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Increased reflection impulsivity in patients with ephedrone-induced Parkinsonism

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ABSTRACT

Aims To examine a syndrome of chronic manganism that occurs in drug addicts in eastern Europe who use intravenous methcathinone (ephedrone) contaminated with potassium permanganate. In many cases the basal ganglia, especially the globus pallidus and the putamen, are damaged irreversibly. Routine neuropsychological assessment has revealed no cognitive deficits, despite widespread abnormalities on brain imaging studies and severe extrapyramidal motor handicap on clinical examination. **Design** Case–control study. **Setting** Ephedrone patients and patients with opioid dependence were recruited from Lviv, Ukraine. **Participants** We tested 15 patients with ephedrone-induced toxicity, 13 opiate-dependent patients who were receiving opioid replacement therapy and 18 matched healthy volunteers. **Measurements** The 'beads task', an information-gathering task to assess reflection impulsivity, was used and feedback learning, working memory and risk-taking were also assessed. **Findings** Opiate-dependent patients differed from controls on three of four tasks, whereas ephedrone patients differed from controls on only one task. More specifically, both patient groups were more impulsive and made more irrational choices on the beads task than controls ($P < 0.001$). However, ephedrone patients had no deficits in working memory ($P > 0.1$) or risk-taking ($P > 0.1$) compared with controls. Opioid-dependent patients had significantly worse working memory ($P < 0.001$) and were significantly more risk-prone than controls ($P = 0.002$). **Conclusions** Ephedrone patients may have similar deficits in information-gathering and decision-making to opiate-dependent patients, with preservation of working memory and risk-taking. This may reflect specific damage to anterior cingulate– basal ganglia loops.

Keywords Beads task, ephedrone-induced Parkinsonism, reflection impulsivity, risk-taking, substance abuse, working memory.

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INTRODUCTION

Methcathinone, also known as ephedrone and mephedrone, is one of several homemade synthetic cathinones with amphetamine-like stimulant activity. Ephedrone users inject themselves several times a day in binges over several days. In eastern Europe, it is generally manufactured on a small scale using commercially available nasal decongestants including phenylpropranolamine (PPA) and pseudoephedrine, potassium permanganate, used as an oxidant and disinfectant [1] and vinegar. During this reaction, as a side product, manganese ions are formed, which then accumulate in the brain and cause dystonia, postural instability, a quiet slurred pallidal speech, dopaminergic unresponsive bradykinesia and later a typical 'cock gait' [2]. There have been no postmortem examinations so far, but magnetic resonance imaging (MRI) of the brain revealed that the disorder affects

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mainly the globus pallidus, the substantia nigra and, to a lesser degree, the subthalamic nucleus, the putamen and the caudate nucleus [3]. Dopamine transporter (DAT) scans confirm an intact nigrostriatal pathway [2]. Although the white matter appears to be normal on T1-weighted MRI scans, diffusion tensor imaging studies showed extensive white matter changes, particularly in the frontal and premotor areas, and widespread damage to cortico–pallidal connections [4]. Despite these extensive abnormalities on brain imaging, only mild deficits in executive function have been reported [3–6]. Individual case reports have indicated a tendency towards impulsivity [7], but this has never been studied systematically. However, drug addiction is associated with executive, memory and decision-making dysfunction [8]. Opiate- and amphetamine-dependent patients have difficulties in planning, learning and memory [9] which persist during opiate replacement therapy [10]. Opiate-dependent patients also make more risky decisions, which may reflect abnormal patterns of orbitofrontal cortex activation [11].

We have compared patients with ephedrone-induced extrapyramidal symptoms to substance abusers without neurological deficits who were taking opioid replacement therapy and healthy volunteers on working memory (WM), feedback learning, risk-taking and the 'beads task'. The beads task explores the amount of information participants gather before making a decision, sometimes referred to as 'reflection impulsivity' [12–14]. Jumping to conclusions has been reported previously in patients with schizophrenia [15–17], patients with Parkinson's disease (PD) with and without impulsive compulsive behaviours [18] and substance abusers [16]. We combined the WM and the beads tasks because it has been suggested that jumping to conclusions might be a specific strategy to reduce WM load [19]. We also used emotionally salient and neutral distractors in the WM task, given the negative effects of task irrelevant information on WM performance [20]. We sought to distinguish between reflection impulsivity and risky choice, which are two components of cognitive impulsivity [21]. We also assessed reward and punishment learning separately, as it is unclear whether potential abnormalities on tasks measuring reflection impulsivity or risk preference are driven by impaired negative or enhanced positive feedback learning.

