The Effects of Modafinil Treatment on Neuropsychological and Attentional Bias Performance During 7-Day Inpatient Withdrawal From Methamphetamine Dependence

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The cognitive benefits of modafinil to patients undergoing 7-day inpatient withdrawal from methamphetamine (MA) dependence were examined as part of a double-blind, randomized, placebo-controlled pilot trial. Recent evidence has identified modafinil-related improvements in treatment outcomes for MA-dependent patients; however, the benefits to cognition function, which is critical to treatment success but known to be impaired, has yet to be examined. The first 20 participants recruited to the study were administered either 200 mg of modafinil (once daily) or placebo, and a neuropsychological test battery (including an MA version of the emotional Stroop task) at admission ($n = 17$) and discharge ($n = 14$). Follow-up interviews were conducted at 1-month postdischarge ($n = 13$). After participant withdrawals (3 in each group), treatment was associated with a significant improvement in immediate verbal memory recall and nonsignificant trend toward improvement on executive function and delayed memory tasks. No benefit was seen for measures of verbal learning, visual memory, processing speed, or verbal fluency. All participants showed a significant attentional bias for MA-related stimuli on the emotional Stroop task. The magnitude of bias predicted both retention in treatment and relapse potential at follow-up but was not significantly ameliorated by modafinil treatment. While nonsignificant, the effect sizes of modafinil-related improvements in executive function and memory were consistent with those found in more robustly powered studies of cognitive benefits in attention-deficit/hyperactivity disorder and schizophrenia, supporting the need for further research.

Keywords: methamphetamine, neuropsychological performance, emotional Stroop, attentional bias, modafinil

Use of the stimulant drug methamphetamine (MA) in Australia is more than twice that of other developed countries (United Nations Office on Drugs & Crime, 2007), with over 6% of the population having used MA in their lifetime. The most recent survey of MA use indicates Australia has 81,000 weekly users (0.5% of population) and 178,000 monthly users (1.0%; AIHW, 2008), with 56% of "regular" users meeting the criteria for MA dependence (McKetin, Kell, & McLaren, 2006; McKetin, McLaren, Kelly, Hall, & Hickman, 2005; McKetin, McLaren, Lubman, & Hides,

2006). Effective treatment for MA dependence is critical to circumventing the individual and community harms associated with its use; however, recent statistics indicate low levels of treatment seeking and poor treatment compliance among this group (AIHW, 2007). One factor contributing to this paradox is the absence of a specific pharmacotherapy for MA withdrawal (Lee, Pennay, Harney, Kenny, & Johns, 2007; McLaughlin, McKenna, & Leslie, 2000).

Withdrawal from MA is reported to result in a low level of physical symptomatology that features agitation, insomnia, and fatigue, but includes a more severe level of psychological symptoms, including depression, anxiety, anhedonia, and cognitive dysfunction (McGregor et al., 2005; McGregor et al., 2008). Given the high level of treatment dropout, previous pharmacotherapy has focused on mood and insomnia with medications such as antidepressants, with mixed success (Shoptaw, Kao, Heinzerlin, & Ling, 2009).

Modafinil is a nonamphetamine psychostimulant that was initially approved for the treatment of narcolepsy but was subsequently shown to have success in clinical trials treating cocaine dependence (Anderson et al., 2009; Dackis, Kampman, Lynch, Pettinati, & O'Brien, 2005; Dackis et al., 2003). The pharmacological mechanism(s) of modafinil's action has yet to be clearly determined (see Minzenberg & Carter, 2007, for a review), with effects on multiple neurotransmitter systems including catecholamine, serotonin, glutamate, GABA, orexin, and histamine systems. The cognitive enhancing effects of modafinil have been associated with its action on the binding (or blocking) of dopamine and norepinephrine transporters (Hermant, Rambert, & Duteil, 1991; Madras et al., 2006), and resulting in increased extracellular dopamine in cortical regions critical to cognition (Volkow et al., 2009).

