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Are methamphetamine users compulsive? Faulty reinforcement learning, not inflexibility, underlies decision making in people with methamphetamine use disorder

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Abstract

Methamphetamine use disorder involves continued use of the drug despite negative consequences. Such 'compulsivity' can be measured by reversal learning tasks, which involve participants learning action-outcome task contingencies (acquisition-contingency) and then updating their behaviour when the contingencies change (reversal). Using these paradigms, animal models suggest that people with methamphetamine use disorder (PwMUD) may struggle to avoid repeating actions that were previously rewarded but are now punished (inflexibility). However, difficulties in learning task contingencies (reinforcement learning) may offer an alternative explanation, with meaningful treatment implications. We aimed to disentangle inflexibility and reinforcement learning deficits in 35 PwMUD and 32 controls with similar sociodemographic characteristics, using novel trial-by-trial analyses on a probabilistic reversal learning task. Inflexibility was defined as (a) weaker reversal phase performance, compared with the acquisition-contingency phases, and (b) persistence with the same choice despite repeated punishments. Conversely, reinforcement learning deficits were defined as (a) poor performance across both acquisition-contingency and reversal phases and (b) inconsistent postfeedback behaviour (i.e., switching after reward). Compared with controls, PwMUD exhibited weaker learning (odds ratio [OR] = 0.69, 95% confidence interval [CI] [0.63–0.77], p < .001), though no greater accuracy reduction during reversal. Furthermore, PwMUD were more likely to switch responses after one reward/punishment (OR = 0.83, 95% CI [0.77–0.89], p < .001; OR = 0.82, 95% CI [0.72–0.93], p = .002) but just as likely to switch after repeated punishments (OR = 1.03, 95% CI [0.73–1.45], p = .853). These results indicate that PwMUD's reversal learning deficits are driven by weaker reinforcement learning, not inflexibility.

KEYWORDS
cognitive inflexibility, compulsivity, methamphetamine use disorder, reinforcement learning, reversal learning

1 | INTRODUCTION

People with methamphetamine use disorder (PwMUD) continue to use methamphetamine despite experiencing growing negative consequences from their drug use (i.e., mental/physical illness, legal and financial problems, relationship loss).[1,2] This behaviour is defined as compulsive substance use and is a hallmark of addiction.[3] Internationally, there are concerns that the prevalence of methamphetamine use disorder (MUD) is increasing, particularly due to the growing availability of high-purity crystal methamphetamine and its related harmful patterns of use.[4,5] Furthermore, although current treatments reduce short-term methamphetamine use and psychological distress,[6] most clients relapse within 1 year of treatment.[7,8] This difficulty in controlling drug use warrants a more nuanced understanding of 'compulsivity' amongst PwMUD.

While several cognitive processes likely underlie compulsive behaviour (i.e., habit formation, avoidance),[9] contingency-based cognitive inflexibility appears the most prominent cognitive driver of compulsivity in addiction.[10] This is because inflexibility refers to a difficulty in updating behavioural responses that were initially associated with reward but are now associated with punishment.[10] It is defined separately from more basic reinforcement learning deficits, which involve the ability to learn which actions or stimuli are associated with obtaining reinforcers.[11] Contingency-based inflexibility has typically been measured using reversal learning tasks, whereby initial stimulus-outcome associations are learnt (either implicitly or explicitly; acquisition phases) and then changed throughout the measure (reversal phases).[10,12] Errors in the reversal phase (i.e., responding to previously reinforced stimuli post-reversal) are often used as the behavioural index for inflexibility on these paradigms.[12]

Previous research using reversal learning tasks has extensively examined the effects of methamphetamine exposure in rodents and non-human primates. Amongst these individuals, weaker reversal learning has been frequently reported and interpreted as an indication towards broader inflexibility and/or compulsivity.[13–19] In addition, abnormal performance on these paradigms has been linked to dysregulation of striatal dopamine (D2-type) and frontal serotonin systems likely caused by methamphetamine consumption.[15,19]

However, despite the consistent cross-species evidence for inflexibility and the popularity of the compulsivity account of methamphetamine addiction, only one study has examined contingency-based reversal learning in humans.[20] This work also found worse reversal learning performance amongst PwMUD, when compared with healthy controls. However, closer inspection of learning rates also suggested that PwMUD made more errors in the tasks' acquisition phase, indicating that PwMUD may instead have fundamental deficits in reinforcement learning. Reappraisal of the animal literature also suggests reinforcement learning deficits versus (or in addition to) inflexibility.[17,19,21] For example, weaker reversal performance by methamphetamine-treated monkeys can be alleviated when given enough practice to master their knowledge of acquisition contingencies.[17]

Understanding whether PwMUD have deficits in reinforcement learning and/or cognitive inflexibility is important for several reasons. From a treatment perspective, the improvement of either construct requires different, targeted approaches. For example, reinforcement learning difficulties may benefit from the implementation of contingency management (CM) programmes,[22] which may overcome participants' weakened learning responses via more immediate and/or obvious reinforcements. In contrast, cognitive inflexibility may require extinction/response prevention therapies, such as cognitive behavioural therapy (CBT).[23] From an ethical standpoint, describing someone's learning as inflexible (or drug use as 'compulsive') may be more likely to generate feelings of hopelessness among patients and clinicians, relative to a perspective of reduced learning.[24]

Unfortunately, prior research using reversal learning tasks may have used methods which conflated cognitive inflexibility and reinforcement learning. This is because appropriate reversal learning requires the ability to (a) initially learn task contingencies (reinforcement learning) and (b) update behaviour when contingencies change (cognitive flexibility). Thus, traditional measures (i.e., errors in reversal phase)[12] are likely impacted by both processes.

