Recreational drug use and cognitive functions

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Adnan Levent

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I declare that this thesis has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree.

Contents

Abstract

Recreational drug use is thought to harm the neurotransmitter communication systems that are important for cognitive processes. The previous studies on the effects of drug use on cognitive functions are rather inconclusive and suffer from methodological challenges, such as small sample sizes, unrepresentative sample types, short abstinence periods, and poor control for confounding factors. Therefore, this study aimed to investigate the effects of recreational drug use on cognitive functions, in particular PM, using mixed research methods while trying to address those methodological difficulties. The study consists of two interrelated studies. In the first study, 53 drug users and 47 non-users were recruited and examined on executive functions (EFs), retrospective memory (RM) and prospective memory (PM), using questionnaire- and lab-based measures. The results revealed that drug users performed poorly in autobiographical memory and verbal learning tests. They also displayed PM deficits, but only in the lab-based measure. On the contrary, they were unimpaired in various EFs measures which might be associated with light drug use. In the second study, seven drug users were interviewed on different components of PM (e.g., RM, attention) to understand how they manage to remember and execute delayed intentions in everyday life from their point of view to unfold the observed discrepancy between the questionnaire- and lab-based PM measures in the first study. It was evident that RM, cues availability at retrieval, time awareness, and attention play a crucial role in PM, thus impairments in such domains might be associated with poor PM performance in drug users. The study also uncovered the cognitive factors (i.e., metacognition and motivation) that explain the observed discrepancy. Together, those impairments may affect the cognitive performance of drug users in a general manner as well as the core aspect of drug abuse-the propensity to continue using drugs despite their increasingly detrimental effects.

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List of Abbreviations

5HT	5-hydroxytryptamine; Serotonin
ACC	Anterior Cingulate Cortex
AidPM	Use of Memory Aiding Strategies.
AM	Autobiographical Memory
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid
AMT	Autobiographical Memory Test
aPFC	Anterior Prefrontal Cortex
AVLT	Auditory Verbal Learning Task
BRIEF	Behavioural Rating Inventory of Executive Function
CB	Cannabinoid Receptors
CBD	Cannabidiol
CR	Correct Rejection
CVLT	California Verbal Learning Test
DA	Dopamine
DLPFC	Dorsolateral Prefrontal Cortex
dmPFC	Dorsomedial Prefrontal Cortex
DMPV	Dynamic Multiprocess Framework
DRM	Roediger and McDermott Paradigm
DS	Digit Span
EB	Event-based
EB PM	Event-based Prospective Memory
ECS	Endocannabinoid System
EFs	Executive Functions
ESK	Event-specific Knowledge
FA	False Alarm
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-aminobutyric Acid
GHB	Gamma Hydroxybutyrate

GHQ	General Health Questionnaire
Glu	Glutamate
LSD	Lysergic Acid Diethylamide
LT Epi	Long-term Episodic PM Failures,
LT PM	Long-term Prospective Memory
LTD	Long-term Depression
LTM	Long-term Memory
LTP	Long-term Potentiation
MDMA	3,4-Methylenedioxymethamphetamine
MWM	Morris Water Maze
NAc	Nucleus Accumbens
NMDA	N-methyl-D-aspartate
OFC	Orbitofrontal Cortex
PAM	Preparatory Attentional and Memory
PCC	Posterior Cingulate Cortex
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PMQ	Prospective Memory Questionnaire
PRMQ	Prospective and Retrospective Memory Questionnaire
PSQI	Pittsburgh Sleep Quality Index
RANCOVA	Quade's Rank Analysis of Covariance
RAPM	Raven's Advanced Progressive Matrices
RAVLT	Rey Auditory Verbal Learning Test
RPA-ProMem	Royal Prince Alfred Prospective Memory Test
RM	Retrospective Memory
RT	Reaction Time
SERT	Serotonin Transporter
ST Hab	Short-term Habitual PM Failures,
ST PM	Short-term Prospective Memory

STD	Short-term Depression
STM	Short-term Memory
STP	Short-term Potentiation
SUD	Substance Use Disorder
TA	Thematic Analysis
TB	Time-based
THC	Delta-9-tetrahydrocannabinol
TM PM	Event-based Prospective Memory
VFT	Verbal Fluency Test
VPA	Verbal Paired Associates
WCST	Wisconsin Card Sorting Task
WM	Working Memory

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Chapter 1- Introduction

1.1. Prevalence of drug use in the world and the United Kingdom

Recreational drugs are chemical substances used for enjoyment, rather than for medical reasons. Alcohol, tobacco and caffeine can be classed as recreational drugs, but this thesis only covers illegal recreational drugs (e.g., cocaine, cannabis).

Illegal recreational drug use remains popular regardless of its negative consequences. According to the World Drug Report 2021 by the United Nations Office on Drugs and Crime, 275 million people have used drugs at least once in the past year, up from 226 million in 2010 (22% increase). This corresponds to 5.5% of the worldwide population aged 15–64, representing nearly 1 in every 19 people. Of those, 36.3 million people are projected to engage in problematic use and suffer from drug use disorders, meaning that their pattern of drug use is detrimental, or they might experience drug dependence and/or require treatment (United Nations Office on Drugs and Crime, 2021). Globally, it is estimated that there were around 585,000 deaths attributed to drug use in 2017 (United Nations Office on Drugs and Crime, 2020). By 2030, the number of people using drugs is projected to increase by 11 per cent around the world and 40 per cent in Africa alone (United Nations Office on Drugs and Crime, 2021). Cannabis is the most commonly used drug in the world, followed by cocaine, MDMA, ketamine and amphetamine.

In line with the global figures, the most recent surveys covering Wales, Scotland and England reported the highest prevalence of drug use in the past 10 years. Roughly 3.2 million people aged 16 to 59 years have taken a drug in 2019. This corresponds to 9.4 per cent of the population aged 16 to 59, representing 1 in every 11 people (Public Health England, 2020). The Report further noted that drug use was much more common among younger adults, approximately one in five adults aged 16 to 24 years have used drugs at least once in 2019

(21 per cent; around 1.3 million people). The estimated cost of illegal drug use to society is around £20 billion in the United Kingdom (Black, 2020) and $193 billion in the United States per year when taking the criminal justice and health costs together (National Institute on Drug Abuse, 2020).

The brain regions and neural processes that are affected by drug use overlap extensively with those that support cognitive functioning. Therefore, it has been suggested that drug use leads to cognitive impairments (Gould, 2010). It is crucial to comprehend the neurobiology of cognitive functions in order to understand the consequences of recreational drug use on those functions. In the following, the neurobiology of various cognitive functions will be outlined. Then, the impact of widely used recreational substances on the brain will be presented. The chapter ends with an overview of the rest of the thesis.

1.2. Neurobiology of cognitive functions

1.2.1. Memory

Memory is one of the most crucial cognitive functions in a person's life. Without memory, it would be impossible to carry out essential tasks like communicating with others, learning, or developing a personality. Memory refers to the capability to encode, store and recall information (Alberini, 2011). In order to form a new memory, information must be altered into an appropriate form, which occurs through the encoding process (learning it, by perceiving it and associating it with the past knowledge). When information is correctly encoded, it must be stored in memory for later use (maintaining it over time). However, one is not aware of much of this stored information until he/she retrieves it (the process of getting information out of memory storage and bringing it back into conscious awareness). There are two major types of memory retrieval: recognition (the ability to recognise previously encountered events, objects, or people) and recall (the ability to remember something without any cues). Consolidation has also been thought to be a part of the memory system (Müller &

Pilzecker, 1900). Memory consolidation refers to the process by which recently learned experiences (or short-term memories) are transformed into more stable, long-lasting forms (or long-term memories), presumably by chemical and structural changes in the brain (e.g., the synaptic connections between neurons are strengthened; Dudai, 2004).

Some theorists (Atkinson & Shiffrin, 1968; Tripathy & Öğmen, 2018) propose that there are three main stores of memory: sensory memory, short-term memory (STM) and long-term memory (LTM). Those memory systems work independently as well as in parallel to support cognition and behaviours; thus it is hard to be definitive about their roles (Packard & Goodman, 2013; Squire & Dede, 2015). However, research over the previous two decades has revealed crucial details about the functions of these memory systems, which will be covered next.

All incoming information from the environment is processed in sensory memory which is defined as the capacity of keeping ongoing information in the mind for a few milliseconds. Three types of sensory memory are: iconic (visual information), echoic (auditory information) and haptic (memory of skin sensation; Radvansky, 2015). With sensory memory, one is able to remember an appearance of a pen after one-second observation. However, most information in sensory memory is unanalysed, thus it fades away in seconds unless one pays attention to it. If so, the information moves from sensory memory to STM where it can be held for seconds to minutes online (Revlin, 2012). STM differs from LTM in two ways; capacity, and duration. A capacity difference indicates that the number of items that can be stored in short-term storage is limited and a duration difference means that information in short-term storage decays as time passes (Cowan, 2008).

