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Feasibility and acceptability of approach bias modification during methamphetamine withdrawal and related methamphetamine use outcomes

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ABSTRACT

Approach bias modification (ApBM), a computerised cognitive training task which aims to reduce automatic, impulsive responding to drug-related cues, has been found to reduce alcohol consumption among individuals seeking treatment for their drinking. However, this approach has not been trialled in patients with methamphetamine use disorder (MUD), where altered impulsivity and reward processing are well-established. As such, this study aimed to examine the feasibility and acceptability of four consecutive days of ApBM training during a residential admission for methamphetamine withdrawal. Abstinence rates were examined 2-weeks and 3-months post-discharge. In terms of uptake, 52 of the 99 eligible patients approached agreed to participate and 47 of these 52 commenced training. Uptake and training completion rates (62%) were lower than those achieved in similar trials of ApBM for residential alcohol withdrawal, suggesting there are challenges to its delivery in this setting. This is likely due to the severity of acute methamphetamine withdrawal syndrome and associated behavioural characteristics. However, participants' ratings of the task and reports of post-session craving suggest acceptability was high. Abstinence rates were 61% at 2 weeks and 54% at 3-months, which compare favourably with the abstinence rates observed in a previous large treatment outcome study. The evidence of acceptability and apparent effectiveness suggest future trials of ApBM with MUD patients are warranted. However, ApBM may be more feasible in certain settings or among particular sub-groups where patients are more clinically stable and therefore more likely to complete the training (e.g., residential rehabilitation, after acute withdrawal has subsided).

1. Introduction

Globally, the use of amphetamines, particularly methamphetamine, has escalated, with the number of users rising from 24 to 34.2 million between 2006 and 2017 (UNODC, 2007; UNODC, 2018). In Australia, presentations to alcohol and other drug (AOD) treatment by people with methamphetamine as their primary drug of concern (PDOC) have more than doubled between 2011–12 and 2016–17 (AIHW, 2013; AIHW, 2018), becoming the second most common PDOC (after alcohol). Withdrawal management (i.e., "detoxification") is the second most common treatment accessed by people with amphetamines as PDOC, after counselling (AIHW, 2018). However, the MATES project, Australia's largest treatment outcome study of people with methamphetamine use disorder (MUD), showed that < 20% of people remained abstinent 3-months following residential withdrawal programs, with > 50% using methamphetamine at least weekly by this point (McKetin et al., 2012). This highlights the need for brief, adjunctive treatments that delay relapse and that can be easily delivered within

Abbreviations: AAT, alcohol approach-avoidance task; ApBM, approach bias modification; AtBM, attentional bias modification; AUD, alcohol use disorder; CBM, cognitive bias modification; MCQ, methamphetamine craving questionnaire; MoCA, Montreal cognitive assessment; MUD, methamphetamine use disorder; SCID-5-RV, structured clinical interview for DSM-5 disorders – research version; SDS, severity of dependence scale; TLFB, timeline follow-back; VAS, visual analogue scale

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these settings.

According to the dual process model, addiction arises from both an underactive 'top-down' executive control system and an overactive 'bottom-up' impulsive motivational system (Bechara, 2005). Overactivity in the impulsive system arises as a result of numerous associative learning experiences, in which the rewarding effects of the drug are paired with various sensory cues, including environmental and social contexts. These drug-related associations become sensitised (i.e., very easily, rapidly and strongly activated), such that re-exposure to these cues (or even memory of them) elicits drug craving (Field & Cox, 2008). These drug expectancies lead to cognitive biases, including attentional bias (the tendency for our attention to be selectively captured by drug-related cues) and approach bias (the automatic action tendency to approach drug-related cues due to their attributed motivational salience) (Cox, Klinger, & Fadardi, 2015; Wiers, Rinck, Dictus, & van den Wildenberg, 2009). Over time, with heavy ongoing substance use, an individual's behaviour becomes increasingly governed by these cognitive biases making relapse more likely when trying to abstain (Field & Cox, 2008). These cognitive biases become particularly influential on behaviour in the context of poor executive control (e.g., planning, decision-making and impulsivity), which is a common characteristic among people with MUD, alongside altered reward processing (Potvin et al., 2018). Research has shown that attentional and approach bias can be dampened through cognitive bias modification (CBM); computerised training programs that re-train cognitive biases, including approach bias modification (ApBM) and attentional bias modification (AtBM).