In healthy adults, modafinil has been associated with significant improvements in working memory and executive function (Turner et al., 2003), while sleep-deprived participants have shown more general benefits to attention, psychomotor speed, memory, and executive function (Gill, Haerich, Westcott, Godenick, & Tucker, 2006; Randall, Fleck, Shneerson, & File, 2004; Westcott, 2005). More recently, modafinil has been used to treat cognitive dysfunction in conditions such as attention-deficit/hyperactivity disorder (ADHD; Greenhill et al., 2006; Kahbazi et al., 2009), schizophrenia (Hunter, Ganesan, Wilkinson, & Spence, 2006; Morein-Zamir, Turner, & Sahakian, 2007; Turner, Clark, Pomarol-Clotet, et al., 2004) and where fatigue is a side effect of treating the principal condition (Minzenberg & Carter, 2007). We are not aware of any published research examining the effect of modafinil on drug-dependent groups, and the clinical trials of modafinil for cocaine and MA dependence (De La Garza, Zorick, London, & Newton Heinzerling (2010); McElhiney et al., 2009; McGregor et al., 2008; Shearer et al., 2009) have not examined cognitive performance.

Recent randomized trials of modafinil to treat MA-dependent users (De La Garza et al., 2010; Heinzerling et al., 2010; McElhiney et al., 2009; McGaugh et al., 2009; McGregor et al., 2008; Shearer et al., 2009) have shown the drug to be well tolerated with limited side effects and minimal adverse events (particularly at 200 mg), but none have examined the benefits to cognition.

Current research indicates that cognitive processes are fundamental for the ability to inhibit the immediate pursuit of pleasurable stimuli, and for the development of adaptive patterns of behavior—both key factors in drug dependence (Kalivas & Volkow, 2005). Chronic MA users tested during a nonintoxicated state consistently display cognitive deficits in memory, attention and psychomotor speed, as well as marked deficits on clinical neuropsychological and experimental measures of executive control (Salo, Nordahl, Moore, et al., 2002; Simon et al., 2002). One aspect of executive dysfunction that has become of particular interest in drug dependence research has been the attentional bias, or difficulty controlling attention away from, substance-related stimuli (Field & Cox, 2008). Behavioral studies have shown that processing a nonsalient stimulus in the presence of more salient stimuli represents a significant difficulty for those dependent on drugs such as alcohol (Cox, Brown, & Rowlands, 2003), and heroin (Franken, Stam, Hendriks, & van den Brink, 2003), nicotine (Bradley, Field, Mogg, & De Houwer, 2004; Field, Mogg, & Bradley, 2004) and cocaine (Copersino et al., 2004; Franken, Kroon, & Hendriks, 2000; Hester, Dixon, & Garavan, 2006), with greater bias predicting poorer outcomes during drug-treatment programs (Carpenter, Schreiber, Church, & McDowell, 2005; Cox, Hogan, Kristian, & Race, 2002).The attentional bias is argued to reflect the salience of drug-related stimuli. As salience directs attention relatively automatically, a greater level of cognitive control must be imposed to ignore the salient stimulus and instead attend to a less salient stimulus (Field & Cox, 2008). Recent work has also demonstrated that psychological intervention with alcohol users (Schoenmakers et al., 2010) and pharmacological intervention with stimulant users (Ersche et al., 2010) was associated with a reduction in attentional bias that accompanied improved treatment outcomes. This work highlights the potential usefulness of attentional bias as a cognitive index of relapse potential and treatment effectiveness, though to date attentional bias tasks have not been adapted for use with MA using populations.

Administration of cognitive tests during withdrawal indicate a further acute deterioration in cognition, with MA users tested 7 days after their last use showing marked cognitive deficits on tests of psychomotor speed, attention, memory and executive control (Simon et al., 2004). These results highlight the unfortunate coincidence that during withdrawal, when the requirement for control over one's behavior faces the greatest challenge from both physical and emotional urges to resume drug use, cognitive performance, and executive control in particular, are most impaired. Treatment to assist with cognitive dysfunction may directly assist with these difficulties, as well as providing indirect benefits to treatment such as greater cognitive capacity for engagement in cognitive–behavioral therapy, the principal treatment for MA dependence.

The aim of the present study was to examine the cognitive benefits of modafinil to patients undergoing 7-days of

inpatient withdrawal from MA as part of a pilot, double-blind, randomized, placebo-controlled trial examining a range of treatment outcome measures (reported elsewhere).

