

**Prospective Memory and Future Event Simulation in
Frequent Cannabis Users**

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Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Overview

Part one of this major research project is a systematic review of the evidence for cognitive remediation for adults with substance use disorders (SUDs). Given the clinical heterogeneity across the 15 included studies (in terms of intervention characteristics, outcome measures used, and quality of reporting), a narrative approach was used to synthesize results. Although there was some evidence for the intervention improving some cognitive and substance use outcomes, this was not consistent, and the review highlights the lack of robust evidence for cognitive remediation for adults with SUDs. Suggestions for future research are discussed.

Part two is an empirical paper describing a study to assess the effects of frequent cannabis use on prospective memory. Prospective memory was assessed using the Virtual Week task over three groups: dependent cannabis users, non-dependent cannabis users and non-using controls. There were no differences found between groups. The introduction of an imagining technique whereby participants had to imagine performing their prospective memory tasks during encoding did not improve prospective memory performance for any of the groups. The results raise important questions about the cognitive effects of cannabis use, and interpreting the findings of this study in light of the strengths and limitations of the research.

Part three is a reflection and critical appraisal on the major research project process as a whole, addressing some of the factors that led to the smooth running of the project, as well as some of the more challenging aspects that arose.

It is important to note that this was a joint research project with Samantha Mansell.

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Part 1: Literature Review

Cognitive Remediation to Improve Cognitive Functioning in Substance Use Disorders: A Systematic Review of Randomised Controlled Trials

Abstract

Background. Chronic substance use is associated with cognitive deficits that are predictive of poor clinical outcomes, such as drug relapse. Cognitive training interventions aim to remediate these cognitive deficits. **Objectives.** To assess whether cognitive remediation interventions for individuals with substance use disorders (SUDs) improve cognitive function and/or impact on treatment outcomes. **Search Methods.** Searches were undertaken of PsycINFO, MEDLINE and EMBASE, as well as reference lists of primary studies and review articles identified. Searches were done in November 2016. **Selection Criteria.** i) Randomised controlled trials (RCTs) comparing any cognitive remediation intervention to treatment-as-usual or a control group, ii) studies with adults meeting diagnostic criteria for a SUD or undergoing treatment for substance use, and iii) at least one cognitive, treatment or drug use outcome measure. Published trials only were included. **Study Appraisal and Synthesis.** Data was narratively (rather than meta-analytically) synthesised given the variability in interventions, outcomes and quality of reporting. Studies were rated for risk of bias using the Cochrane Risk of Bias tool. **Results.** Fifteen RCTs were identified, including 1355 adults (10 trials on alcohol-dependent patients and five on patients in treatment for other substances). Although some trials had favourable effects for remediation groups on some cognitive and substance use outcomes, these were not consistent. The heterogeneity and bias in the studies and the review limit any inferences that can be drawn. **Conclusions.** At present, there is no conclusive evidence that cognitive remediation should be indicated as an adjunct to addiction treatment. Further research may be warranted, and recommendations regarding the design of future studies is given.

Introduction

Substance use disorders (SUDs) are a global health concern. An estimated 240 million people (4.9% of the world's adult population) have an alcohol use disorder (Gowing et al., 2015), and between 16 and 39 million people have other SUDs (United Nations Office on Drugs and Crime, 2014). In addition to the well-known physical, psychological and social effects of SUDs, long-term drug and alcohol use has also been associated with deficits across a number of cognitive domains, including decision-making, response inhibition, planning, working memory, and attention (Rezapour, DeVito, Sofuoglu & Ekhtiari, 2016; Sofuoglu, DeVito, Waters, & Carroll, 2013).

Neurocognitive models of addiction highlight how 'top-down' cognitive deficits (i.e. deficits in processing information that has already been brought into the brain by one or more of the sensory systems) impacts the cycle of addiction, maintaining problematic substance use and poor treatment prognosis. For example, the Impaired Response Inhibition and Salience Attribution framework (Goldstein & Volkow, 2002) considers addictive disorders to arise from a top-down impairment of cognitive and motivational functions implicated in tracking, updating and modulating the salience of reinforcers, and in the ability to inhibit pre-potent responses. Thus, impairments in executive cognitive function may partially account for individuals' problematic tendency to continue to use substances despite the negative consequences. Within these models, there is a distinction between the two interacting mechanisms: automatic 'bottom-up' stimulus-driven processes (e.g. triggered by drug cues), and controlled or executive top-down cognitive processes (e.g., linked to working memory and inhibition).

Models of addiction that implicate dysregulation of top-down processes are generally supported by cognitive and neuroimaging evidence (Littel, Euser, Munafo & Franken, 2012). In addition, the severity of cognitive deficits has been associated with the duration and amount of drug use, suggesting a causal link between drug use and neurocognitive deficits (Bolla, Brown, Eldreth, Tate & Cadet, 2002; Bolla, Rothman & Cadet, 1999). Some evidence also suggests deficits could be pre-existing (Ersche et al., 2012). In recent studies using the Montreal Cognitive Assessment (MoCA), cognitive impairment was detected in 68% and 73% of alcohol-dependent patients and 77% of drug-dependent patients following detoxification (Alarcon, Nalpas, Pelletier & Perney, 2015; Manning, Teo, Guo, Wong & Li, 2016), with consistent findings of the poorest performance in visuospatial processing, attention, memory and executive functioning.

Cognitive deficits may interfere with addiction treatment by reducing the ability of the patient to encode, consolidate, integrate and employ information in the treatment sessions as well as their everyday lives (Fals-Stewart & Lam, 2010). Associations of moderate effect size have been found between general cognition and substance use treatment adherence, reward-based decision making, and alcohol and drug relapse (Dominguez-Salas, Díaz-Batanero & Verdejo-García, 2016), further supporting the idea that deficits in cognitive functioning could be a contributing factor to the maintenance of SUDs.

Despite this, cognitive deficits are not generally targeted by addiction treatments. The most common psychosocial interventions available in the NHS in England specifically target drug-use behaviours, and include: Motivational Interviewing (Miller & Rollnick, 2012), relapse prevention (Marlatt & Gordon, 1985), and humanistic and 12-step approaches (NICE, 2007). It is plausible that cognitive

training as an adjunct to treatment may provide a cognitive ‘strengthening’ to patients with cognitive impairments, which may in turn enable them to adhere to treatment more effectively.

Broadly classified as ‘cognitive remediation’ (also known as ‘cognitive training’, ‘cognitive re-training’ or ‘cognitive rehabilitation’), interventions typically involve repeated practise or strategy training on cognitive exercises which aim to improve or restore functioning within a specific cognitive domain or across multiple domains. Such interventions tend to target executive or controlled cognitive processes, such as working memory or attention, and a distinction can be made between these and other interventions which target bottom-up automatic cognitive mechanisms (e.g. Cognitive Bias Modification; Wiers, Gladwine, Hofmann, Salemink, & Ridderinkhof, 2013).

Although remediating cognitive deficits through cognitive training makes theoretical sense, it is important to address the effectiveness of such interventions through systematically identifying, appraising and synthesizing the existing research. Evidence for cognitive remediation in other disorders is limited. For example, there are inconclusive findings reported in Cochrane systematic reviews of cognitive remediation for dementia (Bahar-Fuchs, Clare, & Woods, 2003), stroke (das Nair, Cogger, Worthington & Lincoln, 2016) and schizophrenia (McGrath & Hayes, 2000).

Previous Reviews

Searches indicate that there are no systematic reviews on cognitive remediation for SUDs. Several narrative articles exist reviewing the emerging literature and neuropsychological mechanisms, including cognitive remediation for alcohol addiction (Allen, Goldstein & Seaton, 1997; Bates, Buckman & Nguyen, 2013) and

across drug and alcohol addiction (Campanella, 2016; Rezapour et al., 2016; Sofuoğlu et al., 2016; Verdejo-Garcia, 2016; Manning, Verdejo-Garcia & Lubman, 2017; Voci, 2008). However, these reviews do not set minimum quality criteria for study design or specify their search strategy, and are therefore at risk of selection bias.

Implications

By collating the existing research and rating the quality of the evidence, the review may have implications for future research. It is also hoped that inferences will be drawn on the effectiveness of cognitive interventions for obviating cognitive deficits, which may have implications for the content of addiction treatment programmes.

Objectives of the Review

Building upon neuropsychological models of addiction and existing narrative reviews, the objective of this systematic review is to answer the following question: do cognitive remediation interventions for SUDs remediate cognitive deficits and/or impact upon treatment outcomes?

Method

Eligibility Criteria

Studies were assessed for inclusion in terms of the research design, population characteristics, intervention, outcome measures used and publication status.

Research Design

Included studies were randomised controlled trials (RCTs) or cluster-randomised trials that randomised to an experimental and control/comparison group. Non-randomised or quasi-randomised trials were excluded due to the increased risk of bias.

Population

Included studies were required to have: (i) an adult sample, and (ii) participants who met criteria (e.g. DSM-III, DSM-IV or ICD-10) for a diagnosis of a substance use disorder (SUD), dependency, or addiction on a substance excluding nicotine, or who were undergoing treatment for substance use. Studies were excluded if participants had a psychotic disorder, traumatic brain damage, a neurological impairment or a learning disability.

Intervention

Studies were included that assessed any cognitive remediation intervention that directly or indirectly targeted top-down cognitive functioning. Interventions could be delivered in any format (e.g. pen-and-paper or computerised). The comparison group(s) of included studies could be treatment-as-usual or an alternative intervention.

Outcomes

Primary outcomes were measures of cognition, treatment outcomes, and substance use. To be included in the review, studies must have included at least one cognitive, treatment or substance use outcome measure.

Publication

Studies were restricted to published full-text journal articles written in English.

No date limits were set.

Search Methods

Papers were identified through a search of three electronic databases: MEDLINE (1946 to November 2016), EMBASE (1980 to November 2016) and PsycINFO (1806 to November 2016), using the Ovid interface in November 2016. The search terms used, including key words and synonyms, were: ‘cognitive remediation’, ‘substance use’ and ‘relapse prevention’. The first two terms were selected to capture the intervention and population. ‘Relapse prevention’ was added to the search string to identify studies that may have offered a cognitive training intervention as part of a relapse prevention programme. The full search terms are listed in Appendix 1.

Study Quality

The methodological quality of the studies was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011). The risk of bias was assessed in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and attrition, selective outcome reporting, and other biases. A second reviewer SM (my research project partner) independently assessed the risk of bias for each study, and any disagreements were resolved by discussion or consulting our research supervisors for a third opinion.

Each potential source of bias was graded as ‘high’, ‘low’ or ‘unclear’. A quote from the study paper or justification for the judgement is given for each bias domain, and presented in a risk of bias table for each study (see Appendix 2). Where risk of

bias judgments were ‘unclear’, the study authors were emailed if their contact details were provided in the papers, and any responses received were recorded.

Analyses

Given the clinical heterogeneity in the studies, including differences in the components and implementation of the interventions and comparisons, the outcome measures used, and quality of reporting, the results are discussed narratively rather than combined statistically with meta-analyses.

Results

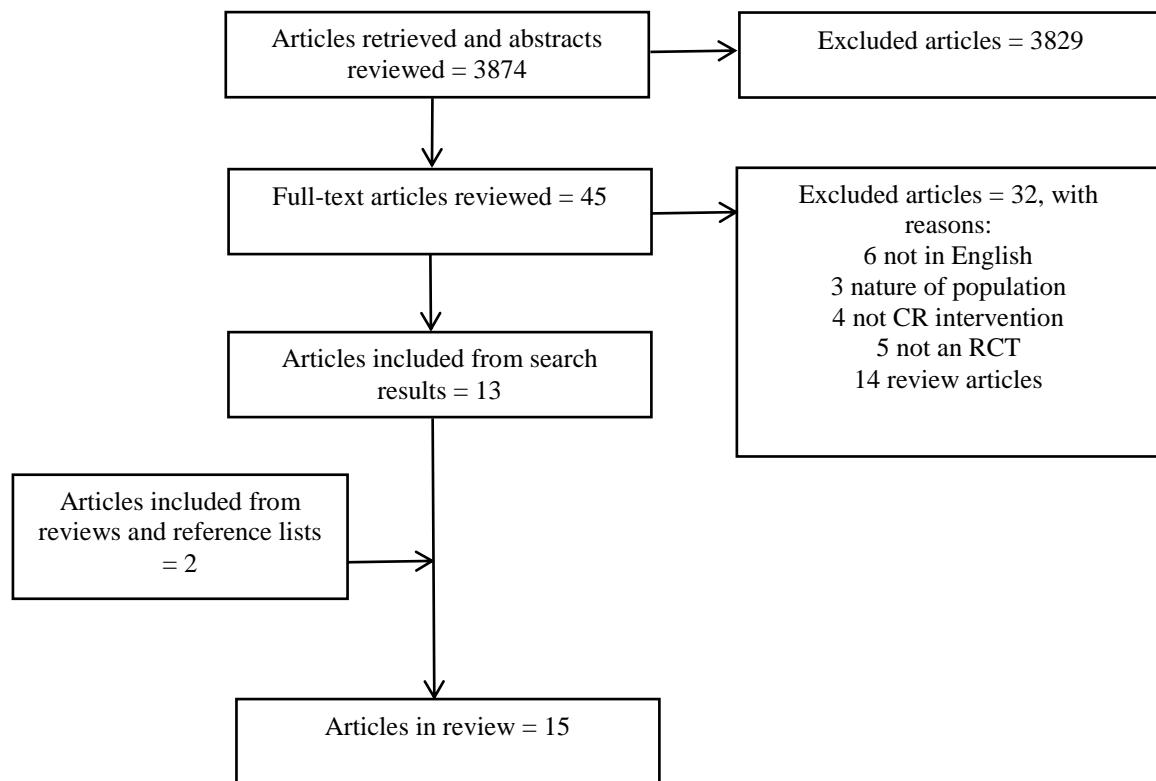
Results of the Search

After duplicates had been removed, a total of 3874 citations were identified. All titles and abstracts were screened. Forty-five full-text articles were retrieved; 13 of these met the inclusion criteria and 32 articles were excluded. To ensure that all relevant articles were included, existing literature reviews and reference lists from included papers were examined and screened against the inclusion criteria. Two more articles were identified. This resulted in a total of 15 studies being included in the review (Figure 1).

Included Studies

Fifteen studies ($n = 1355$) met the inclusion criteria for the review. Fourteen studies were RCTs and one study a cluster-randomised controlled trial (Czuchry & Dansereau, 2003). Studies were published between 1987 and 2016, and ranged in

Figure 1. Study Flow Diagram



population size from eight to 450 (median: 66). Three studies were conducted in Europe (Gamito et al., 2014; Rupp, Kurz, Hinterhuber & Fleischhacker, 2012; Steingass, Bobring, Burgart, Sartory & Schugens, 1994), 11 in North America (Bell, Vissicchio & Weinstein, 2016; Czuchry & Dansereau, 2003; Fals-Stewart & Lucente, 1994; Fals-Stewart & Lam, 2010; Goldman & Goldman, 1987; Grohman & Fals-Stewart, 2003; Rass et al., 2015; Roehrich & Goldman, 1993; Stringer & Goldman, 1998; Wetzig & Hardin, 1990; Yohman, Schaeffer & Parsons, 1988), and one in India (Mathai, Rao & Gopinath, 1998).

Tables 1 and 2 display the study characteristics and main findings. Given the large proportion of studies testing samples in treatment for alcohol use, the studies are presented according to alcohol studies (Table 1) and other substances (Table 2). Effect

sizes (Cohen's d or partial eta-squared η_p^2) were rarely reported, but appear in Table 1 and 2 if available. There was wide variation in statistical procedures used and in the quality of reporting. Therefore, the statistics for the main findings are not presented.

Table 1. Included Studies - Alcohol

Study and Country	N	Population ^a	Clinical Diagnosis	Groups (N Starters/Completers)	Description of Interventions/Comparators	Length	Cognitive Target(s)	Outcome Measures ^b	Main Findings
Bell et al. (2016); USA	34	Outpatients 97% male 55.2 years (SD = 1.7)	Alcohol-use Disorders (MINI)	CCT (16/15) WT (18/16)	Active: Computerised cognitive training (<i>Brain Fitness & InSight</i>) plus work therapy & TAU Control: Work therapy only & TAU	13 weeks (CCT for M = 41.2 hours, plus work therapy M = 190.9 hours; WT only, M = 252.9 hours)	Auditory & visual: learning, attention and memory (e.g. elementary sensory processing tasks, to increasing memory-load story recall tasks)	3 PT, FU (3 months)	PT significant effect of condition on verbal learning & memory score, sustained at 3-month FU
Gamito et al. (2014); Portugal	68	NR 80% male 45.4 years (SD = 10.1)	Alcohol Dependence (DSM-IV)	CS (33/26) TAU (35/28)	Active: mHealth (mobile health) serious-games based cognitive stimulation programme with mobile technology Control: TAU	10 60-minute sessions over 4-6 weeks	Executive functioning: attention (e.g. slot machine task), working memory (e.g. visual memory task) & logical reasoning (e.g. word-object correspondence)	36, 40, 50, 58 PT	No effect of group on MMSE or cognitive flexibility, processing speed or attention. CS group had significant increase in FAB scores,

									whereas TAU group did not
Goldman & Goldman (1987); USA	66	Inpatients 100% male <40 years	Alcohol Dependence (DSM-III)	CRT1 (NR/NR) CRT2 (NR/NR) TAU1 (NR/NR) TAU2 (NR/NR) CG (13/NR)	Active groups: 2 cognitive remediation groups (different sites) received 2 sessions of training of 3 visuospatial tasks Control groups: 2 TAU groups (different sites) & an non-alcoholic control group (no remediation)	2 45-minute sessions	Visuospatial processing (training on the component parts of Trails B: visual scanning speed & accuracy, verbal series alternation, integration of scanning & symbol manipulation)	39 PT	The 2 remediated alcoholic groups performed similarly to the matched, non-alcoholic controls on Trails B, while non-remediated alcoholic groups were worse than normal at both time lags
Mathai et al. (1998); India	8	Inpatients 100% male 40.0 years (SD = 5.5)	Alcohol Dependence (ICD-9)	CT (4/4) TAU (4/3)	Active: Cognitive training of various tasks, increasing in difficulty levels Control: TAU	Daily for 1-hour over 6 weeks	Attention, memory (verbal & visual), information processing, & executive function	1, 23, 26, 27, 29, 48, 73 PT, FU (1 month)	Significant improvement PT in CT group in 3/14 tests; serial processing, memory & number of neuro-psychological deficits.

2 of the patients in the CT group were abstinent at 1month FU whilst 2 had relapsed

Roehrich & Goldman (1993); USA	80	Inpatients 100% male 42.5 years (SD = 10.8)	Alcohol Dependence (DSM-III-R)	NEURO-REM (15/15) ECO-REM (15/15) PBO-REM (16/16) CG (15/15)	Active groups: Standard neuropsychological remediation group received self-guided workbooks (NEURO-REM), & an ecologically relevant remediation group who also were given self-guided workbooks (ECO-REM) Control groups: Attention placebo tasks group, & a no remediation control group	4 1hr sessions, over 3 weeks	NEURO-REM: Visual scanning, visuospatial skills, psychomotor speed, cognitive flexibility, & problem solving ECO-REM: attention, reasoning, & problem solving	23, 38, 68 PT	Both remediation groups showed more improvement for each experience-dependent measure than the PBO-REM & control groups. Transfer effects to RP measures significantly better scores for remediation groups compared to control groups, with a slight advantage for standard neuro-psychological
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stimulation procedures									
Rupp et al. (2012); Austria	41	Inpatients with mild impairment on baseline task	Alcohol dependence (DSM-IV)	CRT (20/20) TAU (21/17)	Active: Computer-assisted cognitive remediation (<i>Cogpack</i>), trained over 62 exercises Control: TAU	12 45-60 minute sessions, over 4 weeks	Attention, executive function & memory	2, 10, 13, 18, 25, 30, 32, 38, 39, 51, 52, 53, 54, 58, 72 PT	Improvements in alertness ($\eta_p^2=0.1$), divided attention ($\eta_p^2=0.1$), working memory ($\eta_p^2=0.1$) & delayed memory ($\eta_p^2=0.12$) for CRT group (medium range effect sizes), but not inhibition and several other cognitive measures
Steingass et al. (1994); Germany	29	Inpatients 82.8% male 52.5 years (SD = 8.1)	NR	AMT (14/NR) WL (15/NR)	Active: Cognitive training sessions, once per week of training, memory games & scanning tasks in a small group (up to 10 people)	Twice per week of training, once per week of games, for 6 weeks	Attention and memory; 12 tasks and several games (e.g. picture recall, face-name associations, learning details of group members)	5, 11, 12, 17, 19, 20, 28, 37, 55 PT	Memory training group had improved performance in verbal memory tests & reproduction of drawings, but not on other measures

Control: Waiting-list control										
Stringer & Goldman (1998); USA	40	Inpatients with baseline scores within one SD of the mean of their age	DSM-III Alcohol Dependence	CRG1 (NR/NR)	Active groups: One group taught a strategy for constructing block designs and given guided practice (CRG1) & one group given practice but without training (CRG2)	2 30-minute remediation sessions	Visuospatial perception & problem solving	53	Remediated groups improved significantly compared to the control group	No difference between the two remediation groups: in supplemented strategy training & simple practice
Wetzig & Hardin (1990); USA	45	Inpatients with impairment at baseline	NR	EXP (15/NR) PRAC (15/NR) TAU (15/NR)	Active: Training on a hierarchical cumulative learning programme on the Wisconsin Card Sorting Test (WCST)	45-minutes twice over two days	Abstract reasoning & conceptual flexibility (shifting)	50	EXP group demonstrated significantly improved performance over the PRAC and TAU groups on the 3 measures	PT

										taken from the WCST
Control groups: practice only on WCST (PRAC) & a TAU group										
Yohman et al. (1988); USA	76	Inpatients 100% male	National Council on Alcoholism Criteria for Alcoholism 42.7 years (SD = 9.3)	MT (25/NR) PT (26/NR) TAU (25/NR) CT (36/NR)	Active groups: Memory (MT) or problem solving training (PT), introducing specific techniques & provided guided & unguided practice	12 hours over 10 daily sessions	Memory (verbal & visual) and problem solving	4, 5, 7, 11, 14, 15, 23, 39, 41, 42, 43, 44, 48, 52, 9, 46, 56	PT	Problem solving group improved more on the problem solving cluster than did either of the other two groups
					Control groups: TAU, & a non- alcoholic control group (no remediation)					

^aTreatment type, Percentage male, mean age. Where age (mean/SD) was reported per group, a formula was used to compute an average for whole sample.