Short-term memory is expanded into a bigger concept called working memory (WM) which combines the ability to keep information for a very short period of time while allowing the controlling and planning of that information (Miller et al., 1960). Several models of WM

have been proposed, but the multi-component model has been the most widely accepted (Funahashi, 2017). Baddeley and Hitch (1973) first offered the three-component WM model. The model consists of an attentional control system, the 'central executive' that works like a traffic cop that coordinates the flow of information into or out of working memory, aided by two subsidiary slave systems, the 'visuospatial sketchpad' and 'phonological loop'. The visuospatial sketchpad is responsible for holding visual information that can be divided into different visual, spatial, and possibly kinaesthetic components; and the phonological loop is where verbal and acoustic information is held, using a temporary store and an articulator rehearsal system (Breedlove & Watson, 2013; Camina & Güell, 2017). Later, the episodic buffer has been added to the model where information from a variety of sources are stored. Thus, it provides a temporary interface between the slave systems and LTM. The episodic buffer is presumed to be controlled by the central executive which is in charge of combining information from different sources into coherent episodes. The buffer works as a modelling space that is independent from LTM, but forms a central phase in long-term episodic learning (Baddeley, 2000a). It should be noted that the visuospatial sketchpad and the phonological loop have their unique links to LTM without going through the buffer (see Figure 1).

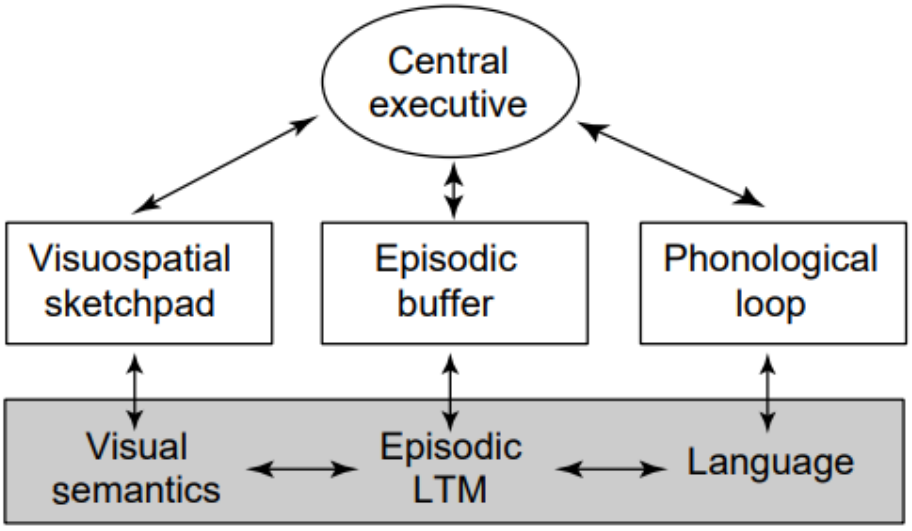

Figure 1: The current version of the multi-component working memory model (Baddeley, 2000a).

WM has often been associated with executive function, decision-making, intelligence, problem-solving, comprehension, and learning (Cowan, 2014). WM relies most heavily on the prefrontal cortex (PFC). More precisely, it has been established that Broca's and Wernicke's areas are responsible for verbal and acoustic information (Baddeley, 2000); the dorsolateral prefrontal cortex (DLPFC) has been mainly implicated in tasks demanding executive control such as information updating (Murty et al., 2011) and integration of information (Jimura et al., 2018); the anterior cingulate cortex (ACC) has been regarded as an "attention controller"(Osaka et al., 2003); and the parietal cortex (PAR) has been considered as the workspace for perceptual processing (Andersen & Cui, 2009). Furthermore, the occipital lobe has been associated with the visuospatial sketchpad (Chai et al., 2018) which is made up of two pathways; the dorsal stream which is thought to be involved with perceiving motion and spatial relationships between object, and the ventral stream which processes information involved with object form and recognition (Catani et al., 2003).

LTM, in contrast to STM/working memory, has an endless capacity to store information for extended periods. It can be broken down into two broad categories; declarative or explicit memory and non-declarative or implicit memory. Declarative memory is the memory of factual information, previous experiences and concepts that can be consciously recalled or declared to others (Camina & Güell, 2017). Declarative LTM is further separated into semantic and episodic memory. Episodic memory consists of personal memories of events and experiences, such as memories of the first holiday or a friend's birthday party. These memories usually include information regarding the event's time and location, as well as other details about the event itself (Dickerson & Eichenbaum, 2010). On the other hand, semantic memory refers to memories of general facts, concepts, knowledge and meaning about the external world (Baddeley et al., 2015). Things that are common

knowledge, such as the names of colours, the sounds of letters, the capitals of countries, and other basic facts gained over a lifetime, are included in semantic memory. With semantic memory, people are able to recall factual information (e.g., Germany is a country) without knowing exactly when and where they learnt this information. The combination of episodic and semantic memory produces autobiographical memory which refers to memory for one's personal events, such as remembering the name of the college you studied (semantic component) or the detail of the graduation ceremony, such as where and when it takes place (episodic component; Willoughby et al., 2012).

Non-declarative memory is another type of LTM that includes all unconscious memories, as well as certain skills or abilities (Squire & Dede, 2015). There are four types of non-declarative: procedural, associative, non-associative, and priming (Camina & Güell, 2017). For example, associative memory refers to the storage and retrieval of information through a relationship with other information. The formation of associative memory is mediated by two types of conditioning: classical and operant conditioning. Classical conditioning is a form of associative learning between stimuli and behaviour. Meanwhile, operant conditioning is a learning process whereby new behaviours develop in terms of their consequences (e.g., rewards and punishments; Camina & Güell, 2017).

Synaptic plasticity is thought to be a foundation for memory which refers to the capacity of the brain to modify itself structurally and functionally via long-term potentiation (LTP) and long-term depression (LTD), in response to intrinsic or extrinsic stimuli (von Bernhardi et al., 2017) which last from hours to months (Abraham, 2003). The LTP is a process by which synaptic connections between neurons are strengthened with frequent activation (Langille & Brown, 2018). The LTD is also important for synaptic plasticity as neural circuits that contain memories are established by strengthening some synapses and weakening others. If synapses consistently grew and made new connections as a result of

LTP, they somehow would reach their maximum efficacy and stop encoding new information. Therefore, specific sets of synapses must be selectively weakened by a low-frequency stimulation (Purves et al., 2001b). There are numerous mechanisms, not entirely understood, behind the synaptic plasticity seen with LTP and LTD. One well-known mechanism involves the neurotransmitter glutamate and its receptors. It is believed that LTP and LTD can be expressed either presynaptically, as changes in glutamate release possibility, or postsynaptically, as changes in glutamate receptor number (Padamsey & Emptage, 2014). Synaptic strength within neuronal circuits can also be modified via short-term facilitation or potentiation (STP) and short-term depression (STD; Tecuapetla et al., 2007). They both, in contrast to LTP and LTD, last on the order of milliseconds to a few minutes.

There is collective agreement among researchers that the hippocampus and surrounding structures are crucially involved in memory (e.g., the memory consolidation, and the formation of new memories via synaptic plasticity; Eichenbaum et al., 2007; Lüscher & Malenka, 2012; Shors & Matzel, 1997; Vargha-Khadem et al., 1997), along with several brain areas including the PFC which plays a role in both encoding and retrieving memories (Allen & Fortin, 2013; Brand & Markowitsch, 2008) and the amygdala where personal memories are given an emotional flavour and learning on the basis of punishment and reward occurs (Sergerie et al., 2008; Staniloiu & Markowitsch, 2020). The findings from a wide range of studies shows that episodic and semantic memory depend critically on the hippocampus. For example, it has been found that patients with dense amnesia as a result of hippocampal damage are unable to make new memories (Duff et al., 2020).