Several studies have shown that ApBM can reduce approach bias (Wiers, Rinck, Kordts, Houben, & Strack, 2010) and reduce relapse after treatment for people with alcohol use disorder (AUD) (Eberl et al., 2013; Manning et al., 2016; Rinck, Wiers, Becker, & Lindenmeyer, 2018; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011). In ApBM programs developed for AUD, participants repeatedly practice "avoiding" alcohol-related images displayed on a computer screen (using a joystick to "push" these images "away"). We recently conducted the first pilot study of ApBM for AUD patients undergoing residential withdrawal and found that delivering 4 sessions of ApBM in this context was both feasible and effective in reducing rates of relapse post-discharge (Manning et al., 2016). ApBM has also been found to be superior in reducing drinking compared to AtBM, at one- and three-month follow-up (Wiers et al., 2015). Furthermore, ApBM has shown promise in a number of tobacco smoking cessation trials (Kong et al., 2015; Machulska, Zlomuzica, Rinck, Assion, & Margraf, 2016; Weckler et al., 2017) and in a recent pilot randomised controlled trial (RCT) for cannabis use disorder (Sherman, Baker, Squeglia, & McRae-Clark, 2018). While a recent small study found no evidence for the efficacy of AtBM in MUD patients undergoing residential rehabilitation (Dean et al., 2018), to date, ApBM has not yet been examined in MUD populations. Given the costs of conducting RCTs, it is firstly important to establish whether ApBM is acceptable to patients with MUD (i.e., if exposure to methamphetamine images is well-tolerated or too distressing) and if ApBM is feasible in settings where it potentially may be applied, including residential withdrawal.

The aim of the present study was to examine the feasibility and acceptability of ApBM during residential withdrawal from methamphetamine. We predicted high rates of uptake and completion of training (demonstrating feasibility), low rates of withdrawal from the study and positive ratings of the ApBM task from participants (demonstrating acceptability). Rates of abstinence from methamphetamine at 2-week and 3-month follow-ups were also examined and compared to rates reported following residential withdrawal in the MATES study (McKetin et al., 2012).

2. Method

2.1. Design, participants, and setting

This study was a single-group, open-label feasibility trial. Forty-seven patients from three inpatient withdrawal units in the Melbourne metropolitan area with moderate or severe MUD were recruited and commenced ApBM training. Treatment as usual at the recruitment sites primarily focused on medical management of acute withdrawal symptoms (e.g. with medications such as benzodiazepines) and participants typically also attended daily group therapy sessions addressing psychosocial issues (e.g. relapse prevention, life planning skills, art therapy, etc.). Planned treatment duration was typically 7 to 10 days, but due to unplanned early discharges by some participants, and longer treatment duration among other participants, actual duration of treatment among those who commenced training ranged from 3 to 15 days (mean = 8.2 days, SD = 2.9 days). Participants were required to be proficient in English and able to provide a phone number to be contacted for follow-up. Exclusion criteria were neurological illness, intellectual disability, traumatic brain injury (with loss of consciousness of 30 min or more), or being too acutely unwell or unstable to participate. Clinicians at the recruitment sites screened participants for these exclusion criteria and referred those who were eligible to the research team.

2.2. Measures

2.2.1. Demographic characteristics and clinical history

A researcher-administered questionnaire recorded date of birth, identified gender, country of birth, Aboriginal or Torres Strait Islander status, education, relationship status, employment, housing, age of onset of methamphetamine use and methamphetamine-related problems, history of prior withdrawal treatment, other drugs of concern, family history of substance use disorder, and psychiatric diagnoses.

2.2.2. MUD diagnosis and severity

The Structured Clinical Interview for DSM-5 Disorders – Research Version (SCID-5-RV) (First, Williams, Karg, & Spitzer, 2015) substance use disorder module was used to confirm the presence of moderate-severe MUD severity (i.e. at least 4 criteria) and to quantify the number of MUD criteria participants met during the past year. The Severity of Dependence Scale (SDS) (Gossop et al., 1995) was also used to measure severity of psychological dependence on methamphetamine during the past year.

2.2.3. Recent substance use

The timeline follow-back (TLFB) (Sobell & Sobell, 1996) method was used to assess the frequency and quantity of methamphetamine and other psychoactive substances consumed in the 30 days immediately preceding admission at the baseline interview; the 14 days following discharge at the 2-week follow-up; and the 30 days preceding the 3-month follow-up.