To amend this, and thus disentangle inflexibility and reinforcement learning deficits, we conducted detailed novel trial-by-trial analysis of a reversal learning task amongst a cohort of PwMUD. We reasoned that inflexibility would manifest as (a) a significant reduction in learning rates between the acquisition-contingency and reversal phases, whereby the latter shows significantly poorer learning, and (b) the maintenance of a certain action despite receiving multiple instances of punishment. In contrast, reinforcement learning deficits would manifest as (a) consistently poor learning rates across both acquisition-contingency and reversal phases and (b) an inconsistent pattern of behaviour after feedback (i.e., increased switching after reward/punishment). Based on prior clinical research in PwMUD[20] and detailed models of learning/inflexibility in nonhuman primates,[17] we hypothesised that PwMUD's behaviour on the reversal learning task would reflect reinforcement learning deficits, rather than cognitive inflexibility, compared to drug-naïve controls.

2 | MATERIALS AND METHODS

2.1 | Design

Cross-sectional, observational design to characterise differences between PwMUD and drug-naïve controls on a reversal learning task.

2.2 | Participants

Thirty-five PwMUD (M_{Age} = 33.26, standard deviation [*SD*] = 7.78, 24 males) were compared with 32 drug-naïve controls (M_{Age} = 31.44, *SD* = 9.54, 20 males). PwMUD were recruited from public and private drug and alcohol treatment services across Melbourne, including inpatient detoxification/rehabilitation and outpatient counselling settings.

The key criterion for inclusion of PwMUD was admission into treatment for methamphetamine use. However, two PwMUD had yet to formally commence treatment, and we based their inclusion on scores >4 on the Severity of Dependence Scale for methamphetamine dependence.[25,26] Table 1 presents PwMUD's patterns of methamphetamine consumption and treatment information, while Table 2 reports PwMUD's secondary substance and medication use. All PwMUD reported crystal methamphetamine as the predominant form used. Drug-naïve controls with similar sociodemographic characteristics (sex, age, education, IQ) were recruited using online and community advertisements. Exclusion criteria for all participants included diagnosis of schizophrenia or intellectual disability. PwMUD were required to have been abstinent for longer than 48 h but less than 12 months.

2.3 | Procedure

The Eastern Health Human Research Ethics Committee approved the study (E52/1213). Recruitment occurred between June 2017 and September 2018. We tested PwMUD at their treatment facility and controls at Monash University. However, when these premises were not convenient, we also used community libraries. Participants were

TABLE 2 Additional substance and medication use amongst PwMUD

	N (or *M*)	% (or *SD*)
Other illicit subs. use		
Cannabis	10	28.57%
GHB	8	22.86%
MDMA	6	17.14%
Cocaine	4	11.43%
Heroin	1	2.86%
SDS alcohol	1	2.70
SDS cannabis	1.6	3.20
Prescribed medication		
Anti-dep	11	31.43%
Anti-psychotic	4	11.43%
Anti-convulsive (lamotrigine)	1	2.86%
Benzodiazepine (diazepam)	1	2.86%

Note: Other Illicit Substance Use refers to substances taken more than 10 times in the past 12 months. Scores can range between 0 and 15. Anti-Dep includes escitalopram, sertraline, fluoxetine, mirtazapine, venlafaxine, duloxetine. Anti-Psychotic includes aripiprazole and quetiapine.
Abbreviations: PwMUD, people with methamphetamine use disorder; SDS, Severity of Dependence Scale.

TABLE 1 Descriptive statistics of sociodemographic and methamphetamine use characteristics in PwMUD and drug-naïve controls

Demographics	PwMUD	Controls	Test statistic	Bayes factor
Sex (F/M)	11/24	12/20	$\chi 2$ = .027, *p* = .60	
Age	33.26 (7.78)	31.44 (9.54)	*U* = 460.5, *p* = .21	BF10 = 0.44
Years of education	14.06 (2.15)	15.00 (2.11)	*U* = 699, *p* = .078	BF10 = 1.75
Verbal IQ	109.29 (5.46)	108.78 (6.29)	*U* = 562.5, *p* = .98	BF10 = 0.27
Depression (CES-D)	19.83 (11.79)	9.22 (6.66)	*U* = 220, *p* < .001	BF10 = 615.90
Meth. Use (PwMUD only)	***M* (or *N*)**	***SD* (or %)**	**Range**	
Severity of dependence (SDS)	9.97	3.05	[4–14]	
Daily dose (grams)	0.44	0.29	[0.10–1.50]	
Frequency (days/month)	19.54	10.34	[3–31]	
Duration (years)	8.56	5.34	[0.58–22]	
Last use (days)	37.48	44.81	[3–180]	
Treatment type				
Inpatient rehab	23	65.71%	-	
Outpatient Counselling	6	17.14%	-	
Multiple	4	11.43%	-	
No treatment	2	5.71%	-	
Route of admin.				
Smoking	32	91.4%	-	
Injecting	3	8.6%	-	

Note: Two PwMUD also reported HIV + status. SDS scores can range between 0 and 15; with those above 4 indicating likely MUD.[26]
Abbreviations: CES-D, Centre for Epidemiologic Studies Depression Scale; PwMUD, people with methamphetamine use disorder; SDS, Severity of Dependence Scale.

screened before undergoing a standardised assessment session which lasted between 1 and 1.5 h. Reimbursement included a $20 (AUD) gift card.