^bOutcome measures are listed in Table 3. Outcome measures in bold are composite or cluster measures where individual outcomes were not reported.

MT – Mid-treatment

PT – Post-treatment

FU – Follow up

NR – Not reported

TAU – Treatment-as-usual

Table 2. Included Studies - Other Substances

Study and Country	N	Population ^a	Clinical Diagnosis	Groups (N Starters/Completers)	Description of intervention/Comparators	Length	Cognitive Target(s)	Outcome Measures ^b	Main Findings
Czuchry & Dansereau (2003); USA	452	Inpatient probationers 69% male --	NR Mixed substances	CSM (232/NR) TAU (220/NR)	Active: <i>The TCU Cognitive Skills Modules</i> (CSM): 10 self-study booklets covering 'critical skills' Control: TAU	5 weeks to complete 10 booklets. 16.8 weeks of treatment, 12.6 weeks of aftercare	Memory, comprehension, self-regulation, goals setting & planning approaches	64, 65, 66 MT, PT	CSM increased residents' involvement in treatment including engagement, cooperation, respect for other residents. CSM more effective at MT than PT
Fals-Stewart & Lucente (1994); USA	80	Inpatients mandated to treatment with general cognitive impairment 29.3 years (SD = 6.0)	NR Mixed substances --	CACR (20/18) PMRAC (20/18) CTAC (20/18) TAU (20/18)	Active: Computer-assisted cognitive rehabilitation (13 tasks) Control groups: Progressive muscle relaxation (PMRAC), computer training control (CTAC) and a TAU group	Twice weekly for 50 minutes over 25.2 weeks	Attention, motor skills, spatial orientation & word memory	23, 39, 47, 53, 57, 60 MT, PT	CACR group, on average, received higher scores on the neuropsychological test battery across the measurement interval (0-6 months) than the other conditions ($\eta^2=0.5$). However, the CACR was not significantly different from control conditions at 6-months (PT)

on the neuropsychological battery									
Fals-Stewart & Lam (2010); USA	160	Inpatients 59% male 32.8 years (SD = 7.0)	One or more Substance Use Disorders (DSM-IV)	CACR (80/75) CATT (80/72)	Active: Computer-assisted cognitive rehabilitation (PSSCogReHab) Control: Computer-assisted typing tutorial	3 times weekly for 50 minutes over 9 weeks	Visuospatial, complex attention, problem solving & memory	59, 60, 61, 62, 63, 67, 69, 72 PT, FU (3, 6, 9 12 months)	CACR had greater improvement in cognitive scores at PT. CACR had lower Addiction Severity Index scores & higher percentage of days abstinent at 12-month FU
Grohman & Fals-Stewart (2003); USA	120	Inpatient 70.8% male 32.2 years (SD = 5.2)	Substance use disorders (DSM-IV)	CACR (40/?) CATT (40/?) TAU (40/?)	Active: Computer-assisted cognitive rehabilitation (PSSCogReHab)-sequence of 13 rehabilitation tasks Control groups: Computer-assisted typing tutorial - trained to type through fixed sequence (CATT), & a TAU group	3 times weekly for 50 minutes over 8 weeks	Attention, motor skills, spatial orientation, & word memory	63, 67 PT	CACR stayed in treatment longer than CATT & were more likely to leave due to 'graduation'

Rass et al. (2015); USA	56	Outpatients 46.4% male 43.4 years (SD = 8.0)	NR Stable Methadone (opioid)	CCRT (37/28) ACC (36/28)	Active: Computerised cognitive remediation: <i>(Cogmed QM)</i>	25 45- minute sessions, 3- 5 times per week	Working memory (verbal & visuospatial)	6, 16, 19, 20 21, 22, 24, 31, 33, 34, 35, 38, 39, 45, 69, 70, 71	Some cognitive outcomes (including working memory tasks similar to the training) showed improved performance at PT. Drug use increased in ACC & remained constant in CCRT
Control: Active computer control									

^aTreatment type, Percentage male, mean age. Where age (mean/SD) was reported per group, a formula was used to compute an average for whole sample.

^bOutcome measures are listed in Table 3. Outcome measures in bold are composite or cluster measures where individual outcomes were not reported.

MT – Mid-treatment

PT – Post-treatment

FU – Follow up

NR – Not reported

TAU – Treatment-as-usual

Participants

All studies recruited participants with diagnosed SUDs (alcohol or other substances), or patients in treatment for a SUD. Two studies (Goldman & Goldman, 1987; Stringer & Goldman, 1998) also included non-SUD control groups. Ten studies recruited patients in treatment for alcoholism (Bell et al., 2016; Gamito et al., 2014; Goldman & Goldman, 1987; Mathai et al., 1998; Roehrich & Goldman, 1993; Rupp et al., 2012; Steingass et al., 1994; Stringer & Goldman, 1998; Wetzig & Hardin, 1990; Yohman et al., 1988), four studies recruited patients with mixed substance use (Czuchry & Dansereau, 2003; Fals-Stewart & Luente, 1994; Fals-Stewart & Lam, 2010; Grohman & Fals-Stewart, 2003) and one study recruited patients on a stable dose of methadone for opioid addiction (Rass et al., 2015).

All studies recruited participants through substance use treatment centres. Twelve studies recruited inpatients in residential treatment programmes (Czuchry & Dansereau, 2003; Fals-Stewart & Luente, 1994; Fals-Stewart & Lam, 2010; Goldman & Goldman, 1987; Grohman & Fals-Stewart, 2003; Mathai et al., 1998; Roehrich & Goldman, 1993; Rupp et al., 2012; Steingass et al., 1994; Stringer & Goldman, 1998; Wetzig & Hardin, 1990; Yohman et al., 1988), and two studies recruited outpatients (Bell et al., 2016; Rass et al., 2015). One study did not report residential status of the treatment programme (Gamito et al., 2014).

The mean age of the randomised populations ranged from 29.3 to 55.2. No studies mentioned recruiting adolescents under the age of 18. Most studies excluded patients with a history of epilepsy, head injury or neurological history unrelated to substance use.

Four studies required participants to be impaired cognitively at baseline. One study (Rupp et al., 2012) had a requisite for at least a ‘mild’ impairment on one of the

cognitive tasks at baseline (one SD below the mean), another study (Stringer & Goldman, 1998) required WAIS-R vocabulary scores within one SD of the mean of their age, a third study (Wetzig & Hardin, 1990) required a baseline deficit in the Wisconsin Card Sorting Test ‘as per the profile of alcoholic performance’ and the fourth study (Fals-Stewart & Luente, 1994) recruited only those displaying a general cognitive impairment defined as a *T* score less than 40 on a summary score of cognitive measures.

Interventions

The studies tested a variety of cognitive remediation interventions, varying in cognitive focus, delivery format and duration of the intervention.

Twelve studies tested an intervention tapping a number of cognitive domains and skills (Bell et al., 2016; Czuchry & Dansereau, 2003; Fals-Stewart & Luente, 1994; Fals-Stewart & Lam, 2010; Gamito et al., 2014; Grohman & Fals-Stewart, 2003; Mathai et al., 1998; Rass et al., 2015; Roehrich & Goldman, 1993; Rupp et al., 2012; Steingass et al., 1994; Yohman et al., 1988), whereas the other three studies tested an intervention which involved guided or repeated practise of one task or a few very similar tasks (Goldman & Goldman, 1987; Stringer & Goldman, 1998; Wetzig & Hardin, 1990).

Six studies tested interventions delivered via a computer programme (Bell et al., 2016; Fals-Stewart & Luente, 1994; Fals-Stewart & Lam, 2010; Grohman & Fals-Stewart, 2003; Rass et al., 2015; Rupp et al., 2012) and one study an intervention using mobile technology (Gamito et al., 2014). Five studies tested non-computerised interventions with relatively few details about the procedure and format (Goldman & Goldman, 1987; Mathai et al., 1998; Stringer & Goldman, 1998; Wetzig & Hardin,

1990; Yohman et al., 1988). Two studies administered self-study workbooks (Czuchry & Dansereau, 2003; Roehrich & Goldman, 1993), and one study delivered the intervention in group format to groups of up to 10 participants (Steingass et al., 1994).

Of the studies which delivered a computerised intervention, four of these were proprietary: *Brain Fitness* and *InSight* (Bell et al., 2016), *Cogpack* (Rupp et al., 2012), *PSSCogReHab* (Fals-Stewart & Lam, 2010; Grohman & Fals-Stewart, 2003) and *CogMed QM* (Rass et al., 2015).

Whereas most studies delivered the intervention over several weeks, three studies only offered two sessions of cognitive remediation (Goldman & Goldman, 1987; Stringer & Goldman, 1998; Wetzig & Hardin, 1990) and one study four sessions (Roehrich & Goldman, 1993).

Comparison Groups

Of the eight studies with two arms, five compared the intervention to treatment-as-usual (Bell et al., 2016; Czuchry & Dansereau, 2003; Gamito et al., 2014; Mathai et al., 1998; Rupp et al., 2012), two studies to a group that controlled for attention (Fals-Stewart & Lam, 2010; Rass et al., 2015) and one to a waiting-list control (Steingass et al., 1994).

Seven studies had more than two arms; three studies had two cognitive remediation groups and treatment-as-usual, non-alcoholic control or attention-control comparator groups (Goldman & Goldman, 1987; Roehrich & Goldman, 1993; Yohman et al., 1988), two studies had practice-only groups in addition to intervention and treatment-as-usual groups (Stringer & Goldman, 1998; Wetzig & Hardin, 1990), and two studies compared intervention groups to attention-control and treatment-as-usual groups (Fals-Stewart & Luente, 1994; Grohman & Fals-Stewart, 2003).

Outcomes

Eight studies measured cognitive outcomes only (Bell et al., 2016; Gamito et al., 2014; Goldman & Goldman, 1987; Mathai et al., 1998; Steingass et al., 1994; Stringer & Goldman, 1998; Wetzig & Hardin, 1990; Yohman et al., 1988). Cognitive outcomes either related to the domain of cognition targeted by the intervention or more general cognitive functioning, in order to determine generalisation beyond the trained domain. Two studies measured treatment outcomes only (Czuchry & Dansereau, 2003; Grohman & Fals-Stewart, 2003). Five studies measured cognitive as well as treatment or substance use outcomes (Fals-Stewart & Lucente, 1994; Fals-Stewart & Lam, 2010; Rass et al., 2015; Roehrich & Goldman, 1993; Rupp et al., 2012). All assessments were undertaken post-intervention, and three studies measured outcomes at follow-up: one month (Mathai et al., 1998), three months (Bell et al., 2016), and up to 12 months (Fals-Stewart & Lam, 2010).

There was considerable variation in outcome measures used. A total of 59 different cognitive outcome measures (including composite scores), nine treatment outcomes and five substance use outcomes were reported over the studies. These have been broadly categorised under the subheadings in Table 3, which lists the outcome measures in full. The number key in Table 3 corresponds to the outcomes listed by study in Table 1 and Table 2.

Table 3. Outcome Measures

Declarative Memory	
<u>Learning and Recall</u>	
1	Cued recall (Menon & Rao, 1997)
2	Munich Verbal Memory Test (Ilmberger, 1988)
3	Hopkins Verbal Learning Test Revised (Benedict, Schretlen, Groninger, & Brandt, 1998)
4	Luria Memory Words (Luria, 1976)
5	Weschler Memory Scale: Logical Memory (Wechsler & Strone, 1987)
6	Word recall and recognition (Snodgrass & Corwin, 1988)
7	Verbal Paired Associates (Yohman & Parsons, 1985)
8	Weschler Memory Scale: Verbal paired associates learning (Wechsler & Stone, 1987)
9	'Learning and memory' cluster score (Yohman et al., 1988)
<u>Visuospatial Memory</u>	
10	Complex Figure Test recall (Lezak et al., 2004)
11	Weschler Memory Scale: Visual reproduction (Wechsler & Stone, 1987)
12	Street-Map Test (Baumler, 1974)
Working Memory	
13	Two-back paradigm in working memory subtest of the Test Battery on Attentional Performance (Zimmermann & Fimm, 1993)
14	Symbol-Digit Paired Associates (Ryan & Butters, 1980)
15	Face-Name Paired Associates (Schaeffer & Parsons, 1987)
16	Visuospatial Working Memory Task (Rapport et al., 2008)
17	Categorised Verbal Memory Test (Channon, Daum & Polkey, 1989)
18	Digit Span Forward and Backward from German WAIS-R (Tewes, 1994)
19	Digit Span Forward (Weschler, 1981)
20	Digit Span Backward (Weschler, 1981)
21	N-back Task (Jonides et al., 1997)
22	Operation Span: proportion of correctly recalled words (Turner & Engle, 1989)
Attention	
<u>Processing Speed/Simple Attention</u>	
23	WAIS Digit Symbol (Weschler, 1981)
24	Digit Symbol Substitution Task (McLeod, Griffiths, Bigelow & Yingling, 1982)
25	Alertness Test, subtest of Test Battery on Attentional Performance (Zimmermann & Fimm, 1993)
26	Simple and choice reaction time (Mathai et al., 1998)
<u>Sustained Attention</u>	
27	Figure Identification task (Weintraub & Mesulam, 1988)
28	D2-Test (Brickenkamp, 1962)
<u>Divided Attention</u>	
29	Triads Task and Rhythm Detection Task (Misra & Raso, 1994)
30	The Divided Attention Test, subtest of Test Battery on Attentional Performance (Zimmermann & Fimm, 1993)

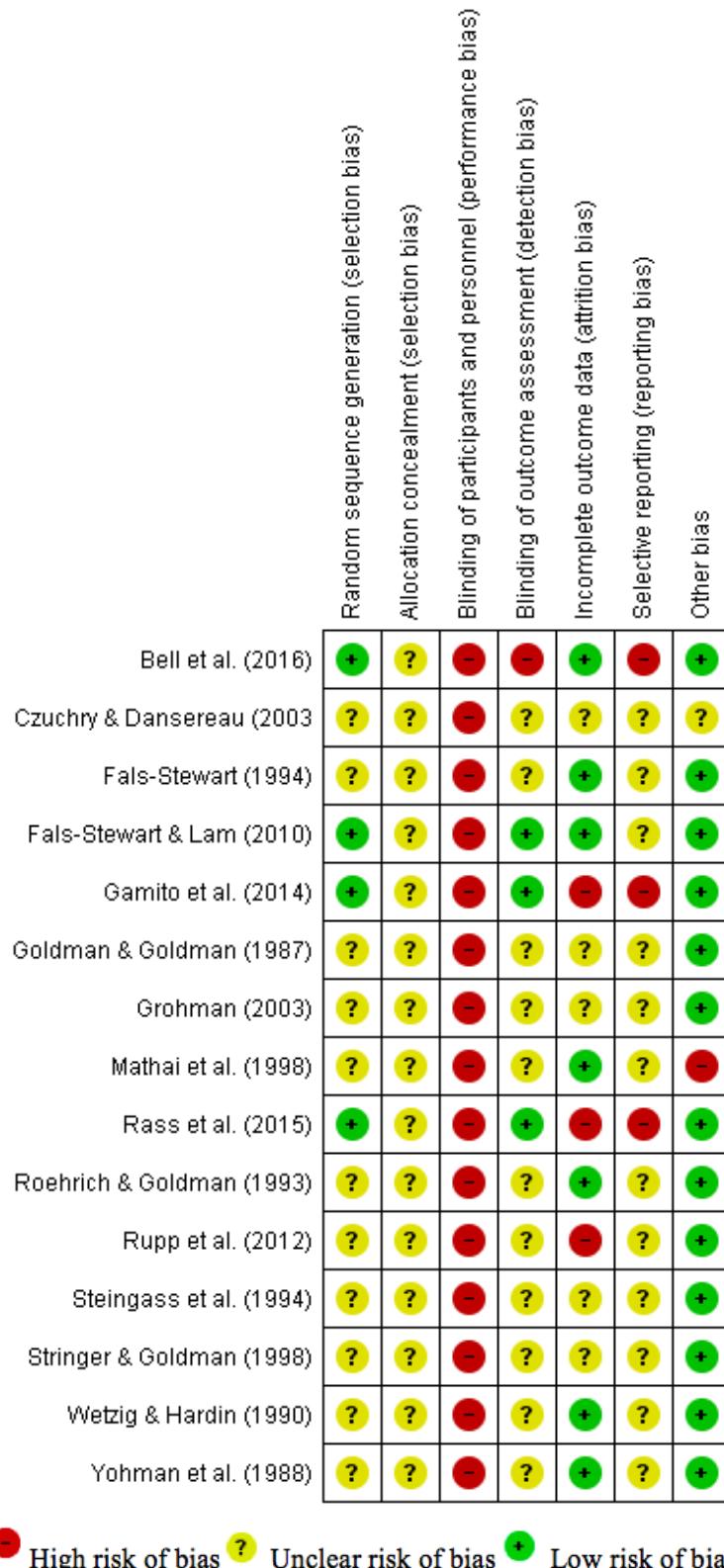
- Executive Function**
- Inhibition and Impulsivity
- 31 A Continuous Performance Task (Epstein et al., 1998)
- 32 Incompatibility test (spatial Stroop task) in the Test Battery on Attentional Performance (Zimmermann & Fimm, 1993)
- 33 Hypothetical Delay Discounting Task (Johnson & Bickel, 2002)
- 34 Quick Discounting Operant Task (Johnson, 2012)
Decision making
- 35 Iowa Gambling Task (Bechara et al., 1994)
- Frontal
- 36 Frontal Assessment Battery (Dubois, 2000)
- 37 Colour-Word-Association Test (Linden et al., 1990)
- 38 Trail Making Test A (Halstead, 1947)
- 39 Trail Making Test Part B (Reitan & Wolfson, 1995)
- 40 Color Trail Test (Satz, Uchiyama & White, 1996)
- Problem Solving and Reasoning
- 41 Twenty Questions (Laine & Butters, 1982)
- 42 Hypothesis Testing Procedure (Levine, 1966)
- 43 Adaptive Skills Battery (Jones & Lanyon, 1981)
- 44 Conceptual Level Analogy Test (Willner, 1970)
- 45 Raven's Standard Progressive Matrices (Raven, 1998)
- 46 Problem Solving cluster score (Yohman et al., 1988)
- Concept Formation and Abstraction Ability
- 47 The Category Test (Halstead, 1947)
- 48 Concept Formation Test (Rao, 1976)
- 49 Abstraction Test (Shipley, 1940)
- Cognitive Flexibility and Fluency
- 50 Wisconsin Card Sorting Test (Heaton, 1993)
- 51 Phonemic fluency (Lezak, Howieson & Loring, 2004)
- 52 Semantic fluency (Strauss, Sherman & Spreen, 2006)
- Visuospatial Construction and Planning
- 53 WAIS Block Design (Wechsler, 1981)
- 54 Complex Figure Test copy (Lezak et al., 2004)
- 55 Rey Figure Test copy (Lezak, 1983)
- 56 Perceptual motor cluster score (Yohman et al., 1988)
- Global Cognition**
- 57 Mean *T* score for battery of tests (Fals-Stewart & Lucente, 1994)
- 58 MMSE (Folstein, 1975)
- 59 The Neuropsychological Assessment Battery-Screening Module (White, Stern & Staff, 2003)
- Treatment Outcomes**
- 60 Staff Rating Scale (Sacks & Levy, 1979)
- 61 Working Alliance Inventory-Short Form (Busseri & Tyler, 2003)
- 62 Client Assessment Summary (Kressel, De Leon, Palij & Rubin, 2000)
- 63 Length of stay in treatment (days)

- | | | |
|----|--|--|
| 64 | Readiness for treatment (TCU Self Rating Form; Czuchry & Dansereau 2000) | Substance Use |
| 65 | Peer ratings of treatment engagement (Czuchry, Dansereau, Sia & Simpson, 1998) | 69 Timeline Followback Interview: Percent Days Abstinent, Drug Use (Sobell & Sobell, 1996) |
| 66 | Community ratings of treatment engagement (Czuchry & Dansereau, 2000) | 70 Addiction Severity Index (McLellan et al., 1992) |
| 67 | Graduation rate | 71 Urine drug screen |
| 68 | Relapse Prevention Content Test (Roehrich & Goldman, 1993) | 72 Obsessive Compulsive Drinking Scale German Version (Mann & Ackermann, 2000) |
| | | 73 Abstinence/Relapse |

Risk of Bias in Included Studies

A summary of the risk of bias across studies is presented in Figure 2.

Figure 2. Risk of Bias Summary



Allocation

Three studies (Bell et al., 2016; Fals-Stewart & Lam, 2010; Gamito et al., 2014) were deemed to be at low risk of bias for random sequence generation. This was based on adequate randomisation methods in the published reports (namely use of random number generator/urn randomisation). Twelve studies were rated as having an unclear risk of bias, as they were described as ‘randomised’ but with insufficient details about methods to make a judgment about possible bias (Czuchry & Dansereau, 2003; Fals-Stewart & Luente, 1994; Goldman & Goldman, 1987; Grohman & Fals-Stewart, 2003; Mathai et al., 1998; Roehrich & Goldman, 1993; Rupp et al., 2012; Steingass et al., 1994; Stringer & Goldman, 1998; Wetzig & Hardin, 1990; Yohman et al., 1988). All 15 studies were rated as unclear for allocation concealment as no details were reported on concealing the allocation sequence prior to assignment.