2.2.4. Cognitive impairment

The Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) was used to measure cognitive impairment. MoCA scores can range from 0 to 30, with scores below 26 indicating cognitive impairment.

2.2.5. Methamphetamine craving

The Methamphetamine Craving Questionnaire (MCQ) was used to assess cravings for methamphetamine. This is an adapted version of the Cocaine Craving Questionnaire (Sussner et al., 2006), created for this study, with the word "cocaine" replaced with "methamphetamine". Scores on the MCQ can range from 1 to 7, with higher scores indicating stronger craving. In addition, a single-item visual analogue scale (VAS)

for methamphetamine craving was administered before and after every ApBM session to monitor whether the sessions were triggering/inducing craving. Participants were asked to mark a line, which was anchored at the left and right ends with “not at all” and “extreme”, respectively, to indicate the current strength of their methamphetamine cravings. Scores on this measure could range from 0 to 100, with higher scores indicating stronger craving.

2.2.6. Acceptability ratings

Following the final session of the intervention, participants completed a 3-item rating of their experience of ApBM assessing whether or not they believed that it had (i) improved their attention, (ii) reduced their craving for methamphetamine, and (iii) was interesting. Response options were “strongly agree”, “agree”, “unsure”, “disagree”, and “strongly disagree”.

2.3. Intervention

For the ApBM we adapted the alcohol approach-avoidance task (AAT) (Wiers et al., 2010), using methamphetamine-related imagery in place of alcohol imagery. Participants were instructed to attend to the orientation (landscape or portrait) of the frames of a series of digitally-presented images, and respond to the pictures, using a joystick. Participants were instructed to perform a push motion (i.e., arm extension) in response to landscape-oriented images (which always contained methamphetamine-related images, e.g., crystal and powder methamphetamine, paraphernalia such as glass pipes and syringes, images of people smoking glass pipes or injecting). This push motion progressively shrank the size of the image, to simulate the image “receding” into the “distance”, thus creating the impression that the stimulus was being “avoided”. Participants were instructed to perform a pulling motion on the joystick in response to portrait-oriented images (which always contained non-drug stimuli, which were images of fruit or vegetables), which progressively increased the image size simulating an “approach” effect. The task had 40 unique methamphetamine-related images and 40 unique fruit/vegetable images, each presented 3 times per session (i.e., 240 image presentations per session) in a random order, with a 500 millisecond inter-trial interval. Incorrect responses caused a large red cross to briefly appear on screen before the presentation was repeated. Each session began with 8 practice trials featuring empty ‘frames’ to remind participants of the task requirements. The AAT was presented to participants using E-Prime 2.0 software (Psychology Software Tools, 2016).

2.4. Procedure

Clinical staff at the recruitment sites notified researchers when potentially-eligible patients were admitted for methamphetamine withdrawal. Researchers approached patients no sooner than the third day of their admission to provide a verbal and written explanation of the study and asked them to sign a written consent form if they agreed to participate. Prior to the first training session, researchers administered the demographic and clinical questionnaire, TLFB, SCID-5-RV, and MoCA, and collected contact details for follow-ups. Participants self-administered the MCQ and SDS prior to commencing the first session of ApBM.

The first session of ApBM commenced on the same day or the day after the baseline questionnaires. Sessions lasted around 15 min and were repeated once daily on the following 3 days (4 consecutive sessions in total). Due to the sites' schedule of activities (e.g. group therapy and psychoeducational sessions) that participants were expected to attend, sessions were scheduled to avoid disruption of or clashes with these activities, and thus could occur at any time of day, depending when was most convenient, but typically occurred between 10:00 AM and 7:00 PM. Immediately before and after each training session, participants completed the single-item VAS craving measure. After the fourth training session they completed the MCQ and rated the acceptability of the training and were remunerated with a $30 supermarket gift card. Due to the variation in participants' duration of residential treatment, the number of days between the last completed session of ABM and discharge ranged from 0 to 8 days (mean = 2.1 days, SD = 1.9) A researcher contacted participants to conduct telephone interviews assessing drug use outcomes 2-weeks and 3-months post-discharge. Participants were sent a $10 gift card for each completed follow-up. This study was approved by the Eastern Health Human Research Ethics Committee (E03-2017) and St Vincent's Hospital Melbourne Human Research Ethics Committee (207/17).