In this study we were interested in assessing differences between former addicts with ephedrone toxicity and current drug-dependent patients. Clinical impression has suggested that most patients with ephedrone-induced basal ganglia damage lose their craving for illicit substances and cease abusing drugs. It is unclear whether their physical disability or damage from the accumbens–pallidum circuitry is responsible for this change in behaviour. Studies in rodents have shown that the globus pallidus plays a key role in the reinforcing effects of illicit drugs [8], and its damage might therefore abolish craving.

We hypothesized that both patient groups are likely to have orbitofrontal cortex dysfunction, considering its important role in drug preoccupation and impulsivity [22], given the widespread abnormalities on neuroimaging studies in ephedrone [4] and drug abusers [23]. Further, we predicted that ephedrone patients would perform similarly to opiate-dependent patients in tasks measuring reflection impulsivity, as jumping to conclusions is known not to recover even after prolonged abstinence in substance abusers [13]. On other tasks, such as risk-taking and feedback learning, we speculated that ephedrone patients would perform better than opiate-dependent patients, given the differences in drug craving and shorter duration of illicit drug abuse. We also expected that both patient groups would perform worse on the WM task, especially when salient distractors were presented but would, conversely, remember distractors significantly better than healthy controls.

METHODS

All participants provided written informed consent. The protocol was approved by the UCLH Trust or Ukrainian local ethics committee. All participants scored more than 26 of 30 on the Mini Mental State Examination (MMSE) [24] and were tested once, usually mid-mornings. Participants received a modest reward (between £10 and 15) depending on their performance.

Patients

Ephedrone patients were recruited from a small database of attendees at the University Clinic Lviv and almost all patients agreed to take part several days prior to testing. Opiate-dependent patients who were interested in participating were chosen randomly among patients attending the psychiatric out-patient clinics in Lviv.

Ephedrone

Fifteen patients with ephedrone-induced extrapyramidal symptoms were recruited from the department of Neurology of Lviv Regional Clinical Hospital, Ukraine. All patients had moderate to severe extrapyramidal symptoms, moderate to severe impairment in postural stability, dystonia and had decrement in finger-tapping with some axial rigidity, induced by ephedrone. Fourteen patients developed extrapyramidal symptoms after intravenous methcathinone abuse, one patient after recurrent oral intake.

A detailed neurological examination was performed by a movement disorder specialist on the day of testing. No patient had a resting tremor or was treated with dopamine replacement therapy. One patient was wheelchair-bound. Seven of 15 patients developed a characteristic 'cock-gait' and had a pallidal speech, similar to patients with progressive supranuclear palsy. No patient had taken any illicit drugs within the last 2 years. Five ephedrone patients consumed other illicit drugs for a short time in the past, but were never dependent on these drugs.

Manganese levels in pubic hair samples were measured in nine of 15 patients, confirming the diagnosis of manganese toxicity. For further details see [5].

Opiate-dependent patients

Thirteen male patients with a recent history of illicit drug abuse meeting DSM-IV-TR criteria for opioid dependence [25] were recruited from the Replacement Therapy Unit of Lviv, regional Clinical Narcological Dispensary and the department of Lviv Regional Clinical Narcological Dispensary, Ukraine. All patients had clinically normal cognitive function, and were on opioid replacement therapy with buprenorphine. Neurological examination was normal in all patients. Twelve of 13 patients had a long-standing history of intravenous opioid abuse (Table 1). All tests were performed prior to their dose of buprenorphine. Only those patients who were able to tolerate a delay of their buprenorphine dose were included. Patients who suffered from clinically evident withdrawal symptoms were excluded. None of these patients reported taking any illicit substances at the time of testing.

Controls

Results were compared with 18 age-matched healthy male volunteers. A similar sample size using identical tasks was used previously in PD patients [18,26].