1.2.2. Executive functions

Executive functions (EFs; collectively referred to as executive control or cognitive control) is another domain in cognitive functioning which are a set of mental skills that are needed to organise, activate, integrate and manage other mental functions and behaviour,

therefore seen as the CEO of the brain. The EFs play an important role in a person's ability to perform everyday tasks, such as organising, planning, prioritising, paying attention and remembering details, and governing emotional responses (Ferguson et al., 2021). It has widely been accepted that there are three core EFs (Lehto et al., 2003): WM, cognitive flexibility and inhibition. In general, they cooperate to accomplish goals, for example, WM aids inhibitory regulation because it requires awareness of the goal to determine what is pertinent or acceptable to suppress (Diamond, 2013). As mentioned, WM is responsible for the active maintenance and management of information over a very short period of time (McCabe et al., 2010). Cognitive inhibition (also called inhibitory control, including interference control and self-control) refers to the ability to control thoughts, behaviour, attention, and/or emotions to override a strong inner tendency or external lure, and instead perform what is more appropriate (or use this the ability to tune out stimuli that are irrelevant to the mind's current state or the process/task at hand (Diamond, 2013). There are two types of inhibition: (1) response inhibition (also known as behavioural inhibition or motor inhibition) which is the suppression of inappropriate motor responses or actions that are no longer adaptive to the situation (Aron et al., 2014); and (2) attentional inhibition (also known as interference control or interference suppression) which is the resistance to interference from stimuli in the external environment (Nigg, 2017). Cognitive flexibility is another component of EFs which is defined as the brain's ability to switch from thinking about one concept to another (Gonzalez et al., 2013). With cognitive flexibility, one is able to adapt his or her thinking and behaviour in response to the environment that constantly changes (Cools, 2015).

The PFC is the brain region most frequently associated with EFs (Cristofori et al., 2019). Most evidence for the anatomical association between EF and PFC comes from studying individuals with a brain injury. The injuries in the dorsolateral PFC (DLPFC) and

orbitofrontal cortex (OFC) are associated with EF deficits (Barbey et al., 2012). Individuals with lesions to the OFC and the ACC show impairments in social and motivated behaviours. Damage to the DLPFC can lead to higher-order cognitive impairments involving cognitive control (Larson et al., 2006), inhibition (Picton et al., 2007), and WM (Barbey et al., 2013). However, non-frontal brain regions are also found to be linked with EFs (Champod and Petrides, 2007). For example, the limbic region of the medial temporal lobe (e.g., amygdala, hippocampus) is strongly linked with the PFC and these connections are very important for emotional response regulation and mnemonic interactions (Barbas and Zikopoulos, 2007). Moreover, the basal ganglia has been thought to mediate inhibitory executive functioning (Aron et al., 2016; Wiecki & Frank, 2013). These findings suggest that both frontal and non-frontal brain areas are crucial for intact executive functions.

1.3. The neurobiology of recreational drugs

Neurotransmitters are chemical messengers in the nervous system that enable neurons to communicate with each other. The brain needs neurotransmitters to regulate many necessary functions, including breathing, heart rate, digestion, sleep cycles, appetite, muscle movement, mood, memory, learning, concentration, and many other functions (Sheffler et al., 2022). However, recreational drugs can alter the natural circulation of those neurotransmitters, resulting in changes in mood, consciousness, perception, cognition, or behaviour. In this section, the widely used recreational substances and their effects on the brain and cognitive functions will be discussed. It should be noted that there is limited evidence on the effects of drugs on cognitive processes, using neurochemical and neuroimaging techniques.

There are three main groups of recreational drugs; stimulants that increase neurotransmission levels (e.g., caffeine, ecstasy, cocaine); depressants that decrease neurotransmission levels (e.g., cannabis, heroin); and hallucinogens that distort perceptions of

reality, resulting in perceptual abnormalities (e.g., LSD, ketamine). Due to the nature of this project, only illegal recreational drugs are covered.

A drug produces its physiologic effects by binding to a receptor. A drug's ability to influence a given receptor depends on the drug's affinity (the ability to bind to a receptor) and the drug's efficacy (the capacity to produce an effect). Although the drug's affinity and efficacy are determined by the drug's chemical structures, they can be modulated by other factors, such as other drugs use, disorders, genetic mutations, and ageing (McCuistion et al., 2017). Drugs act in two ways; agonistic (full and partial) and antagonistic (competitive and non-competitive). An agonist drug mimics or enhances the message carried via the neurotransmitters by binding to a receptor and causing a biological response, whereas an antagonist drug blocks the effects of a neurotransmitter by binding a receptor and preventing its activation (Holloway & Peirce, 1998).

1.3.1. Marijuana

Marijuana ($C_{21}H_{30}O_2$) is the most widely used illegal drug and is derived from the Cannabis Savita plant. This plant's parts are used in preparing different drugs. Marijuana (also known as cannabis) is made from leaves, stems and seeds; whereas, hashish mainly is made from flower tops. Marijuana is commonly smoked, resulting in the activation of hundreds of compounds in the bloodstream, however, the delta-9-tetrahydrocannabinol (THC) is the main psychoactive ingredient of marijuana (Abood & Martin, 1992). This compound activates cannabinoid receptors (CB) that are a part of the endocannabinoid system (ECS), along with the endocannabinoids (e.g., anandamide and 2-arachidonoylglyerol) and enzymes. The stimulation of these receptors with THC in the body and the brain causes a variety of behavioural effects, for instance, decreased motor activity, memory impairment, analgesia, hypothermia, distortions in time perception, vision and hearing (Schweinsburg et al., 2008) as well as euphoria, increased sex desire and appetite

(Karila et al., 2014). The cannabinoid receptors, members of G protein-coupled receptor family, have at least two subtypes; CB1 that is found in the nervous system, including cerebellum, hippocampus, substantia nigra, cerebral cortex and basal ganglia (Herkenham, 1992); and CB2 that is found in the immune system and has anti-inflammatory functions (Cabral & Griffin-Thomas, 2009; Turcotte et al., 2016).

As discussed earlier (see 1.2.1 Section), synaptic plasticity mechanisms (e.g., LTP, LTD, STP and STD), mediated by the release of glutamate neurotransmitter (Padamsey & Emptage, 2014), are thought to be a foundation for memory (Abraham, 2003). Those processes can be divided into subgroups based on their induction and expression as well as the synaptic locus of the key alteration that underlies the change in efficacy (Gerdeman & Lovinger, 2003). While some forms of synaptic plasticity are initiated and sustained by only presynaptic or postsynaptic mechanisms, others by retrograde messengers that are released from postsynaptic neurons and then act on the presynaptic neuron to modulate the presynaptic neurotransmitter release system (Alger, 2002; Kemp & Bashir, 2001; Kourosh-Arami et al., 2021). It is now well-established endocannabinoids act as retrograde messengers in the brain (Alger, 2012; Kano et al., 2009; Katona and Freund, 2012). When released from postsynaptic neurons, they activate presynaptic cannabinoid CB1 receptors which, in turn, lead to a transient and long-lasting reduction of neurotransmitter release at both inhibitory and excitatory synapses in a short-term and long-term manner in several brain structures, including the hippocampus, prefrontal cortex and amygdala (Chevaleyre et al., 2007; Heifets & Castillo, 2009; Kano et al., 2009; Piette et al., 2020; for review see Chevaleyre et al., 2006). The neurotransmitters reported to be mediated by the CB1 receptor include glutamate (Lévénés et al., 1998), GABA (Szabo et al., 1998), and dopamine (Cadogan et al., 1997).

Numerous studies have attempted to explain the molecular processes behind this mechanism by using electrophysiological and biochemical techniques. For example, Heifets

and Castillo (2009) found that, in the hippocampus, cannabinoids mobilise from the postsynaptic neuron to suppress neurotransmitter release from presynaptic neurons by constant action potential firing or strong depolarization, through a poorly comprehended system that depends on increased intracellular calcium ion concentration (Heifets & Castillo, 2009). This process is also known as "depolarisation-induced suppression of inhibition (DSI)" which particularly relates to the inhibition of GABA release from presynaptic interneurons. There is also a mechanism that suppresses excitation, called "depolarization-induced suppression of excitation (DSE)" which particularly relates to the inhibition of glutamate release from excitatory neurons. Both DSI and DSE have been thought to mediate short- and long-term synaptic plasticity (Lafourcade, 2009). For example, long-term changes in synaptic strength due to DSI and DSE have been associated with associative memory formation in the amygdala and hippocampus (Martin et al., 2000). Furthremore, Marsicano et al. (2002) found that the ECS has a central function in extinction of aversive memories as CB1-deficient mice exhibited strongly impaired short- and long-term extinction in auditory fear-conditioning trials, with intact memory acquisition and consolidation. In another study, the role of the ECS in working memory was assessed by comparing wild-type mice to CB1 receptor knockout mice in several Morris water maze (MWM) tasks in which animals are required to search for a hidden platform to escape the maze when the location of the hidden platform is changed throughout the task. Despite being repeatedly shown the new platform location, CB1 receptor knockout mice continued to return to the original platform location, exhibiting significant deficits in a reversal task (Varvel & Lichtman, 2002). Together, the evidence summarised above shows marijuana exerts its effects through the activation of the ECS which is a major signalling system in learning and memory (Marsicano and Lafenêtre, 2009; Mechoulam and Parker, 2013; Kruk-Slomka et al., 2017). Hence, recreational cannabis use might impair those cognitive processes.