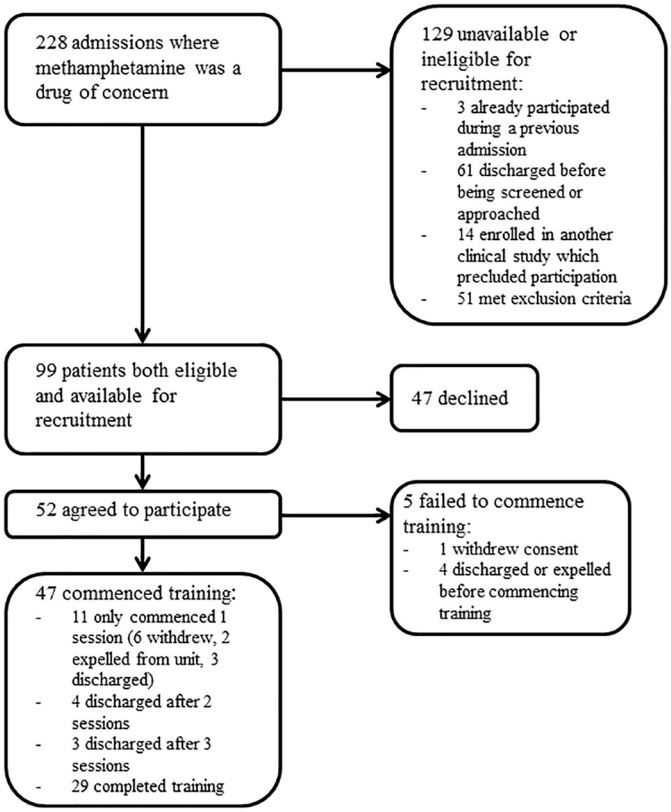

Fig. 1. Screening and recruitment flow diagram.

3. Results

3.1. Uptake

Of the 99 patients eligible and available for recruitment, 52 (53%) provided consent to participate and 47 (47%) commenced training (see Fig. 1 for participant flow).

3.2. Participant characteristics

The demographic and clinical characteristics of the 47 participants who commenced ApBM training are shown in Table 1. Nearly all participants were unemployed, and approximately one quarter were in unstable accommodation (i.e., homeless, boarding house, shelter or refuge). Approximately three-quarters reported having a current psychiatric diagnosis, with depression (57%), anxiety disorders (47%), post-traumatic stress disorder (17%), and psychotic disorders (13%) being the most common types of diagnoses. Nearly two-thirds had undergone previous episodes of detoxification for substance use (although not necessarily for methamphetamine).

More than half cited additional drugs of concern; including cannabis (30%), heroin/other opioids (26%), alcohol (17%), GHB (4%), and

Table 1
Participants' characteristics.

	M/n	SD/%	Range
Age (years)	34.67	7.35	23.60–50.06
Gender (n/% female)	22	47	
Born in Australia (n/%)	43	91	
Aboriginal or Torres Strait Islander	6	13	
Unemployed (n/%)	42	89	
Did not complete year 12 at school	38	81	
No stable accommodation (n/%)	12	26	
Any current psychiatric comorbidity[a] (n/%)	34	74	
Additional drugs of concern (n/%)	26	55	
Current daily[b] tobacco smoker	43	91	
Family history of SUD (n/%)[a]	34	74	
Age of first use of any illicit or non-prescribed amphetamine-type substance (M/SD)	19	6	10–40
Total days of methamphetamine use in the month prior to admission (M/SD)[a]	21.04	8.92	3-30
Total estimated grams of methamphetamine used in the month prior to admission (M/SD)[a]	11.37	12.90	1.00-60.00
Mean grams of methamphetamine used per use day in month prior to admission (M/SD)[c]	0.53	0.48	0.06-2.00
SDS score	10.00	2.97	3–15
SCID-5-RV number of MUD symptoms	10.36	0.99	7–11
Any previous detoxification episodes	25	62	
MoCA score[c]	25.18	3.84	10–30

M: mean, MoCA: Montreal Cognitive Assessment, MUD: methamphetamine use disorder, SCID-5-RV: Structured Clinical Interview for DSM-5 Disorders (Research Version), SD: standard deviation, SDS: Severity of Dependence Scale, SUD: substance use disorder.

[a] Data missing for 1 participant, thus N = 46 for these data.