For demographic characteristics see Table 1.

WM task

WM was assessed using a task which uses abstract geometric figures and emotional distractors during the memory interval. This allowed us to assess the effects of distractibility, and in particular emotionally valenced distractibility on WM. Twenty-four trials of the WM task were performed on a laptop computer, after an explanatory demonstration. Participants were asked to memorize either two or three geometric figures which were shown for 3 seconds, followed by a delay of 2 seconds. Then another geometric figure was presented and participants were asked whether this figure was within the set that they had to remember previously. During the delay, one or two positive, neutral or negative distractors obtained from the validated International Affective Picture System were shown [27]. Salient and neutral pictures contained mainly human characters. Positive pictures contained food or sexual subjects, negative pictures included scenes of violence.

After the 24 trials participants were shown a series of distractor images and were asked whether they thought they had seen these images before. Distractors had been shown previously in half of the series of 24 (12 of 24).

Table 1 Demographic characteristics with details about past history of substance abuse in patients.

	Controls	*Ephedrone*	*Opiate-dependent patients*	*t-value, χ^2 and F-value*	*P-value*
Participants (*n*)	18	15	13		
Age (years)	32.3 ± 5.5	34.0 ± 7.2	32.0 ± 7.1	0.34	0.71
Gender (male)	18	13	12	2.4	0.3
Education	13.8 ± 2.8	12.2 ± 1.4	12.0 ± 1.9	5.1	0.01*
Drug abuse (years)			12.0 ± 5.1		
Replacement therapy (years)			1.4 ± 1.3		
Ephedrone abuse (years)		1.5 ± 1.2			
Ephedrone stopped (years)		6.2 ± 2.6			
Parkinsonism (years)		7.0 ± 2.4			
Substance abuse (patients)		15	13		
i.v. opioid		4	12		
i.v. heroin		2	4		
Cannabis		3	3		
Cocaine		1	1		
Morphine		0	1		
Ephedrone (i.v/oral)		14/1	0		

All values are mean ± standard deviation. Significant differences are labelled with '*'. Controls, ephedrone, opiate-dependent patients; i.v.: intravenous.

Beads task

We used the beads task to assess the amount of information gathered by subjects before committing to a decision. This is often called 'reflection impulsivity' [28], and several studies have shown that subjects with substance dependence commit to decisions without gathering much information [13,18]. The beads task was administered on a laptop computer and was explained on a series of slides on the screen. Participants were told that a sequence of beads would be drawn from one of two cups, one containing predominantly green and the other predominantly blue beads. All bead draws for each sequence were drawn from the same cup. For each sequence of draws, participants were first shown a bead, either green or blue. After seeing the bead, they could choose to draw another bead from the cup, or they could choose to guess the cup that was being drawn from. This was repeated until they guessed a cup or they drew 10 beads, after which they had to guess which cup was being drawn from. We recorded the number of beads drawn before the participant guessed a cup and whether the choice represented a rational (e.g. if more blue beads were drawn the participant guessed blue) or irrational (i.e. guessing the less likely cup colour) choice. For further details see [18].

Participants had to play four blocks, with two blocks containing an 80 : 20 ratio of beads within each cup and two blocks a 60 : 40 ratio. Each block had three trials. They were told that they would win 10 units if they guessed the correct cup. Incorrect choices by participants resulted in either a loss of nothing (in two blocks) or a loss of 10 units (in two blocks) and participants were informed of the loss condition before each trial. Participants knew that they could draw up to 10 beads before making a decision. They were, however, 'charged' 0.2 units for each additional draw, so additional draws reduced the amount they would win, although by only a small amount.

Risk task

A gambling task was used to probe the risk preference/aversion of the subjects [29]. Studies have shown that addicts make decisions in the Iowa Gambling task which suggest that they are risk-prone [30]. However, the Iowa Gambling task includes both elements of risk and feedback learning. Therefore we analysed each element separately. In each trial subjects were given a choice between two gambling options, which were presented on the left and right of the screen. Each option had either a single certain outcome or two possible outcomes. For example, if the subjects had a 20% chance of winning 10 units and an 80% chance of winning 5 units, the pie would be split 80/20. The certain options were displayed as solid circles, representing the 100% outcome. Immediate feedback was given after selecting the preferred gamble. For details see [26].