Method

Participants

Twenty participants (6 women, mean age = 34.3, range = 21–48) were recruited from two drug withdrawal treatment sites via advertising and word of mouth. Both treatment sites are short-term (5- to 7-day stay) residential withdrawal units located in metropolitan Melbourne. Patients who sought inpatient treatment for MA dependence were offered the opportunity to participate in the trial. Inclusion criteria for the study required patients to be 18 years and over, met the *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition* (*DSM–IV*) diagnosis of current MA dependence but the absence of dependence on any other drug except nicotine and marijuana, and had used MA in the past 48 hours (confirmed via saliva test, *iScreen OFD*, Instant Technologies, Norfolk, VA). Exclusion criteria included not suffering from active psychosis or current major depression, current or past history of conditions with the potential to impair cognition (e.g., stroke, traumatic brain injury, ADHD, epilepsy), returning positive urine screen samples for any drug other than MA, nicotine, or marijuana or presenting with any contraindications for modafinil treatment (e.g., previous adverse reaction, pregnancy, breastfeeding).

Participants were fully informed of the nature of the research and provided written consent for their involvement in accordance with the requirements of the Health Human Research Ethics Committee of Western Health. Participants reported other drug use in the month prior to interview, with the self-reported use detailed in Table 1. Not shown in Table 1 are the frequencies of other illicit drug use. At screening, by self-report about the past 30 days, overall frequency of cocaine use was 7%, heroin 14%, ecstasy 35%, benzodiazepines 71%, alcohol 64%, and cannabis 64%. The groups were not significantly different on these frequency rates.

Treatment

During the 7 days of inpatient treatment, participants took a 200 mg tablet of modafinil, or the matched placebo, once daily upon awakening, from the 1st to the 5th day. On the 6th and 7th days participants in the modafinil treatment group received a 100 mg tablet, to titrate the dose prior to discharge. Modafinil and placebo was purchased, prepared, randomized and dispensed by the study pharmacist. All investigators, doctors, nursing staff, researchers and participants were blind to the medication assignment. Randomizations were created in blocks of four using a computerized randomization program. All participants received general support as usual from the nursing and medical staff and upon completion of the trial were offered standard referral for ongoing support and treatment. Following inpatient discharge, participants did not receive either modafinil or placebo medication.

Assessment Measures

Questionnaires. A battery of questionnaires, the results of which are presented elsewhere, was administered at treatment entry and discharge. They included a range of demographic, drug use history and mental health questions as well as daily clinical measures addressing withdrawal and physiological changes.

Neuropsychological tests. A battery of clinical neuropsychological measures were administered to participants on the day of admission (prior to receiving modafinil or placebo treatment) and on the day of discharge. The measures were chosen to sample performance from a range of cognitive domains previously shown to be impaired in MA dependent participants, including (i) *verbal and visual memory*: Rey Auditory Verbal Learning test (RAVLT), Rey Complex Figure test (RCFT), (ii) *working memory*: Digit Span test, (iii) *psychomotor speed*: Digit-Symbol Substitution test, and (iv) *executive function:* Controlled Oral Word Association test (COWAT), Trail Making test, Stroop Test. Alternate forms were used for all measures and counterbalanced across participants. The baseline assessment also included an administration of the National Adult Reading Test (version 2) to assess premorbid verbal IQ.

MA stroop task. The cocaine-related emotional Stroop task described by Hester, Dixon, & Garavan, 2006) was adapted for the current study. The task presented 3 blocks of 90 trials, interspersed by short rest breaks. The stimuli in the MA-related emotional Stroop included words from each of the following categories: MA-related (e.g., meth, ice) and neutral words (e.g., box, telephone), incongruent (classic Stroop) color words, and congruent color words. The MA-related words, "meth," "ice," "wizz," "powder," "speed," and "louey" were derived from the six most frequently nominated words from a questionnaire completed by 15 active MA-users seen at Turning Point Alcohol and Drug Centre. Each task block presented 72 congruent color trials, pseudorandomly interspersed with 18 "critical" trials (six words from each of the three other word categories). Training prior to the main task familiarized participants with responding to the color of the word stimuli via the keypad of a standard keyboard, with colored stickers indicating the four different response buttons. A single trial presented the word stimulus on a black background where it remained until the participant responded, following which a 250-ms blank screen and a 500-ms fixation cross would be presented prior to the next word stimulus.