Blinding

The behavioural nature of the interventions could not be kept blind from participants and personnel. As a result, blinding of participants and personnel was rated as high risk of bias by default. Regardless of the inability to blind participants and personnel, it was possible to reduce bias for all outcomes by recruiting someone not otherwise involved in the study to measure outcomes without knowledge of allocation. Three studies were rated as low risk of bias for reporting outcome assessors as blind (Fals-Stewart & Lam, 2010; Gamito et al., 2014; Rass et al., 2015). For eleven studies, it was not reported and thus the bias was rated as unclear (Czuchry & Dansereau, 2003; Fals-Stewart & Luente, 1994; Goldman & Goldman, 1987; Grohman & Fals-Stewart, 2003; Mathai et al., 1998; Roehrich & Goldman, 1993; Rupp et al., 2012; Steingass et al., 1994; Stringer & Goldman, 1998; Wetzig & Hardin, 1990; Yohman et al., 1988).

One study was rated as high risk of bias as outcome assessors were not blind to participants' intervention group (Bell et al., 2016).

Incomplete Outcome Data

Three studies were deemed to be high risk for attrition bias. Both Gamito and colleagues (2014) and Rass and colleagues (2015) had high levels of attrition and excluded dropouts from the analyses, and Rupp and colleagues (2012) had uneven levels of attrition between groups and it was not reported whether dropouts were included in the analysis. Seven studies were considered to be low risk for attrition bias (Bell et al., 2016; Fals-Stewart & Luente, 1994; Fals-Stewart & Lam, 2010; Mathai et al., 1998; Roehrich & Goldman, 1993; Wetzig & Hardin, 1990; Yohman et al., 1988). This was due to low rates of attrition (<20%) which was balanced across groups or as imputation was likely to have appropriately accounted for missing data. Five studies were rated as having unclear risk of bias (Czuchry & Dansereau, 2003; Goldman & Goldman, 1987; Grohman & Fals-Stewart, 2003; Steingass et al., 1994; Stringer & Goldman, 1998) as levels of attrition or subsequent numbers analysed were not reported.

Selective Reporting

Three studies were rated as being at high risk of bias for selective outcome reporting; these were the only studies that had prospectively registered a trial protocol. One study (Gamito et al., 2014) omitted reporting the post-treatment MMSE from the paper despite stating this as a primary outcome in the protocol (see Appendix 2 for more details, including author correspondence), another study (Bell et al., 2016) did not report all outcomes stated in the protocol in the paper, and a third study (Rass et

al., 2015) reported several outcomes in the paper that were not pre-specified in the registered protocol.

For the remaining 12 studies, the risk of selective reporting was rated as unclear as outcomes could not be checked against a prospectively registered protocol (Czuchry & Dansereau, 2003; Fals-Stewart & Luente, 1994; Fals-Stewart & Lam, 2010; Goldman & Goldman, 1987; Grohman & Fals-Stewart, 2003; Mathai et al., 1998; Roehrich & Goldman, 1993; Rupp et al., 2012; Steingass et al., 1994; Stringer & Goldman, 1998; Wetzig & Hardin, 1990; Yohman et al., 1988). There is a tendency for these to be older studies, conducted when reporting standards were not as strict as they are for current RCTs.

Other Sources of Bias

One study was considered to be at high risk of other types of bias (Mathai et al., 1998) as the intervention group received additional interventions to the treatment-as-usual group, and had a small sample size ($N = 8$). The other 14 studies were rated as low risk of bias, as no other biases were identified such as baseline imbalances.

Effects of Interventions

The study findings were considered by outcome. For convenience and clarity, these were classified under the domains of: declarative memory, working memory, attention, executive function, global cognition, treatment outcomes and substance use outcomes. Where possible, risk of bias judgments were integrated into the study results.

Declarative Learning and Memory

Six studies assessed verbal learning and memory outcomes. Three studies testing interventions that broadly targeted attention and memory reported post-treatment improvements for the cognitive remediation groups but not comparison groups (Bell et al., 2016; Mathai et al., 1998; Steingass et al., 1994). Where follow-up assessment was performed, improvement was sustained at 3 months (Bell et al., 2016). One study (Rupp et al, 2012) found a significant improvement only for delayed verbal recall, and non-significant effects between groups for verbal immediate recall, learning and recognition.

One study did not find a significant improvement in the cognitive training group (Rass et al., 2015). Another study (Yohman et al., 1988) which reported a composite measure of visual memory and working memory found no effect of either memory training or problem solving training (the two active intervention groups) for the intervention compared to control group.

Two studies reported measures relating to visuospatial memory recall, and neither found an effect of the intervention (Steingass et al., 1994; Rupp et al., 2012).

Working Memory

Three studies assessed working memory. One study found improvements on two measures of working memory (two-back paradigm and Digit Span Backwards) for the cognitive remediation group compared to control group, who were trained over multiple cognitive domains (Rupp et al., 2012). Another study trained participants specifically in working memory (Rass et al., 2012) and of the five measures of working memory assessed, there were improvements for the intervention group in two of these

measures (Digit Span Backwards and Visuospatial Working Memory Task) and not for the other three (Operation Span, Digit Span Forwards and N-back Task).

One study (Steingass et al., 1994) of attention and memory training for alcoholics found no effects of the intervention over three measures of working memory.

Attention

Four studies reported measures of processing speed/simple attention. Two studies found no significant effect of the intervention on these measures (Rupp et al., 2012; Rass et al., 2015), and two reported an effect. One of these (Mathai et al., 1998) found improvements on simple reaction time for the intervention group (however, note the high level of bias in this study), and the other (Roehrich & Goldman, 1993) found both remediation groups had significant improvements on Digit Symbol substitution compared to control groups.

For the two studies reporting measures of sustained attention, there were no significant intervention effects (Mathai et al., 1998; Steingass et al., 1994), nor were there effects for two studies measuring divided attention (Mathai et al., 1998; Rupp et al., 2012).

Executive Function

Two studies measured response inhibition and impulsivity over five different outcome measures (Rass et al., 2015; Rupp et al., 2015). Neither study found significant effects of the intervention compared to control groups.

Five studies reported measures of frontal lobe functioning. One study (Gamito et al., 2014) found significant improvements from baseline to follow-up in the Frontal

Assessment Battery in the intervention but not control group. Three studies administered the Trail Making Test Part B; two found an improvement in remediation groups (Roehrich & Goldman, 1993; Goldman & Goldman, 1987) and one did not (Rass et al., 2015). One study that tapped frontal functioning from the Colour-Word-Association Test did not find an effect of the intervention (Steingass et al., 1994).

Two studies measured outcomes relating to problem solving and reasoning. One study (Yohman et al., 1998) found that a group trained on problem solving did significantly better than the other two (memory training and control) groups on a cluster measure of problem solving. The other study (Rass et al., 2015), however, found an intervention and control group worsened post-treatment on a measure of reasoning.

The only study (Mathai et al., 1998) reporting an outcome relating to concept formation did not find significant effects of the active intervention.

With regards to cognitive flexibility, two studies measured the Wisconsin Card Sorting Test (WCST). Whereas one study (Gamito et al., 2014) found no effect of the intervention group compared to treatment-as-usual, the other (Wetzig & Hardin, 1990) found the experimental group demonstrated significantly improved performance over the practice and control groups on three outcomes from the WCST.

One study (Rupp et al., 2012) measured verbal fluencies (semantic and phonemic) and found no effect of the intervention.

Four studies administered outcomes measuring visuospatial construction and planning. Two studies administered the WAIS Block Design task. One study (Rupp et al., 2012) which trained alcoholics in a general computer-assisted cognitive remediation programme did not find an intervention effect on this measure. Another (Stringer & Goldman, 1998) specifically trained two groups of alcoholics on the task

(one remediation group was taught a strategy for constructing block designs and given guided practice, and one control group practiced but without the training) and found both remediation groups equally effective and significantly better than the control groups. Also, both groups' post-test performance fell to very near that of the non-alcoholic control group, indicating some functional recovery. Two other studies considered outcomes broadly under this cluster; Steingass and colleagues (1994) found no group effect of attention and memory training on the Rey Figure Test copy and Yohman and colleagues (1988) found no effect of problem solving or memory training on a perceptual motor cluster score of outcomes.

Global Cognition

Four studies reported a measure of global cognition. Two of these measured the MMSE (Folstein, 1975). Whereas Gamito and colleagues (2014) found no difference between groups post-treatment following an mHealth multi-domain cognitive intervention, Rupp and colleagues (2012) found a post-treatment improvement in MMSE score in the computer-assisted cognitive remediation group compared to the treatment-as-usual group. One study presented a summary score for a battery of neuropsychological tests rather than reporting outcomes individually (Fals-Stewart & Luente, 1994). At post-treatment the computer-assisted cognitive rehabilitation group were not significantly different from the three control conditions on this main outcome measure. The other study to report a global measure of cognition (Fals-Stewart & Lam, 2010) found a significant improvement on the NAB-SM for a computer-assisted cognitive rehabilitation group versus an active control group at nine-week post-treatment assessment. However, this outcome was not reported at

follow-up assessments (three, six, nine and 12 months) so it is unclear whether the effect was sustained.

Treatment Outcomes

Five studies considered whether cognitive remediation interventions had an effect on substance-use treatment outcomes. One study (Roehrich et al., 1993) tested an instrument assessing acquisition of the elements of relapse prevention (RP), and the remediation groups improved in RP content acquisition and cognitive flexibility compared to control groups, with the standard neuropsychological stimulation group slightly outperforming the ‘ecologically valid remediation’ group. Another study (Czuchy & Dansereau, 2003), a large cluster-RCT which compared probationers receiving Cognitive Skills Modules in addition to inpatient treatment-as-usual, considered: readiness for treatment, peer ratings of treatment engagement and community ratings of treatment engagement. Effects were found for the intervention groups at mid- and post-treatment for readiness for treatment, peer-ratings (of working the programme and for being clean and sober), and increased community engagement and respect, but differences were bigger at mid-term than post-treatment.

For the two studies (Fals-Stewart & Luente, 1994; Fals-Stewart & Lam, 2010) measuring staff ratings of patient participation the cognitive remediation groups had higher scores on each month of measurement. In addition, Fals-Stewart & Lam (2010) found the cognitive remediation group participants had significantly higher scores on another two measures of treatment engagement (WAI-S and CAS).

Finally, for the two studies that considered length in treatment and graduation rate, it was found that the intervention groups stayed in treatment longer and a greater

proportion of patients who received the intervention graduated from the programme successfully (Fals-Stewart & Lam, 2010; Grohman & Fals-Stewart, 2003).

Substance Use Related Outcomes

With regards to substance use outcomes, two studies measured the Addiction Severity Index (McLellan et al., 1992). Whereas one study (Fals-Stewart & Lam, 2010) found that the intervention group showed improvement on some ASI composite measures (Alcohol, Drug, Legal, Family-Social) at 12-month follow-up, the other study (Rass et al., 2015) found that the only composite of the ASI to be significantly different at post-treatment was Employment Status. Both studies also reported intervention groups having fewer drug use days and a higher percentage of days abstinent at post-treatment compared to control participants. Another study (Mathai et al., 1998), which has questionable validity due to high risk of bias, reported no effect of the cognitive intervention on rates of abstinence and relapse at one-month follow up. Finally, Rupp and colleagues (2012) measured alcohol cravings (OCDS-G) and found that compulsions were significantly lower for the intervention group, but not obsessions.

Discussion

Summary of Main Results

This study reviews RCTs of cognitive remediation for adults with SUDs, with a view to understanding whether the interventions lead to improvement in cognition or positively impact treatment outcomes. The review highlights the clinical heterogeneity across the existing studies, and the large number of cognitive outcome

measures used. Using a narrative approach to synthesise results across outcomes (cognitive, treatment and substance-related), overall results are mixed and the evidence for cognitive remediation is weak across many of the comparisons.

For cognitive outcomes, the evidence is limited and inconclusive. There is some evidence for the effect of memory/attention training on remediating verbal learning and memory (over three studies; Bell et al., 2016; Mathai et al., 1998; Steingass et al., 1994), sustained to three months (Bell et al., 2016). There is also some evidence for improvements in measures of frontal lobe function following cognitive remediation (two multi-domain interventions [Gamito et al., 2014; Roehrich & Goldman, 1993] and one specific-task intervention [Goldman & Goldman, 1987]), although this is not consistently found across other studies. With regards to visuospatial construction and planning, there was some evidence for improvements after specific training in a task on post-treatment performance (Stringer & Goldman, 1998) – however, a multi-domain computer-assisted remediation intervention had no effect (Rupp et al., 2012). This may indicate that training on a specific cognitive task may increase one's performance on that task, but that general cognitive programmes may not lead to transfer-effects on measures. There is mixed evidence on studies reporting measures of global cognition and working memory. There is little evidence for visuospatial memory recall, attention and response inhibition/impulsivity.

With regards to treatment and substance use outcomes, there is some indication that cognitive remediation may improve measures indicating treatment engagement and acquisition. More promising is some evidence of improvement in objective measures of length in treatment and graduation rate, which favour cognitive remediation over control groups (these two studies had two of the largest *N*s [Fals-Stewart & Lam, 2010; Grohman & Fals-Stewart, 2003]). Similarly, there is some

evidence favouring cognitive remediation groups with regards to fewer drug use days and a higher percentage of days abstinent.

Overall Completeness and Applicability of Evidence

The limited number of studies within each narrative comparison weakens the extent to which conclusions can be drawn, and thus the applicability of the evidence to true estimates of effectiveness. All studies recruited participants from addiction services, which renders the findings of the review applicable to those engaged in treatment for their substance use. However, participants who volunteered to participate in research may not be representative of all patients with SUDs, potentially representing a more motivated subgroup. Very few studies had follow-up assessments and therefore we cannot make inferences that any of the favourable effects found post-treatment would be sustained. The acceptability of the interventions to individuals with SUDs was not reported in any study. It would be useful to know how participants found the cognitive remediation tasks, for example, whether they would commit to it as part of treatment, or whether they were able to focus and engage with it. Although a few studies reported treatment and substance use outcomes, the evidence remains limited as to whether any of the limited improvements in cognitive functioning translate to meaningful effects in real-life.

Quality of the Evidence

The risk of bias for each study and across bias domains has been reported in detail previously and summarised in Figure 2. None of the included studies reported a power calculation, and there is a chance that the smaller studies may have missed real effects. Seven studies had small samples under 65 participants (Bell et al., 2016;

Mathai et al., 1998; Rass et al., 2015; Rupp et al., 2012; Steingass et al., 1994; Stringer & Goldman, 1998; Wetzig & Hardin, 1990). Three studies had large samples over 100 (Czuchry & Dansereau, 2003 [N = 452]; Fals-Stewart & Lam, 2010 [N = 160]; Grohman & Fals-Stewart, 2003 [N = 120]). Given there were no significant high risk of biases identified for these trials (however, judgements were often unclear due to poor reporting) perhaps more weight should be given to these studies. The latter two studies (Fals-Stewart & Lam, 2010; Grohman & Fals-Stewart, 2003), which both offered computerised cognitive remediation interventions, found favourable effects on treatment and substance use outcomes. The largest trial (Czuchry & Dansereau, 2003), a cluster-randomised study which offered self-study booklets to communities randomised to the intervention, was less promising with some effects for ‘soft’ measures of treatment engagement and more effective at mid-treatment than post-treatment.

Of particular concern is the fact that all three RCTs that pre-registered a trial protocol (Gamito et al., 2014; Bell et al., 2016; Rass et al., 2015) did not all follow the procedure they had pre-specified and omitted reporting of some measures, rendering them at high risk for selective outcome reporting and questioning the study results. There were other concerns with these three papers, including the testing of a large number of outcomes. For example, Gamito and colleagues (2014) reported 14 cognitive measures which increases the chance of finding a chance positive result or “cherry picking” an outcome to report.

Potential Biases and Limitations of the Review Process

There are potential biases and limitations in the review process that should be considered when interpreting the findings.

Cognitive measures were categorised under a single cognitive domain. Categorising outcome measures was a challenge, as several measures are likely to tap several cognitive functions (e.g. both attention and memory), as few tasks require cognitive skills that operate in isolation. These crude decisions made about categorisation will have affected the inferences drawn about the effectiveness as this was done by outcome type.

There was high heterogeneity across the intervention content (for example, some interventions which trained a specific task/domain and others that trained several cognitive skills), delivery format (computerised, self-study booklets, or group-delivered) and amount of intervention received (two sessions of remediation up to 50). This may weaken the strength of conclusions that can be drawn from collating studies by outcome (i.e. grouping what may in practice have been quite different ‘cognitive remediation’ interventions). There was also heterogeneity across the populations samples (e.g. in setting [country and type of treatment programme], type of SUD, and severity of cognitive impairment at baseline) which may have affected the degree of any benefits of remediation.

Three comprehensive databases were searched to identify trials. However, due to time and resource constraints, not all relevant electronic databases were searched and so there is a chance some studies could have been missed. This is a possibility given that two of the included studies, identified from review papers, were not identified in the original search. In addition, grey literature was not searched. This could suggest a risk of publication bias, which may overestimate the effects of interventions (as studies finding a positive result are more likely to be published; Winters & Wier, 2017).

The review was biased to randomised studies only; this may have affected the review findings if higher quality studies differ systematically from other studies on characteristics other than study quality.

Although a second individual rated risk of bias for each study, only one author scanned the search results, made decisions on inclusion and exclusion, extracted data from included studies, and categorised cognitive outcome measures. Ideally these processes would have been done by two authors to reduce human error and implicit individual biases.

Finally, it was a challenge to integrate study risk of bias judgments into results and conclusions. It is important to keep these in mind in weighting the applicability of the evidence.

Conclusions

At present, the findings are not sufficiently consistent to be evidence for recommending cognitive remediation as an adjunct to addiction programmes. However, there is some evidence from a small number of studies that some cognitive remediation interventions may have an effect on treatment outcomes. There is some promise in computerised cognitive remediation programmes that warrant further research. The estimates of effectiveness are not very clear given some of the methodological limitations and significant clinical heterogeneity across studies.

Implications for Practice

There is no clear indication at present that cognitive remediation would be a useful adjunct to treatment. There is, however, substantial evidence that cognitive

impairments are prevalent across SUDs so perhaps focusing on tailoring treatments that have an evidence-base to adapt for this could prove more useful.

Implications for Research

Following the review, several recommendations for future research follow. It would be useful for future studies to use a small set of robust cognitive outcome measures that would allow for direct comparison. It would also be useful, when considering the wider implications of remediating deficits with regards to treatment adherence and reducing substance use, to test whether cognitive outcomes transfer to these more clinically-relevant outcomes. Follow-up assessments should be carried out to determine whether any effects are sustained. In addition, should any robust evidence be found in future trials, an effectiveness trial testing the feasibility and acceptability of the intervention in addiction services would be the necessary next step.

It could also be useful to consider who does and does not respond to cognitive remediation intervention - i.e., whether a severity of deficit or long history of substance use negates the ability to benefit from the intervention.

Although the review focused on interventions that targeted top-down cognitive functions, there is recent suggestion in the literature that interventions targeting both top-down and bottom-up cognitive functions could prove more promising (Manning, Verdejo-Garcia, & Lubman., 2017).

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Part II: Empirical Paper

Prospective Memory and Future Event Simulation in Frequent Cannabis Users

Abstract

Background. Frequent cannabis users have been found to show impaired memory for past events, but it is not clear whether they are also impaired in prospective memory for future events. **Aims.** To objectively assess prospective memory (PM) in frequent cannabis users (one group dependent on cannabis, and one group non-dependent) compared to non-using controls, and to examine the effects of future event simulation (FES) on PM performance. To explore depression, anxiety and ‘schizotypy’ across groups. **Design.** An independent groups design. **Setting.** University College London. **Participants.** Fifty-four participants (18 dependent cannabis users, 18 non-dependent cannabis users and 18 controls) took part and were matched on age, gender, and highest level of education. **Measures.** The Virtual Week was used to assess PM abilities, with and without FES. Other measures: Cannabis Use Potency Questionnaire (CPU-Q), immediate and delayed prose recall, phonemic and category fluency, Spot-the-Word, Beck Depression Inventory (BDI-II), Beck Anxiety Inventory (BAI), and a measure of schizotypy (O-LIFE: Unusual Experiences). **Results.** There were no group differences in PM performance on the Virtual Week, and FES did not improve PM performance. Dependent cannabis users scored higher on depression, anxiety and schizotypy than both other groups (non-dependent cannabis users and controls, who scored similarly). **Conclusions.** When carefully matched on baseline variables, cannabis users do not differ from non-using controls on PM. Suggestions for future research are discussed.

Introduction

Cannabis is the most commonly consumed illicit drug in the world, with an estimated 120-190 million users worldwide (United Nations Office on Drugs and Crime, 2015). Cannabis is a psychoactive drug which comes in various forms, and is either smoked, inhaled as vapour, or ingested orally. It is used medically (e.g. for reducing symptoms in chronic pain and spasticity; Whiting, Wolff & Deshpande, 2015), in religious rituals, and for pleasure. There are around 90 chemical compounds within the plant, known as cannabinoids, but the major active cannabinoid by which the plant exerts its desired psychoactive effects is THC (Δ^9 , tetrahydrocannabinol). THC produces a euphoric high, feeling of relaxation, and intensification of sensations, among other physiological and cognitive effects (Curran & Morgan, 2014; McLoughlin et al., 2014).

High doses of THC can also cause acute, transient psychosis-like symptoms (D'Souza et al., 2005), and there is an association found between high-potency cannabis use and psychosis (di Forti et al., 2015; Ferraro et al., 2013). Frequent cannabis use has also been associated with depression and anxiety. A cohort study ($N = 14,531$; Cheung et al., 2010) found the highest levels of anxiety and mood disorders were in those who smoked cannabis almost every day (18.1%), compared to those smoking more infrequently or not at all (8.7%). Another large cohort study ($N = 42,862$; Grant & Pickering, 1998) found more severe comorbidity was associated with cannabis dependence, hypothesising that cannabis may be used to self-medicate depression. This finding has been replicated recently in a community sample ($N = 521$) of frequent cannabis smokers, with the study finding that mood and anxiety problems

were highest in the dependent users compared to non-dependent users (who smoked the same amount), with the non-dependent users scoring similarly to the general population sample (van der Pol et al., 2013).