Feedback learning task

The ability of participants to integrate positive and negative feedback within a learning context was assessed using an instrumental learning task. The task had four blocks of 24 trials [31]. In each trial participants were shown two stimuli and they had to select one of them. After choosing a stimulus they were informed of the outcome. Each block contained a fixed probability of winning or losing associated with each stimulus, and one stimulus was more often rewarded or punished less often than the other. Participants were asked to select the stimulus that they thought was more likely to win in two 'winning blocks' or less likely to lose in two 'losing blocks'. In 'winning blocks' participants could win either 0.5 units or nothing, in the other two 'losing blocks' subjects should avoid a loss or could lose 0.5 units. Feedback was given immediately. Winning probabilities for the two stimuli were 70/30%.

Data analysis

Statistical analysis was performed using SPSS version 18. For the demographic variables, age, gender and years of education were used as dependent variables and groups (ephedrone, substance abusers and controls) were modelled as a between-subject factor. We used analysis of variance (ANOVA), *t*-test or χ^2 test, where appropriate. Years of education was modelled as a cofactor for all other analyses but did not change any results.

WM task

We used a generalized linear model (SPSS) with a binary logistic distribution. As a dependent variable we used score (correct response = 1 or incorrect response = 0). Distractor (positive, neutral or negative), number of memoranda (two or three geometric figures), choice (yes/no) and actual shown figure (yes/no) were modelled as fixed factors. Groups (ephedrone, substance abusers and controls) were modelled as a between-subject factor and subject was a random factor nested under group.

Beads task

We performed analyses using a generalized linear model (SPSS). As a dependent variable we used either the number of draws before making a decision or opposite colour choice, the number of times participants made an irrational decision (e.g. blue bead shown, green cup selected). As these are both count variables, we used a Poisson model which had a log-linear link function. For

the first analysis, beads ratio (80 : 20 or 60 : 40) and loss condition (loss, no loss) were modelled as fixed factors. Groups (ephedrone, controls, substance abusers) were modelled as a between-factor and subject was a random factor nested under group.

Risk task and feedback learning task

Data analysis for the risk and learning tasks was carried out by fitting parametric decision-making models to the behaviour of each individual subject, and comparing the distributions of parameter fits from the model between groups in a within-subject design. For further details see [26].

RESULTS

Demographics

There was no age difference between the three groups ($F_{(2,44)} = 0.34$, $P = 0.7$), but there was a significant difference in years of education ($F_{(2,42)} = 5.1$, $P = 0.01$). *Post-hoc* analysis showed that controls had significantly more years of education than ephedrone patients ($P = 0.033$) and substance abusers ($P = 0.022$).

WM task

There was a significant effect of group (Wald $\chi^2 = 16.0$, $P < 0.001$), a significant effect of distractor type (Wald $\chi^2 = 17.8$, $P < 0.001$) (Fig. 1) and a significant distractor by number of memoranda interaction (Wald $\chi^2 = 10.0$, $P = 0.007$). Pairwise analysis between the groups showed that opiate-dependent patients performed significantly worse than ephedrone patients and controls (see Table 2). We also analysed how often the distractors could be remembered at the end of the experiment, but found no group differences (Wald $\chi^2 = 4.3$, $P = 0.5$).

Beads task

We first examined the number of draws each participant made in the different conditions (Fig. 2a). We found