Results

Treatment Retention and Compliance

Of the 20 participants recruited to the study, two participants were unable to complete the neuropsychological tests because of illiteracy, and one participant was later found to be ineligible and their data removed. All 17 remaining participants completed the baseline neuropsychological session, three participants did not complete the discharge session, and of these 14 participants one could not be interviewed at the 1-month follow-up session (two participants tested at baseline but not

Table 1

Mean and SEM for Placebo and Modafinil Treatment Groups on: (A) Demographic and Drug Use History, (B) Performance on Neuropsychological Measures at Baseline and Discharge Sessions

	Modafinil		Placebo	
	M	*SEM*	*M*	*SEM*
(A) Demographic Variables				
Age	32.3	2.5	35.3	2.9
Years of education	11.6	0.4	12.3	0.6
Verbal IQ (NART)	99.3	4.6	102.3	4.2
Leeds Dependence Scale	22.1	1.2	23.6	1.5
Brief Symptom Inventory	112.3	13.3	85.7	11.4
Methamphetamine				
Days of use in last month	15.3	1.7	18.0	2.4
No. of uses in last month	89.7	25.3	65.0	20.5
Lifetime duration	10.5	3.2	5.0	1.4
Benzodiazepines	55.4	32.3	28.5	23.4
Alcohol	10.3	4.8	12.8	6.5
Cannabis	221.4	98.4	43.1	28.1
Ecstasy	3.2	1.5	0.1	0.1
Opiates	3.3	2.8	0.0	0.0

	Baseline		Discharge		Baseline		Discharge	
	M	*SEM*	*M*	*SEM*	*M*	*SEM*	*M*	*M*
(B) Neuropsychological measures								
RAVLT Delayed	7.9	1.6	8.6	1.2	7.0	1.6	7.2	1.1
RAVLT Recognition	45.0	1.6	44.1	1.4	44.6	1.6	45.0	1.4
RAVLT Recall B	**3.7**	**0.4**	**5.9**	**0.5**	**4.4**	**0.4**	**4.6**	**0.5**
RAVLT Recall A	9.3	1.4	9.6	1.0	8.3	1.4	8.9	1.0
RCFT Copy	32.2	1.4	31.9	0.8	28.0	1.4	30.6	0.8
RCFT Delay	18.0	2.5	19.6	1.8	16.1	2.5	16.4	1.8
Digits Forward	11.0	0.9	11.0	0.9	11.6	0.9	11.0	0.9
Digits Backward	7.1	0.7	7.3	1.1	6.4	0.7	6.7	1.0
Digit Symbol	55.7	3.5	58.6	3.7	53.9	3.5	54.7	3.7
COWAT Total	44.9	4.8	52.6	6.7	46.3	4.8	52.9	6.7
COWAT Animals	23.7	1.9	26.0	2.3	20.6	1.9	22.9	2.3
Trails A	28.9	2.8	27.7	2.3	32.1	2.8	23.3	2.3
Trails B	64.7	6.7	58.8	9.1	56.9	6.7	66.6	9.1
Trails B-A	35.9	6.0	31.1	8.6	24.7	6.0	43.2	8.6
Stroop Task								
Color	725.9	52.4	681.9	54.9	740.0	62.0	713.1	65.0
Methamphetamine	833.8	54.5	764.4	48.6	833.5	64.5	780.0	57.5
Neutral	776.8	45.4	698.3	39.6	775.1	53.8	751.5	46.8
Incongruent	934.6	71.3	882.2	67.3	1011.3	84.4	966.5	79.7

Note. NART = National Adult Reading Test; RAVLT = Rey Auditory Verbal Learning Test; RCFT = Rey Complex Figure Test; COWAT = Controlled Oral Word Association Test. The measures of drug use in Part (A), unless otherwise stated, represent the self-reported mean number of uses in the last month. The groups did not differ significantly on any of these baseline measures. Significant improvement in neuropsychological performance across sessions as a result of modafinil is highlighted with bolding of text in Part (B).

discharge were also interviewed at follow-up). No adverse events were reported by the sample taking modafinil and participants reported tolerating the medication well.