2.4 | Measures

2.4.1 | Sociodemographic and mental health characteristics

Participants self-reported their age and education, while IQ and intellectual disability were assessed/screened using the *National Adult Reading Test* (NART).[27] Depressive symptomatology was assessed using the *Centre for Epidemiologic Studies Depression Scale* (CES-D).[28]

2.4.2 | Methamphetamine use

Frequency of methamphetamine consumption in the last month of use was collected using *The Timeline Follow Back interview* (TLFB).[29] PwMUD's degree of methamphetamine dependence was assessed using the *Severity of Dependence Scale* (SDS). [25,26]

2.4.3 | Cognitive inflexibility vs. reinforcement learning

The *Probabilistic Reversal Learning Task* (PRLT)[30,31] is a computerised measure that requires participants to learn which of two different coloured squares is more rewarding (see Figure S1 for task diagram). On each trial, participants were presented with two coloured squares (one red and one green; all participants denied colour-blindness) on the left and right of the screen (randomly allocated). They were informed that, on any given trial, one square was 'correct' (i.e., usually associated with a gain of two points and a positively valenced 'winning chime' sound), while the other was 'incorrect' (i.e., usually associated with a loss of two points and a negatively valenced 'boh!' sound). Participants were instructed to select the square they believed was the more frequently rewarded stimulus based on the feedback that they received to that point. After making their response, they then received feedback on their choice, and the next trial would then be presented without an intertrial interval.

Overall, the task was separated into four, 40-trial phases. Phases one and three were acquisition-contingency phases, whereby participants attempted to learn the initial contingencies and reinforcement probabilities associated with each square. Phases two and four were reversal phases, whereby the rewarding/punishing elements of the stimuli were switched, and participants had to update their behaviour. In the first two phases, the reward/punishment rates were set at 80/20% for the correct square and vice-versa for the incorrect square. In the final two phases, the reward/punishment rates changed to 70/30%.[31,32] All phases immediately followed one-another, with no breaks or signalling to participants.

The PRLT has been frequently used in prior addiction research.[31,32]

2.5 | Statistical analysis

To achieve our aim of disentangling reinforcement learning and inflexibility on the PRLT, our analyses focused on exploring behaviour related to accuracy (i.e., selecting the correct stimulus) and feedback (i.e., reward or punishment), across both shorter (i.e., individual trials) and longer time frames (i.e., across phases or multiple trials). As such, our main analyses are divided into two sections: (a) Trial-By-Trial Performance Across and Within Phases and (b) Switch/Stay analyses. How we used each section to investigate inflexibility or reinforcement learning deficits are described in the relevant discussions below. For both of these approaches, we used a recommended series of Generalized Mixed-Effects Model stepwise (backward deletion) comparisons.[33] Briefly, this involved comparing models in a hierarchical order (using AIC/BIC as the measures of model fit measures), beginning with a 'saturated model' (a model including all possible relevant effects). This 'saturated model' was then compared to a simpler model which includes all the same predictors, except for the most complex effect/interaction. If the reduced model was of equal or better fit, it was then used for comparison with a further simplified version. We present results from both 'saturated' and any 'best-fitting' models to conservatively confirm results. We used the *lme4* package[34] in *R*[35] to create the models, while relevant quantitative predictors were zero-centred, and p values obtained via z-test approximations. Alpha was set at α = .05 for main analyses and α = .017 for post-hoc contrasts due to multiple comparisons. Potential confounders (i.e., age, education, IQ and depression) were compared using Mann–Whitney U-tests and Bayes Factors in *JASP*.[36] To corroborate our main results, we applied a more traditional analysis of variance (ANOVA) and t test approach, which is described in the relevant results (Section 3.4). We also conducted control analyses to investigate if attention, motivation, severity of methamphetamine dependence and severity of any potential comorbid cannabis dependence were impacting PwMUD's behaviour (Section 3.5).

2.5.1 | Trial-by-trial performance across and within phases

These analyses investigated group differences on trial-by-trial accuracy within and across phases. Model construction began by assuming that participants' within-phase learning curves were negatively accelerated (a trend previously observed on PwMUD's choice data when performing reversal learning[20]). Essentially, this theorises that early experiences contribute the most information when learning new behaviours.[37] To achieve this, we modelled Accuracy (choosing correctly or not on each trial) as a binomial variable (using a logit link function) and logarithmically transformed trial (so that the underlying learning process is assumed to be linear relative to log-trial). This transformation of the effect of trial outperformed both its original linear counterpart and a polynomial-based approach (another way to model negatively accelerating curves, see Supporting Information). Therefore, further mentions of 'Trial' will reference the use of this logarithmic transformation.