[b] Reported using tobacco on the majority of the 30 days prior to admission.

[c] Data missing for 2 participants, thus N = 45 for these data.

cocaine (2%). Forty-two (89%) participants cited methamphetamine as their PDOC, while the remaining 5 participants all cited it as their second-most concerning substance. Among these 5 participants for whom methamphetamine was the second drug of concern, 2 cited opioids as their PDOC and 3 cited cannabis as their PDOC. SDS and SCID-5-RV scores and past-month methamphetamine use data shown in Table 1 suggest high severity of MUD, with all participants meeting the DSM-5 criterion for severe MUD (i.e., ≥6 of the 11 possible symptoms) and 29 (62%) endorsing all 11 symptoms. Smoking and injecting were the only routes of administration reported for past-month use, with 56% reporting exclusively smoking, 31% exclusively injecting, and 13% both smoking and injecting. MoCA scores suggested a high rate of cognitive impairment, with half (49%) of participants scoring in the impaired range (i.e., 25 or less).

3.3. Completion and withdrawal rates

Of the 47 participants who commenced training, 29 (62%) completed the 4-session protocol. Failure to complete all 4 sessions was due to early discharge from the withdrawal unit (15%), missing sessions due to being asleep, unwell, or uncooperative (6%), being expelled from the withdrawal unit due to possession of drugs (4%) or withdrawing consent (13%). Reasons for withdrawal were recorded by researchers and, of the 6 participants who withdrew, 4 (9% of the 47 participants who commenced training) reported that this was due to the task being triggering or distressing, while the other 2 participants cited stressors unrelated to study participation as the reason for withdrawal.

3.4. Cravings

MCQ scores were generally low (session 1: N = 46, mean = 2.63, SD = 1.25; session 4: N = 29, mean = 2.10, SD = 0.84), but a paired-samples *t*-test showed that the decline between these sessions in the 29 participants who completed the MCQ both pre and post-training was

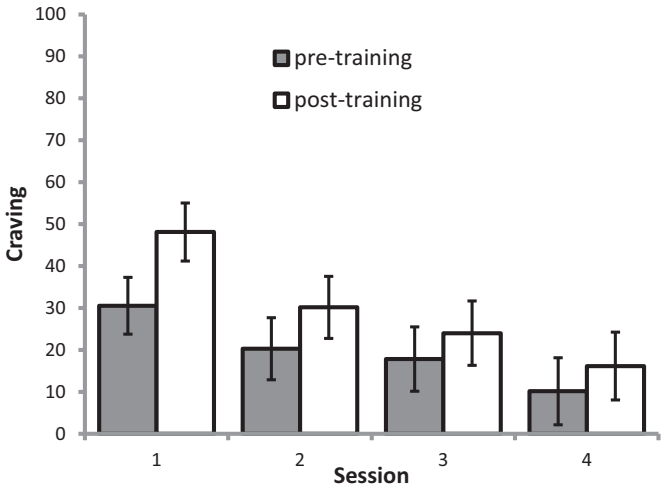

Fig. 2. Mean ratings on the single-item visual analogue scale before and after each session. Error bars show 95% confidence interval of the means.

statistically significant ($t(28) = 4.11$, $p < .001$). Mean ratings on the single-item craving VAS are shown in Fig. 2. Linear mixed modelling showed that pre-training craving ratings diminished over sessions 1–4 ($p = .005$, $p = .001$, and $p < .001$ for contrasts comparing sessions 2, 3, and 4 to session 1, respectively). There was a significant increase in craving after session 1 ($p < .001$), but tests of the interactions between the within-session increase in craving and the contrasts between session 1 and later sessions showed that the acute within-session increase in craving was significantly smaller in sessions 3 ($p = .030$) and 4 ($p = .036$) than in session 1. The within-session increases in cravings during sessions 3 and 4 were non-significant (both ps > .122).

3.5. Participants' task ratings

Ratings of the training tasks were collected from 36 participants (see Fig. 3). In terms of acceptability, 75% either 'agreed' or 'strongly agreed' that the task improved their attention and 78% 'agreed' or 'strongly agreed' that it was interesting. However, only around one-third (36%) felt it reduced their cravings for methamphetamine.