Follow-up interviews conducted 1 month after discharge indicated 7 of the 13 (3 of 6 placebo, 4 of 7 modafinil) available participants reported using MA in the period following inpatient discharge. Participants also provided a saliva drug test at the follow-up interview, which provided confirmation of MA use during the 48-hr prior. No participant who reported abstaining from MA had a positive saliva test, however 3 participants who self-reported MA use did not test positive due to the MA use being outside the test window.

Neuropsychological Tests

To examine the effect of experimental treatment of neuropsychological test performance, repeated measures analysis of variance (ANOVA) with session (baseline, discharge) as the within-subjects factor and treatment group (Modafinil, Placebo) as the between-subjects factor, was used. Only one measure from the RAVLT memory test, RAVLT Recall B, displayed a significant interaction effect between session and group, $F(1, 10) = 3.72, p < .05$), with performance improving from baseline to discharge for the modafinil group, but not controls. All other test outcomes indicated neither a main effect of session nor an interaction between session and group. The effect sizes (partial eta squared) for interaction effects was typically below $\eta^2 = .10$, and only three measures: RAVLT Recall B ($\eta^2 = .30$), Trails B-A ($\eta^2 = .17$), and Trails B ($\eta^2 = .11$) were above that threshold.

In general, performance on the battery indicated improvement across time for both groups. The data on mean percentage change from baseline to discharge is presented in Figure 1.
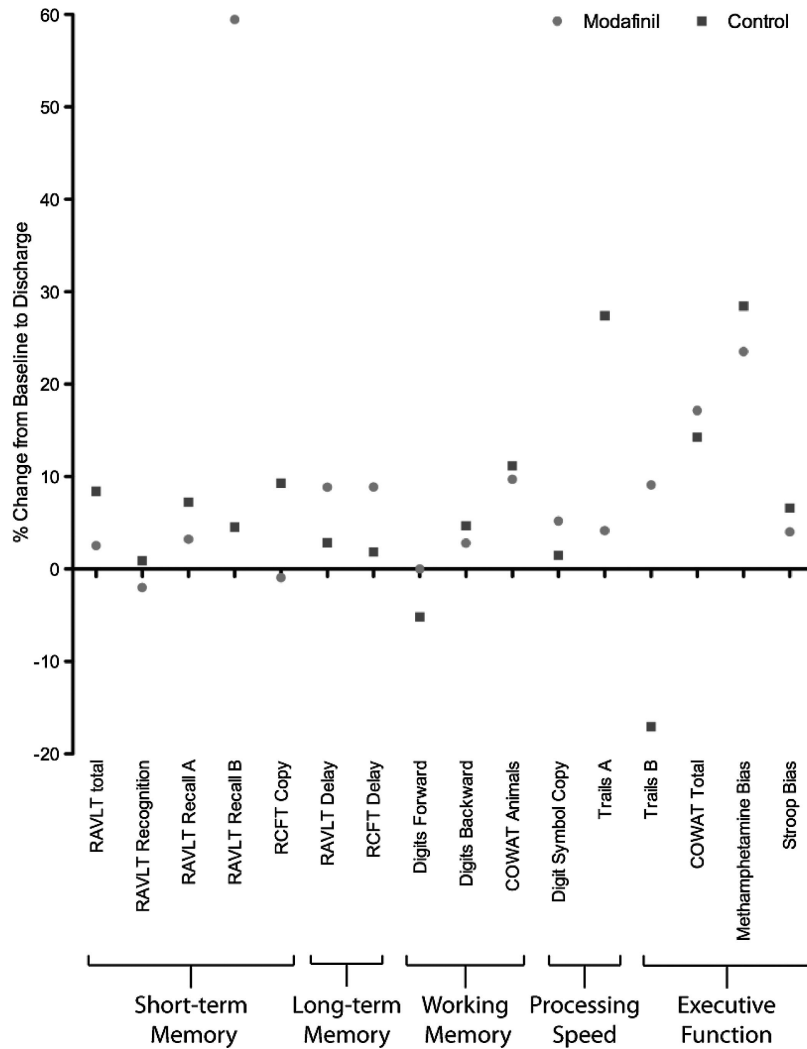
Figure 1. The mean percentage change in cognitive performance from the baseline to discharge session is presented for Modafinil and Placebo treatment groups. Percentage change measures from the Trail Making Test and Emotional Stroop task, where decreases in response time indicate improvement, have been inverted for consistency across measures.