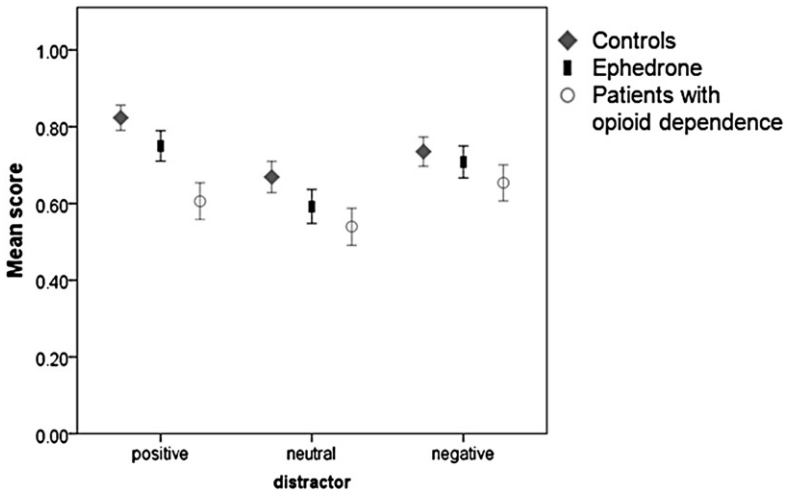

Figure 1 Working memory (WM) performance with positive, neutral and negative distractors. Error bars are ± 1 standard error

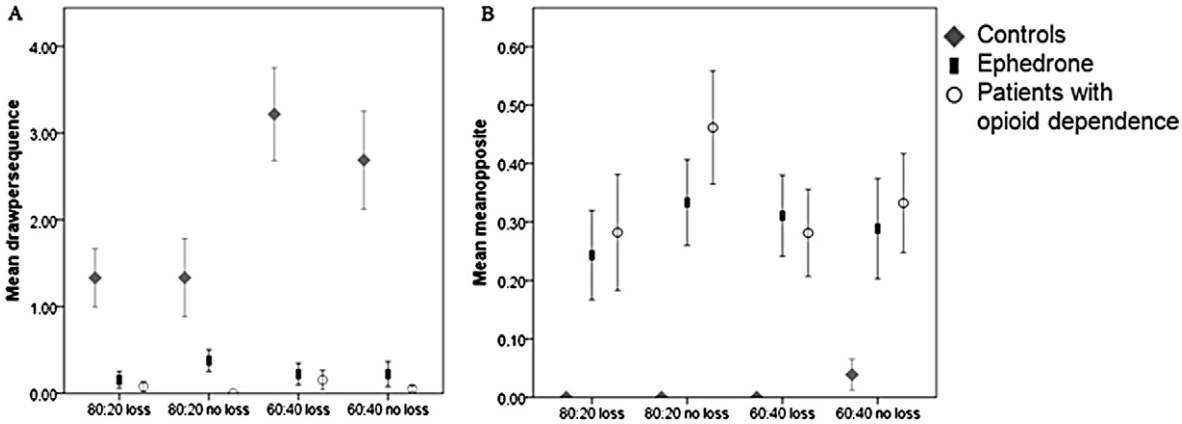

Figure 2 Beads task. (a) Average number of draws per condition by group. (b) Number of times participants chose the opposite colour. Error bars are ± 1 standard error

Table 2 Summary of pairwise comparisons between groups.

Group (χ^2, F-value and P-value)	*Opiate-dependent patients*	*Controls*
Ephedrone		
WM	$\chi^2 = \mathbf{6.2}$, $\mathbf{P = 0.013}$	$\chi^2 = 2.3$, $P = 0.12$
Draws	$\chi^2 = 3.2$, $P = 0.076$	$\chi^2 = \mathbf{45.3}$, $\mathbf{P < 0.001}$
Opposite colour	$\chi^2 = 0.54$, $P = 0.46$	$\chi^2 = \mathbf{30.1}$, $\mathbf{P < 0.001}$
Risk-taking	$F_{1,29} = 2.03$, $P = 0.496$	$F_{1,31} = 4.67$, $P = 0.116$
Opioid-dependent patients		
WM		$\chi^2 = \mathbf{15.4}$, $\mathbf{P < 0.001}$
Draws		$\chi^2 = \mathbf{30.0}$, $\mathbf{P < 0.001}$
Opposite colour		$\chi^2 = \mathbf{34.1}$, $\mathbf{P < 0.001}$
Risk-taking		$\mathbf{F_{1, 30} = 14.75}$, $\mathbf{P = 0.002}$

Both patient groups performed significantly worse on the beads task ('draws', 'opposite colour') than controls. Patients with opioid dependence had worse working memory (WM) than both other groups and were more risk-prone than controls. Significant *P*-values are highlighted in bold type.