After this, we defined accuracy as the output variable for these analyses and built models using a mixture of the following fixed effects: Phase (1–4), Trial within Phase (1–40), Group (PwMUD vs. drug-naïve controls) and any relevant covariates and interactions. Participant was always included as a random intercept.

To test inflexibility, we included a set of contrasts which investigated different patterns of change in accuracy rates across phases. The main contrast of interest, C1 (1, −1, 1, −1), compared phases one and three (acquisition contingencies) versus phases two and four (reversed contingencies). Contrast C2 (1, 1, −1, −1) modelled the effect of contingency degradation in the second half of the task (i.e., 80/20% versus 70/30% phases). Contrast C3 (1, −1, −1, 1) was theoretically irrelevant, but included to ensure the contrasts were comprehensive and orthogonal.[38] C1 is presented in the results section, while C2 and C3 are reported in Table 3. To aid in interpretation, a significant odds ratio (OR) > 1 for C1 would indicate that correct responses were more likely in phases one and three, relative to two and four (i.e., evidence that participants are showing reversal cost). In group interactions, greater inflexibility by PwMUD, relative to controls would be indicated by a C1 × Group OR > 1.

In contrast, to test reinforcement learning difficulties in these analyses, we used the Group × Trial interaction. This investigates whether groups showed differences in their accuracy across the trials (i.e., accuracy should increase with the number of trials). An OR < 1 would indicate towards PwMUD exhibiting weaker learning, relative to controls.

TABLE 3 Comprehensive statistics for the saturated and best-fitting model (trial-by-trial performance)

	Saturated model			Best-fitting model		
Predictors	***Odds Ratios***	***CI***	***p***	***Odds Ratios***	***CI***	***p***
Intercept	3.31	2.67 – 4.10	**<.001**	3.27	2.65 – 4.05	**<.001**
Group	0.54	0.39 – 0.73	**<.001**	0.54	0.40 – 0.74	**<.001**
Depression	1.08	0.93 – 1.26	.311	1.08	0.93 – 1.26	.308
Trial	1.96	1.82 – 2.10	**<.001**	1.94	1.81 – 2.08	**<.001**
Phase						
C1	1.32	1.23 – 1.41	**<.001**	1.24	1.19 – 1.30	**<.001**
C2	1.31	1.22 – 1.41	**<.001**	1.27	1.21 – 1.33	**<.001**
C3	1.20	1.12 – 1.29	**<.001**	1.20	1.15 – 1.25	**<.001**
Phase x Trial						
C1 x Trial	0.93	0.87 – 1.00	.049	0.93	0.89 – 0.98	**.002**
C2 x Trial	1.06	0.99 – 1.14	.075	1.06	1.02 – 1.11	**.005**
C3 x Trial	0.82	0.77 – 0.88	**<.001**	0.87	0.83 – 0.91	**<.001**
Trial x Depression	0.98	0.93 – 1.03	.412	0.98	0.93 – 1.03	.408
Group x Phase						
C1 x Group	0.91	0.83 – 0.99	.032			
C2 x Group	0.95	0.86 – 1.03	.225			
C3 x Group	0.99	0.91 – 1.09	.858			
Group x Trial	0.69	0.62 – 0.76	**<.001**	0.69	0.63 – 0.77	**<.001**
Group x Phase x Trial						
C1 x Group x Trial	1.00	0.92 – 1.10	.939			
C2 x Group x Trial	1.01	0.92 – 1.10	.886			
C3 x Group x Trial	1.11	1.02 – 1.22	**.016**			
Random Effects						
σ^2	3.29			3.29		
$\tau_{participant}$	0.29			0.28		
ICC	0.08			0.08		

Note: Bolded *p*-values are viewed as significant (≤.05 in typical analyses, ≤.0167 in contrasts). C1 (1, -1, 1, -1) compares acquisition-contingency to reversal phases; C2 (1, 1, -1, -1) compares easy and hard phases; C3 (1, -1, -1, 1) is theoretically irrelevant, necessary to complete contrasts and compares phases 1 and 4 with phases 2 and 3.

2.5.2 | Switch/stay analysis

These analyses aimed to investigate group differences on shifting after reward and punishment, the latter reflecting inflexibility. The dependent variable was defined dichotomously as Stay (0; repeating the previous choice) or Switch (1; making a different choice to the previous trial). The main predictor was Accumulated Feedback. This was coded as 3 (three consecutive punishments whereby participant did not change response in the last two trials), 2 (two consecutive punishments whereby participant did not change response in the last trial), 1 (previous trial punished) and 0 (previous trial rewarded). The best fitting model was selected using a combination of the following effects: Accumulated Feedback, Group and any relevant covariates. Participant was entered as a random intercept.