Word Emotional Stroop Task

Accuracy performance for both users and controls was close to ceiling (over 96%) for all categories except Stroop trials, which was around 90% (modafinil = 89%, placebo = 92%). Accuracy rates did not indicate any significant main effects of group, and the interaction between these factors did not reach significance for MA-related words, $F(1, 10) = 2.30$, $p = .15$, $\eta^2 = .19$).

The mean reaction time (RT) and standard error scores for correct responses from both the control and modafinil groups are presented in Table 1. The RTs were analyzed using a $2 \times 2 \times 4$ repeated-measures ANOVA, with group (modafinil, placebo) the between-participants variable and stimulus type (MA, neutral, congruent, incongruent) and session (baseline, discharge) the within-participant variables. There were significant main effect for stimulus type

$F(3, 30) = 41.9$, $p < .01$, and session, $F(1, 10) = 9.31$, $p = .01$, but not group, $F(1, 10) = 0.19$, $p = .66$. The mean RT data indicate response times for the discharge session were significantly faster than during baseline, and response times for all stimulus type conditions were significantly different ($p < .01$ for all post hoc comparisons), with congruent, neutral, MA and incongruent the order from fastest to slowest. The interaction between group and stimulus type was nonsignificant, $F(1, 10) = 0.55$, $p = .47$.

To examine executive dyscontrol for MA-related stimuli an attentional bias score was calculated by subtracting the response time to neutral words from MA-related words. Participants showed a significant attentional bias for MA-related words at both baseline: 57ms ($SD = 68$), $t(11) = 2.90$, $p = .01$, and discharge: 50 ms ($SD = 44$), $t(11) = 3.95$, $p < .01$. A repeated measures 2 session $\times$ 2

Group ANOVA indicated neither a main effect of session, $F(1, 10) = 0.54$, $p = .48$, group, $F(1, 10) = 0.57$, $p = .57$, nor an interaction between session and group, $F(1, 10) = 1.91$, $p = .20$, $\eta^2 = .19$. The same pattern of results was demonstrated for Incongruent "Stroop" trials, whereby both sessions indicated a significant difficulty responding to the words (greater than neutral), but no main effect of session, group, or interaction.

A Pearson correlation coefficient analysis examined the relationship between bias scores and behavioral measures of treatment retention and relapse. Relapse is defined as self-reported use of MA following inpatient discharge. The baseline MA-bias score significantly correlated with the number of days retained in treatment ($n = 15$, $r = -.60$, $p = .019$), but did not reach significance for self-reported relapse at follow-up ($n = 13$, $r = -.42$, $p = .17$). The relationship between individual differences in the discharge MA-bias score and the number of self-reported MA uses during the period between discharge and follow-up ($n = 13$, $r = .54$, $p = .07$), also failed to reach significance. The direction of these relationships indicate that greater bias for MA-related words was related to increased risk of early discharge from treatment, relapse following treatment and MA usage postrelapse.

The Incongruent Stroop bias score was not significantly related to any of the aforementioned measures of MA-use behavior.

Discussion

The results of this pilot randomized controlled trial indicate that a 7-day inpatient withdrawal treatment administering modafinil to dependent MA users improved performance on a measure of immediate verbal memory (RAVLT List B recall). Measures of delayed memory recall (RAVLT delayed recall, RCFT delayed recall) and executive function (Trails Making Test Part B, Stroop bias and accuracy scores) all demonstrated a nonsignificant trend toward improved performance during modafinil treatment; however, the effect sizes were in the small category ($\eta^2 = .10-.20$).