1.3.2. Cocaine

Cocaine ($C_{17}H_{21}NO_4$) is a stimulant drug that is found in the leaves of the Erythrozylon coca plant. Cocaine comes in different forms, for example, powdered cocaine which is ingested by snorting and crack cocaine which is consumed by smoking or directly injecting into the bloodstream. Cocaine exerts its effects by blocking or slowing down the monoamine transporters (e.g., DAT, SERT, and NET), in particular those for DA. In doing so, cocaine increases levels of DA as well as 5HT, and NE in the brain (Woolverton and Johnson, 1992). Upon consumption, cocaine produces mental alertness, intense happiness, extreme energy, hypersensitivity to sound, touch and sight. Cocaine extensively diffuses throughout the brain when taken, but its main target appears to be the limbic system (Kalivas & McFarland, 2003). The dopamine-rich Nucleus Accumbens part (NAc; the major component of the ventral striatum) of the limbic system seems to be the most related to the cocaine high. Increases in DA secondary to phasic DA neuron firing play a key role in encoding reward, saliency and motivation in this part of the brain (Di Chiara, & Imperato, 1988; Schultz et al., 1997; Sarno et al., 2022). Therefore, it plays a crucial role in reinforcement learning (Grogan et al., 2017; Saunders et al., 2018). In the short-term, cocaine use increases DA neuron activities that create artificial reinforcement learning signals that are of greater duration and magnitude compared to what is observed in response to natural events (Volkow et al., 2004; 2010). Whereas, in the long-term, it has been found to lead to a decrease in DA neuron activities (e.g., decreases in DA release and in DA D2 receptors in the striatum; Volkow et al., 1997). The decreases in DA release in the striatum have been associated with the decreased sensitivity to 'natural' reinforces (e.g. food, sex) and motivational salience for nondrug-related environmental stimuli in drug abusers (Garavan et al., 2000; Volkow et al., 2004)- perhaps due to repeated drug use that raise the thresholds required for dopamine neuron activation and signalling (Volkow et al., 2009).

Furthermore, a growing body of evidence suggests that DA is one of the most important neurotransmitters that regulates neuron activity involved in WM (Goldman-Rakic, 1995; Klaus & Pennington, 2019; Meyer-Lindenberg et al., 2005). Evidence for this claim comes from numerous sources, including studies on patients with Parkinson's disease which is characterised by a gradual loss of dopaminergic neurons and a functional impairment in the dopaminergic system. For example, a study found that dopaminergic system dysfunction in early PD was related to WM impairments (Brück et al., 2005). Moreover, Landau et al. (2009) used the Positron Emission Tomography (PET) tracer 6-[18F]fluoro-L-m-tyrosine to measure dopamine synthesis capacity in the striatum (putamen, caudate) during different phases of a WM task in healthy older participants. The results revealed that there was a positive correlation between caudate dopamine synthesis and WM capacity. In monkeys, disruption of dopaminergic transmission by focal D1 antagonist application in dorsolateral PFC impairs spatial working memory (Sawaguchi & Goldman-Rakic, 1991).

Moreover, DA neurons display increases of firing in response to salient stimuli in certain parts of the brain, such as the hippocampus and ventral tegmental area (VTA; Kamiński et al., 2018) which are associated with the encoding of new, episodic-like information into long-term declarative memory. Otmakhova and Lisman (1996) showed that D1/D5 dopamine receptor activation increases the magnitude of early LTP at CA1 hippocampal synapses by enhancing glutamatergic transmission which, in turn, facilitates the encoding of new information in LTM (Otmakhova & Lisman, 1996). A wide range of studies supports this hypothesis. For instance, Li et al. (2003) found that the level of DA rises when animals were exposed to new environments. However, this improved memory for novel environments was lost when hippocampal dopamine receptors were blocked. In summary, cocaine has a significant impact on monoamines, specifically DA which plays a key role in

reinforcement learning, working memory and the formation of new memories, thus its abuse can result in deficits in those domains.

1.3.3. MDMA

MDMA (3,4-Methylenedioxymethamphetamine; $C_{11}H_{15}NO_2$) is a synthetic stimulant drug that is a derivative of amphetamine. MDMA commonly comes in crystallised or tablet form. The powder form, referred to by its chemical name, MDMA, mostly contains pure MDMA, whereas the tablet form, also known as ecstasy or Molly is usually mixed with various other substances. The effects of MDMA on the different neurotransmitters and receptors are not fully understood (Liechti et al., 2000). However, it has been argued that MDMA exerts its effects by binding to the monoamine transporters, in particular, those for 5HT to block their reuptake as well as stimulate their release by getting into the axon terminal and interacting with the vesicle as MDMA has a greater affinity for the monoamine transporters than 5HT (Gudelsky & Yamamoto, 2008). Consequently, MDMA increases levels of 5HT (mostly), DA and NE (Kalant, 2001). MDMA also triggers the release of the hormones oxytocin and vasopressin, which are associated with trust, love, sexual arousal and other social experiences (Wolff et al., 2006).

The particular serotonergic contribution to memory and learning was first confirmed by Eric Kandel in the 1970 s. He found that 5-HT significantly contributed to memory formation by increasing the level of cyclic adenosine monophosphate (cAMP) in the sensory neurons of Aplysia (Cedar and Schwartz, 1972) which, in turn, triggers the cAMP-dependent protein kinase that facilitates synaptic transmission in terms of sensitisation (Brunelli et al., 1976). After repetitive stimulations, this causes protein synthesis-dependent LTP of synaptic strength (Schacher et al., 1988). For example, lowering 5 HT globally by using acute tryptophan depletion (ATD; which prevents 5-HT production in brainstem neurons and results in a short-term and reversible reduction of cerebral 5-HT; Van Donkelaar et al., 2011)

leads to memory impairments. For instance, Borghans et al. (2017) assessed seventeen participants, who received ATD or a placebo, on a verbal learning task. The results revealed decreased scores for the immediate recall as well as for the delayed recall after ATD. This study supports evidence from previous observations (Amin et al., 2006, McAllister-Williams et al., 2002, Riedel et al., 1999, Sambeth et al., 2009). While lowering 5 HT globally impairs memory, the increased level of 5HT by SSRIs has been associated with enhanced memory (Harmer et al., 2002). Data from several studies suggest that MDMA use leads to long-lasting reductions in neocortical serotonin signalling (Benningfield & Cowan, 2013; Biezonski & Meyer, 2011). For instance, a meta-analysis by Roberts et al. (2016b) revealed that MDM/ecstasy users displayed significant SERT reductions in 11 out of the 14 regions in the brain, including every neocortical (in particular in the occipital cortex) and limbic region. Those findings are in line with a previous review (Camarasa et al., 2012). Similar findings were obtained in preclinical studies. For instance, male Sprague-Dawley rats were treated with saline or MDMA (15 mg/kg × 4 doses in one day) and examined on different learning paradigms, including the MWM one week after MDMA administration. MDMA-treated rats performed worse than SAL-treated rats in the MWM reversal learning task (Able et al., 2006). In summary, MDMA interacts with numerous neurotransmitter systems particularly 5-HT which has an important role in various cognitive functions, therefore, its abuse can lead to impairments in those cognitive processes.

1.3.4. Amphetamines

Amphetamines are a group of man-made stimulant drugs that can be classified into three categories; amphetamine ($C_9H_{13}N$; e.g., speed), methamphetamine ($C_{10}H_{15}N$: e.g., crystal meth), and dextroamphetamine (C_9NH_{13}). Crystal meth (also known as Tina, glass, or ice) and speed are the most popular amphetamines. Amphetamines act like cocaine and MDMA as they also block the re-uptake process of DA (mostly), NE and 5HT (Sitte &

Freissmuth, 2015) by binding to DAT, SERT and NET; and produce similar effects, but last much longer (six to eight hours). Furthermore, they stimulate the release of DA, 5HT and NE from presynaptic terminals by interacting with intracellular compounds, in resulting high levels of these neurotransmitters at synapses (Ferrucci et al., 2019). It has been demonstrated that augmented levels of monoamines, in particular DA and NE due to amphetamine intakes at the synaptic terminal, are responsible for euphoria, reduced fatigue, mood improvements, increased libido and the general sense of wellbeing (De Wit et al., 2002; Heal et al., 2013; Pester et al., 2018).

In rodents, methamphetamine reduces numerous indices of DA terminal integrity, especially in the striatum (O'Dell et al., 1993; Camarasa et al., 2010). The striatal alterations produced by prolonged exposure of rats to methamphetamine include decreases in dopamine content (Kogan et al., 1976), dopamine metabolites (Ricaurte et al., 1982) and loss of dopamine transporters (Escubedo et al., 1998). In addition to DA, methamphetamine is also toxic to 5-HT-containing neurons (Ricaurte et al., 1982). The mechanism of methamphetamine damage to 5-HT neurons is still not completely understood, but it has been suggested that the release of DA is an intermediate step in the cause of 5-HT degeneration (Sonsalla et al., 1986), thus blocking DA synthesis inhibits 5-HT degeneration (Schmidt et al., 1985).

