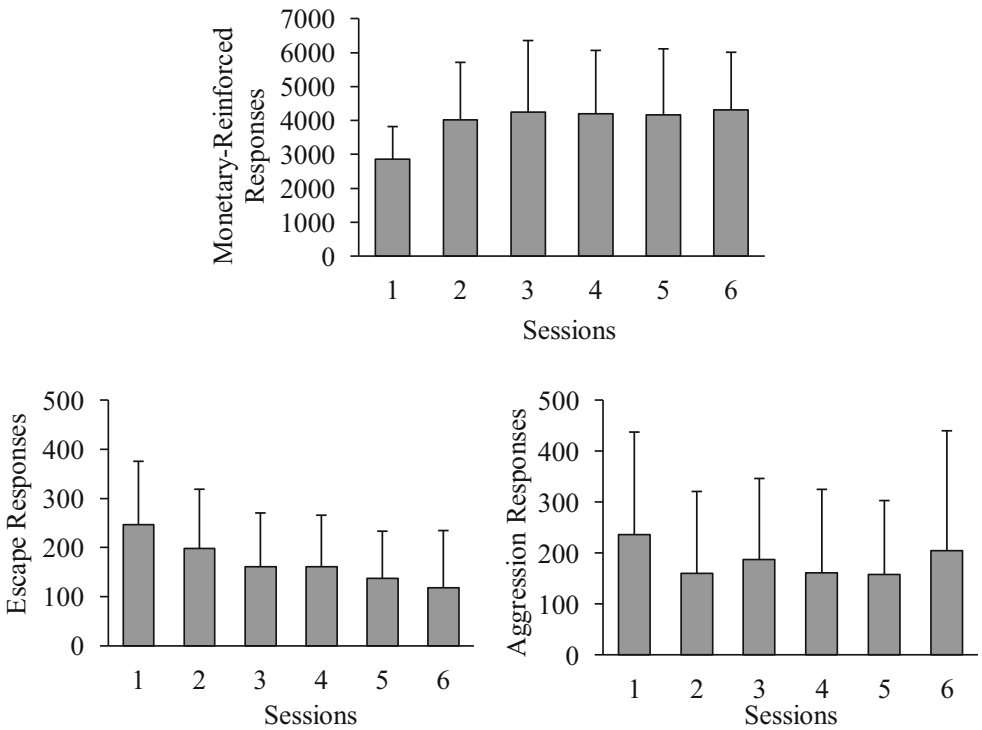

Fig. 2 Mean and standard deviation of monetary-reinforced, escape, and aggressive responses on the PSAP across the six total sessions

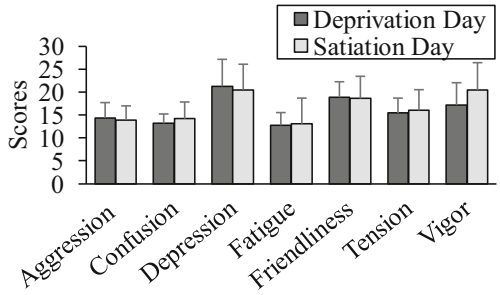

Fig. 3 Mean and standard deviation of responses on the Profile of Mood States (POMS) taken before the Point Subtraction Aggression Paradigm (PSAP) task on deprivation day and satiation day

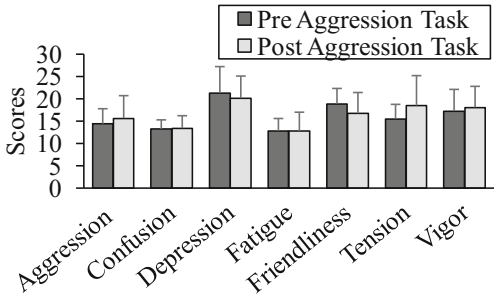

Fig. 5 Mean and standard deviation of responses on the Profile of Mood States (POMS) taken on drug deprivation day before and after completing the Point Subtraction Aggression Paradigm (PSAP) task

measured on two separate occasions, once just before (deprivation day) and once just after (satiation day) patients received their daily methadone dose. Changes in responding on the aggressive, escape-maintained, and monetary-reinforced responses on the PSAP were compared across the two time periods. There were no differences in responding on any measure across deprivation and satiation days.