The neuropsychological performance of the current sample is also consistent with previous evidence of cognitive deficits observed in active and abstinent MA users (for reviews, see Meredith, Jaffe, & Ang-Lee, 2005; Nordahl, Salo, & Leamon, 2003; Scott et al., 2007), particularly in the domains of memory and learning (Gonzalez, 2004; Kalechstein, Newton, & Green, 2003), psychomotor speed (Volkow, Chang, Wang, Fowler, et al., 2001), and executive function (Cherner et al., 2010; Monterosso, Aron, Cordova, Xu, & London, 2005; Salo, Nordahl, Possin, Leamon, M., & Gibson, 2002; Salo et al., 2005; Simon et al., 2004; Simon, Dean, Cordova, Monterosso, & London, 2010). With prolonged abstinence (of at least 12 months), there is some recovery of function (Iudicello et al., 2010); however, over shorter periods of abstinence neuropsychological performance has been shown to decline further (Mccann et al., 2007; Simon et al., 2004; Simon et al., 2010). MA-related cognitive deficits have also been linked to a variety of cortical differences between MA users and matched controls, including fronto-cortical dysfunction (London et al., 2005; Monterosso et al., 2007; Paulus, Tapert, & Schuckit, 2005; Thompson, 2004), dopaminergic transporter levels (Mccann et al., 2007; Volkow, Chang, Wang, Fowler, Franceschi, et al., 2001; Volkow, Chang, Wang, Fowler, et al., 2001), and striatal dopamine receptor levels (Lee et al., 2009).

The small sample size in the current pilot study did not provide the statistical power to detect small effects; however, it is of note that previous studies with larger samples have detected clinically significant benefits from modafinil treatment to cognitive performance in patients with ADHD (Turner, Clark, Pomarol-Clotet, et al., 2004b)–Digit Span Forwards $\eta^2 = .28$, delayed pattern recognition memory $\eta^2 = .24$, Stop Signal RT $\eta^2 = .26$) and Schizophrenia (e.g., Turner, Clark, Dowson, Robbins, & Sahakian, 2004): Digit Span Forwards $\eta^2 = .19$, Digit Span Backwards $\eta^2 = .13$, Tower of London extra dimensional shifts $\eta^2 = .26$).

These previous results highlight the potential to identify significant improvements in performance as a result of modafinil treatment, given the magnitude of effect sizes we have detected in the pilot study, with additional data collection. While larger studies of modafinil treatment for MA dependence have been conducted (De La Garza et al., 2010; Heinzerling et al., 2010; McElhiney et al., 2009; McGregor et al., 2008; Shearer et al., 2009), none have to date examined the influence on cognitive function. While our results are preliminary, it is hoped that the trend of results from this pilot study prompt larger scale studies to include cognitive testing. Recent work by Ersche and colleagues (2010) has demonstrated the potential to improve cognitive performance (specifically reducing attentional bias for drug-related stimuli), in stimulant dependent patients using pharmacological intervention. Given the relationship between cognitive control, attentional bias and abstinence in stimulant users (Carpenter et al., 2005; Copersino et al., 2004; Streeter et al., 2008), evidence for the efficacy of such medications in improving cognition would be of great value.

The procedure of tailoring the modafinil dose from 200 mg to 100 mg on the two days prior to the discharge testing session may also have diminished the benefit derived from modafinil to cognitive performance. Animal and blinded controlled trials in healthy and nonpsychiatric populations (e.g., narcolepsy) have demonstrated dose-related effects on cognition when moving from 100 mg to 200 mg (Minzenberg & Carter, 2007).

Our participants' drug-use histories showed that, at baseline, the modafinil group had a greater duration (10 vs. 5 years) and recent frequency of MA use, as well as nonsignificantly higher levels of recent benzodiazepine, cannabis, ecstasy and alcohol use. These factors might indicate a higher severity of illness in the modafinil treated group, which has the potential to obscure any medication effect and bias outcomes toward a null result.

The finding of a significant attentional bias for MA-related stimuli adds to a growing literature demonstrating similar drug-specific effects in almost all drug dependent groups (Field & Cox, 2008). A strong relationship between

baseline levels of MA-related attentional bias and treatment retention, and discharge levels of bias and relapse rates is consistent with similar findings in heroin (Marissen et al., 2006), nicotine (Waters et al., 2003) and alcohol (Cox et al., 2002) samples. These findings support the association between attentional bias and drug craving and highlight the potential of using this cognitive task as an objective index to track changes in craving and in turn risk for relapse (Field, Munafo, & Franken, 2009).

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