Schröder et al. (2003) investigated the effects of a neurotoxic regimen of methamphetamine on hippocampus-dependent memory tasks including object recognition as well as on the brain. Male rats were administered with methamphetamine (4 x 4.0 mg/kg) or saline and taught the object recognition task one week and three weeks later. During training, rats explored two same copies of the identical object. In the retention test phases, one of these objects was switched by a novel object. The results revealed that drug-treated rats failed to discriminate between the familiar objects and novel during both STM (one week after drug

injections) the and LTM test (three weeks after drug injections). They also found that methamphetamine significantly damaged DA terminals in the striatum and 5-HT terminals in the hippocampus (30 – 40% losses of binding) at both one and three weeks after the drug injections (Schröder et al., 2003). In another study, rats treated with methamphetamine displayed impaired learning in MWM at 72 hrs and 1 week after treatment. However, this memory impairment was prevented by administering memantine (the substance that is used for preventing amphetamine-induced neurotoxicity in the brain; Camarasa et al., 2010). Studies with human subjects found similar findings. For example, Volkow et al. (2001) demonstrated that compared to the comparison subjects, methamphetamine abusers showed significant dopamine transporter reduction in the striatum (mean differences of 21.1% in the putamen and 27.8% in the caudate). Another study investigated the pattern of structural brain changes associated with amphetamine abuse and cognitive impairments that related to those changes, using magnetic resonance imaging (MRI) and new computational brain-mapping techniques. They found that amphetamine abusers had 7.8% smaller hippocampal volumes than healthy non-user controls. Memory performance on a word-recall test was mapped and correlated with the observed hippocampal impairments (Thompson et al., 2004). In summary, methamphetamine can be toxic to a wide range of neurotransmitter systems, including DA and 5-HT that can lead to various cognitive impairments when abused.

1.3.5. GHB

GHB or Gamma Hydroxybutyrate ($C_4H_8O_3$) is a natural compound of the human brain and acts as a neurotransmitter and neuromodulator (Mamelak, 1989). It is also a medicinal product and synthetic drug. GHB is in liquid form (commonly known as 'liquid ecstasy') and consumed as a shot with a mixture of non-alcoholic drinks. GHB is produced easily from its precursors; 1,4-Butanediol and gamma-butyrolactone which can be found in super glue removers, nail polish and floor cleaning products. These precursors are naturally

converted into GHB when ingested, exerting the same effects as GHB (Schep et al., 2012). GHB interacts with two major receptors in the brain (Cash et al., 1999); the GHB (excitatory) that is most numerous in the hippocampus and cortex (Carter et al., 2009; Hechler et al., 1992; Andriamampandry et al., 2007); and GABAB receptors (inhibitory) as GHB's chemical structure is very similar to GABA ($C_4H_9NO_2$). GHB acts as an agonist at both receptors with high and low affinity respectively (van Noorden et al., 2016). Following binding to these receptors, GHB prevents glutamatergic neurotransmission in hippocampal (Berton et al., 1999) and neocortical neurons (Li et al., 2007) which has been closely linked to synaptic plasticity (Padamsey & Emptage, 2014) as discussed earlier (see in 1.2.1 Section). GHB also alters various neurotransmitter systems, particularly 5HT, NE, DA and Ach. Although previous studies have produced inconsistent findings, the data suggest that GHB has significant effects on the dopaminergic system (van Noorden et al., 2016). It has been found that GHB initially inhibits the release of DA at the synapse, but increases the neuronal production of DA. This is followed by either a dose-dependent stimulation of DA release (high doses stimulate, low doses inhibit) or time-dependent (the release of DA increases with time; Hechler et al., 1991). Furthermore, though the neuropharmacological sequelae are unclear, there is evidence that GHB induces changes in glutamate (Ferraro et al., 2001) and acetylcholine levels (Nava et al., 2001; Schep et al., 2012) in the hippocampus, thereby affecting memory. Indeed, several studies demonstrated that GHB administration leads to learning and memory impairment (Kueh et al., 2008; Pedraza et al., 2009; Sircar and Basak, 2004). For example, the effect of repeated administration of GHB (10 mg/kg) was examined on various parameters: neurological damage, WM, and spatial memory, using neurological tests, the hole-board and the Morris water maze test. The results revealed that the administration of GHB for 15 days produces neurological impairment and neuronal damage in the hippocampal CA1 and the prefrontal cortex (PFC) region of male rats. It was suggested

that neuronal death found in these regions may partially explain the observed spatial and WM problems after 15 days of GHB administration (Pedraza et al., 2009). A study by van Nieuwenhuijzen et al. (2010) suggests long-lasting impairment (at least 8 weeks) in object recognition memory in rats after administration of the drug.

Although GHB is classified as a depressant, its behavioural effects are biphasic (physically stimulating or sedating). At low doses, it may produce feelings of euphoria, lowered inhibitions, increased self-confidence, high libido, memory lapses, general disorientation, dizziness, vomiting and muscle spasms; and at high doses, it can induce extensive muscle relaxation, confusion, disorientation, vomiting, sleepiness, dizziness, loss of balance, impaired learning and memory (Carter et al., 2009). A GHB overdose can result in irritation, agitation, unconsciousness (temporary coma), shallow breathing confusion, vomiting, hallucinations, memory loss and death (Carter et al., 2009).

1.3.6. Ketamine

Ketamine ($C_{13}H_{17}C_{l2}NO$) can also be classified as a hallucinogenic which is commonly used by veterinarians and medical practitioners as an anaesthetic. It is also used recreationally to get 'high'. Ketamine, which comes in liquid and powder forms, exerts its analgesic, psychotomimetic, amnestic and schizophrenic effects mostly by interacting with Glu. It is a non-competitive antagonist at N-methyl-D-aspartate (NMDA) Glu receptors (Morgan et al., 2012) which are essential mediators of synaptic transmission and plasticity (Paoletti et al., 2013). Morris et al. (1986) found that NMDA-receptor antagonists interrupt hippocampal LTP. It is well established that NMDA-receptor-mediated LTP is involved in both long-term memory and WM in humans (Lisman et al, 1998), thus ketamine has been associated with impairments in those domains. For instance, Morgan et al. (2004) run a double-blind, placebo-controlled, independent groups design study with 54 healthy participants to test the effects of infusions of two doses (0.4, 0.8 mg/kg) of ketamine on

memory systems. They found that ketamine produced a dose-dependent deficit to WM and episodic as well as slowed down semantic processing. It also reduced procedural learning and recognition memory. A number of existing studies have also shown that the administration of ketamine impairs episodic (Hetem et al. 2000; Honey et al. 2005; Malhotra et al., 1996) and working memory (Adler et al., 1998; Krystal et al., 1994, 1998, 2000; Ma et al., 2015; Roussy et al., 2021; Wang et al., 2013).

Ketamine also has less prominent actions at other receptor sites, for example, it acts as an antagonist at muscarinic and nicotinic acetylcholine receptors as well as it may facilitate GABA inhibition (Orhurhu et al., 2022). Moreover, ketamine may increase neurotransmitters such as NE, DA and 5HT in the brain (Pham & Gardier, 2019; Rabiner, 2007). Similar to GHB, it has dose-dependent effects; at low doses, it has euphoric and dissociative effects (feeling detached from reality), whereas at high doses, it has the hallucinogenic (feel, see, smell, taste or hear things that are not there or are different from how they are in reality) and immobilising effects (Morgan et al., 2012; Orhurhu et al., 2022).

1.3.7. LSD

Lysergic acid diethylamide (LSD) is a semisynthetic hallucinogenic substance derived from lysergic acid which is found in ergots (fungal parasite of the seed heads of cereal grasses). It is a clear odourless, water-soluble material and comes in tablets, capsules, liquid and blotting paper forms. The effects of LSD are largely achieved through its predominantly agonistic activity at serotonin receptors, in particular, 5-HT2A receptors (Halberstadt, 2015; Passie et al., 2008) as its chemical structure ($C_{20}H_{25}N_3O$) is very similar to 5HT ($C_{10}H_{12}N_2O$). Due to this similarity, they bond with each other very strongly which explains LSD's long-lasting effects, between 6 to 10 hours (Wacker et al., 2017). The activation of 5-HT2A receptors is associated with increased cortical glutamate levels seemingly by a presynaptic receptor-mediated release from thalamic afferents (Nichols, 2004) and increased effective

connectivity from the thalamus to cortical areas (Preller et al., 2019). A study assessed the acute effects of LSD (100 µg) on cognition, using a double-blind, randomised, placebo-controlled, within-subject design in 25 healthy subjects. To understand the specific role of LSD, subsequently the role of the 5-HT2A receptor in cognition, they blocked this receptor subtype via the pre-treatment of LSD with the 5-HT2A receptor antagonist ketanserin (40 mg). All participants underwent the following conditions: placebo + placebo, placebo + LSD, and ketanserin + LSD. The results revealed that LSD significantly impaired cognitive flexibility, and working memory, compared to controls. The results further showed that all LSD-induced cognitive deficits were disappeared with the 5-HT2A antagonist ketanserin pre-treatment. Those findings highlight the effects of LSD via the 5-HT2A receptor system on executive functions (Pokorny et al., 2020). Similarly, object recognition and recall were affected after LSD administration (100 micrograms) (Jarvik et al., 1955).