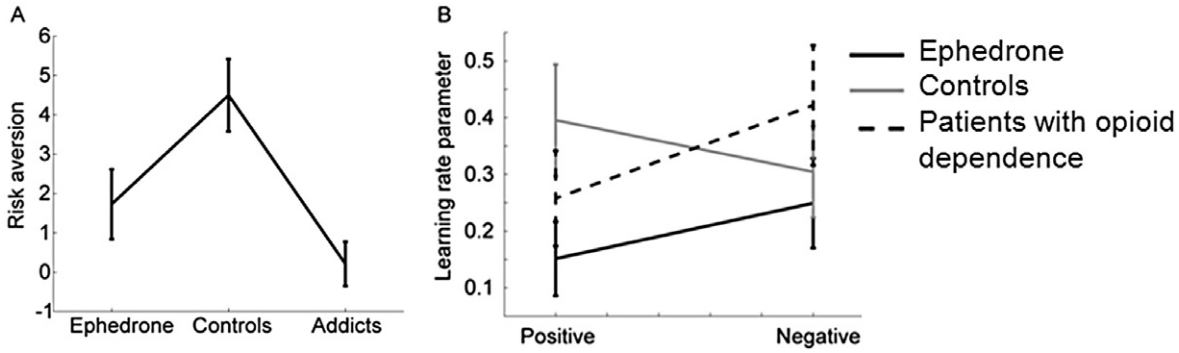

Figure 3 (a) Plot showing risk preference across the groups. (b) Learning behaviour across the three groups

significant main effects of group (Wald $\chi^2 = 73.0$, $P < 0.001$), beads ratio (Wald $\chi^2 = 4.5$, $P = 0.033$), a significant group × loss condition interaction (Wald $\chi^2 = 6.5$, $P = 0.037$) and a significant group × ratio interaction (Wald $\chi^2 = 9.5$, $P = 0.009$).

Pairwise comparisons between the three groups showed a significant group × loss interaction between the ephedrone group and opiate addicts (Wald $\chi^2 = 5.5$, $P = 0.019$) and a significant group × ratio interaction between the ephedrone and the control groups (Wald $\chi^2 = 9.3$, $P = 0.02$) (Table 2).

Opposite colour choice

We subsequently examined the number times participants chose the opposite colour, or the less probable cup, given the beads that had been drawn (Fig. 2b), and found a significant main effect of group (Wald $\chi^2 = 34.6$, $P < 0.001$) (Table 2).

Risk task

There were group differences in preference for risky gambles ($F_{2,\ 45} = 7.06$, $P = 0.002$). Opiate-dependent patients were more risk-prone than controls, but there were no other significant differences (Fig. 3a, Table 2).

Learning task

Performance on the learning task was analysed by fitting separate learning rate parameters to the positive and negative feedback conditions [32]. All groups learned equally well ($F_{2,\ 43} = 1.78$, $P = 0.173$) and there was no difference in how groups responded to either learning to win or learning to avoid losing, measured as a group × feedback type interaction ($F_{2,\ 43} = 1.07$, $P = 0.345$). There was also no difference in how positive versus negative feedbacks were integrated ($F_{1,43} = 0.6$, $P = 0.438$) (Fig. 3b).

DISCUSSION

To our knowledge, this is the first study to analyse WM, feedback learning, risk-taking and information-gathering systematically in patients with ephedrone toxicity. Results were compared with patients with opioid dependence and healthy volunteers.

There was no difference in WM performance between controls and ephedrone patients, even when salient distractors were shown. Both groups performed significantly better than opiate-dependent patients. Previous studies have demonstrated poor attention in substance abusers when required to ignore salient stimuli during WM tasks [33]. Our results are also consistent with previous studies that have shown impaired WM performance in opiate-dependent patients [34]. All patients on opioid replacement therapy were tested prior to their daily buprenorphine dose, and therefore might conceivably have had subtle withdrawal symptoms and low brain dopamine levels [8] Thus, impaired WM performance in this group might be explained by the inverted 'U-shape' hypothesis, suggesting that both too low or excessive dopamine levels can impair cognitive function [35]. It is, however, also possible that subclinical anxiety due to withdrawal might have contributed to poor WM performance.