Three new contrasts examined differences in Accumulated Feedback. C1 (−3, 1, 1, 1) compared behaviour after one reward to one/two/three instances of consecutive punishments. C2 (0, −2, 1, 1) compared behaviour after one punishment to two/three consecutive punishments. C3 (0, 0, −1, 1) compared behaviour after two consecutive punishments to three consecutive punishments. For interpretation, ORs > 1 for C1, C2 and C3 would indicate that participants are (C1) more likely to switch after any amount of accumulated negative feedback relative to reward (or less likely to switch after reward compared to any accumulated negative feedback); (C2) more likely to switch after two or three instances of accumulated negative feedback relative to a single instance (or less likely to switch after one negative accumulated feedback compared to two or three) or (C3) more likely to switch after three instances of accumulated negative feedback relative to two (or less likely to switch after two negative feedbacks compared to three). In the Contrast × Group interactions, ORs > 1 would indicate that such contrast effects are larger for PwMUD, and ORs < 1 would indicate the contrast effects are larger in controls. Evidence towards inflexibility would be manifest if PwMUD were more likely to repeat actions despite multiple negative feedbacks, relative to controls (statistically, C3 OR > 1 and C3 × Group OR < 1). Evidence toward reinforcement learning deficits would be primarily manifest if the PwMUD group were more likely to switch after reward, relative to controls (statistically, C1 OR > 1, C1 × Group OR < 1).

3 | RESULTS

3.1 | Descriptive statistics between groups

Groups were matched in sex, age, education and IQ, but not for depression scores (Table 1) which were added as a covariate in subsequent analyses.

3.2 | Trial-by-trial performance across and within phases

Figure 1 displays the observed proportion of correct responses for each phase and trial of the task, and each group. Visually, drug-naïve controls showed steeper learning functions in all phases, as well as greater 'reversal costs' at the start of each phase. Such observations likely reflect that controls were performing more accurately by the end of each phase, and therefore required a greater adjustment of their behaviour after reversal.

To identify which variables best explained these group differences we began the model comparisons (see Table 4 for comparisons and Table 3 for statistics of saturated and best-fitting models). First, we checked whether there were indeed learning differences between PwMUD and controls. As such, a 'Saturated No-Group-Learn' model and a 'Saturated Group-Learn' model were compared. The Saturated No-Group-Learn Model included Accuracy as the outcome variable;

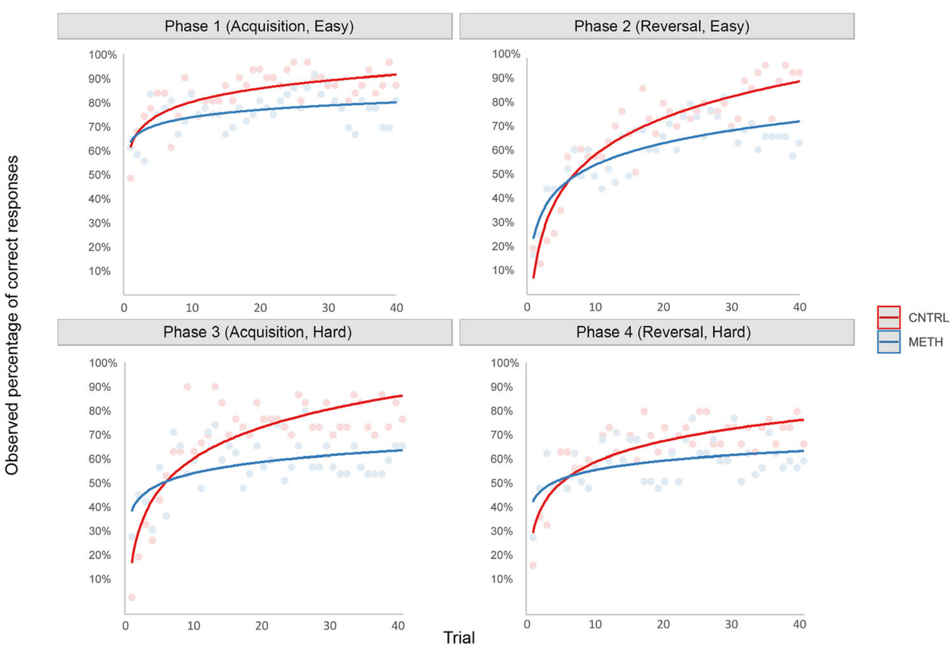

FIGURE 1 Observed percentage of correct responses as a function of phase, trial, and group. The dots represent the observed percentage of correct choices at each trial per group (statistically, a function of phase, trial and group). The lines represent logarithmic trendlines maximising the fitting for each phase and group

TABLE 4 Fitting indices for models analysing trial-by-trial performance across and within phases (reversal learning inflexibility)

Model	*df*	AIC	BIC	χ^2	*p*
Saturated no-group-learn	11	12,276	12,356		
Saturated group-learn	19	12,214	12,352	77.689	<.001 (group > no-group)
Simplified group-learn 1	16	12,214	12,343	5.818	.121 (1 ≥ saturated)
Simplified group-learn 2.1	15	12,266	12,376	54.622	<.001 (2.1 < 1)
Simplified group-learn 2.2[a]	13	12,214	12,330	6.494	.090 (2.2 ≥ 1)
Simplified group-learn 2.3	13	12,262	12,357	54.409	<.001 (2.3 < 1)

Note: p values correspond to contrasts regarding the superiority of the more complex model relative to the simpler one. See text for a description of model compositions.
[a]Best-fitting model.