Long-term cannabis use has also been linked to acute impairment of cognitive functioning, including decision-making (Whitlow et al., 2004), executive functioning (Bolla, Brown, Eldreth, Tate & Cadet, 2002), memory (Curran et al., 2016), and word fluency (Croft, Mackay, Mills & Gruzelier, 2001). These cognitive effects are thought to be mediated by Type 1 cannabinoid (CB1) receptors, which are found in frontal and temporal brain regions (Mechoulam & Parker, 2013). A meta-analysis of 13 studies indicates that these acute cognitive effects may be reversed after a period of abstinence (Schreiner & Dunn, 2012), and the length of abstinence is associated with the extent of the reversal of the cognitive effects (Schoeler, Kambeitz, Behlke, Murray & Bhattacharyya, 2016).

Smoking high-potency forms of cannabis (i.e. with high levels of THC) has been associated with a greater severity of dependence and more pronounced cognitive effects, compared to smoking less potent forms of the drug. Higher levels of cannabidiol (CBD) can moderate some of the negative effects of THC (Curran et al, 2016; Freeman & Winstock, 2015). Although general rates of cannabis use are falling in the UK (Home Office, 2014), there is increasing popularity of more potent forms of cannabis with THC levels of 15% or more, often called ‘skunk’. Rising THC concentrations have been found from cannabis seizure data in the UK (Hardwick & King, 2008), Europe (EMCDDA, 2014) and the USA (ElSohly et al., 2016).

One of the most frequently reported and robust effects seen in cannabis users relates to memory performance (Bolla et al., 2002; Curran et al., 2016; Schoeler, Kambeitz, Murray & Bhattacharyya, 2016). Laboratory-based studies on memory

suggest that long-term use of cannabis may have significant effects on memory, including impairments in encoding, storage, manipulation and retrieval (Solowij & Battisti, 2008). However, despite the wealth of evidence on the effects of cannabis use on retrospective memory, research into the effects on future-based memory processes remains relatively neglected.

One vital aspect of everyday memory is prospective memory (PM), which is the ability to enact intended actions at a certain point in the future, i.e. forming an intention followed by the execution of that intended action after a delay (Rendell & Henry, 2009). To-be-remembered actions may be event-based (e.g. collecting a prescription when passing a GP surgery), time-based (e.g. meeting a friend at 18:00) or activity-based, requiring an action to be performed following the accomplishment of another activity (e.g. calling the doctor after posting a letter). As such, these forms of PM depend on whether the cue for PM performance is the appearance of a certain stimulus (event-based), the passage of a certain amount of time (time-based) or the end of an activity (activity-based). Actions may be regular (e.g. taking medication every morning), or irregular (e.g. one-off actions, such as a dentist appointment).

It is thought that PM ability is reliant on retrospective memory to retain knowledge of the intention, the cue, and executive planning and motivation functions, to coordinate intended actions (Burgess, Simons, Coates & Channon, 2005). Deficits in PM may hold broad implications for occupational, interpersonal and/or health related functioning through failure to enact intended actions (Fish, Manly & Wilson, 2009).

PM is an emerging area in substance use research. Impairments in PM performance have been found in alcohol dependence (Griffiths et al., 2012), methamphetamine users (Rendell, Mazur & Henry, 2009), long-term opiate users

(Terrett et al., 2014), heavy social drinkers (Platt, Kamboj, Italiano, Rendell & Curran, 2016) and MDMA users (Montgomery, Hatton, Fisk, Ogden, & Jansari, 2010). Aside from the everyday implications, PM deficits may also impair a user's ability to apply planned relapse prevention strategies in those aiming to reduce or stop their substance use.

To date, several studies have investigated PM in cannabis users (Bartholomew, Holroyd & Heffernan, 2010; Bedi & Redman, 2008a; Bedi & Redman, 2008b; Cuttler, 2012; Fisk & Montgomery, 2008; Gallagher et al., 2014; Hadjiefthyvoulou, Fisk, Montgomery & Bridges, 2011; McHale & Hunt, 2008, Montgomery & Fisk, 2007; Montgomery, Seddon, Fisk, Murphy & Jansari, 2012; Rodgers et al., 2001; Rodgers et al., 2003). However, many of these studies have significant methodological limitations, making it difficult to attribute any observed effects specifically to cannabis use.

There is an important distinction to be made between studies using self-report PM questionnaires (e.g. the Prospective Memory Questionnaire [PMQ]; Hannon, Adams, Harrington, Fries-Dias & Gipson, 1995), which tap into a range of PM errors in everyday life, and those using objective measures of memory performance in the laboratory setting or in a real-world context. Several studies of PM in cannabis users have used self-report measures, and the results are inconsistent. Two self-report studies have found cannabis use to be associated with PM deficits (Fisk & Montgomery, 2008; Montgomery & Fisk, 2007) and three did not find an impairment in users (Bedi & Redman, 2008a; Rodgers et al., 2001; Rodgers et al., 2003). In the two studies finding a PM deficit using the PMQ (Fisk & Montgomery, 2008; Montgomery & Fisk, 2007) a non-standard and loose definition of cannabis use was used (lifetime use of cannabis regardless of frequency and chronicity, in a sample of poly-drug users). Self-report

measures which tap self-perception of PM are prone to inaccuracy in reporting due to failures in accurately recalling lapses in memory, and as self-rated cognitive abilities tend to pick up on performance anxiety. These two studies also suffered from other critical methodological limitations such as the questionable validity of the PMQ (Uttl & Kibreab, 2011).

More objective measures of PM have been used to examine performance in cannabis users, such as a video-based task (Titov & Knight, 2001) that requires participants to move through a shopping precinct and carry out pre-assigned tasks, and another video-based task requiring participants to play the role of an office worker for a day with a list of tasks to be completed for the office manager (Jansari, Agnew, Akesson, & Murphy, 2004). A systematic review and meta-analysis (Platt, 2014) of objective PM measures found cannabis users to perform significantly worse than healthy controls on irregular event-based PM tasks over six studies ($g = .43$, 95% CI [.02, .83], $Z = 2.07$, $p < .001$), but with large statistical heterogeneity between studies ($I^2 = 76\%$). While two of these studies found cannabis use to have no effect on PM (Cutler et al., 2012; Gallagher et al., 2014), four studies reported either small (Hadjieffyvoulou et al., 2011), medium (Bartholomew et al., 2010; Bedi & Redman, 2008b) or large effects (Montgomery et al., 2012). With regards to irregular time-based PM performance (five studies), cannabis adversely affected performance ($g = .43$, 95% CI [.02 - .83], $Z = 3.31$, $p = < .001$). Effect sizes were medium to large, with only one study reporting no effect (Cuttler et al., 2012). One study (Gallagher et al., 2014) examined regular PM (time-based), and the effect was small ($g = .31$, 95% CI [-.10 - .71]).

Many of the studies in the systematic review failed to use a reliable and objective measure of participants' cannabis use to determine their allocation to

cannabis or comparison groups. For example, the studies varied from defining cannabis groups as using ‘some cannabis use in the past year’ (Bartholomew et al., 2010), to ‘at least once a month for the past six months’ (McHale & Hunt, 2008) to ‘at least four times in the last month’ (Montgomery et al., 2012). Similarly, tasks varied from a short 10-minute PM video task, to ones tapping PM over a much longer time period (e.g. returning an envelope to the researcher one, two and three weeks after a short-term memory task with any words they could recall; Gallagher et al., 2014).

A separate series of studies, not on cannabis users, have shown deficits in PM may be overcome by a planned and deliberate cognitive rehearsal strategy. Future event simulation (FES) involves pre-experiencing future events using a structured mental imagery task (Schacter, Addis, & Buckner, 2008). FES involves instructing the participant to vividly imagine performing a future action during encoding. The constructive episodic simulation hypothesis supposes that episodic memory combines the details of past experiences (e.g. objects, people and locations) to depict potential future events (Schacter et al., 2008). There is evidence that FES may improve PM performance on an objective measure of PM, the Virtual Week (VW; Rendell & Craik, 2000) for event-based tasks in heavy drinkers (Platt et al., 2016), and for those acutely administered alcohol on event-based tasks (Paraskevaides et al., 2010). However, on a study also assessing VW performance in alcohol-dependent individuals compared to social drinkers (Griffiths et al., 2012), there was no effect of FES on PM for the dependent group, but an improvement for social drinkers on time-based PM.

Aims

The present study sought to determine PM performance measured by the VW in both dependent and non-dependent frequent cannabis users (both groups using

cannabis four or more days a week) compared to non-using controls, and whether any task performance increment was observed through use of FES. Given the role of memory and executive function in PM processes, these domains of cognition were also assessed to determine their contribution to any observed differences in PM. We also explored levels of depression, anxiety and schizotypy ('psychosis-proneness') across the groups.

Importantly, this is the first study to assess both regular and irregular time- and event-based PM in frequent cannabis users (dependent and non-dependent) and to explore the effects of FES on performance. The cannabis users were to both use frequently (four or more days a week)

Findings from this study may have clinical relevance for substance use treatment, which is especially pressing given that demand for cannabis use treatment in addiction services continues to rise (NDTMS, 2015). Within the relapse prevention model, applying coping skills when faced with situations at high risk of relapse would rely in part on PM skills (Blume, Schmaling, & Marlatt, 2005), as would implementing intended strategies in generic cognitive behavioural therapy. If it were to be found that FES can improve PM, it could be suggested as a clinically useful addition to existing psychosocial treatments for cannabis users by compensating for a deficit in the ability to simulate future events. However, it is important to note that the systematic review in Part 1 of this paper on cognitive remediation for substance use found no conclusive evidence at present that cognitive training should be indicated as an adjunct to addiction treatment.

Hypotheses

Drawing on previous research outlined above, we hypothesised that cannabis users would have a deficit in irregular event- and time-based PM compared to controls. We hypothesised that dependent users would show a greater irregular PM deficit than non-dependent users. Although there is only one study on which hypotheses related to regular PM task performance can be based (Gallagher et al., 2014), we hypothesised a similar pattern in the current study, that there would be poorer regular PM performance in cannabis users compared to controls. We had no hypotheses regarding FES due to a lack of directly relevant research; however, we intended to compare it directly with Griffiths and colleagues (2012) who found that alcohol-dependent individuals did not benefit from FES but that the comparison group of social drinkers did for time-based irregular PM. Finally, we hypothesised that dependent cannabis users would score higher on depression and anxiety than non-dependent cannabis users and controls, in line with previous research findings.

Method

Participants

Sample Size

Sample size was calculated using a statistical power analysis on G*power (Faul, Erdfelder, Lang & Butchner, 2007), specifying $p = .05$ and power = .80. Using a medium effect size ($\eta_p^2=0.11$) from an analysis detecting a difference between cannabis users compared to a control group on an objective measure of PM (Bartholomew et al., 2010), projected sample size to detect an interaction between

group and baseline PM performance was $N = 42$. However, as there was greater uncertainty for the other analyses (e.g. as there has been no PM study with FES on cannabis users), a larger sample size was recruited to partially overcome any underestimation of effect size in the power calculation. We therefore invited 56 participants (18 per group) to take part in the study.

Recruitment

Participants were recruited throughout 2016. Posters were displayed on noticeboards at local university campuses in the central London area and distributed around some public areas such as Camden Lock, and adverts were posted on social media websites (Twitter, Facebook and Gumtree). Snowball sampling was also used.

Interested individuals were emailed the Study Information Sheet (see Appendix 3), and, if still interested, a telephone screening interview was arranged.

Telephone Screening: Inclusion and Exclusion Criteria

A telephone screening was used to determine eligibility for the study and took approximately five minutes. A copy of the screening script is in Appendix 4. Our inclusion criteria for the cannabis sample was to be using the drug four or more days a week (i.e. more days than not). We also collected additional information about cannabis use during the telephone screening: age at which participants started using cannabis, number of grams per week, and score on the 5-item Severity of Dependence Scale (SDS; Gossop et al., 1995). We classified users as dependent (score ≥ 3) or non-dependent (score < 3). According to Swift and colleagues (1998), a score of three or above indicates probable cannabis dependence, with sensitivity of 64% and specificity of 82% when compared to the ‘gold standard’ diagnostic criteria for cannabis

dependence (DSM-III-IR). Demographic information was collected for all individuals screened including age, gender, and highest level of education. We also asked all individuals about their alcohol use and use of other drugs. Control participants were required to have limited illicit drug use (twice a month or less) and no history of a substance dependence.

All participants were required to speak English fluently. Exclusion criteria included: being under 16 years old, a current or historical diagnosis of dependence on any substance other than cannabis or tobacco, weekly alcohol consumption exceeding 21 units for women or 28 units for men (NHS-recommended guidelines at the time), a history of traumatic brain injury or stroke, a current or recent (last three weeks) experience of psychosis, in current treatment (psychological therapy or pharmacological) for a mental health problem other than anxiety or depression, a diagnosis of a learning disability, reading difficulties, or current use of antipsychotic medication or benzodiazepines.

All participants were asked to refrain from consuming any illicit drugs and alcohol on the day of the testing session, and gave their verbal agreement for this at the end of the telephone screening.

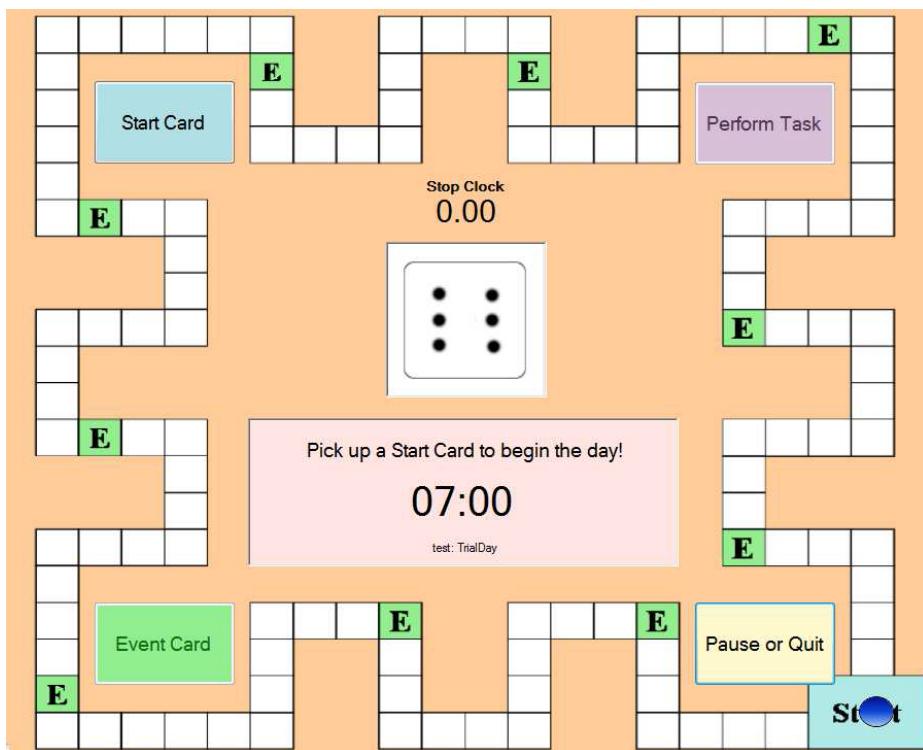
Participants from each of the three groups (dependent cannabis users, non-dependent cannabis users, and controls) were selected as closely as possible to match each other in age, gender and highest level of education.

Measures

Prospective Memory

The Virtual Week (VW; Rendell & Craik, 2000) is a virtual board game that requires participants to move a counter around a board by rolling an electronic die. Participants work their way around the board, with one circuit of the board representing one virtual ‘day’. The virtual time of day is shown on a clock in the centre of the board and the time passes as the counter moves around the board. Over the virtual day, there are ten green ‘E’ squares on the board to pass through. When a participant’s counter falls on or passes an ‘E’ square, they are instructed to click on the event card button on the board. This event card symbolises a time-appropriate event occurring in the virtual day, e.g. the first event cards depict morning activities such as eating breakfast, and the last event cards depict evening activities such as eating dinner. Each event card requires the participant to select a multiple-choice answer in response to a given activity, such as what to eat for breakfast. Throughout each virtual day, participants are assigned a number of tasks they must remember to perform at points later in the day (as a measure of PM). In the version of the VW used in this study, each day contained four ‘time-based’ tasks to be performed at specified times of day (as displayed on the central 24-hour clock), and four ‘event-based’ tasks to be performed in response to particular events (depicted on the Event Cards). See Figure 1 for a screenshot of the VW.

Figure 1. The Virtual Week Board Game



At the start of the game, participants are informed of four regular PM tasks that need to be carried out on each virtual day (one circuit of the board). Two of these are time-based tasks (taking an asthma inhaler pump at 11:00 and 21:00) and two are event-based tasks (taking antibiotics with breakfast and dinner). The remaining four tasks are different on each virtual day and are thus irregular PM tasks. These tasks are designed to simulate more occasional tasks that occur in everyday life, e.g. having a haircut at 15:00 (time-based) or picking up some pencils from the shop (event-based). There are two time-based and two event-based irregular tasks, two of these are presented at the beginning of the virtual day and the other two at other points throughout the day. Participants perform tasks by clicking the 'Perform Task' button within an Event Card, or the Perform Task button on the main board. The Perform Task button lists a number of tasks that the participant can choose to perform.

The VW automatically registers whether a task is correctly performed, missed or performed late. The key variable of interest is the proportion of correctly completed irregular time-based, regular time-based, irregular event-based and regular event-based tasks. Given that the VW was developed in Australia, some of the task details were amended prior to running the study to make it more appropriate for a UK sample. See Appendix 5 for a list of all the VW tasks.

Episodic Memory

The Story Recall subtest of the Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn & Baddeley, 2003) is a measure of verbal episodic memory. Participants listen to a short passage and are asked to immediately repeat back everything they can remember. They then repeat the recall task after a delay. Using the RMBT scoring guidelines where the passage is broken into 21 sections, participants are awarded one point for accurate recall of each section, or half-points for partial recall (or a synonym). Scores are computed separately for the immediate and delayed conditions.

Executive Function

Verbal fluency tasks involve the retrieval of words based on phonemic or semantic criteria, placing demands on executive processes as they require efficient verbal retrieval and recall, self-monitoring (i.e. responses that have already been given), self-initiation and inhibition of responses. In phonemic fluency, participants are asked to name as many words (excluding proper nouns) as they can beginning with a letter (e.g. 'g') in 60 seconds. The score is the total number of responses, minus repetitions and incorrect responses. In category fluency, participants are asked to name

as many words in a specific category (e.g. ‘vegetables’) in 60 seconds. In addition to these well-known fluency tasks, drug-related fluencies were also measured (Goldstein, Woicik, Lukasik, Maloney & Volkow, 2007). In alcohol-fluency participants are asked to name as many alcohol-related words as they can in 60 seconds, and in cannabis-fluency (for the groups of participants that use cannabis), participants are asked to name as many cannabis-related words as they can in 60 seconds. The order of each fluency task was counterbalanced by topic.

Premorbid Intelligence

The Spot-the-Word test (STWT; Baddeley, Emslie & Nimmo-Smith, 1993) is a task requiring participants to select the real word from each of 60 letter-string pairs containing one word and one non-word. The STWT has demonstrated convergent validity with the Wechsler Adult Intelligence Scale (Yuspeh & Vanderploeg, 2000).

Cannabis Use

In the Cannabis Potency Use Questionnaire (CPU-Q; Mokrysz, Freeman, Shaban & Curran, in preparation) participants are asked to select one of three pictures that best represents the type of cannabis they use most frequently, and to then estimate the approximate percentage of time they use each of the three types (Figure 2). Each picture shows different preparations of cannabis: high-potency floral preparation which typically contains very high levels of THC and little or no CBD, often referred to as ‘skunk’ (Picture A), compressed resin or ‘hash’, typically containing higher levels of CBD and lower levels of THC (Picture B) and traditional dried herbal material, referred to as ‘bush weed’ or ‘Thai weed’, which contains much lower levels of THC but little or no CBD (Picture C).

Figure 2. Preparations of cannabis used in the CPU-Q.



The use of pictures allows for an indirect indication of the THC and CBD levels in the cannabis used by participants, and avoids complications that differing terminologies for each variation may have on these estimations.

Anxiety

The Beck Anxiety Inventory (BAI; Beck & Steer, 1993) is a 21-question multiple-choice self-report scale that measures current levels of general anxiety. The BAI covers 21 symptoms of anxiety, asking the participant to state how severely they have been bothered by each symptom over the past three days. The BAI has been used in previous studies into anxiety and cannabis use (Dafters, Hoshi, & Talbot, 2004; Troisi, Pasini, Saracco & Spaletta, 1998). The BAI has high internal consistency ($\alpha = .92$) and high test-retest reliability over one week ($r = .75$). The BAI also exhibits a moderate correlation with the revised Hamilton Anxiety Rating Scale ($r = .51$) (Beck, Epstein, Brown & Steer, 1988).

Depression

The Beck Depression Inventory (BDI-II; Beck, Steer & Brown, 1996) is a 21-item self-report questionnaire measuring the severity of a range of depressive symptoms experienced over the previous two weeks. Each question is scored 0 to 3. It demonstrates good criterion validity with a correlation of 0.71 against the Hamilton Psychiatric Rating Scale for Depression (Beck et al., 1996). The BDI-II has been used in previous studies exploring depression in cannabis users (Buckner, Keough, & Schmidt, 2007; Troisi et al., 1998).

Schizotypy

The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Mason, Claridge, & Jackson, 1995) is a measure of schizotypy, or ‘psychosis-proneness’. The O-LIFE has four subscales: unusual experiences, cognitive disorganisation, introvertive anhedonia and impulsive nonconformity. Studies have found higher scores on schizotypy (using a different measure: the schizotypal personality questionnaire) in individuals who use cannabis with high concentrations of THC (Skosnik, Spatz-Glenn, & Park, 2001), and an association between levels of schizotypy (the Unusual Experiences subscale of the O-LIFE) and ratings in a future thinking task (Winfield & Kamboj, 2010). The Unusual Experiences subscale has been found to be a reliable and brief (i.e. time-efficient) scale to explore psychosis-proneness (Mason, Linney, & Claridge, 2005).