The normal WM performance in the ephedrone group is in keeping with other studies showing normal scores on MMSE and frontal assessment battery (FAB) scores [6,36]. Interestingly, controls and ephedrone patients performed better when salient distractors were presented. Emotional stimuli can enhance cognitive functions (e.g. precise recall of a moment during an emotional event) but can also worsen WM capacity, particularly when they need to be ignored [20]; thus, our hypothesis that WM performance would decline with salient distractors proved incorrect. One possible explanation is that during high cognitive load the impact of salient distractors is reduced, while activity in the dorsolateral prefrontal cortex increases [37]. An easier version of the task might have led to stronger effects of distractors on WM performance.

We also found a relative improvement of WM performance with positive distractors. Implicit exposure to positive images might induce striatal dopamine release and might boost WM performance indirectly, given the role of striatal dopamine in WM [38]. However, there was no similar effect in opiate-dependent patients. It is possible that in this group, due to changes of the amygdala during addiction [8], salient photographs might be stimulating to a lesser extent and therefore fail to lead to a memory-enhancing effect. Chronic buprenorphine has also been shown to reduce the salience of the drug-associated cues [39], and might have reduced attention to salient cues.

Decision-making on the beads task is processed via a circuit involving the anterior cingulate, the parietal cortex, the insula and the ventral striatum [14]. Controls who gathered more information had more parietal cortex activation [14]. The anterior cingulate is necessary for optimal decision-making and to integrate risks [40]. Thus, damaged connections from the anterior cingulate to the striatum and globus pallidus–cortical circuits in substance abusers and ephedrone patients [4,5,41], albeit due to different mechanisms, could explain the impaired performance on the beads task.

In our study, controls drew significantly more beads than patients. Both patient groups also made more irrational decisions and chose the less likely cup more often than controls. Although group differences between ephedrone patients and substance abusers only reached trend levels, ephedrone patients gathered more evidence in the no loss conditions than patients with opioid dependence.

Various deficits in decision-making have been reported in substance abusers [42]. Impaired decision-making has also been found in patients with ventromedial prefrontal cortex lesions [43]. 'Delusional thinking', defined as a belief based on incorrect inference [25], has been reported in treated PD patients with impulsive–compulsive behaviours [44,45] who also chose the opposite cup significantly more often than controls [18]. It has also been correlated positively with fewer draws on the beads task in delusional patients with and without schizophrenia [16]. Our results are in line with other studies showing a positive correlation of jumping-to-conclusion behaviour and prefrontal cortex dysfunction during task performance [46]. Thus, lesions within the anterior cingulate circuit in the ephedrone patients [4] might explain poor performance on the beads task, while the dorsolateral prefrontal loop, necessary for WM, may be relatively intact. This discrepancy between impairment in 'reflection impulsivity' but intact WM function is consistent with other studies suggesting a dissociation of WM and decision-making processing within the prefrontal cortex [47]. Increased reward-seeking behaviour with a reduced sensitivity to negative feedback or, more probably, insensitivity to unpredictable future consequences are possible explanations [47]. However, the feedback learning task where reward and punishment learning was assessed separately did not reveal any group differences.

We also examined risk-taking behaviour across groups and found that only opiate-dependent patients made more risky decisions than controls, while group differences between ephedrone and controls only reached trend levels.

A limitation in our study is that we did not assess a full battery of standard neuropsychological tasks and only two tasks assessing cognitive impulsivity were performed.

In summary, we have demonstrated 'reflection impulsivity' in patients with brain damage due to ephedrone toxicity but intact WM and feedback learning. An impaired ability to evaluate risk may contribute to risk-taking behaviours, including risky injecting practices. Additional neuropsychological studies taking into consideration gender differences are needed, and

comparisons with patients with chronic manganese toxicity from other causes [48,49] who have been reported to suffer from compulsive behaviour and emotional lability [50] would be of considerable interest.

Declarations of interest

SOS received honoraria from Britannia Pharmaceuticals, otherwise none. AJL: consultancies: Genus; honoraria: Novartis, Teva, Meda, Boehringer Ingelheim, GSK, Ipsen, Lundbeck, Allergan, Orion; grants: PSP Association, Weston Trust—the Reta Lila Howard Foundation; otherwise none. BBA: grants: Wellcome, and the Intramural Research Program of the NIH; otherwise none. Other authors: none.

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