LSD also has less pronounced agonistic activity at dopamine D2 and D1 receptors (Preller et al., 2018). Its administration produces visual hallucinations and other characteristic alterations in mood, thought, perception, and the sense of self (Barrett et al., 2018; Nichols, 2004). While many users may experience positive outcomes, some report possible adverse reactions including paranoia, depersonalization, panic, anxiety, ego dissolution as well as somatic symptoms such as heart palpitations and dizziness (Carbonaro et al., 2016). These negative symptoms are normally referred to as a bad trip. Using structural equation modelling, Barrett et al. (2016) identified a profile of bad trips involving of seven components: paranoia, death, fear, grief, isolation, insanity, and physical distress. When the drug wear off, the stressful effects of a bad trip usually ease; however, it can continue for weeks or months in some users (Passie et al., 2008). These long-term side effects are known by the clinical terms “Hallucinogen Persisting Perception Disorder” and “Persistent Psychosis” (National Institute on Drug Abuse, 2015).

1.3.8. Psilocybin

Psilocybin ($C_{12}H_{17}N_2O_4P$) is another hallucinogenic drug that is extracted from certain types of mushrooms (also known as magic mushrooms). Psilocybin can either be fresh or dried and consumed raw, mixed with food, or brewed into a tea, and produces similar effects to LSD. New research by Petri et al. (2014) suggests that psilocybin temporarily alters the brain's entire organisational framework by increasing communication between different regions of the brain, including previously disconnected regions (see Figure 2), resulting in things like hearing colours and seeing sounds, which is known as the phenomenon of synaesthesia (Petri et al., 2014).

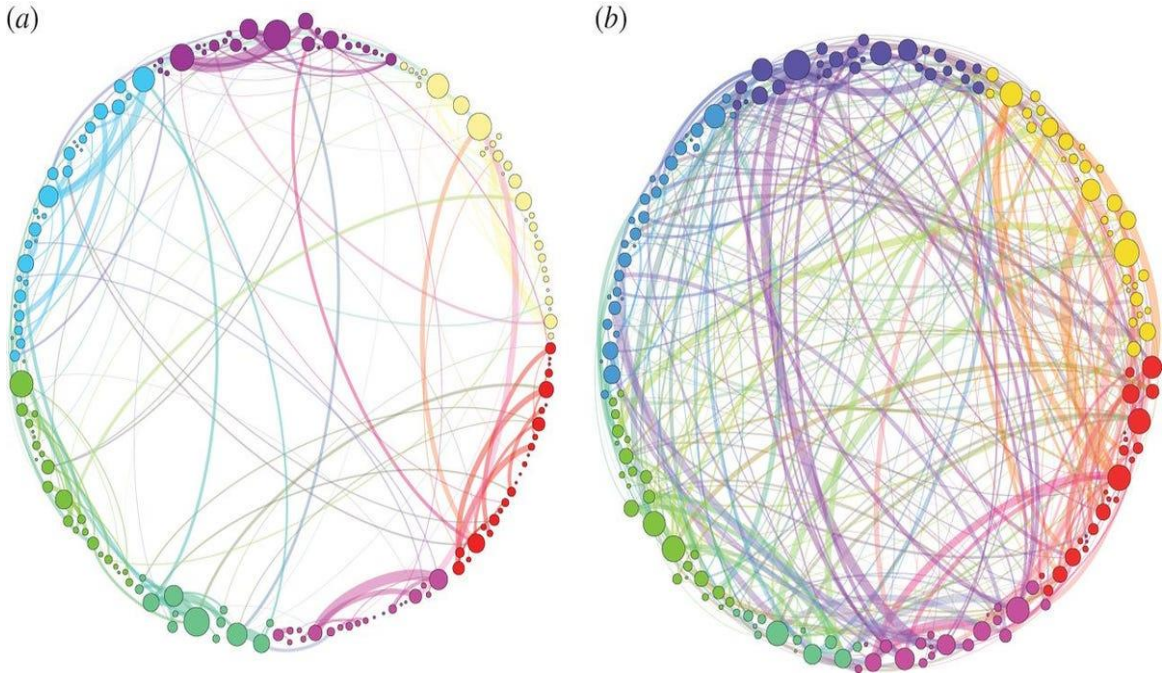

Figure 2: Visualisation of the brain connections in a person on a placebo (a) and in someone given psilocybin (b) (Petri et al., 2014).

Similar to LSD, psilocybin exerts its effects by its partial agonist action at 5-HT2A receptors (Nichols, 2016), which is thought to influence glutamatergic signalling in a variety of cortical and subcortical afferents (Scruggs et al., 2003). A double-blind, placebo controlled within-subject design study compared the neuropsychological effects of multiple doses of psilocybin (10, 20, and 30 mg/70 kg) in 20 hallucinogen users. Orderly, dose-dependent

negative effects of psilocybin were found on various cognitive functions, including WM, episodic memory, and associative learning (Barrett et al., 2018). The highest dose produced the worst performance on those domains.

1.4. Overview of the thesis

In this section, overview of the rest of the thesis will be presented. Chapter 2 provides a literature review on the effects of recreational drugs on retrospective memory and executive functions with behavioural and neurobiological measures. In this Chapter, methodological issues in the previous studies are identified and future directions are given to deal with those issues.

Chapter 3 focuses on prospective memory, which involves both retrospective memory and executive functioning. It presents a systematic review of 27 on the effects of recreational drugs on prospective memory. Similar to Chapter 2, methodological issues in the reviewed studies are identified. Future recommendations are then suggested to address those issues.

Chapters 4, 5, 6 and 7 are the empirical chapters of this thesis. Chapter 4 assesses performance of recreational polydrug users and drug naïve controls on questionnaire-based and lab-based prospective memory measures while addressing methodological challenges facing previous studies. The performance of polydrug users and drug naïve controls was assessed on executive functions in Chapter 5 and on retrospective memory in Chapter 6, using various lab-based tests. These three studies were parts of one big study, but presented as three individual studies.

The result from Chapter 3 and 4 revealed that there is a discrepancy between questionnaire-based and lab-based PM measures in drug users. In chapter 7, an attempt is made to understand this discrepancy by using a detailed qualitative interview approach

assessing the different components of PM (short-term memory, long-term memory, attention, cognitive shifting).

The final chapter, Chapter 8, discusses the overall findings, integrating the results of the quantitative and qualitative studies. It aims to present a new perspective on how to understand the impact of recreational drugs on cognitive functions and their implications. The challenges in the current literature are also discussed.

Chapter 2: The Effects of Recreational Drugs on Retrospective Memory and Executive Functions: A Review

As described in the previous chapter, recreational drugs influence the brain regions and neural processes that support various cognitive functions. Previous research have provided important information on the biological and psychological consequences of illegal recreational drug use on those functions. While Chapter 2 will review studies on retrospective memory and executive functions, Chapter 3 will review studies only on prospective memory. In this chapter, the relevant literature will be examined under three subsections: retrospective memory, executive functions and neuroimaging and neurochemical studies. In the final section of this chapter, the overall methodological issues will be summarised.

2.1. Retrospective Memory

Memory can be classified under two broad concepts: retrospective and prospective memory. Retrospective memory involves memory of events, people or experimental stimuli that were experienced in the past, such as remembering the detail of a friend's birthday party or recalling a list of words presented in an experiment. Whereas, prospective memory involves remembering to carry out a planned action or recall a planned intention at some future point in time. It should be noted that the distinction between retrospective and prospective memory is not clear-cut as prospective memory essentially contains some elements of retrospective memory which will be reviewed separately in Chapter 3. Despite the shared elements between the two kinds of memory, there are various distinguishing features, for example, while in prospective memory the process of remembering is initiated by the participant, in retrospective memory the investigator initiates this process. In this

section, studies with drug users, employing retrospective memory measures will be reviewed. Retrospective memory is declarative memory and includes semantic and episodic memory. Retrospective memory is usually evaluated by learning, retention, and retrieval (Adan et al., 2016) where participants encoding the given information (learning phase), storing it (retention phase) and then retrieving it (retrieval phase)There are various ways to assess retrospective memory, such as through verbal learning (e.g., Delis et al., 2017), source memory(e.g., Johnson et al., 1993) and false memory tests (e.g., Roediger & McDermott, 1995) in which participants are asked to learn a list of words (learning phase) to recall those words in the testing phase after a break. Additionally, retrospective memory can be measured via autobiographical memory tests (e.g., Williams & Broadbent, 1986) where participants are asked to recall personally experienced past events. Therefore, this section reviews five areas of retrospective memory: verbal learning, associative learning, false memory, source memory, and autobiographical memory.