Other Measures

As the data was collected as part of a joint research project on future thinking in cannabis users, participants also completed an additional task where they were required to imagine hypothetical future events. This is reported elsewhere (Mansell,

2017). See Appendix 6 for a declaration of each person's contributions to the joint research project.

Focus Group and Pilot Testing

Prior to finalising the study protocol, a small focus group was held with two cannabis users who smoked frequently. They were recruited from an advert on social media. We met for 90 minutes at University College London (UCL) during which the proposed trial protocol was discussed, ensuring instructions were clearly understood, and the feasibility of the episodic foresight task (not reported here) was assessed. No changes or revisions to any tools or tasks were made after discussion with the group.

The testing session was then piloted on three volunteers, which helped to determine the position of breaks during the testing session.

Procedure (Figure 3)

The study received ethical approval from the UCL Research Ethics Committee (ethical approval number: 5402/001; Appendix 7) in January 2016 under an amendment to an existing approval. Written informed consent (Appendix 8) was obtained prior to participants taking part. All participants attended a one-off testing session at the Clinical Psychopharmacology Unit at UCL. This lasted approximately two and a half hours including breaks, and participants were compensated £20 for their time. Scripts for the testing session were used for every participant to ensure consistency.

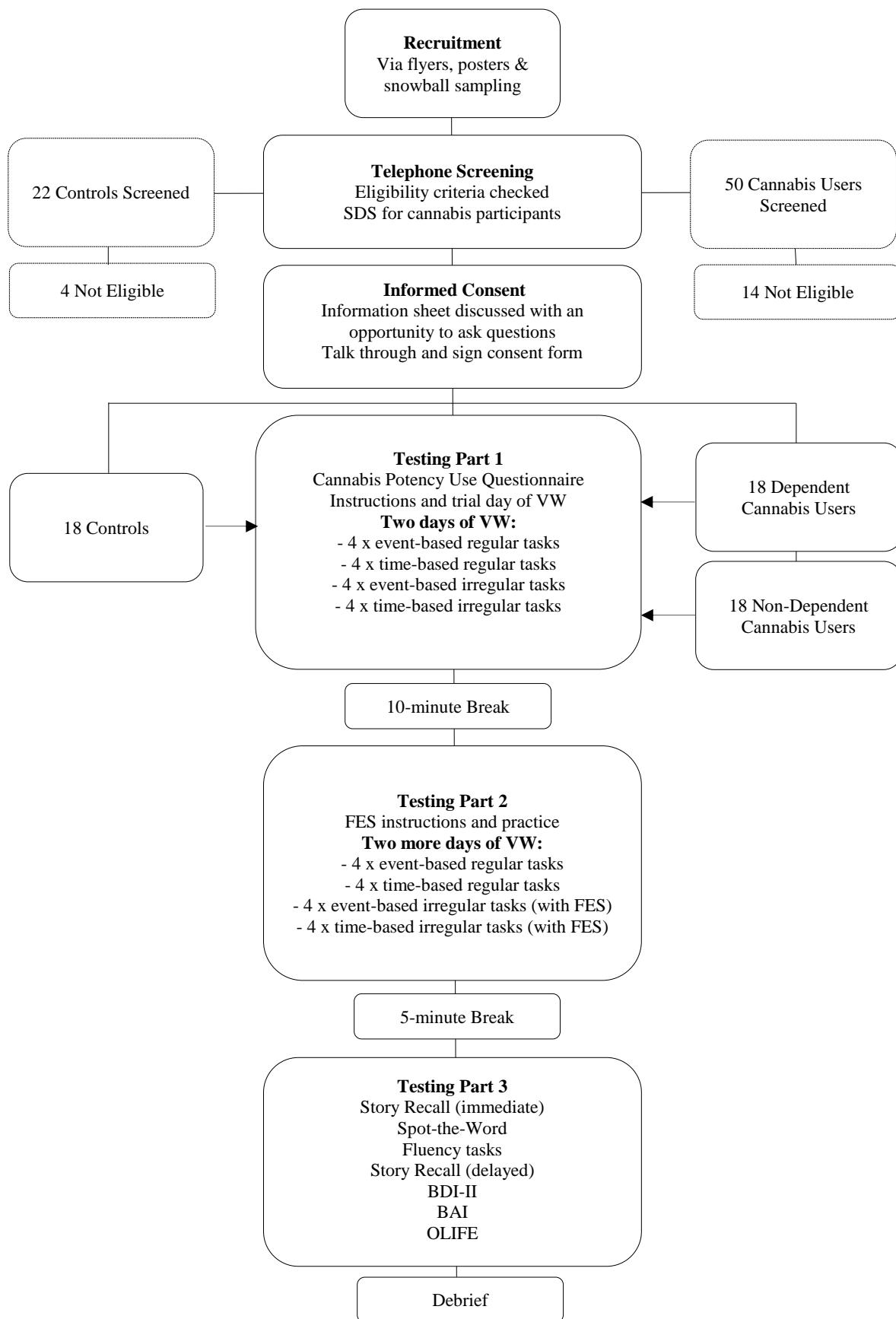
Participants from the cannabis groups were first asked to complete the CPU-Q. All participants were then introduced to the VW (see Appendix 9 for the script

used). A trial day was completed to orient participants to the task; they followed the instructions on-screen and had an opportunity to ask questions. Participants were not permitted to start the VW until they could successfully articulate all of the regular PM tasks to ensure they had encoded the information. They were also asked to read aloud every event card in the game. Participants then completed their first two virtual days. The tester did not provide feedback on accuracy.

After a 10-minute break, participants were introduced to the imagining technique (FES) which they were instructed to use for all irregular events presented over the next two days of the VW. This involved imagining oneself performing a task in as much detail as possible, including details like the setting and course of events, the time of day, and the people and objects around. Participants were encouraged to set the task in their own daily life, and were given the example that if they were set the task of food shopping in the VW, they should imagine themselves shopping in the supermarket they would typically shop in. Participants then carried out two more days of the VW, prompted by the tester to imagine each irregular task for 10-seconds after the task had been set. After completing the VW, participants carried out future thinking task not reported here. They were then given a five-minute break. Participants were finally administered the remaining tasks in the following order: Story Recall (Immediate), Spot-the-Word, fluencies (verbal, category, alcohol, cannabis [cannabis participants only]), Story Recall (Delayed), BDI-II, BAI and O-LIFE Unusual Experiences. The order of the fluency tasks was counter-balanced.

At the end of the testing session, participants were debriefed and asked whether they would like to receive a summary of the results after study completion (see Appendix 10 for the results summary sent to participants).

Figure 3. Study Flow Diagram



*After the VW, the participants completed a future thinking task (not reported here)

Statistical Analyses

All analyses were performed on IBM SPSS Statistics Version 22. There was no missing data. Before exploring baseline data and running the main analyses, variables were checked for normality by observing histograms and calculating skewness and kurtosis Z-scores. Taking sample size into consideration, Z-scores of ≥ 3.29 were used to index non-normality (Kim, 2013). Using this criterion, frequency of type of cannabis used as a percentage of all occasions (CPU-Q), amount of cannabis (grams per week), and the BAI data violated assumptions of normality. For non-normal variables measured in only two groups (i.e. cannabis-related variables), non-parametric Mann-Whitney U tests were used to compare groups and central tendency and dispersion were described using medians and inter-quartile ranges (IQR). For all the other variables, parametric chi-squared tests were used to compare categorical variables, and t -tests (two group comparisons) or ANOVAs (three group comparisons) were used to detect group differences for continuous data. For parametric tests, means and SDs were reported.

The assumption of homogeneity of variance (as evidenced by Levene's test) and normality according to our criteria ($Z \leq 3.29$) was met for all VW variables. VW data was analysed with repeated measures ANOVAs, with Bonferroni-adjusted pairwise comparisons (with adjusted p -values) to explore post-hoc effects. To explore relationships between significant variables, Spearman's ρ correlations were conducted (on both parametric and non-parametric variables, to allow for direct comparison). Correlations were conducted with an adjusted alpha of 0.01 to minimise Type-I error. Data was also examined for extreme values. One participant's score in one of the VW variables was 4 SDs from the mean, and was Winsorized to the next highest non-outlying value.

Results

Group Demographics (Table 1)

The groups were well matched on baseline variables. There was no statistical difference between the number of males and females across the dependent cannabis group (nine males and nine females), non-dependent cannabis group (10 males and eight females) and control group (six males and 12 females), $\chi^2 (2, N = 54) = 1.94, p = 0.38$. Similarly, the groups did not differ on age, $F(2, 51) = 0.15, p = 0.89$, highest level of education, $\chi^2 (4, N = 54) = 2.20, p = 0.67$, Spot-the-Word score, $F(2, 51) = 1.00, p = 0.37$, or units of alcohol consumed per week, $F(2, 51) = 0.12, p = 0.89$.

Table 1. Group Demographics, Alcohol Use and Spot-The-Word scores across the Dependent Cannabis, Non-Dependent Cannabis and Control Groups

	Dependent Cannabis Users (n = 18)	Non- Dependent Cannabis Users (n = 18)	Controls (n = 18)
	n (%)	n (%)	n (%)
Gender:			
Male	9 (50)	10 (55.6)	6 (33.3)
Female	9 (50)	8 (44.4)	12 (66.8)
Highest level of education:			
GCSE or vocational qualification	1 (5.6)	2 (11.1)	3 (16.7)
A Level	8 (44.4)	5 (27.8)	5 (27.8)
Degree	9 (50)	11 (61.1)	10 (55.6)
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
Age (years)	24.2 (5.1)	23.9 (3.7)	23.4 (3.7)
Spot-the-Word score	49.5 (3.5)	47.2 (5.8)	48.6 (5.3)
Alcohol (units consumed per week)	10.1 (8.1)	9.8 (6.9)	11.0 (8.8)

Cannabis Use (Table 2)

There were no differences between dependent and non-dependent cannabis users in the type of cannabis most commonly used, with both groups primarily using high-potency skunk. The proportions of hash and herbal preparations varied marginally but this was not significant, $\chi^2 (2, N = 36) = 4.13, p = 0.13$. There were no differences between cannabis groups in: the frequency that each preparation of cannabis was used as a percentage of total cannabis use occasions, for skunk, $U = 141, p = 0.52$, herbal, $U = 132.5, p = 0.36$, and hash, $U = 156.5, p = 0.86$; mean age of onset of cannabis use, $t(34) = 6.48, p = 0.52$; amount of cannabis (grams) used a week, $U = 152.5, p = 0.77$; or the number of days of cannabis use a week, $t(34) = 1.31, p = 0.2$. The mean SDS score in the dependent group was 4.3 ($SD = 1.5$), and in the non-dependent group 0.8 ($SD = 0.8$), $t(34) = 8.60, p < .001$. The SDS had high internal consistency ($\alpha = 0.89$).

Table 2. Cannabis Use in the Cannabis Groups

	Dependent Cannabis Users (n = 18)	Non-Dependent Cannabis Users (n = 18)
	n (%)	n (%)
Type of cannabis most commonly used (CPU-Q):		
Picture A – ‘Skunk’	15 (83.3)	17 (94.4)
Picture B – ‘Hash’	0	1 (5.6)
Picture C – ‘Herbal’	3 (16.7)	0
	Median (IQR)	Median (IQR)
Frequency of use of each cannabis type (%):		
Picture A – ‘Skunk’	80.5 (23)	85.0 (28)
Picture B – ‘Hash’	10 (13)	7 (16)
Picture C – ‘Herbal’	8 (23)	0.5 (10)
Amount used a week (grams)	5 (4.75)	4 (4.63)
	M (SD)	M (SD)
Days used per week	6.5 (0.7)	6.06 (1.3)
Age started using cannabis	15.6 (2.2)	16.1 (1.9)
SDS Score***	4.3 (1.5)	0.8 (0.8)

Note: *** $p < .001$, ** $p < .01$, * $p < .05$

Neuropsychological Tests (Table 3)

On tasks assessing episodic memory, there were no differences across all three groups in immediate story recall, $F(2, 51) = 1.89, p = 0.16$, or delayed story recall, $F(2, 51) = 1.39, p = 0.26$. Similarly, there were no differences between dependent cannabis users, non-dependent cannabis users and control participants on measures of executive functioning: phonemic fluency, $F(2, 51) = 2.28, p = 0.11$, category fluency, $F(2, 51) = 1.27, p = 0.29$, and alcohol fluency, $F(2, 51) = 0.48, p = 0.62$. The cannabis sample additionally completed a measure of cannabis fluency, and their mean scores did not differ between the dependent and non-dependent groups, $t(34) = 0.193, p = 0.85$.

Table 3. Episodic Memory and Executive Functioning in Dependent Cannabis, Non-Dependent Cannabis and Control Groups

	Dependent Cannabis Users (n = 18)	Non- Dependent Cannabis Users (n = 18)	Controls (n = 18)
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
Episodic memory:			
Story recall – immediate	7.3 (2.5)	7.5 (2.7)	8.9 (3.1)
Story recall – delayed	6.5 (2.2)	6.3 (2.4)	7.6 (3.2)
Executive functioning:			
Phonemic fluency – letter	14.8 (5.8)	12.0 (3.7)	15.1 (4.5)
Category fluency – ‘vegetables’	15.6 (5.1)	13.6 (4.6)	15.9 (4.6)
Category fluency – ‘alcohol’	20.5 (7.6)	19.3 (4.9)	21.7 (8.8)
Category fluency – ‘cannabis’	20.8 (7.8)	21.3 (7.7)	-

Depression, Anxiety and Schizotypy (Table 4; Figure 4)

There were group differences in depression, anxiety and schizotypy as measured by the BDI-II, $F(2, 51) = 15.6, p < 0.001$, BAI, $F(2, 51) = 9.89, p < 0.001$, and O-LIFE Unusual Experiences, $F(2, 51) = 11.65, p < 0.001$. Bonferroni-adjusted

pairwise comparisons and *p*-values for each ANOVA indicated that the dependent cannabis group had significantly higher levels of depression, anxiety and schizotypy than both the non-dependent group (*p* <0.001; *p* <0.001; *p* = 0.001) and controls (*p* = 0.001; *p* = 0.006; *p* <0.001). The control group and non-dependent group did not significantly differ on depression (*p* = 0.28), anxiety (*p* = 1.0) or schizotypy (*p* = 1.0). Cronbach's alpha indicated high internal consistency for the BAI (α = 0.8), BDI-II (α = 0.87) and O-Life Unusual Experiences (α = 0.89).

Table 4. Depression, Anxiety and Schizotypy in Dependent Cannabis, Non-Dependent Cannabis and Control Groups

	Dependent Cannabis Users (<i>n</i> = 18)	Non- Dependent Cannabis Users (<i>n</i> = 18)	Controls (<i>n</i> = 18)
	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)
Depression:			
BDI-II Total Score***	11.2 (4.9)	2.9 (3.6)	5.5 (5.1)
Anxiety:			
BAI Total Score***	9.9 (6.3)	3.0 (3.6)	4.6 (4.5)
Schizotypy:			
O-LIFE – Unusual Experiences***	5.1 (2.4)	2.1 (2.8)	1.6 (1.6)

Note: *** *p* <.001, ** *p* <.01, * *p* <.05

Using the clinical cut-offs for depression on the BDI-II (Table 5), 94 percent (*n* = 17) of both the non-dependent cannabis and control participants scored in the 'minimal' range and six percent (*n* = 1) scored within the 'mild' range of depression. In the dependent cannabis user group, 33% of individuals (*n* = 6) scored within the mild depression range, with the remaining 67% of the group (*n* = 12) scoring in the minimal range. A chi-squared test indicated the difference between groups was significant, χ^2 (2, *N* = 54) = 7.38, *p* = 0.026. None of the participants across the whole

sample scored ‘moderately’ (score of 20-28) or ‘severely’ depressed (score of 29 or over).

Figure 4. Mean (SE) scores for the BDI-II (Depression), BAI (Anxiety) and O-Life Unusual Experiences (Schizotypy) in the Dependent Cannabis, Non-Dependent Cannabis and Control Groups

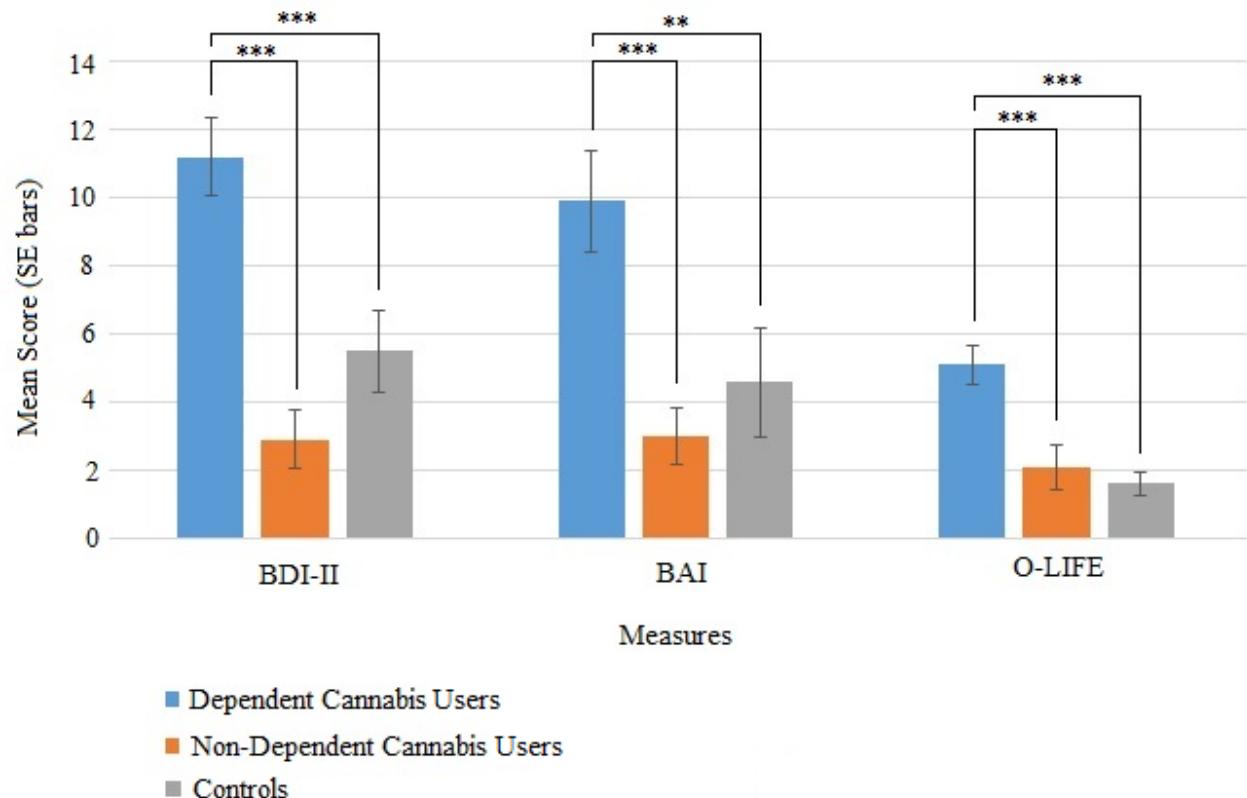


Table 5. Clinical Categories for Depression on the BDI-II across Dependent Cannabis, Non-Dependent Cannabis and Control Groups

	Dependent Cannabis Users (n = 18)	Non-Dependent Cannabis Users (n = 18)	Controls (n = 18)	
Score range	Clinical Category	n (%)	n (%)	n (%)
0-13*	Minimal	12 (66.7)	17 (94.4)	17 (94.4)
14-19*	Mild	6 (33.3)	1 (5.6)	1 (5.6)

Note: *** $p < .001$, ** $p < .01$, * $p < .05$

Pre-FES Virtual Week (Table 6)

The data from the pre-FES VW days (i.e. the first two days administered, prior to the introduction of FES) were first analysed to assess any baseline group differences in PM performance. The dependent variable was the proportion of tasks that were completed correctly. A 2x2x3 repeated measures ANOVA with the within-subjects factors of task regularity (irregular, regular), task cue (event-based, time-based) and between-subjects factor of group (dependent cannabis, non-dependent cannabis, controls) was run. There was a significant main effect of task cue, $F(1, 51) = 10.07, p = 0.003$, with Bonferroni-adjusted pairwise comparisons indicating that the proportion of correct responses was greater on event-related tasks ($M = 0.82, SD = 0.19$) than time-related ($M = 0.72, SD = 0.25$).

There was no main effect of task regularity, $F(1, 51) = 0.39, p = 0.845$, or interaction effects between group and task cue, $F(1, 51) = 1.07, p = 0.352$, group and task regularity, $F(1, 51) = 2.68, p = 0.078$, cue and task regularity, $F(1, 51) = 3.403, p = 0.071$, or a three-way interaction between task regularity, task cue and group, $F(1, 51) = 0.093, p = 0.912$.

Table 6. Comparison of Dependent Cannabis, Non-Dependent Cannabis and Control Groups on Mean (SD) Proportion of Irregular and Regular PM tasks Completed Correctly in the Pre-FES VW

PM task	Dependent Cannabis Users (n = 18)	Non-Dependent Cannabis Users (n = 18)	Controls (n = 18)
	M (SD)	M (SD)	M (SD)
<i>Irregular:</i>			
Event-based	0.82 (0.17)	0.86 (0.21)	0.85 (0.23)
Time-based	0.61 (0.31)	0.78 (0.21)	0.69 (0.33)
<i>Regular:</i>			
Event-based	0.88 (0.15)	0.74 (0.25)	0.75 (0.34)
Time-based	0.76 (0.28)	0.72 (0.28)	0.72 (0.36)

Virtual Week with FES

To assess the impact of FES on PM performance, the proportion of irregular VW tasks completed correctly before the introduction of FES was compared to the FES condition. This was done for event-based tasks and time-based tasks separately, with two 2x3 repeated measures ANOVAs with the within subject factors of imagining (no-FES, FES) and the between-subjects factor of group (dependent cannabis, non-dependent cannabis, controls).