3.6. Follow-up methamphetamine use

Of the 47 participants, 6 withdrew and 2 participants' follow-ups were not pursued due to uncooperative or threatening behaviour, and follow-ups were therefore pursued only for the remaining 39 participants, of whom 31 completed the 2-week follow-up (79% of those pursued, 66% of the total sample). Of these 31 participants, 19 (61%) reported no methamphetamine use during the 2-weeks since discharge. Of the 12 who did report using methamphetamine, half (n = 6) used it on only 1 day in that 2-week period (mean = 2.7 days use). The mean total amount of methamphetamine used among these participants per using day was 0.20 g (SD = 0.10).

Of the 39 participants pursued for 3-month follow-ups, 26 were successfully contacted, with time since discharge ranging from 90 to 156 days (mean = 98.7; median = 94.5) at the time of the follow-up. Fourteen participants (54%) reported abstaining from methamphetamine in the 30 days prior to the follow-up, although this estimate is limited by the low 3-month follow-up rate (follow-up only completed by 67% of the 39 pursued, or 55% of the total sample of 47). Of the 12 who reported using methamphetamine, mean days of use in the past 30 days was 12.1 days (median = 5 days) and a paired-samples *t*-test showed that this was a significant reduction compared to their frequency of methamphetamine use in the 30 days prior to admission to the withdrawal unit ($t(9) = 2.767$, $p = .022$). The mean total amount

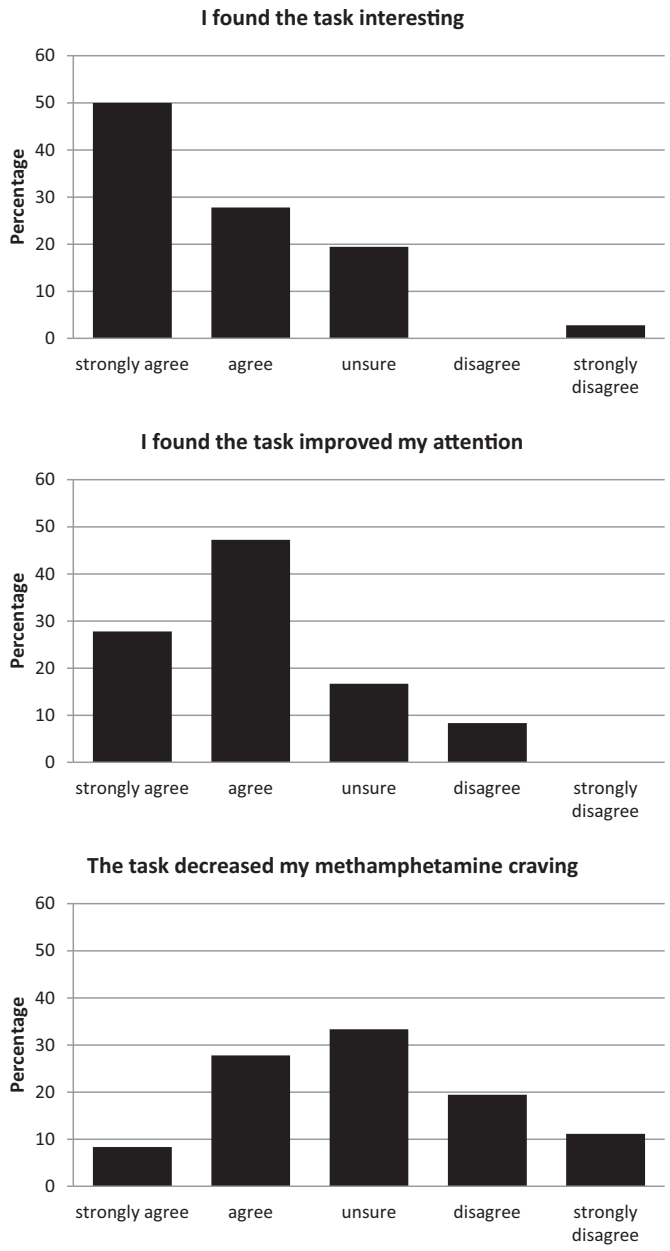

Fig. 3. Proportion of participants endorsing each rating option for whether approach bias modification was interesting (top), improved attention (middle), and reduced craving (bottom).

of methamphetamine consumed over this 30-day period among those who used any was 0.21 g (SD = 0.30) per using day. Among those who used any methamphetamine at the 3 month follow-up, changes in mean grams used per using day ($t(7) = 1.775$, $p = .199$), relative to the 30 days prior to admission to the withdrawal unit were non-significant, but numbers of participants for these analyses were very small and lacking in statistical power.