2.1.1. Verbal Learning

When studying explicit forms of retrospective memory in the laboratory, the investigator presents some materials for learning, such as a list of words. After a delay of some duration, participants are then put in a retrieval mode and asked to recollect the given materials intentionally via free or/and cued recall or recognise them. Verbal learning is most commonly assessed by list-learning tasks such as the California Verbal Learning Test (CVLT), the Rey Auditory Verbal Learning Test (RAVLT), the Wechsler Memory Scale (WMS), the Verbal Learning and Memory Task, the Auditory Verbal Learning Task (AVLT), the Hopkins Verbal Learning Test-Revised or the Wechsler memory subscales (e.g., Verbal paired associates). These tasks measure the learning, recall and recognition of a list that is shown to participants repeatedly.

It has previously been observed that users of illegal recreational drug exhibit poorer performance on tests of verbal learning compared to non-user participants. For instance, Rodgers (2000) examined the three groups of young people (15 regular users of ecstasy who had used ecstasy an average of 20 times over a five-year period, 15 regular users of cannabis who had used cannabis on average four days per week over an 11-year period, and 15 illicit drug naïve controls) on the WMS and found that both cannabis and ecstasy user groups scored worse on verbal memory relative to the control group. However, it must be noted that participants in the drug user groups were required to stop using cannabis for 1 month prior to testing to avoid the confounding effect of recent cannabis use on cognitive functions. Thus, observed memory impairment could be due to the withdrawal symptoms (e.g., irritability, anxiety and insomnia; Sexton et al., 2019) which have been thought to influence on cognition (Mantua & Simonelli, 2019; Rock et al., 2014). Moreover, Solowij et al. (2002, 2011) run a couple of studies on the effects of cannabis use on verbal learning and found that cannabis use impairs verbal learning. For instance, in one of the studies, 52 adolescent cannabis users, 67 alcohol users and 62 non-user controls matched for education, age, and IQ were tested on a learning task, using the RAVLT. Cannabis users performed significantly worse on all tests, indicating impaired learning, retention and retrieval. The degree of deficit was related to the frequency, duration, quantity, and age of onset of cannabis use. Median self-reported abstinence from cannabis was 20.3 h in the study, suggesting recent use of cannabis (Solowij et al., 2011). Hence, the acute effects of the drug might have interfered with participants' cognitive performance (Garavan et al., 2008). In another study, regular recreational ecstasy users (who used ecstasy over six months or longer with a minimum frequency of twice a month in the last two years or who used ecstasy on the least 25 occasions within the last two years)recalled fewer words after the first presentation of the learning list (immediate recall trial) and the delay (delay recall trials) and they required more repetitions to learn the list

compared to only cannabis user (matched for cannabis use with the ecstasy user group) and non-user controls (Gouzoulis-Mayfrank et al., 2000). However, it should be noted that ecstasy users displayed a poorer performance in all three general intelligence measures, compared to controls.

The reviewed literature suggests that verbal memory deficits are more apparent in stimulant drug users (e.g., cocaine and ecstasy), for instance, Reske et al. (2010) compared one hundred fifty-four young occasional, nondependent stimulants users and 48 stimulant-naive participants in the CVLT. They found that stimulant users displayed significant verbal memory deficits, most noticeably in the verbal recall and recognition scores. They also found that marijuana use did not affect CVLT performance. Moreover, McCardle et al. (2004) compared the performance of 17 participants with a history of MDMA use with the performance of 15 non-MDMA drug users. Results indicated that the MDMA group displayed poorer delayed recall and verbal learning than controls after accounting statistically for the effects of cannabis and depression. Similar results were obtained in many other studies with cocaine (Kumar et al., 2019; Woicik et al., 2009), ecstasy (Fox, Toplis, et al., 2001; Gouzoulis-Mayfrank et al., 2003; Quednow et al., 2006; Rouse & Bruno, 2011; Yip & Lee, 2005; for review, see Kalechstein et al., 2007) and methamphetamine users (Basedow et al., 2021; Hoffman et al., 2006; Volkow et al., 2001; Woods et al., 2005). This could be due to that those are the most commonly used drugs (Public Health England, 2020), thus, the majority of studies might have been conducted on those stimulants, but not on other drugs.

Moreover, Kuypers et al. (2016) pooled the data from 65 drug-naïve participants and 65 polydrug ecstasy-users in past placebo-controlled experimental studies to investigate whether ecstasy impairs verbal memory. In those studies, participants were given either MDMA or placebo and examined in the Word Learning Task. Ecstasy users were asked to refrain from any drug use at least one week prior to testing sessions. The results revealed that

while MDMA intoxication impaired verbal memory, long-term MDMA use had no effect as the memory performance of ecstasy users who received a placebo did not differ from drug-naïve controls. There was also no association between quantifiers of lifetime ecstasy use (e.g., years of use, times used) and deficient memory performance. The authors attributed this to a low lifetime ecstasy use history in the present sample. One of the possible limitations of the study is that the premorbid intelligence levels of participants were not measured which might have affected the results.

Moreover, a couple of studies attempted to investigate whether drug-induced impairments disappear once drug use was stopped. A study tested 22 recent MDMA users, 16 ex-MDMA users who had stopped taking MDMA for more than 12 months and 13 control subjects. Recent and ex-MDMA users displayed significantly poorer performance than controls on immediate and delayed recall in the RAVLT. This suggested that the influence of MDMA on memory may be long-lasting (Reneman et al., 2001). Another study also supported this finding where ex-ecstasy users who reported a lifetime exposure of at least 250 ecstasy tablets, and stopped using it at least 20 weeks before the study were significantly impaired on verbal recall, compared to drug-naive controls (Thomasius et al., 2003). Furthermore, Thomasius et al. (2006) found that impairments of verbal memory in ex-ecstasy users may persist for longer than 2.5 years after cessation of ecstasy consumption. Interestingly, a longitudinal study found that cognitive impairment (measured via a German version of the RAVLT) due to cocaine use is reversible within 1 year (Vonmoos et al., 2014).

In summary, the majority of studies showed that verbal learning deficits could be one of the negative effects of drug use, specifically for those who consume stimulant drugs.

2.1.2. Associative learning

Associative learning is a type of learning in which two unrelated elements become connected through a process called conditioning. Croft et al. (2001) assessed 18 cannabis

users, 11 MDMA/cannabis users and 31 drug naïve controls on spatial and non-spatial associative learning tests in which participants were asked to learn associations between six colour pairs (non-spatial) or six spatial pairs (spatial). While there were no significant differences between cannabis users and MDMA/cannabis users, the combined MDMA/cannabis and cannabis groups performed worse than the controls. However, the study had a short abstinence period (i.e., 48 hours).

In another study, heavy cocaine (average use of 9.27 grams per week) abusers' scores were significantly below the normative group scores on associative learning (Ardila et al., 1991). However, it should be noted that all subjects in the study were cocaine addict. A 2-year follow-up study also shows that visual paired associates learning is impaired in new MDMA users (Wagner et al., 2015).

Similar to other cognitive impairments in drug users, associative learning deficits are also more apparent in stimulant users, in particular ecstasy users. For example, in multiple studies, ecstasy users scored worse than non-ecstasy polydrug users on associative learning tests (Fox et al., 2002; Gallagher et al., 2012; Montgomery, Fisk, & Newcombe, 2005; Wagner et al., 2013). However, most of those studies had a short abstinence period (e.g., 24 or 48 hours; Gallagher et al., 2012; Montgomery, Fisk, & Newcombe, 2005). Moreover, a pharmacological MRI study with a placebo-controlled, crossover design showed that THC administration did not affect associative memory task performance in thirteen volunteers (Bossong et al., 2012). Overall, those studies indicate the harmful long-term effects of drug use on associative learning.