Participant as a random intercept; and the following fixed-effects: Trial, Phase, Depression, Phase × Trial and Depression × Trial (the only Depression interaction identified in prior analysis). The Saturated Group-Learn Model included all the No-Group factors as well as all relevant Group effects and interactions (Group, Group × Phase, Group × Trial and Group × Phase × Trial). When compared, the Saturated Group-Learn Model provided a better fit, indicating that group effects/interactions likely described our data.

We then attempted to remove any unnecessary effects from the Saturated Group-Learn Model, beginning with the most complex interactions. Simplified Group-Learn Model 1 removed the three-way interaction (Group × Phase × Trial) without losing fit and was thus used for the following comparisons. Removal of Group × Trial (Simplified Group-Learn Model 2.1) and Phase × Trial (Simplified Group-Learn Model 2.3) reduced fit, meaning these predictors were useful in explaining participants behaviour. In contrast, removal of Group × Phase (Simplified Group-Learn Model 2.2) did not reduce model fit and was removed due to parsimony. In this manner, Simplified Group-Learn Model 2.2 became the best-fitting model.

Because Simplified Group-Learn Model 2.2 did not include the interactions of Group × Phase and Group × Phase × Trial, it appeared there were no differences between PwMUD and controls in their performance between phases (i.e., no inflexibility). In contrast, the retention of the Group × Trial interaction (OR = 0.69, 95% confidence interval [CI] [0.63–0.77], $p < .001$) suggested that PwMUD had difficulties in learning action–outcome associations throughout the entire task (i.e. reinforcement learning deficits).

To confirm these results, we also examined the Saturated Group-Learn Model which retained the relevant contrast interactions within Group × Phase and Group × Phase × Trial. While the primary contrast, C1, was significant (OR = 1.32, 95% CI [1.23–1.41], $p < .001$), indicating a reduction in accuracy between acquisition-contingency and reversal phases across all participants, it did not interact with Group (OR = 0.91, 95% CI [0.83–.99], $p = .032$; $\alpha = .016$ for post-hoc contrasts) or Group × Trial (OR = 1.00, 95% CI [0.92–1.10], $p = .939$). Notably, the trending interaction between C1 × Group indicated in the opposite direction to inflexibility amongst PwMUD (indicating either a floor effect due to poor baseline learning, or that PwMUD were indeed more flexible).

3.3 | Switch/stay analysis

Saturated Group Switch and Saturated No-Group Switch models were built and compared, based on a similar rationale to the previous section (see Table 5 for model comparisons and Table S1 for statistics of saturated and best-fitting models). The Saturated No-Group Switch Model included Switch/Stay as the output variable, Participant as a random intercept and the following fixed-effects predictors: Accumulated Feedback, Depression and Accumulated Feedback × Depression. The Saturated Group Switch Model included all these predictors plus all Group-relevant predictors/interactions and was again the better fit.

Simplified Group Switch Model 1 removed the three-way interaction (Accumulated Feedback × Group × Depression), retained model fit and was used for further comparison. However, removal of the Accumulated Feedback × Group interaction did reduce fit (Simplified Group Switch Model 2), indicating a substantial contribution of this

TABLE 5 Fitting indices for models involved in analyses of sensitivity to accumulated feedback (switch/stay analysis)

Model	*df*	AIC	BIC	χ^2	*p*
Saturated no-group switch	9	11,328	11,394		
Saturated group switch	17	11,301	11,424	43.431	<.001 (group >no-group)
Simplified group switch 1[a]	14	11,297	11,399	2.2828	.516 (1 > saturated)
Simplified group switch 2	11	11,322	11,402	30.814	<.001 (1 > 2)

Note: p values correspond to contrasts regarding the superiority of the more complex model relative to the simpler one. See text for a description of model compositions.
[a]Best-fitting model.

interaction and identifying Simplified Group Switch Model 1 as the best-fitting model.

In Simplified Group Switch Model 1, Group interacted with both C1 (comparing switch/stay after one reward to one/two/three punishments; OR = 0.83, 95% CI [0.77–0.89], $p < .001$) and C2 (comparing switch/stay after one punishment to two/three punishment; OR = 0.82, 95% CI [0.72–0.93], $p = .002$). There was no significant group interaction when comparing two/three cumulative punishments (OR = 1.03, 95% CI [0.73–1.45], $p = .853$).

Such results indicated that PwMUD were more likely to switch after a single instance of reward/punishment compared with controls but were no more likely to switch after two or three consecutive punishments. This appeared to again rebuke inflexibility amongst PwMUD and further indicate towards reinforcement learning abnormalities.

When comparing these results with the original Saturated Group Switch Model, we also found similar findings, with significant interactions between C1 × Group (OR = 0.81, 95% CI [0.74–0.87], $p < .001$), C2 × Group (OR = 0.77, 95% CI [0.67–0.90], $p = .001$) but not C3 × Group (OR = 0.91, 95% CI [0.61–1.35], $p = .629$).

Figure 2 presents overall switch/stay behaviour by group, using predicted values from the Saturated Group Switch Model.