For event-based irregular tasks, there was no main effect of FES, $F(1, 51) = 1.98$, $p = 0.165$, nor an interaction between FES and group, $F(1, 51) = 0.258$, $p = 0.774$. Similarly, for time-based irregular tasks there was no main effect of FES, $F(1, 51) = 0.337$, $p = 0.564$, nor an interaction between FES and group, $F(1, 51) = 0.861$, $p = 0.429$.

Correlations (Table 7)

An exploratory analysis looked at the extent to which cognitive variables were associated with intellectual functioning (Spot-the-Word score) and amount of cannabis use (grams per week). PM (overall proportion correct on the VW), episodic memory (immediate and delayed story recall) and executive functioning (average fluency score) were correlated with Spot-the-Word score for all groups, and also with amount of cannabis used for the cannabis groups.

Table 7. Spearman's *rho* Correlations between Spot-the-Word, Cannabis Use (Grams per Week) and Cognitive Measures across Dependent Cannabis, Non-Dependent Cannabis and Control Groups

		Dependent Cannabis Users (n = 18)		Non-Dependent Cannabis Users (n = 18)		Controls (n = 18)
		STW score	Cannabis use (grams pw)	STW score	Cannabis use (grams pw)	STW score
Prospective memory:	VW overall proportion correct	0.02 (p = 0.94)	-0.19 (p = 0.43)	0.41 (p = 0.09)	-0.01 (p = 0.97)	0.54 (p = 0.06)
Episodic memory:	Story Recall: Immediate	0.23 (p = 0.37)	-0.13 (p = 0.61)	0.69** (p = 0.002)	-0.22 (p = 0.37)	0.44 (p = 0.06)
	Story Recall: Delayed	0.57** (p = 0.01)	-0.87 (p = 0.73)	0.60** (p = 0.008)	-0.08 (p = 0.74)	0.51* (p = 0.03)
Executive function:	Average fluency score	0.43 (p = 0.08)	-0.16 (p = 0.54)	-0.29 (p = 0.25)	0.31 (p = 0.22)	0.18 (p = 0.49)

Note: *** p <.001, ** p <.01, * p <.05. STW = Spot-the-Word. pw= per week

Discussion

This is the first study to examine PM (regular, irregular, time- and event-based) and the effects of FES on PM ability in dependent and non-dependent frequent cannabis users compared to non-using controls. The three groups were well-matched on key variables including age, premorbid intelligence, highest level of education and alcohol use. There were no differences between groups in PM ability. The introduction of an FES condition requiring participants to mentally rehearse tasks did not lead to improvements in PM scores. All groups scored similarly on other cognitive measures: episodic memory and executive functioning (fluency tasks). Dependent and non-dependent cannabis users both primarily smoked high-potency skunk, and did not differ on other cannabis use variables such as amount smoked per week.

Dependent cannabis users scored higher than non-dependent users and non-using controls on depression, with 33 percent falling into the category for ‘mild depression’ on the BDI-II compared to just six percent in each of the other two groups. Dependent cannabis users also scored higher on anxiety and schizotypy (‘psychosis proneness’) than the non-dependent and control group.

After finding no PM differences across groups, we wondered whether differences in intelligence may be offsetting impairments in PM. We therefore explored as a post-hoc analysis whether there were associations between premorbid intelligence and all cognitive measures (PM, episodic memory, executive function), compared to amount of cannabis use (grams per week) and cognitive measures. Correlations indicated there were no associations between cannabis use and cognitive measures for the dependent and non-dependent groups. Premorbid intelligence, however, was moderately positively correlated with delayed episodic memory score

across all three groups. For non-dependent users, there was a moderate positive correlation between premorbid intelligence and immediate episodic memory. In none of the groups did pre-morbid intelligence correlate with PM. Thus, a post-hoc hypothesis that intellectual functioning in the cannabis groups was driving PM ability was not evidenced by the data.

Effects of Cannabis Use on Prospective Memory

Previous literature generally indicates that people who use cannabis perform more poorly on tasks of PM than those who do not use the drug, suggesting that use of cannabis leads to a deficit in the ability to enact planned future actions. A recent meta-analysis of studies using objective (e.g. video-based) measures of PM found deficits in cannabis users for both irregular event and irregular time-based tasks (Platt, 2014). Our findings (across both irregular and regular PM) are not consistent with this, finding no differences between frequent dependent cannabis users, non-dependent users and controls. We can also compare our findings to recent studies with similar designs using the VW in alcohol dependence (Griffiths et al., 2012) and heavy drinkers (Platt et al., 2016) which did find specific PM deficits.

There may be several explanations for our findings. Firstly, there may indeed be no effect of frequent cannabis use on PM, in contrast to the relatively well-established effects of cannabis use on retrospective memory processes. Indeed, our findings are consistent with the three studies of PM that used self-report rather than objective measures of PM performance (Bedi & Redman, 2008a; Rodgers et al., 2001; Rodgers et al., 2003). In addition, two (out of six) PM studies using objective assessments (Cutler et al., 2012; Gallagher et al., 2014) measuring irregular event-based PM, and one (out of five) studies measuring irregular time-based PM also did

not find differences between cannabis users and control groups (Cuttler et al., 2012). Interpreting the mixed existing literature is difficult given the broad range of definitions of ‘cannabis user’ used for determining inclusion across studies, the different measures of PM used, and additional methodological weaknesses. However, it does appear that in our study, when carefully controlling for demographic factors and within our sample of self-selecting young adults, cannabis use does not seem to affect PM as measured by the VW task.

Another explanation of our findings is that there may be an effect of cannabis use on PM, but that it was not detected in this study due to insufficient power, ceiling level performance, or validity issues in the VW task. The proportion of correct responses on the VW was relatively high across groups, especially on event-based irregular PM. However, similarly high scores were also found in the comparable studies in alcohol (Platt et al., 2016; Griffiths et al., 2012). Future studies might consider increasing the number of PM tasks and over a more extended (virtual) period, thus increasing the difficulty level which may elicit different performance across groups. In addition, none of the previously reported PM in cannabis studies have used the VW paradigm, which perhaps places different demands on executive processes. For example, when people are required to perform a task at a certain time or event on the game, they select the ‘Perform Task’ button and a series of options appear. The VW thus has prompts, rather than requiring the participant to freely recall and execute the relevant task. Given shortfalls in reporting of other PM measures, it is unclear whether the other tests of PM also do this.

There is also questionable validity of the VW task in relation to real life PM, despite its psychometric properties (Rendell & Henry, 2009). Everyday PM requires an individual to perform intended actions over several hours or days, often with several

active intentions each with different levels of importance. The time aspect and complexity of the construct of PM is not captured by the Virtual Week, which assesses PM using a simple lab task with each virtual day lasting approximately 15 minutes and with tasks bearing potentially little relation to real-life PM in participants' lives. Therefore, it could also be useful to conduct future research aiming to replicate the findings of the current study as indicated above, and to corroborate the findings with an ecologically-valid measure of PM over a longer time-lag. For example, in a PM task used in Marsh and colleagues' study (1998) participants filled in activity sheets documenting their tasks for the upcoming week and the task importance on a 7-point scale. Participants returned one week later and recorded whether each plan had been completed, and reasons for not completing a task, which may give some insight into a more real-life PM over a longer time scale. The study findings would be strengthened by an additional measure of PM such as this.

It is important to consider the characteristics of the sample used in our study when interpreting the results on PM. The participants were relatively high functioning and well-educated, with 50-61% of each group having at least one university degree. In addition, the cannabis groups did not exhibit episodic memory or executive impairment relative to the control group, which is not consistent with previous studies of frequent cannabis users (for a review see Curran et al., 2016). Some large cohort studies demonstrate that cannabis users have lower educational attainment and are more likely to leave school early (Lynskey, Coffey, Degenhardt, Carlin & Patton, 2003).

To test the hypothesis that our sample included a cognitively-able subgroup of cannabis users for whom the cognitive effects of using cannabis are less pronounced (or non-existent), we conducted post-hoc correlational analyses exploring whether

intellectual functioning was driving the PM ability in the cannabis groups. These did not confirm this idea. This is consistent with a large meta-analysis (Schoeler et al., 2016) which found that years of education did not moderate the cognitive effects of cannabis, and another study finding no correlation between educational qualifications and PM (Reese & Cherry, 2002).

Another hypothesis is that in previous studies of PM in cannabis users, groups may have been mismatched on years of education. A systematic review (Broyd, van Hell, Beale, Yucel & Solowij, 2016) of the effects of cannabinoids on cognition, which considered 105 studies, found that more than 50% of studies did not report IQ or years of education. However, where studies did match on IQ or controlled for differences between groups, impairments remained for immediate and delayed memory and verbal learning and memory (PM was not measured). We did find an association between premorbid intelligence and episodic memory in non-dependent users only. Of the studies into PM and cannabis reviewed in this paper, two did not report premorbid functioning or educational attainment (McHale & Hunt, 2008; Bartholomew et al., 2010), one reported only premorbid functioning (Montgomery et al., 2012), two reported both and there were no differences between groups (Gallagher et al., 2014; Hadjiefthyvoulou et al., 2011), and the final two reported a measure of premorbid functioning and educational attainment but they were different between groups (Cuttler et al., 2012; Bedi & Redman, 2008). This is not consistent for the studies finding differences compared to those not, again complicating the interpretations of findings in the literature. It will be important that future studies measure these variables to ensure comparability between groups of users and controls.

Effects of Future Event Simulation on Prospective Memory

There were no improvements in PM performance across dependent cannabis users, non-dependent cannabis users and control participants after the introduction of FES. Cognitive rehearsal for tasks has been shown to improve some aspects of VW performance in heavy drinkers and those acutely administered alcohol (Platt et al., 2016; Paraskevaides et al., 2010), but not for those dependent on alcohol (Griffiths et al., 2012). It may be that this cognitive rehearsal strategy did not have a benefit in our participants. However, since compliance with instructions or quality of the simulations was not assessed it is difficult to gauge the true impact of this strategy. We can link this to findings from Part 1 of this paper, a systematic review of cognitive remediation for substance-using populations, which found no conclusive evidence in support of the intervention. The previous studies using FES in the VW in substance use (Griffiths et al., 2012; Platt et al., 2016) asked participants questions about their strategy use (e.g. open questions about their strategies, and ratings of vividness of the imagery). These questions were not introduced in our study due to time-restrictions limiting the number of tasks in the testing session (as part of a joint project). In hindsight, however, a brief question about participants' ability to carry out the FES and what strategy they used could have been useful to help interpret our findings. Platt and colleagues (2016) found no correlations between VW performance and the vividness ratings taken in their study, and point out that in FES participants are asked to imagine the future events set in their day-to-day life. However, these do not occur, rather an event card on the VW is a prompt which may require a different cue for task completion than in the imagined setting. According to the constructive episodic simulation hypothesis, episodic memory combines the details of past experiences (e.g. objects, people and locations) to depict potential future events (Schacter et al., 2008). It could be that the

tasks on the VW have no direct relevance to participants' episodic memories (e.g. 'telephoning Bill about babysitting'), rendering imagining the potential future event a difficult task.

Cannabis Use and the Effects of Cannabis Use on Mental Health

Cannabis use variables measured in this study did not differ between users classified as dependent on the drug and those non-dependent. We had predicted that dependent users would smoke the higher-THC concentrated skunk (which has been associated with more pronounced cognitive effects), and were thus surprised to find that 83 percent of dependent users and 94 percent of non-dependent users primarily smoked skunk. This may be because skunk is increasingly the most readily available form of cannabis (Hardwick & King, 2008; Curran et al., 2016), unlike some of the less potent forms such as hash which have lower levels of THC and higher levels of CBD. It is likely therefore that other factors are leading to dependency within our sample, rather than the type of cannabis used.

The finding that dependent users scored higher on schizotypy, yet smoked equally potent cannabis as the non-dependent group, could indicate this subgroup are affected in a different way by their cannabis use. This dependent group may have a pre-existing reactivity to cannabis that renders them more prone to experiencing psychotic-like symptoms – or, indeed, these symptoms were pre-existing and the group were more vulnerable to becoming dependent on the drug after starting cannabis use.

In line with previous evidence (Grant & Pickering, 1998; van der Pol et al., 2013), we found that dependent cannabis users were more depressed and anxious than non-dependent users. Cannabis may be used to self-medicate depression and anxiety (Grant & Pickering, 1998), and perhaps if cannabis use is serving this function in

people who are exhibiting more symptomology, they are more likely to develop a dependence on the drug. We could also hypothesise that the group of frequent smokers who exhibit depression and anxiety symptomology worry more about their cannabis use and thus score on the SDS as dependent (e.g. questions in the SDS include: ‘Do you worry about your use of cannabis?’ and ‘Do you wish you could stop?’). Schoeler and colleagues (2016) found in a meta-regression that lower levels of depression attenuated the adverse effects of cannabis on memory (this was not the same for anxiety). It is interesting therefore that in our sample, the group with the highest levels of depression (dependent cannabis users) did not exhibit memory deficits. If the study was repeated with a greater difficulty of tasks and PM load, it would be useful to see whether any relationship between depression symptomology and PM performance would be prevalent.

It would also be useful to carry out a prospective longitudinal study to decipher whether higher levels of depression, anxiety and schizotypy precede or are followed by the initiation of frequent cannabis use in those who go on to develop a dependence.

Methodological and Broader Considerations

A key strength of the study is that groups were well-matched on baseline variables (age, gender, highest level of education, and premorbid intelligence). Frequency of cannabis use was clearly defined (four or more days per week), unlike other studies in this field. We also examined the effect of dependency across cannabis users who were balanced for frequency of use.

There are some limitations of the study to consider. The recorded amount of cannabis used by participants was self-reported, and some people had difficulties identifying how much they smoked. This was because cannabis tends to either be sold

as an ‘eighth’ (however, may not actually weight an eighth of an ounce) or per a certain cost (e.g. a £20 bag worth). Estimates in grams were therefore approximate. Similarly, healthy controls have been found to underestimate their alcohol use (Feunekes, van’t Veer, van Staveren & Kok, 1999) due to social desirability, which could have masked differences between controls and cannabis users on the VW.

It is also important to consider the order of the VW tasks and nature of the FES condition. The ‘control’ days of the VW (without FES) always came first, followed by the ‘experimental’ condition (the two FES days). This was to remove any carry-over effects of the FES task. However, due to keeping this order the same, there could have been practise effects, although the lack of improvement between the control and experimental conditions does not necessarily support this. As mentioned above, we do not know the extent to which participants successfully carried out the FES task as instructed. If they were not carrying it out as planned, and encoding the tasks as they had during the first two VW days, that could explain the lack of improvement following the introduction of FES.

We must be cautious about generalising beyond the population sample who participated in the study – a group of relatively well-educated university and publicly-recruited young adults who frequently use cannabis (on average six days a week). We cannot assume the same results would be found in an older sample of frequent cannabis users. In addition, the study tested a sample of self-selecting cannabis users which could possibly be a more motivated group than the average frequent cannabis user.

More broadly, it is important to consider the widespread use of memory aids that people commonly use to assist enacting intended future actions. One could argue there is less of a requirement for PM skills given the accessible and available aids in which to remind ourselves of tasks (e.g. paper diaries, calendars, phone reminders, and

phone diaries). It would be useful to investigate how the prevalent use of such aids is affecting the extent to which we require our cognitive PM abilities, and whether there are associations between memory aid use and PM performance in studies. Additionally, the implications for any differences in PM may be less detrimental given the alternative options for reminding ourselves of to-be-remembered tasks.

Clinical Implications

The results of this study may be relevant when considering cognitive interventions for cannabis users. The findings would not support the use of cognitive rehearsal for improving PM task performance, or to assist users in improving their PM for applying addiction treatment strategies. However, it is important to note our sample of cannabis users were not accessing help for their cannabis use so the findings may not necessarily be applicable to samples in treatment for reducing their use. Our findings do fall in line with the review of the literature (Part 1 of this paper) which found no consistent evidence for the effect of cognitive remediation for cognitive deficits. However, it could be that as our sample did not have deficits, this was not applicable.

There are implications from our findings for assessing mental health in dependent frequent cannabis users. It is likely this group may need support for their depression and anxiety, and may be using cannabis to cope with symptomology (although causality was not established in this study). Cannabis users who present at addiction or GP services should be screened for their mental health and referred appropriately to their local services. It may be that by addressing their depression/anxiety, their cannabis use will not escalate to a point where it becomes problematic.

Conclusions

This study was the first to test frequent cannabis users (dependent and non-dependent) on various forms of PM, and compare them to non-using controls. When carefully matched on demographic variables, we found no evidence for a PM deficit as measured by the VW in our sample of young adults, nor evidence that an imagining task has any further effect on performance. Future research should aim to explore whether increased task difficulty on the VW leads to any differences or a replication of findings in this paper, alongside a measure of real-life PM and a question about strategy use in FES.

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Part 3: Critical Appraisal

Introduction

In this critical appraisal, I will reflect on the background context to choosing the research topic, and my experiences over various stages of the research process. I will consider the strengths of the study, and factors that assisted it running smoothly – notably, working alongside a project partner and team. I will also discuss some of the more challenging aspects of the research process, and expand on some of the limitations of the study methodology. I will finally consider future directions for cannabis and PM, and reflect on the wider social and political implications of research into substance use that have come to my attention during this process.

Background Context to the Research

Prior to starting the DClinPsy, during my Master of Science degree in Evidence-Based Social Intervention, I learnt the importance of conducting high-quality research to best estimate the effects of intervening into social, community or mental health problems. Using the skills acquired during this programme, I went on to work as a Research Assistant (RA) contributing to the development of NICE clinical guidelines for mental health disorders, and later as an RA on a clinical RCT. Although I had pre-doctoral experience in secondary research and working on a primary research trial, I had never planned and followed a clinically-relevant primary research project through from start to finish, so was excited to gain experience of this on the DClinPsy.

Building upon an interest in addictions, which was the topic area of my MSc dissertation (a systematic review of parenting programmes for substance-misusing mothers; Braidwood, 2011) and after starting a first year DClinPsy placement in an NHS drug addiction service, I was drawn towards research in the UCL Clinical Psychopharmacology Unit. Drug misuse and its costs - to the individual, their families

and communities - is a major challenge to the modern world, and I heard first-hand the stories from patients about the effects of their chronic drug use, which often started in the context of very traumatic histories.

I decided to explore my interest into the effects of substance use by researching an aspect of cognition - prospective memory (PM) - in frequent cannabis users, and the effects of future event simulation (FES) as a technique for improving PM. A fellow trainee, Samantha Mansell, also expressed interest in future memory processes in cannabis users, so we decided to collaborate and undertake a joint research project. As our supervisors pointed out, research is rarely undertaken by a single person and there are great benefits of discussing ideas and problem solving as a team, so I was excited to be part of a joint project.

Planning, Recruitment and Testing

Two previous DClinPsy trainees (with support from the UCL Clinical Psychopharmacology Unit) had explored PM and future event simulation in alcohol use (Griffiths, Hill, Morgan, Rendell, Karimi, Wanagaratne & Curran, 2012; Platt, Kamboj, Italiano, Rendell, & Curran, 2016). The effects of frequent cannabis on PM in were yet to be explored, and we aimed to carry out a study using the same objective measure of PM (the Virtual Week) to allow for direct comparison.

After several months of reading around the topic, discussing the proposed ideas with our supervisors, the Clinical Psychopharmacology Unit team, and my project partner, the measures and finer details of the study were set out. During this process, we researched into drug dependency and decided to recruit both dependent and non-dependent cannabis users. We made decisions about categorisation, e.g. that four days a week would count as ‘frequent’ use as it denotes more days smoking a week than

not, and as frequency of use rather than amount of use per se that is linked to increase chance of dependency (Curran et al., submitted). Although these initial decisions were ground in the literature and discussed with the team, I felt a sense of responsibility in making the ‘right’ decisions and wanting to state very explicitly our inclusion criteria prior to recruitment in order to reduce bias and indecision upon assessing each potential participant. My confidence grew in making such decisions (e.g. about study inclusion) with practice and directly referring to our criteria.

Throughout the early stages of setting up the research project, I really felt the benefits of planning with a team rather than as an individual; it helped us to question, justify, bounce new ideas off each other and make decisions. As the Clinical Psychopharmacology Unit already had an ethics approval for ‘investigating the determinants and psychological consequences of ketamine and high-potency cannabis use’, we submitted an amendment to the existing submission with the details of our study. This was approved shortly after it was sent (one week later), and thus ethics approval was rather straightforward in this study.

The next stage of the research process was recruitment and testing; Samantha and I enlisted help from an MSc student Jon Waldron to assist us with this. In carrying out a joint research project, and with the support from Jon, we were able to increase our sample size to far greater than would have been possible if we had worked as individuals, as the workload of testing was shared. Working as a three, we set ourselves deadlines and goals for testing and together planned our recruitment initiatives. We helped to motivate each other, often simultaneously testing participants in the same slots in separate rooms, so we could set up together and debrief. We also were aware of the importance of consistency of testing sessions, so prepared a detailed script to the testing session that we all followed, and of being organised with our materials to

ensure we had the right order of measures for each participant's counterbalanced condition. We observed each other during the pilot period, where we each piloted one participant with the others in the room, again to ensure consistency.

I have reflected on how living in an age of social media and the internet made our recruitment a much easier process; when we re-posted our advert on social media or enlisted a new website for the advert (e.g. introduced an advert on Gumtree, half-way through recruiting after a brief lull in interest), we got a surge of new emails from potential participants. We also used more traditional methods such as handing out flyers and putting up adverts, on university noticeboards and in some public spaces (such as Camden Lock and a '4-20' cannabis event in Hyde Park). We did not struggle with recruitment, and our recruitment drives and flexibility (such as working some evenings and weekends, and having three potential testers' availability to work with) aided the process. There were, however, a few challenges during the testing period. Several participants cancelled at the very last minute, or did not show up, which was frustrating as it meant a time-slot was lost. After this, aside from the confirmation email we sent out when participants agreed to attend a slot, we introduced a second reminder on the evening before or morning of their testing session, which seemed to have an impact on attendance rates and more notice of cancellation if they were not going to attend.