These findings contrast with studies in nonhumans which have found that aggression increases under opioid withdrawal (Felip et al., 2000; Tidey & Miczek, 1992). Species differences or differences in measures of aggression may be responsible for the discrepant results. It is also possible that the 24-hr deprivation experienced during MMT was not severe enough to influence aggressive responding on the PSAP. In this study, there were no changes in self-reports of mood at the end of the 24-hr dosing cycle (see below). Because negative mood changes were anticipated, no other subjective or objective measures of withdrawal were collected. Thus, it is uncertain whether participants experienced significant opioid withdrawal. Several human studies have found that objective and subjective signs of withdrawal (Dyer et al. 1999; Hiltunen et al., 1995, 1999) poorer decision-making abilities (Gorzelańczyk, Fareed, Walecki, Feit, & Kunc, 2014), and self-reports of increased tension, anger, and irritability (Dyer et al., 2001) occur at the end of the 24-hr methadone dosing cycle; however, not all studies have found these effects (McMillan & Gilmore-Thomas, 1996; Torrens et al., 1998). These findings suggest that in some cases 24 hours may be insufficient to generate significant deprivation. It is interesting to note that studies with nonhumans that have found increases in aggressive responding under opioid withdrawal either investigated behavior after the administration of an opioid antagonist, or after prolonged periods of deprivation. For example, Tidey and Miczek (1992) found that aggression toward a conspecific in mice continued to increase as a function of time since the removal of a morphine pellet at 5, 48, and 96 hrs.

It remains to be seen whether longer deprivation periods and more severe withdrawal are associated with increased aggression in humans. Studies have shown that subjective and objective withdrawal effects grow more severe with time since last dose in MMT patients (e.g., Dyer et al., 2001; Hiltunen et al., 1995, 1999). For example, Hiltunen et al. (1999) found that withdrawal effects began increasing approximately 8 hrs after methadone dose was received and continued to increase until the following dose was given. Withdrawal effects were assessed using the subjective opiate withdrawal scale (SOWS), which is a scale that measures physical withdrawal symptoms as well as changes in mood, and the objective opiate withdrawal scale (OOWS), which is a scale that measures observable physical signs of withdrawal. Dyer et al. (2001) showed increases in negative mood states on the POMS such as anger, tension, and depression until the following dose of methadone was taken. Future research could assess the effects of longer periods of deprivation on aggression by studying aggression in a population that is experiencing extended withdrawal for treatment, such as individuals undergoing heroin detoxification or initiating treatment using an opioid antagonist, such as naltrexone. It would also be useful for future studies to include a variety of subjective and objective measures of withdrawal to better relate aggressive behavior to withdrawal severity.

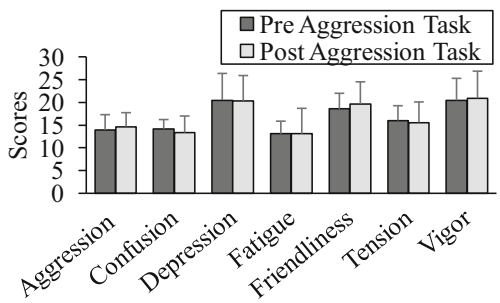

Fig. 4 Mean and standard deviation of responses on the Profile of Mood States (POMS) taken on drug satiation day before and after completing the Point Subtraction Aggression Paradigm (PSAP) task