3.4 | Traditional analyses of reversal learning

We also compared our original analyses with two 'traditional' approaches for reversal learning data. The first compared the number of errors in both acquisition-contingency and reversal phases between PwMUD and controls. We found that PwMUD made significantly more errors in both acquisition-contingency (PwMUD: $M = 26.23$, $SD = 9.64$, Controls: $M = 18.31$, $SD = 10.41$; $t(65) = 3.23$, $p = .002$) and reversal phases (PwMUD: $M = 32.09$, $SD = 9.74$, Controls: $M = 25.59$, $SD = 11.11$; $t(65) = 2.49$, $p = .013$). These results mirror our original findings whereby PwMUD exhibited performance deficits throughout the task.

We also compared our analyses to a Mixed-ANOVA-based approach, previously used in people with Cocaine and Gambling Disorders on the PRLT.[39] Factors were the same as our modelling approach, except that Trial was replaced with Block (a grouping of 8 trials, 5 blocks per phase), and the dependent variable was the number of correct responses per block, ranging from 0 to 8. The results (see Table S2 for comprehensive statistics) again support our original findings, with the effect of Block differing across groups, $F(2.50, 162.27) = 7.32$, $p < .001$; akin to weaker learning in the PwMUD group, but with the effect of Phase not being different across groups, $F(2.77, 180.31) = 0.15$, $p = .92$; which reveals no difference in inflexibility between groups, or any three-way interaction, $F(9.44, 613.75) = 1.07$, $p = .39$.

3.5 | Control analyses

After obtaining these results, we then conducted further analyses to (a) ensure our findings were not due to factors such as inattention or disengagement from our PwMUD participants and (b) investigate the impact of common clinical covariates (Severity of Dependence of methamphetamine and cannabis and Time Since Last Use of methamphetamine) on PwMUD's performance. We found that (a) PwMUD and controls had similar attention and motivation during the PRLT (indicated by nonsignificant differences in overall reaction times and choice-outcome behaviour consistent with learning); (b) the pattern identified in PwMUD (weak learning and increased switching) was exacerbated in more severe users, though time since last use had no significant effects on performance and (c) severity of any comorbid cannabis dependency were not impacting accuracy or stay/switch behaviour amongst PwMUD. These analyses are provided in the Supporting Information.

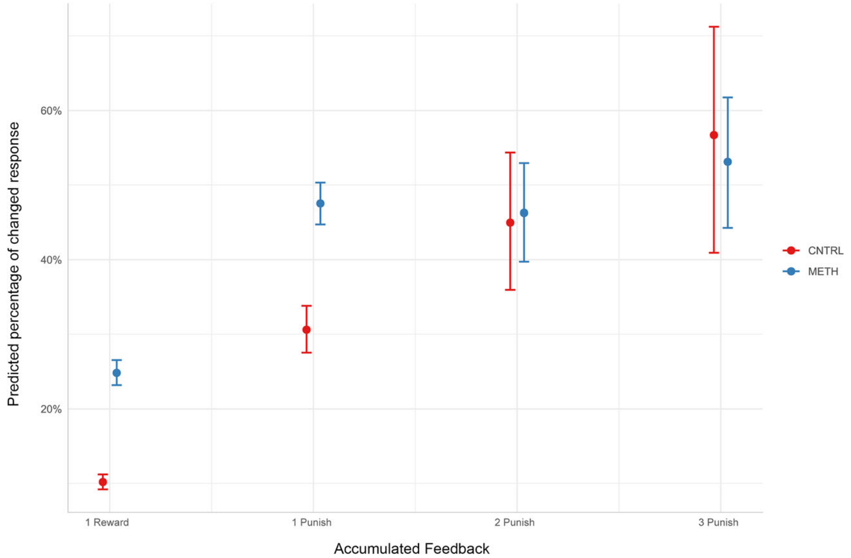

FIGURE 2 Predicted percentage of changed response (and confidence intervals) in the current trial as a function of accumulated feedback. This figure visualises the predicted percentage of each groups' switch/stay behaviour for each level of the accumulated feedback predictor, in the saturated model (see Table S1). This is achieved by tuning the saturated model's parameters using a maximum likelihood approach in order to best approximate participants observed choices. Results are similar across visualisations in observed, best-fitting and saturated versions of this figure

4 | DISCUSSION

This study aimed to disentangle the contribution of reinforcement learning and inflexibility (as a proxy of compulsivity) to reversal learning performance in PwMUD, compared with drug-naïve controls. We found that PwMUD deficits were due to weaknesses in reinforcement learning, as demonstrated by (a) poorer learning rates across the task and (b) a more inconsistent pattern of behaviour after feedback (i.e., greater switching after one instance of reward/punishment). In contrast, our results did not support inflexibility, as PwMUD (a) did not have a greater decline in their accuracy after the reversal of task contingencies and (b) did not perseverate after repeated punishments. Together, these findings challenge the prevailing view that MUD is associated with inflexibility.