4. Discussion

This open-label pilot study aimed to test the feasibility and acceptability of a novel ApBM intervention for methamphetamine use delivered during residential withdrawal. The uptake (i.e., the proportion of eligible participants who engaged in ApBM training) was approximately half of that observed in our earlier study (Manning et al., 2016) with patients undergoing alcohol withdrawal (47% versus 93%) despite both studies being conducted in the same setting. Similarly, the proportion completing the 4-session protocol was also lower (62% versus 83% in the alcohol study). Thus, in terms of feasibility, our findings suggest there are challenges with conducting this intervention in people with MUD, at least in a residential withdrawal setting. Difficulties in recruiting and retaining participants are perhaps not surprising, given the characteristics of methamphetamine withdrawal during the acute phase (or well known 'crash'), where individuals are often very fatigued, somnolent and emotionally labile (McGregor et al., 2005; Zorick et al., 2010). While we did not formally document reasons for declining participation, anecdotally, these factors were major contributors. Higher rates of behavioural instability were also observed relative to our previous alcohol ApBM study, with 25% of participants who commenced ApBM subsequently self-discharging or being expelled prior to completing the 4 sessions of training. While alcohol withdrawal symptoms can often be well-managed with medications, methamphetamine withdrawal symptoms may be less amenable to currently-available medication regimens. Our low rates of successful follow-up also speak to the difficulty of conducting research in this population following medical detox. Indeed, we have previously observed lower rates of completion of research follow-ups among AOD treatment clients with methamphetamine as their PDOC, relative to clients with other PDOCs (Lubman et al., 2014) and among those with MUD, lower follow-up rates have been observed in participants recruited from residential withdrawal compared to those recruited from other treatment types (McKetin et al., 2012).

Anecdotally, some participants noted that images of active intravenous methamphetamine use (people injecting) were "highly-triggering" and for a minority (9%) this contributed to them withdrawing from the study due to finding the images upsetting or triggering craving. This is consistent with studies that have shown stronger elicited cravings when exposed to more salient and proximal drug-related images (Staiger & White, 1991). It is therefore not surprising that in the current study, craving ratings increased immediately following the first session of training, when participants were exposed to the methamphetamine-related imagery for the first time, but this effect diminished over subsequent sessions, with no significant increase in cravings after the 3rd and 4th sessions. While craving levels declined over the 4 sessions, our ability to attribute this to ApBM is limited by the lack of a control group. Moreover, while participants' opinions were divided regarding whether the training contributed to reducing their cravings for methamphetamine, approximately three quarters who provided ratings felt it was interesting and improved their attention (i.e., sustained focus on the task). Together, these data suggest that acceptability of this intervention was high. Nevertheless the small number of participants who withdrew due to "triggering" of cravings, and the marked average within-session increase in cravings during the first session of ApBM serve as a warning of possible risks inherent in future studies, or clinical application, of ApBM in this population. In the residential treatment setting in which we conducted this study, we were able to immediately refer participants for support from clinical staff if they reported distress or uncontrollable cravings, but future studies could also incorporate post-session relaxation or mindfulness techniques to improve participant safety. Bowen, Chawla, and Marlatt (2011) outline several brief breathing, relaxation, and "urge surfing" exercises, such as the SOBER exercise, that could be easily used in this context, and would be particularly important in non-clinical settings where rapid referral to site clinicians is not an option.

Given the overall significant decreases in craving, as measured by the MCQ and visual analogue scale ratings, it's unclear why a majority of participants did not report that the training reduced their cravings on the acceptability questionnaire. It may be that there were subgroups for whom there was no change in, or even worsening of, craving, despite an average overall reduction effect in the whole sample, and future research in larger samples could examine what factors predict whether or not ApBM reduces craving in individuals. It is also the case that this

acceptability question was open to interpretation, and some participants may have considered overall changes in craving across all 4 sessions when answering it, while others may have considered acute within-session increases in craving instead.