Another possible explanation for the lack of effect of methadone deprivation on aggressive responding in this study is that the participants may have had a low tendency to engage in aggressive behavior. Prior research has suggested that drug-related changes in aggression may depend on preexisting aggressive tendencies, and that drugs may increase aggression only in individuals who are already prone to act aggressively (Hoaken & Stewart, 2003). For example, Dougherty, Bjork, Bennett and Moeller (1999) found that the level of alcohol-induced aggression on the PSAP was positively correlated with rates of aggressive responding under placebo conditions. To determine whether aggressive tendencies contributed to deprivation effects in the present study, aggressive responding under satiation was correlated with changes in aggressive responding under deprivation. The two measures were not significantly correlated. Additional research with a larger sample showing a wider range of aggressive response rates is needed to better determine if there is a meaningful relation between the two variables.

Overall, rates of aggressive responding on the PSAP in this study were much lower than in prior studies with opioid users. In this study the average number of aggressive responses were 193.4 on the satiation day (and 175.6 on deprivation day), whereas previous studies investigating aggressive responding in nondeprived methadone maintenance patients (of whom 23 %–35 % displayed multiple symptoms of ASPD) found that rates exceeded 300 per 25 min session (e.g., Gerra et al., 2004; Gerra et al., 2001; 2007). In fact, aggressive responding in this study was similar to responding by the control participants in previous studies. Thus, opioid withdrawal may have had minimal effect in this study because participants were not especially likely to respond aggressively.

Trait measures of aggression as measured by the Buss–Perry Aggression Questionnaire (AQ), however, were very similar to AQ scores reported in opioid users in prior studies (Bácskai, Czobor, & Gerevich, 2011; Clair et al., 2009). Thus, although levels of aggressive responding on the PSAP were lower than those reported in prior studies, measures of trait aggression appeared consistent with the elevated measures reported in opioid users. Prior studies have shown, however, that trait measures of aggressive responding are sometimes (Gerra et al., 2001, 2004, 2007), but not always correlated (e.g., Lieving, Cherek, Lane, Tcheremissine, & Nouvion, 2008; Tcheremissine et al., 2005) with rates of aggressive responding on the PSAP. This study also found no correlation between measures of trait aggression on the AQ and aggressive response rates.

Prior research has shown that opioid use tends to decrease cognitive motor performance and psychomotor speed (Mintzer & Stitzer, 2002; Specka et al., 2000). A recent study showed changes in decision-making abilities across the 24-hr methadone dosing cycle, with a higher rate of faulty decisions occurring premethadone dose compared to postdose (Gorzelańczyk et al., 2014). Despite this, there was no effect of methadone satiation or deprivation on monetary-reinforced responses in this study. These results are consistent with a previous study which also found that monetary-reinforced responses on the PSAP were not affected by acute administration of an opioid (codeine; Spiga et al., 1990).

Monetary-reinforced responses increased as a function of exposure to the task. Alternatively, escape responses decreased. These changes presumably occurred because participants learned that earnings could be increased by responding more on the monetary-reinforced option and less on the escape option (additional escape responses within the provocation-free period offered no additional protection from money losses). It is unclear why aggressive responding did not show the same decrease across sessions as escape responding, given that additional aggressive responses during provocation-free periods also were ineffective at initiating another provocation-free-period.