Our efforts to match participants on age, gender, alcohol consumption and highest level of education meant that towards the end of the recruitment process we had to actively seek participants (e.g. low-alcohol consuming, less-educated controls) and screen more people to find participants that fit our criteria. Also, we found that more of the cannabis participants that we screened were non-dependent according to our criteria, and so we had to turn away otherwise eligible non-dependent users who

we screened during the latter stages of recruitment and wait for dependent users to come forward. Given that we started testing participants ahead of schedule, the cancellations and more screenings we had to carry out for matched-participants did not majorly delay our study progress.

We also gained useful qualitative information about participants during the testing sessions, in informal conversations when walking them in and out of the building. A few spoke passionately about their use of cannabis, and wanted to actively participate in research to ‘prove’ that cannabis was not associated with adverse effects. I wondered if our participants represented a sample of cannabis users who were motivated and keen to contribute to research, but may not, potentially, be representative of other users who are less so. This is hard to overcome in studies with self-selecting participants, and it would be interesting to see what a similar study carried out in a clinical setting, where people are seeking help for their drug use, would find.

Limitations and Future Directions

If the study were to be repeated, a question about use of strategy in FES would be an important addition. We cannot assume from the data as it stands that FES as a technique when carried out as intended has no effect on performance, as we do not know what participants were carrying out during the 10-seconds where they were instructed to imagine the task context, and how they were doing it (e.g. visually imagining the context, or repeating the words). A challenge of being part of a joint research project was the length of our testing session, which was already two and a half hours, and thus some additional ideas for measures were cut. However, in

hindsight, this was important and would have been included if we were to re-run the study.

As indicated in the empirical paper, another limitation of the Virtual Week is that the ‘perform task’ button which is available on the board for the duration of the game presents participants with several options of tasks to carry out. There is a chance that participants looked at this feature to remind themselves of upcoming tasks, serving as a prompt, before they necessarily had the intention of performing a task. This would of course confound the results, if some participants used this feature (as more of a prospective recognition rather than recall task), whereas others may have not paid it attention. It could be argued that this potential recognition element resembles real-life PM in that people so often use diaries and calendars to prompt their memory, where they are met with their list of tasks or plans. It would be interesting to see how the results differed (if at all) if participants had to type the task which was required of them at the appropriate point in the game, without a task list presented, thus removing any potential for uncontrolled prompting.

A few of the minor study task and event card details were changed from the original Virtual Week version that we used, such as food choices for lunch, which were changed to suit a British sample than Australian, where the programme was developed. However, it is questionable how applicable the tasks in general and finer details (e.g. names of people in the game) were to the participants’ lives, and thus whether they were able to generate images of themselves performing such tasks. Also, given the age range of our sample (average age of 24 years), perhaps task selection relevant to this age would have rendered the measure of PM and use of FES more applicable. It is also important to consider that FES is hypothesized to work by formation of a mental representation of the context in which the task is to be completed which prompts task

completion when that context is later encountered (Paraskevaides et al., 2010). In the board game, however, tasks are presented in the form of words, as are later cues to task completion (i.e. event cards), yet FES requires a visual representation. It may be questioned, then, whether the visual context imagined during FES is appropriately later triggered when encountering the related event card.

As already indicated, given the relatively high proportion of correct responses on the Virtual Week across all groups, it would be useful to repeat the study with a greater task load and perhaps for more virtual days, to see if the similarity in performance across groups remains when the cognitive load and difficulty is higher. In addition, it would be interesting to carry out the study on a clinically-dependent sample who were seeking help for their cannabis use, compared to our samples who were not in treatment but were identified as dependent from a brief screening measure. Results in a clinical setting would have more relevance and applicability to clinical samples.

Finally, when reflecting on how the sample in the study relates to the patients I have seen in my addiction placement (and in my Early Intervention for Psychosis service, where a number of patients I was working with had a history of cannabis use), I have considered ethnicity. An important omission to our study was not recording ethnicity, especially when we are considering whether our sample was a representative sample and whether we can generalize the results to the real population.

Wider Implications and Reflections

During and after carrying out this study, I have considered wider issues such as the political implications around researching into drugs, and the importance of publishing studies that find no differences between groups (or no effects of

interventions) in research more generally. This first came to light when screening participants for the study, where a few individuals questioned whether it was safe for them to participate anonymously given they were using an illegal drug and checking that their name would not be held or used against them.

Despite the prevalence of drug use worldwide and consequent importance of researching the effects, the area is complicated by politics due to the illegality of most drugs, and political stances against changing policy in line with evidence if it comes contrary to existing beliefs or supposed public opinion. The government's chief drug advisor and scientist Professor David Nutt was sacked by the home secretary in 2009 after publishing a classification of harms and consequent ranking of drugs based on this (Nutt, 2009) which indicated that alcohol and tobacco were more harmful than many illegal drugs (including ecstasy and cannabis). Coming from an evidence-based background and perspective, I believe it is highly important that research into drugs is well-conducted, published, and used to inform policy and peoples' decisions. Given that this current study finds there was no differences between cannabis users and control participants, the political implications seem especially relevant. It is also important all well-conducted study findings are published in scientific journals or widely available, as we know that the literature is biased towards publishing studies that find effects rather than non-effects (Winters & Wier, 2017). We can only best assess the effects of an intervention, or in this case the effects of a substance, if we have all the existing evidence available to us to pool together. Carrying out this research has reminded me of the importance of publishing research, especially persisting in doing so if journals reject a paper which does not show an effect between groups.

Conclusions

In summary, I have genuinely found each stage of this research project (such as planning, recruiting, testing, analysing and interpreting the results) a really enjoyable process. There are some key strengths to the study, as mentioned, as well as improvements and suggestions for future research. I have learnt skills which I will certainly take beyond the DClinPsy course and into my future career as a Clinical Psychologist, where I hope to actively contribute to clinically-related research and to share the findings regardless of the direction of the results. I have really valued working as part of a small team during the earlier stages of the research project, and have greatly appreciated the support throughout from both of my supervisors Professor Valerie Curran and Dr Sunjeev Kamboj, as well as the rest of their team.

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Appendices

Appendix 1: Search Strategy

Appendix 2: Risk of Bias Tables

Appendix 3: Study Information Sheet

Appendix 4: Telephone Screening Script

Appendix 5: The Virtual Week Tasks

Appendix 6: Declaration of Joint Research Project

Appendix 7: Ethics Approval

Appendix 8: Consent Form

Appendix 9: Virtual Week Script

Appendix 10: Study Results Summary for Participants

Appendix 1. Search Strategy

1. exp Cognitive Rehabilitation/
2. exp Brain Training/
3. (cognit* adj2 stimulation).ti,ab.
4. (cognit* adj2 rehabilitation).ti,ab.
5. (cognit* adj2 remediation).ti,ab.
6. (cognit* adj2 training).ti,ab.
7. (cognit* adj2 retraining).ti,ab.
8. (cognit* adj2 enhancement).ti,ab.
9. (cognit* adj2 support).ti,ab.
10. exp "SUBSTANCE ABUSE AND ADDICTION MEASURES"/ or exp "SUBSTANCE USE DISORDER"/
11. exp Drug Dependency/ or exp Drug Rehabilitation/ or exp Drug Addiction/ or exp Drug Abuse/ or exp Addiction/ or exp Alcoholism/ or exp Alcohol Abuse/
12. (drug adj2 abuse).ti,ab.
13. (abuser* or abusing or addict* or depend* or habit* or misuse or user*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
14. (abuse not (child* or sex*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
15. (adiazepam or alcohol* or alprazolam or amphetamin* or analgesic or anaesthetic or antriamycin or anxiolytic* or ativan or barbituat* or bentazepam or benzodiazepin* or bromazepam or brotizolam or buprenorphin* or camazepam or cannabi* or chlordiazepoxid* or cinolazepam or clobazam or clonazepam or clorazepam or clotiazepam or cloxazolam or cocaine* or codeine or crack or crystal or cyprazepam or depressant* or diacetylmorphin* or diazepam* or doxefazepam or estazolam or etizolam or fentanyl or flunitrazepam or flurazepam or flutazoram or flutoprazepam or fosazepam or GHB or gisisopam or halazepam or hallucinogen* or haloxazepam or heroin* or hydrocodone or hydromorphone or hydroquinone or hypnotic* or inhalant* or ketamin* or ketazolam or librium or loflazepate or loprazolam or lorazepam or lormetazepam or marihuana* or marijuana* or meclonazepam or medazepam or meperidine or mephedrone or mescalin* or metaclazepam or methadone or methamphetamine* or methaqualone or mexazolam or midazepam or midazolam or morphine* or narcotic* or nerisopam or nimetazepam or nitrazepam or nitrates or (nitrous adj oxide) or nordazepam or opiate* or opioid* or opium or oxazepam or oxazolam or oxazepam or oxycodone or oxycontin or oxzepam or painkiller* or (pain adj killer*) or PCP or pethidin* or Percocet or phencyclidin* or pinasepam or poly* or prazepam or propazepam or propoxyphene or psychoactive* or psychostimulant* or quinazolinone or ripazepam or ritalin or sedative* or serazepin* or solvent* or stimulant* or substance* or temazepam or tetrazepam or tofisopam or tramadol or triazolam or triflubazam or valium or vicodin).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
16. exp Relapse Prevention/
17. (relapse adj prevent*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 16 or 17
19. 10 or 11 or 12

20. (13 or 14) and 15

21. 19 or 20

22. 18 and 21

Appendix 2. Risk of Bias Tables

Bell et al. (2016)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation of six performed by independent statistician
Allocation concealment (selection bias)	Unclear risk	No allocation concealment procedures were described
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 patients were excluded from the analysis (out of 34): 1 in CCT group, 2 from WT group. One withdrew after randomisation before starting the intervention (not reported which group), one patient due to hospitalisation and one declined the PT testing as he was employed. 2 more participants were lost at 6 month FU, last observation carried forward used in analysis. Low risk due to low attrition
Selective reporting (reporting bias)	High risk	Protocol registered NCT01410110. Author sent some additional outcomes after correspondence; not all measured were reported in the publication (days of sobriety; alcohol use)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel would have been aware of group condition
Blinding of outcome assessment (detection bias) All outcomes	High risk	'Assessments were performed by.... this person was not blind to participant condition'
Other bias	Low risk	No other significant sources of bias were identified

Czuchry & Dansereau (2003)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Communities were “randomly assigned”. No details of how random sequence was generated
Allocation concealment (selection bias)	Unclear risk	No reporting of how allocation was concealed prior to assignment
Incomplete outcome data (attrition bias)	Unclear risk	Dropout was not reported, nor how any (potential) missing data was analysed. Ns used in analyses not provided
All outcomes		
Selective reporting (reporting bias)	Unclear risk	No protocol registered. Results for all stated outcomes reported although not all raw scores not given
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel would have been aware of their condition
All outcomes		
Blinding of outcome assessment (detection bias)	Unclear risk	Counsellors and an on-site research assistant administered all measures. It is likely they would have not been blind to community condition, although this is not reported
All outcomes		
Other bias	Unclear risk	Depending on whether the counsellors and peers were blind (likely not), there may have been additional bias in the results from the peer and counsellor outcome ratings

Fals-Stewart & Luente (1994)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	‘Randomly assigned’. No details of randomisation procedure i.e. how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	No allocation concealment procedures were described

Incomplete outcome data (attrition bias) All outcomes	Low risk	Relatively low and evenly spread attrition: 8 subjects did not complete the study (2 in each group) and were not included in the analysis
Selective reporting (reporting bias)	Unclear risk	No protocol registered
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>'Staff and patients were told that the study was designed to determine the effect of the different interventions on participants' neuropsychological test performance. They were not told any a priori hypotheses.'</p> <p>However, due to the nature of the intervention, participants would have been aware of which intervention they were receiving</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>It is not reported whether research psychometrician who administered the neuropsychological battery was blind.</p> <p>Clinical staff who rated patients with the SRS were unaware of research hypotheses however it is now reported whether they were aware of group assignment</p>
Other bias	Low risk	No other potential biases identified

Fals-Stewart & Lam (2010)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'The presence of cognitive impairment ... was used in a covariate-adaptive urn randomisation procedure'
Allocation concealment (selection bias)	Unclear risk	No description of how the allocation was concealed. Randomisation occurred after baseline interviews
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>There was a reasonable level of attrition: at PT, 5/80 patients in CACR group & 8/80 in CATT group did not complete outcome measures. Some missing data at follow up: 3 month (CACR N=75, CATT N=72), 6 month (CACR N=74, CATT N=72), 9 month (CACR N=70, CATT N=69), 12 month (CACR N=72, CATT N=73). Multiple imputation (MI) methods were used; multiple</p>

		data sets were generated and analyses of separate datasets were then combined
Selective reporting (reporting bias)	Unclear risk	No trial protocol. All outcomes specified in the paper were reported, although not all raw scores presented
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel would have been aware of their condition
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Research assistants ‘who remained unaware of randomisation assignment’ conducted all baseline and post-treatment interviews
Other bias	Low risk	No other significant sources of bias were identified

Gamito et al. (2014)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation with a random number generator
Allocation concealment (selection bias)	Unclear risk	No reporting of how allocation was concealed prior to assignment. From the paper’s attached CONSORT-EHEALTH Checklist V1.6.2 Report: “not applicable”. Author’s reply to email (4/1/17) did not clarify: ‘Allocations were determined by random assignments of patients to each of the groups’
Incomplete outcome data (attrition bias) All outcomes	High risk	14/68 patients dropped out of the study (7 from each group). Missing data was not imputed- it was excluded from the analysis
Selective reporting (reporting bias)	High risk	Trial registered NCT01942954. Protocol states aside from the FAB which is reported in the paper, participants would be assessed in “Frontal Lobe Cognitive Functioning (Retention, Attention and Calculation, Language and Visual-spatial abilities)” – but

does not state using which measures. The paper reports ‘cognitive flexibility’ (WCST) and the Color Trail Test (CTT). When asked in email to the author, the reply (4/1/17): “The cognitive domains related to Retention, Attention and Calculation, Language and Visual-spatial abilities are categories of the Mini-Mental State Examination test and were not assessed in our paper. We mention these domains when describing the measure, but were not assessed because it was not our main aim”

Blinding of participants and personnel (performance bias)	High risk	Patients and personnel were not blind to their condition, knowing which was the intervention of interest and the comparator
All outcomes Blinding of outcome assessment (detection bias)	Low risk	From CONSORT-EHEALTH Checklist V1.6.2 Report: “outcome assessors were blind to the experimental group of the participants”
All outcomes Other bias	Low risk	No other potential biases identified

Goldman & Goldman (1987)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	‘Each alcoholic subject was randomly assigned’. No details of the method used to generate the allocation sequence given.
Allocation concealment (selection bias)	Unclear risk	No allocation concealment procedures were described
Incomplete outcome data (attrition bias)	Unclear risk	Attrition was not reported nor were the numbers randomised or subsequently analysed in each intervention group
All outcomes Selective reporting (reporting bias)	Unclear risk	No protocol. All stated outcomes discussed but means/SDs/Ns in analyses not reported
Blinding of participants and personnel (performance	High risk	Participants and personnel would have been aware of their intervention condition

bias)		
All outcomes		
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of outcome assessors was not reported
All outcomes		
Other bias	Low risk	No other potential biases identified

Grohman & Fals-Stewart (2003)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomly assigned' after baseline assessment. No details of the method used to generate the allocation sequence given
Allocation concealment (selection bias)	Unclear risk	No allocation concealment procedures were described
Incomplete outcome data (attrition bias)	Unclear risk	Dropout of the intervention during treatment stay was not reported explicitly. Could assume there was no dropout as under 'Procedure' reports participants engaged in the respective exercises 3 times weekly for 50 minutes, 'all of these participants were guided through the intervention in each of these conditions by a research assistant to ensure that the tasks were completed'
All outcomes		
Selective reporting (reporting bias)	Unclear risk	No protocol registered. All specified measures in the paper are reported. Only measured cognitive functioning at baseline
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel knew which intervention group they were in
All outcomes		
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported. However, outcome measures were all objective (length of stay in treatment; reason for discharge) so blinding not necessarily appropriate
All outcomes		

Other bias	Low risk	None identified
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Mathai et al. (1998)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Allocated at random'. No description of how the randomisation sequence was generated was given
Allocation concealment (selection bias)	Unclear risk	No allocation concealment procedures were described
Incomplete outcome data (attrition bias)	Low risk	1 patient in the control group 'went to his native town after the pre-assessment and came only for the post assessment'. No other mention of incomplete outcome data. 1 person lost to FU
All outcomes		
Selective reporting (reporting bias)	Unclear risk	No protocol. Means and SDs reported for outcomes identified in the paper
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel would have been aware of their treatment condition
All outcomes		
Blinding of outcome assessment (detection bias)	Unclear risk	Whether outcome assessors were blind was not reported in the paper
All outcomes		
Other bias	High risk	Treatment group were 'counselled more frequently' than TAU group [therefore limiting difference between groups as only the presence of the cognitive intervention] Small overall sample size: N=8

Rass et al. (2015)

Bias	Authors' judgement	Support for judgement
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Random sequence generation (selection bias)	Low risk	Participants were randomly assigned using a ‘minimisation procedure’ to balance groups on various parameters
Allocation concealment (selection bias)	Unclear risk	Not reported. Restricted randomisation (minimisation) increases chance of selection bias if next allocation can be predicted with greater than 50% probability. Author emailed but did not answer questions, just referred back to the paper where it was not clear
Incomplete outcome data (attrition bias) All outcomes	High risk	9/37 dropped out of CCRT and 8/38 from ACC group. Only treatment completers were included in analysis – dropouts excluded. High level of attrition
Selective reporting (reporting bias)	High risk	Trial registered on clinicaltrials.gov: NCT01271413. Several outcomes assessed (as reported in the paper, e.g. operation span task, visuo-spatial working memory task) were not pre-specified in the protocol. Author emailed regarding these but did not answer questions, just referred back to the paper where it was not clear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were aware of their intervention allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pre- and post-training assessment sessions were administered by a research assistant blind to training condition, ‘with one exception due to error’
Other bias	Low risk	No other biases identified

Roehrich & Goldman (1993)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	‘Each participant was randomly assigned’, ‘subjects younger than 40 years and those 40 years of age and older were assigned separately to each group to balance for age both within and across groups’. No

description of what method used to do this randomly		
Allocation concealment (selection bias)	Unclear risk	No allocation concealment procedures were described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop out not reported. The N's in the analysis reported are the same as the Ns randomised so can assume there was no dropout or scores were imputed
Selective reporting (reporting bias) Blinding of participants and personnel (performance bias) All outcomes	Unclear risk High risk	No protocol. All outcomes specified in paper were reported in means/SDs Participants and personnel would not be blind to intervention received
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not reported
Other bias	Low risk	No other biases identified.

Rupp et al. (2012)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomly assigned'. No details of randomisation procedure reported. Author emailed but no reply received
Allocation concealment (selection bias)	Unclear risk	No allocation concealment procedures were described. Author emailed but no reply received
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 45 randomised, 4 were excluded prior to starting the intervention as they did not show a mild cognitive deficit. From the 41 who made up the sample, 0 patients in the CR group and 4 in the CG did not provide post-treatment data [1 was discharged from inpatient treatment for drinking alcohol, 3

		terminated treatment prematurely]. Ns are not provided in the Results tables so unknown whether data was imputed or excluded
Selective reporting (reporting bias)	Unclear risk	No known protocol. All specified outcome measures in the paper reported (means/SDs) but not with Ns used in analyses. Author emailed but no reply received
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel would have been aware of their group allocation by nature of the interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Whether outcome assessors were blind to group was not reported. Author emailed but no reply received.
Other bias	Low risk	No other biases identified

Steingass et al. (1994)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were 'randomly assigned'. How the randomisation sequence was generated or the participants randomly assigned was not reported
Allocation concealment (selection bias)	Unclear risk	No reporting of how allocation was concealed prior to assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 participants prior to assessment/intervention were excluded as they were illiterate. No mention of dropout apart from one subject failing to complete one outcome measure (D2 test), it was not reported whether data was imputed so likely to have been left out of analysis
Selective reporting (reporting bias)	Unclear risk	No protocol. All specified outcomes reported (means and SDs)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel would have been aware of their group allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not reported who carried out the outcome assessments and whether they were blind to condition.
Other bias	Low risk	No other biases identified

Stringer & Goldman (1998)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomly assigned'. No details of how randomisation was done are given
Allocation concealment (selection bias)	Unclear risk	No reporting of how allocation was concealed prior to assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The actual Ns assigned to each group are not reported. No mention of attrition
Selective reporting (reporting bias)	Low risk	No protocol. Means depicted for each group on a graph, no SDs for block design (specified outcome measure).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel would have been aware of their group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blind outcome assessors
Other bias	Low risk	No other risks identified (but small N in each group - ~10)

Wetzig & Hardin (1990)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Because of the possible biasing effects of variables such as race, age and education, subjects were matched on the basis on these demographics and then assigned randomly to each of the three groups'. No detail of how the groups were randomly assigned
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout is reported, although Ns in analysis are not reported
Selective reporting (reporting bias) Blinding of participants and personnel (performance bias) All outcomes	Unclear risk High risk	No protocol registered. Means and SDs provided for primary outcomes Participants and personnel would have been aware of their group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported whether outcome assessors were blind.
Other bias	Low risk	None identified

Yohman et al. (1988)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Groups of 3 to 7 alcoholic subjects from successive ward treatment groups were randomly assigned'. No details of how randomisation sequence was generated. Not individual randomisation

Allocation concealment (selection bias)	Unclear risk	Successive ward treatment groups were assigned. No mention of how which group they would fall in to was pre-determined and concealed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout was not reported but Ns provided in Results imply all randomised participants were included so one can assume there was no dropout
Selective reporting (reporting bias) Blinding of participants and personnel (performance bias) All outcomes	Unclear risk High risk	No protocol. Cluster/composite scores presented (means and SDs) for each group Participants and personnel would have been aware of their group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported whether outcome assessors were blind
Other bias	Low risk	None identified

Appendix 3. Study Information Sheet

CLINICAL PSYCHOPHARMACOLOGY UNIT
RESEARCH DEPARTMENT OF CLINICAL, EDUCATIONAL
AND HEALTH PSYCHOLOGY



Information sheet for volunteers

The determinants and psychological consequences of ketamine and high potency cannabis use.