While these findings conflict with reports of inflexibility in animal models of MUD,[13–16,18] they do align with previous research in PwMUD. Specifically, our detection of overall weaker learning trajectories is consistent with the only other reversal learning study amongst PwMUD.[20] Furthermore, PwMUD also exhibit poor performance on other decision-making tasks that involve learning action-outcome relationships (i.e., Iowa Gambling Task),[40,41] as well as decreased dopaminergic populations in critical regions for reinforcement learning.[42] As such, we believe the discrepancy between our results and previous preclinical reports may be due to potential methodological oversights regarding the impact of reinforcement learning in non-human studies. This may have occurred because researchers: used reversal errors as the primary measure of inflexibility,[14] trained the acquisition phase before methamphetamine administration[13,18] or selected performance thresholds that may not capture 'well-learnt' behaviour (i.e., 70% of trials correct).[15,16] Furthermore, due to the relatively small number of PRLT studies in clinical Substance Use Disorder populations, it is difficult to determine whether the deficits we have observed are unique to methamphetamine or generalise across other substances. For example, there is evidence supporting abnormal learning trajectories[32,39] and increased switching behaviour[43] in people with Cocaine and mixed Stimulant Use Disorders. However, support against the presence of inflexibility has been more varied, with mixed results in people with Cocaine Use Disorder,[39,44] and evidence against inflexibility in Amphetamine and Opioid Use Disorders.[44]

Our identification of increased switching after both reward and punishment also provides clues towards which specific dysfunctional processes may underline PwMUD's learning deficits, as well as when this may occur in the addiction process. For example, a recent computational analysis of reversal learning data in Stimulant Use Disorder also found greater win-switch and lose-switch behaviour. This was linked to lower reward sensitivity and higher punishment sensitivity, respectively.[43] In comparison, participants with Binge Eating Disorder (who share clinical characteristics with PwMUD) have also been shown to have greater overall switching, though this was instead associated with deficits in updating the value of alternative (non-chosen) options.[45] Furthermore, while animal models may provide support that learning deficits are the result of chronic methamphetamine use,[15,16,19] recent studies have also identified that such difficulties may predate substance use and play a role towards increased methamphetamine self-administration.[46] Although further clinical research is required, our finding of exacerbated learning deficits in PwMUD with more severe patterns of use appears compatible with both scenarios.

From a theoretical standpoint, our work outlines a new perspective of choice behaviour in PwMUD. Previously, behaviour amongst this population has been described as rigid, habitual or perseverative.[47,48] However, our sample of PwMUD behaved contradictory to such descriptions, acting inconsistently and being overly eager to change responses. As such, it may be that what appears to be 'compulsive' behaviour in PwMUD instead reflects difficulties in learning adaptive behaviour. At a therapeutic level, deficits in probabilistic reinforcement learning may explain why treatments such as CM are efficacious for PwMUD.[22] While this may seem counter-intuitive, due to CM's reliance on similar learning systems required for PRLT performance, these interventions may overcome PwMUD's deficits via increases in the immediacy/tangibility of reinforcement. This is supported by evidence identifying greater benefits amongst stimulant users when reinforcer magnitude and immediacy are increased.[49,50] Finally, at a psychological level, adopting a view that methamphetamine problems are partly due to an amenable learning difficulty may be more motivating to clients and clinicians, compared with a compulsivity narrative sometimes associated with hopelessness.[24]

Study strengths include the fine-grained analysis that allowed us to differentiate reinforcement learning and cognitive inflexibility. Furthermore, we recruited PwMUD from different treatment and sociodemographic settings, increasing the representativeness of our treatment-seeking sample. Finally, identifying controls with similar sociodemographic characteristics prevented the impact of age, sex, education and IQ. Regarding limitations, one major consideration is that our task did not provide participants with any tangible positive rewards for accurate performance (i.e., beyond game points). Thus, it is possible that PwMUD may have been less interested in the task, compared with controls. Still, such a concern is mitigated by our control analyses, which identified adequate attention and motivation in the PwMUD group. Readers should also consider that the PRLT is a generalised measure that does not reference substance use. Therefore, while we identified domain-general learning deficits, it may be that PwMUD's inflexibility is restricted to methamphetamine-based contingencies. Relatedly, while these deficits were present in a novel, dynamic task (i.e., including learning and shifting components), it is possible that PwMUD may struggle adapting behaviours learnt prior to chronic methamphetamine consumption (as found in some rodent studies[13,18]). Furthermore, despite the comprehensiveness of our modelling procedure, our sample size may have had insufficient power to detect more subtle, three-way interactions. Finally, we allowed the inclusion of additional mental health diagnoses and secondary alcohol/drug use in our PwMUD group, without the aid of a standardised diagnostic interviews. Although this makes it difficult to ascribe group differences in task performance solely to MUD, such characteristics are also representative of treatment-seeking populations.[8]

5 | CONCLUSION

We found that decision-making problems frequently ascribed to inflexibility in PwMUD were better explained by deficits in reinforcement learning. These findings challenge the 'compulsive' stereotype often applied to PwMUD and support the use of treatment approaches targeting contingency-based learning.

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AUTHORS CONTRIBUTION

AHR, IV and AVG designed the study. AHR and IV collected the data. JCP ran the analyses and provided interpretation for the results. AHR lead the manuscript writing process with all authors contributing to its final version. All authors also reviewed and approved the final version of this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author. It is not publicly available due to privacy and ethical restrictions.

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