Mild methadone deprivation did not affect participant's self-reported mood on the POMS. This finding is consistent with two previous studies that also found no change in withdrawal symptoms or craving associated with the mild opioid withdrawal related to the 24-hr dosing cycle in MMT (McMillan & Gilmore-Thomas, 1996; Torrens et al., 1998). Contrary to this, several other studies have found that mild withdrawal associated with the 24-hr MMT dosing interval leads to higher tension, anger, and depression on self-report measures such as the POMS (Dyer et al., 2001; Shiran et al., 2012) and higher anxiety levels on the Subjective Opiate Withdrawal Scale (Hiltunen et al., 1995, 1999). Methadone dose (and thus level of withdrawal) may have contributed to these discrepant results. For example, in two of the studies showing an effect of deprivation on mood (Dyer et al., 2001; Hiltunen et al., 1999), half of the participants selected for the study were unhappy with their current dosing level (i.e., reported that the dose was too low) and complained of withdrawal symptoms. Hiltunen et al. (1999) found that participants on lower doses of methadone displayed more severe withdrawal symptoms and were also more likely to be dissatisfied with their dosing levels. Thus, it is possible that changes in mood across the 24-hr methadone dosing cycle are more likely to occur in individuals on low doses or in individuals unhappy with their current dosing level. Further evidence for this hypothesis is shown by studies that have found that subjective and objective measures of opioid withdrawal in methadone maintenance patients across the 24-hr dosing schedule are highly correlated with plasma methadone concentrations (e.g., Hiltunen et al., 1995, 1999). Furthermore, studies have found that mood measured by the POMS improves as methadone dose is escalated in MMT (Greenwald, 2006), or if a

one-time dose increase of 50 % is administered to patients (Strasser et al., 2010). One study that found no effect of deprivation on mood on the Subjective Opiate Withdrawal Scale noted that participants in their study were given higher methadone doses than participants in prior studies (Torrens et al., 1998). Unfortunately, methadone dose and satisfaction with methadone dosage was not assessed in this study. It is possible, then, that opioid deprivation did not affect self-reports of mood in this study because doses were high and participants did not experience withdrawal. Further research is necessary to determine whether negative mood changes across the 24-hr methadone dosing cycle are related to methadone dose.

Aggressive responses on the PSAP were not correlated with POMS scores in any condition, indicating that rates of aggressive behavior were not associated with measures of anger or irritability. There was also no relation between length in methadone treatment and aggression scores on the PSAP, POMS measures, or Buss–Perry measures. This finding is consistent with previous studies which also found no relation between length of opioid use and aggression levels (Gerra et al., 2001, 2004, 2007).

In summary, the mild opioid deprivation associated with methadone maintenance therapy did not produce an increase in aggressive responding in adult humans on a laboratory aggression task. These data suggest that the 24-hr methadone dosing period does not produce deprivation severe enough to induce potentially problematic aggressive behavior. Additional research is needed to determine whether aggressive responding in humans is likely to increase during more severe or prolonged periods of opioid abstinence or in individuals with histories of violent behavior. Future research should also evaluate whether aggression is more likely to change in individuals who are on lower methadone doses or who are unsatisfied with their current dosing level, as these individuals are more likely to show mood changes across the 24-hr MMT dosing cycle.

Compliance with Ethical Standards

Funding This study was funded by a student research award grant from Western Michigan University (no grant number applicable).

Conflict of Interest Author A declares that she has no conflict of interest. Author B declares that she has no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Appendix

Table 2 Individual participant data averaged across three daily sessions during deprivation day and satiation day for PSAP monetary-earning, aggression, and escape responses

Participant number	Monetary-earning deprivation day	Monetary-earning satiation day	Aggression deprivation day	Aggression satiation day	Escape deprivation day	Escape satiation day
901	4,416.00	4,523.67	133.33	76.67	163.33	93.33
902	7,697.67	5,819.67	100.00	156.67	216.67	206.67
903	2,407.33	3,093.33	190.00	196.67	160.00	3.33
904	3,794.67	3,987.33	10.00	33.33	126.67	30.00
905	3,995.00	4,661.00	240.67	0.00	236.67	200.00
906	1,155.00	1,575.33	83.33	399.33	283.00	240.00
907	3,261.67	2,788.67	110.00	130.00	143.33	156.67
908	2,536.33	3,607.33	340.00	276.67	290.00	326.67
909	3,485.00	3,969.67	16.67	273.33	203.33	450.00
910	4,863.00	4,355.67	190.00	116.67	53.00	87.33
911	2,628.33	3,176.67	100.00	110.00	103.33	123.33
912	7,334.33	6,032.33	593.33	550.00	50.00	140.00

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