An investigation of prospective memory and future thinking in cannabis use.

Version 1 November 2015

You are invited to participate in a research study investigating whether cannabis use may affect "prospective memory" or "episodic foresight". Prospective memory is remembering to do something in the future, for example, picking up some milk on the way home from work. Episodic foresight is the capacity to imagine future events.

Before you decide to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss this with the investigators if you have any questions. Please ask us if there is anything that is not clear or if you would like more information. Take time to consider whether you wish to take part.

Thank you for reading this.

The purpose of the research

This study is designed to improve our understanding of potential effects of cannabis on prospective memory and episodic foresight. Prospective memory refers to our ability to remember to do something in the future. Most of our everyday forgetting involves prospective memory failures, such as forgetting to do something you had intended to, or had promised someone you would do. Research has shown that cannabis can affect people's memory for the past but we don't know whether it affects remembering to do something in the future. It is important we start to investigate this to see how we could improve people's prospective memory. We will also be looking at the capacity to imagine future events, for example, how we imagine spending our next birthday. Exploring this capacity is also of interest given its implications for ability to plan and think about our imagined futures.

To achieve these aims, this study will compare prospective memory and episodic foresight in daily cannabis users with non-users.

Why have I been chosen?

You have been chosen to take part because you meet the criteria to participate in the study, and will fall into one of two groups: daily cannabis users or non-users.

How many people will take part?

Sixty participants will be recruited. Forty participants will use cannabis daily, and twenty will be non-users.

Do I have to take part?

No. It's up to you to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time.

What happens to me if I decide to take part?

You will be invited to come in for one visit at UCL's Clinical Psychopharmacology Unit (Gower Street, WC1E 6NT). A member of the team will check whether you have any questions about what you've read on this information sheet before proceeding. We will ask some questions about substance use before starting the tasks. You will then complete some tasks on prospective memory and episodic foresight, as well as others relating to past memory, processing information and emotions.

This will last approximately two hours, with one scheduled break.

Expenses and payments

We will pay you £20 for taking part in the study.

What are the possible risks of taking part?

There are no foreseen risks in taking part in this study.

What happens if I don't want to carry on with the study?

Taking part in this study is voluntary. If you do decide to take part, you are free withdraw at any time. If you do withdraw, no more data will be collected about you.

How will I find out the results?

A summary of the results will be sent to all those who participated in the study, once the study is complete. If the study is published in a journal, you will not be referred to by name or any way identified in the report, nor will the data be traceable back to you. By taking part in the study, you agree to not restrict the use of any anonymised data even if you withdraw from the study.

What if there is a problem or something goes wrong?

Any complaint about the way you have been dealt with in this study will be addressed. If you are harmed taking part in this research project, there are no special compensation arrangements, but if you are harmed by someone else's negligence then you may have ground for legal action. If you wish to complain or have any concerns about any aspects of the way you have been approached or treated during the course of the study, your complaint to the Joint Research Office will be reviewed by the Clinical Research Governance Committee and the UCL Research Governance Committee.

Will my taking part in this study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. All data collected will be securely transferred to and stored on UCL premises and computers. As the study is confidential, all data collected will be secured against any unauthorised access.

For one of the tasks, your spoken response will be audio recorded. This recording will be anonymised, stored on a password protected USB stick, then deleted as soon as it has been transcribed.

Although the overall results may be published in a scientific journal, no individual participants will be identifiable from this. Confidential information linking your identity with clinical details will be separated after the trials, unless we inform you otherwise, in which case we will ask consent to retain such information. As you are being paid for participation, your name and address will be passed to UCL Finance for administration purposes. All data will be collected and stored in accordance with the Data Protection Act 1998.

Who is organising and funding the research?

The study is being organised by University College London and funded by University College London [Project ID: 5402/001] and is funded internally.

Who has reviewed the study?

The UCL Research Ethics Committee [Project ID: 5402/001] has approved the study.

Contact details

Ruth Braidwood (r.braidwood@ucl.ac.uk) and Sam Mansell (Samantha.mansell.14@ucl.ac.uk), Trainee Clinical Psychologists at UCL, are conducting the study and will answer any questions you have about the research and participating. Jonathon Waldron (jonathan.waldron.15@ucl.ac.uk), an MSc student, will be involved in recruitment and testing and is also available to answer any questions. Professor Valerie Curran (v.curran@ucl.ac.uk), Professor of Psychopharmacology, and Dr Sunjeev Kamboj (sunjeev.kamboj@ucl.ac.uk) are supervising the research and may also be contacted with any questions.

Thank you for taking the time to read and consider this information.

Appendix 4. Study Screening Script

STUDY TITLE: An investigation of prospective memory and future thinking in cannabis use.

Protocol ID: 5402/001

Telephone Pre-Screening

Date.....

Screening number.....

Estimated time: 10 minutes

Have you read the information sheet about the study and are you interested in taking part?

YES

NO (**If NO then END**)

If cannabis users:

Please inform volunteers that as part of this telephone pre-screening they will be asked some detailed and sensitive questions about their cannabis use to determine if they are eligible for the trial, and that if they feel uncomfortable about answering any of the questions they have the option not to answer.

If controls:

Please inform volunteers that as part of this telephone pre-screening they will be asked some detailed and sensitive questions to determine if they are eligible for the trial, and that if they feel uncomfortable about answering any of the questions they have the option not to answer.

Volunteer informed:

YES

NO (**If NO then END**)

Age:

Date of Birth:

Gender: Male / Female (circle)

What is your highest level of education?

GCSE

A Level

Vocational training course

Undergraduate degree

Postgraduate degree

Doctorate

Other

We're now going to ask a few questions about your cannabis use.

Do you smoke cannabis?

YES

NO

At what age did you start smoking cannabis?

.....

How many days a week do you smoke?

- 1
- 2
- 3
- 4
- 5
- 6
- 7

How many grams do you individually smoke a week?

.....

How long does it take you to individually smoke an “eighth” (i.e. an eighth of an ounce or 3.5 grams)?

.....

SDS

We're now going to ask a few more questions about your cannabis use and give a few options to answer.

1. Did you ever think your use of cannabis was out of control?

- a. Never or almost never (0 points)
- b. Sometimes (1 point)
- c. Often (2 points)
- d. Always or nearly always (3 points)

2. Did the prospect of missing a smoke make you very anxious or worried?

- a. Never or almost never (0 points)
- b. Sometimes (1 point)
- c. Often (2 points)
- d. Always or nearly always (3 points)

3. Did you worry about your use of cannabis?

- a. Not at all (0 points)
- b. A little (1 point)
- c. Quite a lot (2 points)
- d. A great deal (3 points)

4. Did you wish you could stop?

- a. Never or almost never (0 points)
- b. Sometimes (1 point)
- c. Often (2 points)
- d. Always or nearly always (3 points)

5. How difficult would you find it to stop or go without?

- a. Not difficult (0 points)
- b. Quite difficult (1 point)
- c. Very difficult (2 points)
- d. Impossible (3 points)

Add up the points

SDS score / 15

Thanks for that. We are now going to ask you a few more questions.

Do you drink alcohol?

- YES
- NO

If YES, at what age did you start drinking alcohol?

15

If YES, how many days a week?

- 1
- 2
- 3
- 4
- 5
- 6
- 7

Please give us an estimate of how much* alcohol you drink a week. Give your answer in terms of type and number of drinks consumed. For example, five pints of lager and a large glass of white wine.

2 units .

*21 units woman, 28 units man as broad upper limits for the study

Do you use any illicit (illegal) drugs other than cannabis?

- Any illicit drug
- No illicit drug used

If ANY illicit drug

Drug	How often*

**Find out if they do it more or less than twice a month*

Have you ever been diagnosed/concerned about dependency on any illicit substance other than cannabis or nicotine?

- YES
- NO

If YES Provide details

Are you fluent in English?

- YES
- NO (**if NO then END**)

Are you currently receiving psychiatric medication and/or therapy for a mental health problem?

- YES
- NO

If YES Provide details

Have you ever been diagnosed with a psychotic disorder (e.g. Schizophrenia, Bipolar) or experienced a psychotic episode in the past?

- YES
- Provide details (diagnosis, time elapsed since last episode)

- NO

Have you ever been diagnosed with a learning difficulty?

- YES (**If YES then END**)
- NO

Are you currently using any other prescribed medication?

- YES
- NO

If yes, list them here:

Would you be willing to refrain from using drugs/alcohol on the day of the testing session?

- YES
- NO

Thank you for answering these questions. We will let you know if you meet criteria for the study very soon. If you do, would you be willing to come to UCL for a testing session which will take approximately 2.5 hours? We are based by Goodge Street, just off Tottenham Court Road.

Would you be happy for your contact details to be passed on to other UCL researcher's within our group who are currently running studies for which you may be eligible to participate?

- YES
- NO

Appendix 5. The Virtual Week Tasks

Task type	Monday	Tuesday	Wednesday	Thursday
Regular event-based tasks	Take antibiotics at breakfast Take antibiotics at dinner	Take antibiotics at breakfast Take antibiotics at dinner	Take antibiotics at breakfast Take antibiotics at dinner	Take antibiotics at breakfast Take antibiotics at dinner
Regular time-based tasks	Use asthma inhaler at 11:00 Use asthma inhaler at 21:00	Use asthma inhaler at 11:00 Use asthma inhaler at 21:00	Use asthma inhaler at 11:00 Use asthma inhaler at 21:00	Use asthma inhaler at 11:00 Use asthma inhaler at 21:00
Irregular event-based tasks	Pick up your sister's membership pass whilst at the swimming pool/sports club Tell Kate that Margaret has had a baby girl next time you talk to Kate	Drop in the dry cleaning when you go out shopping Return library book borrowed by Brian when you are at the library	Invite your friend David to dinner when you see him Buy some stationary supplies when you are at the corner shop later today	Ask Jill for the book she borrowed when you have afternoon tea with Jill When you go to use the washing machine, set it to a gentle cycle
Irregular time-based tasks	Haircut at 13:00 Appointment at library for help with computers 15:00	Phone bank at 12:00 to arrange an appointment Put casserole in the oven at 17:00	Meet your friend Michael for coffee at 16:00 Phone David's sister at 18:00 about baby sitting	Submit a report at 15:00 Have an x-ray at 16:00

Appendix 6. Declaration of Joint Research Project

This major research project was a jointly carried out with Samantha Mansell, a fellow DClinPsy trainee. The following stages were completed together: finalising the study protocol, recruiting participants, and testing participants. We also had help in the recruitment and testing phase from Jon Waldron, a Research Methods in Psychology MSc student at UCL. We each tested approximately a third of participants.

Jon wrote up a subset of the complete dataset for his MSc dissertation ($N = 34$; 17 control participants and 17 dependent frequent cannabis users) on the episodic simulation of future events (ESoFE) task (participant-ratings only), which is not reported in this paper. Samantha's thesis reports on the ESoFE task with the full sample, considering both the researcher and participant ratings.

All three reports include the analyses of baseline demographic data, neuropsychological measures (episodic memory and fluency tasks), depression, anxiety and schizotypy.

References

- Mansell, S. (2017). Episodic simulation of future events in dependent and non-dependent daily cannabis users. *Unpublished clinical psychology doctoral thesis, Department of Clinical, Educational, and Health Psychology, University College London.*
- Waldron, J. (2016). Episodic foresight in dependent cannabis users. *Unpublished MSc dissertation, Department of Clinical, Educational, and Health Psychology, University College London.*

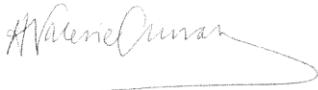
Appendix 7. Ethics Approval

UCL RESEARCH ETHICS COMMITTEE

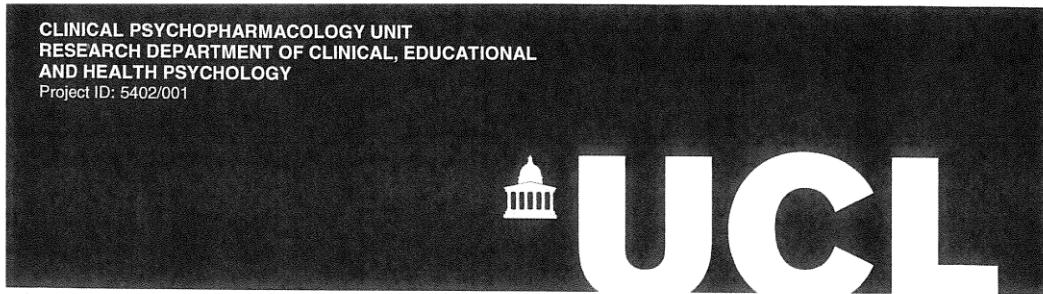


Amendment Approval Request Form

1	Project ID Number: 5402/001	Name and Address of Principal Investigator: Professor Valerie Curran UCL Dept of Clinical Educational and Health Psychology Division of Psychology and Language Science 1-19 Torrington Place London WC1E 7HB
2	Project Title: Investigating the determinants and psychological consequences of ketamine and high-potency cannabis use.	
3	Type of Amendment/s (tick as appropriate) <input checked="" type="checkbox"/> Research procedure/protocol (including research instruments) <input type="checkbox"/> Participant group <input type="checkbox"/> Sponsorship/collaborators <input type="checkbox"/> Extension to approval needed (extensions are given for one year) <input checked="" type="checkbox"/> Information Sheet/s <input checked="" type="checkbox"/> Consent form/s <input checked="" type="checkbox"/> Other recruitment documents <input type="checkbox"/> Principal researcher/medical supervisor* <input type="checkbox"/> Other *	
*Additions to the research team other than the principal researcher, student supervisor and medical supervisor do not need to be submitted as amendments but a complete list should be available upon request.		
4	Justification (give the reasons why the amendment/s are needed) We would like to add new tests which examine memory for, and ability to imagine, future plans in cannabis users (we will not test ketamine users). The information sheet and consent form have been amended accordingly	
5	Details of Amendments (provide full details of each amendment requested, state where the changes have been made and attach all amended and new documentation) 1. The researchers wish to add 2 psychological tests and 1 well-validated self report measure to their ongoing research with frequent cannabis users, which will provide data for two DClinPsy research projects being supervised by the Principal Investigator. The two new tests will enable the investigation of both prospective memory (memory for intended actions) and episodic foresight (a mental imagery task) in dependent and non-dependent cannabis users and non-using controls. It is hypothesized that dependent cannabis users will perform worse than non-dependent and non-using controls respectively on prospective memory and episodic foresight. 2. It is also hypothesized that we will identify a 'cannabis foresight bias' on the episodic foresight task demonstrated through higher scores for cannabis-related future scenarios compared to a neutral future scenarios in both dependent and non-dependent daily users compared to controls. The new testing protocol will be administered in one sitting, and will take approximately 2 hours. It will include the following tasks/measures: 1. Virtual Week Task. An objective measure of Prospective Memory, which uses a computerised board game procedure. Participants are required to.... 2. Episodic foresight Task. This requires participants to imagine future scenarios (one neutral, one cannabis-related, and one alcohol-related) and then provide ratings of the phenomenological qualities of these simulations (e.g. amount of sensory detail, emotional valence, spatial/temporal clarity) on a numerical scale	

	<p>(e.g. Winfield & Kamboj 2010).</p> <p>3. Work and Social Adjustment Scale (WSAS; Mundt., 2002). This is a validated, five-item, self-report measure of daily functioning.</p> <p>The information sheet and consent form have been amended accordingly (attached).</p> <p>To optimise recruitment of participants we will advertise the study in selected appropriate media (e.g. web based drugs forums). We expect that this will speed up the recruitment process and allow us to more efficiently contact and screen potential participants. Please find a copy of the advertisement attached.</p>
6	<p>Ethical Considerations (insert details of any ethical issues raised by the proposed amendment/s)</p> <p>The issue of potential fatigue given the two hour duration of the testing procedure has been taken into consideration and all participants will be offered a standardised break during testing.</p> <p>Participants will be paid £7.50 per hour to take part in the study, which represents an appropriate level of reimbursement for the time/effort that will be required of them.</p>
7	<p>Other Information (provide any other information which you believe should be taken into account during ethical review of the proposed changes)</p> <p>Declaration (to be signed by the Principal Researcher)</p> <ul style="list-style-type: none"> • I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it. • I consider that it would be reasonable for the proposed amendments to be implemented. • For student projects I confirm that my supervisor has approved my proposed modifications. <p>Signature: </p> <p>Date: 4th January 2016</p> <p>FOR OFFICE USE ONLY:</p> <p>Amendments to the proposed protocol have been <u>Approved</u> by the Research Ethics Committee.</p> <p>Signature of the REC Chair, Professor John Foreman: <u>John</u></p> <p>Date: <u>12/1/2016</u></p>

Appendix 8. Consent Form



Consent Form

Version 1 November 2015

The determinants and psychological consequences of ketamine and high-potency cannabis use.

An investigation of prospective memory and future thinking in cannabis use.

Investigators: Prof H Valerie Curran, Dr Sunjeev Kamboj, Ruth Braidwood, Samantha Mansell & Jonathon Waldron.

I confirm that I have read and understand the information sheet for the study and have had the opportunity to ask questions and discuss the study. YES/NO

I agree that I have received satisfactory answers to all my questions or have been advised of an individual to contact for answers to questions about the research and my rights as a participant. YES/NO

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. YES/NO

I understand that the personal information generated from this study will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998. YES/NO

I consent to the information I have submitted being securely transferred to and stored on University College London premises and computers. YES/NO

I understand that I am being paid for my assistance in this research and that some of my personal details will be passed to UCL finance for administration purposes. YES/NO

I agree to take part in the above study. YES/NO

I agree/do not agree (*delete where applicable*) for the results of the study and details of any effective memory strategies to be sent to me at the end of the study to: (*please include post or email address details if applicable*).

.....
.....
.....
.....

Signed (participant)

Date

Signed (investigator)

Appendix 9. Virtual Week Script

General introduction before commencing trial day:

- “VW is a board game played on the computer. The game is about the day-to-day activities of a typical week and it will ask you to remember lots of tasks and ‘perform’ them in the game. You don’t perform them in real life, just in the game.”
- “One circuit of the board represents one virtual day. Your position is represented by this blue token. As the token moves clockwise around the board, you are going through your virtual day. Try to imagine that each event like it’s really happening”
- “We will start with a trial day, which will introduce you to the features of the game. Then you will play 3 virtual days on your own.”

After beginning, point out the board in the centre where important messages are shown and let the participant know to read this when requiring instruction.

- “Please read aloud all instructions, events and tasks as you move round trial day.”

After the second Help Message, make sure the participant understands the help messages, read them aloud. Point out how the time is changing as they move around the board.

After the third Help Message, let the participant know that the token turns dark blue when on the correct square. If they miscount and move incorrectly, the game won’t let them proceed until they’ve landed on the correct square.

At the first Event Card (Breakfast):

- “Please read title and all contents of the event cards out loud.”

Clarify that they need to make a choice about the event, and that they need an odd/even/any number to continue moving around the board. Some participants need to be encouraged to make a choice for the sake of the game, even if it isn’t what they would do in normal life.

At the first Task Card (antibiotics):

Explain how the task is related to the Breakfast event card.

- “So, we must take our antibiotics at breakfast and dinner. If we look back to the event card we selected, it tells us we are currently having breakfast. That means we have to perform this first task right now.”

At the second Task Card (asthma inhaler):

- “These 2 tasks will become your regular tasks for the next two days of the game, after this trial day, so you will need to remember them”

When back to game board, point out the Perform Task button on the board, so that participant knows where to find it later for the time-based task.

Near 11:00 AM. *Explain that time-based tasks can still be performed correctly after the exact time:*

- “*The game takes into consideration that dice rolls are random, so the token won't always land on the exact time. So if a large dice roll takes you past the exact time when a task is due, and you perform it immediately, it is still considered on time.*”

After trial day is complete:

- “Ok now that the trial day is over, you will do four virtual days on your own- I can't assist you with remembering the tasks but I am here if you have other questions about the program”

Make sure participant understands the instruction slides before day 1 – explain the key points:

- They must continue to read aloud all task and events, including the title
- Perform Task button – board and events
- Make sure you always read aloud the title of event cards
- You will be getting a break after two days
- When asked to make decisions on events – try and pick options you would choose in real life as it will make the task check easier

Appendix 10. Study Results Summary for Participants

CLINICAL PSYCHOPHARMACOLOGY UNIT
RESEARCH DEPARTMENT OF CLINICAL, EDUCATIONAL
AND HEALTH PSYCHOLOGY
Project ID: 5402/001



 *An Investigation of Prospective Memory and Future Thinking in Cannabis Use* 

Participants (N=54) were 18 frequent cannabis users who were 'dependent', 18 frequent users who were 'non-dependent', and 18 controls who did not use cannabis →

What do we mean by dependent?
We asked all cannabis users 5 questions about their use of cannabis (The Severity of Dependence Scale; Gossop et al., 1995). Questions were around how difficult it would be to stop using cannabis, levels of anxiety around missing a smoke, and the extent to which cannabis use felt out of control. If people scored ≥3 they were classified as 'dependent' and if they scored <3 as 'non-dependent'.

KEY FINDINGS

1) Prospective memory – the Virtual Week
Prospective memory is remembering to do something in the future, for example, picking up some milk on the way home from work. We tested this with the *Virtual Week* computerised board game.

We found that there were no differences in prospective memory ability between dependent cannabis users, non-dependent cannabis users and controls.

2) Depression, anxiety and unusual experiences
Dependent cannabis users scored higher on measures of depression, anxiety and unusual experiences than non-dependent users and controls (who scored similarly).

3) Future thinking task
We investigated future thinking by asking people to imagine and describe events which might plausibly happen to them in the future, then rate these events on a series of scales. The researchers also rated audio recordings of the event descriptions.

In dependent cannabis users, future events were rated by researchers as containing more contextual information than non-dependent users. Dependent users reported greater mind-wandering than non-dependent users, but this was linked to them having higher anxiety scores.

Non-dependent users provided richer descriptions of their cannabis future events than dependent users.