This was a single-group, open-label trial, not designed to rigorously test efficacy. Nevertheless, we believe the observed rates of abstinence at follow-ups are encouraging and suggest that further research testing the efficacy of ApBM for MUD is worth pursuing. The 3-month abstinence rate compares favourably (more than twice as high) with the abstinence rate of 18% reported by detoxification participants at the 3-month follow-up in the MATES treatment outcome study (McKetin et al., 2012). However, it is important to acknowledge that the observed abstinence rates among those who completed follow-ups may overestimate the true rate of abstinence in the whole sample, since there was a high rate of loss to follow-up, and those lost to follow-up may be more likely to have used methamphetamine. Nevertheless, even taking an extremely conservative assumption that everyone who was lost to follow-up had relapsed, the past-month abstinence rate at the 3-month follow-up (36% of the 39 whose follow-up was pursued, or 30% of the total sample of 47 participants who commenced training) would still be higher than the corresponding rate observed in the MATES study.

Additional study limitations are the small sample size and lack of objective verification of self-reported methamphetamine use. Moreover, screening for some exclusion criteria (e.g. intellectual disability, brain injury) was conducted by site clinicians based on patients' clinical admission notes (patient history) and their clinical impression of patients', rather than standard diagnostic measures. These clinical notes may not have completely detailed information relevant to all eligibility criteria and it is thus possible that we included participants who did not meet all eligibility criteria. We did not measure approach bias in this feasibility study and therefore cannot demonstrate that ApBM reduced any such bias, nor that it existed prior to training. However since approach bias to drug cues has been demonstrated in people with problematic alcohol, nicotine, cannabis and heroin use (Zhang et al., 2018), it is highly likely to have been present in the current sample. Nonetheless it will be important to measure approach bias in a randomised clinical trial to better understand the mechanisms of ApBM's efficacy in this population if it is shown to be effective. Moreover, participants had a wide range of MoCA scores, with half of scores within the range indicative of cognitive impairment. As this was a small, uncontrolled feasibility study, we could not analyse whether this factor altered outcomes or interacted with effects of ApBM. This will be important for future studies to examine, since cognitive impairment is common in this population and it remains unclear whether this limits patients' ability to engage with and benefit from ApBM.

4.1. Conclusion

While the feasibility of ApBM for MUD during acute withdrawal appeared limited, our findings regarding acceptability and effectiveness suggest that further research into this approach is nonetheless warranted. This could include testing feasibility and conducting clinical trials in settings where clients may be more clinically stable, such as residential rehabilitation, where they may be more likely to engage in and complete ApBM. It could also include further research to identify which patients are best suited to and best able to tolerate ApBM during acute withdrawal. Future clinical studies designed to test efficacy should further consider the selection of stimuli used for training. Specifically, consumer input and co-design of future ApBM interventions can ensure the images represent participants' drug use (i.e., crystal or powder methamphetamine) or their route of drug administration (i.e., smoking, injecting or snorting), ensuring better selection of appropriate, relevant and safe (i.e., not too triggering) images and optimal non-drug related approach stimuli. Ideally, future ApBM training will offer individualised image sets tailored to the specific forms of methamphetamine and paraphernalia used by individual patients, in addition to tailored, personalised non-drug 'approach' images in order to maximise engagement and efficacy.

Ethics approval and consent to participate

Ethical approval was obtained from the Eastern Health Human Research Ethics Committee (EHHREC; Reference E03-2017) and St Vincent's Hospital Melbourne Human Research Ethics Committee (207/17).

Consent for publication

Not applicable.

Availability of data and materials

Data collected from individual participants will not be made publicly available, due to conditions of ethical approval regarding confidentiality. Data may only be made available to researchers for additional analyses subject to further ethical approval. Those interested in further analyses of data produced may contact the corresponding author.

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Author's contributions

VM, DIL, AV, and JBBG conceived of the study and secured funding, and developed the protocol with input from PKS and JAGL. VM and JBBG supervised the research team that conducted recruitment and data collection, and were involved in writing and editing the final version of this manuscript. KM recruited participants, collected and analysed data, wrote the first draft of this manuscript, and assisted with further editing of later drafts. JBBG and SCC were also involved in participant recruitment, data collection and analysis and contributed to writing and editing this manuscript. HP recruited participants, collected data and assisted with editing the manuscript. All authors reviewed and edited the manuscript, and approve this final version.

Competing interests

DIL has provided consultancy advice to Lundbeck and Indivior, and has received travel support and speaker honoraria from Astra Zeneca, Janssen, Indivior, Lundbeck, Shire and Servier. However, these organisations have no role in the present study, and do not conceivably stand to gain or lose from the publication of this manuscript. No other authors have any competing interests to declare.

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