2.1.3. False Memory

A false memory is when someone remembers something that did not happen or remembers it in a different way than how it actually happened (Shaw, 2020). In a double-blind, placebo-controlled, within-subjects design, healthy occasional cannabis users (N = 24)

memorised object images that were placed over scenes (e.g., white cat on beach) after administration of placebo or THC (15 mg oral). Two days later, memory of the object images was tested by asking participants to distinguish between previously shown objects or perceptually similar lures (e.g., different white cat). The objects were presented either on their original (e.g., beach) or different scenes (e.g., forest). Participants who received THC showed memory impairment for perceptual details of the objects and context illusion: context reinstatement increased false recognition with high confidence (Doss et al., 2020). In another double-blind, randomised, placebo-controlled trial, the acute and delayed effects of THC on susceptibility to false memory were investigated in 64 healthy occasional cannabis users. Participants, who inhaled the vapour of a single dose of THC or a placebo, were tested immediately (encoding and retrieval while intoxicated) and 7 days later (retrieval sober) via two misinformation tasks and associative word lists. The results revealed that cannabis consistently increases susceptibility to false memories across different paradigms in intoxicated participants (Kloft et al., 2020). Other research with a similar design found that cannabis increases susceptibility to false memories (Cuttler et al., 2021; Doss, Weafer, Gallo, & de Wit, 2018). A recent review by Kloft et al. (2021) also shows that cannabis can increase susceptibility to false memory creation and suggestibility with effect sizes ranging from medium to large.

The studies reviewed above suggest that there is a link between false memory and acute cannabis use. However, the findings on the effects of chronic cannabis use on false memory are inconsistent. For instance, Riba et al. (2015) found that heavy cannabis users (who used it daily for at least the last 2 years) are more prone to experiencing false memories in a modified version of the DRM paradigm, compared to occasional users (<50 occasions of cannabis use in their lifetime). On the contrary, Kloft et al. (2019) compared the performance of three groups: cannabis-naïve controls (n = 53), regular cannabis consumers (at least

1/month) who were sober at least seven days prior to the experiment (n = 50), and regular cannabis consumers who were acutely intoxicated (n = 53) on false memory, using the DRM paradigm and found no group differences.

There is little published data on the effects of other drug use on false memory. For example, a double-blind, placebo-controlled study on the acute and delayed effects of MDMA on false memory could not find evidence for the notion that MDMA increases susceptibility to false memories (Kloft et al., 2022). Taken together, the current literature shows that the acute cannabis use can lead to false memories, however, the chronic effects of cannabis and other drugs (e.g., MDMA, cocaine, GHB) on false memory are unclear or unknown.

2.1.4. Autobiographical memory (AM)

It has been found that AM (i.e., memory for one's personal history) is not properly maintained in people with a history of illegal drug use. For instance, Oliveira et al. (2007) investigated the autobiographical memory of a group of young drug (e.g., cocaine, cannabis, and hallucinogens) dependents(n=25) and a control group of young non-users (n=25; aged between 13 to17 years old), using the Autobiographical Memory Questionnaire (Borrini et al., 1989). The result revealed that the group of drug users had more difficulties accessing long-term information from autobiographical memories than the controls. It should be noted that drug users were diagnosed as having alcohol and/or drug abuse or addiction. Furthermore, Pillersdorf and Scoboria (2019) also found that chronic cannabis users (a minimum of 3–4 times cannabis use per month over the past year; N= 47) exhibited reduced autobiographical memory specificity (inability to recall the detail of a past experience) compared to non-users (N = 52), using the fading affect bias protocol in which participants were asked to recall six emotionally strong memories (pleasant and unpleasant) that happened over the previous year.

It appears that AM impairments might be more common in regular users or drug addicts. For example, a study examined 23 recreational (weekly or less) and 34 regular cannabis users (at least three times per week) and 57 drug naïve controls in the autobiographical interview in which participants were asked to describe a personally experienced event from their previous or a new future event after giving a cue word. The results revealed no significant differences between the control group and recreational users while regular users performed less well than both recreational-users and control non-users (Mercuri et al., 2018). However, the authors noted that there were significant age differences between the regular users and both cannabis-naive and recreational users; the regular user group on average was about 4 years older than the other groups, which might explain the differences between the groups. Also, the duration of lifetime cannabis use in most regular users was between 1 and 5+ years while for most recreational-users was less than 12 months. Moreover, a double-blind placebo-controlled study assessed the acute effects of MDMA on emotional memory during encoding and retrieval in healthy participants who viewed emotionally neutral, negative, and positive images and their labels and were tested with cued recollection and recognition memory tests forty-eight hours after the learning phase. Participants were randomly allocated to one of three groups who were given MDMA (1 mg/kg) either during encoding (N=20), retrieval (N=20), or neither (N=20). They found that MDMA impairs both encoding and retrieval of emotional recollections. However, this seemed to be specific to recollection as there were no group differences on recognition (Doss, Weafer, Gallo, & Wit, 2018). Overall, most studies found AM deficits in regular/heavy drug users, however, more studies with recreational drug users are needed to understand the effects of light drug use on AM.

2.1.5. Source Memory

Source memory is memory for certain contextual details of a stimulus, such as its colour, location, or temporal context in which the stimulus is encountered. Fisk et al. (2014) assessed the performances of 62 ecstasy/polydrug users and 75 non-ecstasy users on a source memory task in which participants attempted to determine whether or not a word had been previously shown and if so, tried to recall the location, format, and temporal position in which the word had occurred. While there was no difference in terms of the number of hits and false positive responses, ecstasy/polydrug users were less able to determine the format in which words had been shown (lower versus upper case). There was a significant negative correlation between the current frequency of cocaine use and list source memory performance (Fisk et al., 2014).

Moreover, a couple of studies were conducted by Morgan et al. to investigate the short- and long-term effects of ketamine use on source memory. In the first study, 20 poly-drug controls and 20 ketamine users were compared on a source memory task (participants were asked to report whether they have heard the word presented before, if so, whether it had been read out in a female or male voice) both on the night of drug use (day 0) and 3 days later. The results revealed that ketamine abusers displayed a persisting deficit in source memory on both days (Morgan et al., 2004). In the second study, 25 frequent ketamine users (more than four times a week), 27 infrequent ketamine users (less than four times a week but at least once a month), 24 abstinent users (abstinent for a minimum of 1 month), 23 polydrug controls (who were matched with the current ketamine-using groups for use of other drug) and 20 non-users of illegal drugs were assessed. They found that the frequent users performed more poorly than abstinent ketamine users and polydrug users. However, the authors pointed out that the frequent ketamine indicated significantly fewer years in education compared to the other groups (Morgan, Muetzelfeldt, et al., 2010).

Furthermore, Cuttler et al. (2021) investigated the acute effects of the high-potency cannabis on cognition functions, including source memory. Eighty cannabis users were recruited and randomly assigned to stay sober or use one of high-potency cannabis products: (1) high-potency concentrates (≥ 60% THC) with CBD, (2) high-potency flower (≥ 20% THC) without CBD, and (3) high-potency flower with CBD. Participants were observed over Zoom videoconferencing while remaining sober or inhaling their product and then were administered cognitive tests. High-potency cannabis flower without CBD and concentrates impaired source memory (Cuttler et al., 2021). Consistent with these findings, Ilan et al., (2004) found that the ability to distinguish new from old words in a memory test was diminished after cannabis smoking. Conversely, another study demonstrated no source memory impairments when comparing the performance of cannabis users before and after smoking cannabis either in low- or high-cannabidiol groups (Morgan, Schafer, et al., 2010).

In summary, most studies found source memory impairment in specific drug users (e.g., ecstasy, ketamine). However, those studies did not have drug naïve controls. Furthermore, the effects of other popular drugs (e.g., cocaine, GHB) on source memory are unknown. Thus, more studies are needed to understand the possible effects of those drugs on source memory while comparing those drug users with drug naïve controls.

2.2. Executive Functions

2.2.1. Cognitive Inhibition

Inhibitory control has been primarily measured by response (e.g., Stop-signal and Go/NoGo tasks) and attention inhibition tasks (e.g., Stroop task). Response inhibition tasks involve the suppression of inappropriate motor responses or actions that are no longer adaptive to the situation, for example, in the Stop-signal task, participants perform a shape judgment task (the primary task) in which they are asked to discriminate between a square

and a circle by pressing a left key for a square and a right key for a circle as fast and accurately as possible. Occasionally, the primary task stimulus is followed by an auditory stop signal and participants are instructed to withhold their responses (Verbruggen et al., 2008). Attention inhibition tasks involve the resistance to interference from stimuli in the external environment. For instance, in the Stroop task, participants are presented with 100 trials in which colour names (green, red, yellow, blue) in different font colours appear on the computer screen for 3 seconds one by one. They are instructed to press the key as quickly and as accurately as possible that corresponds to the colour of the ink that the word appears in on each trial, ignoring the word that is displayed (Stroop, 1935).

Data from several studies suggest that cocaine users are impaired in cognitive inhibition. For example, Sellaro et al. (2014) assessed recreational cocaine polydrug users (n = 17) and cocaine-free controls (n = 17), matched for age, sex, alcohol consumption, and intelligence on the Simon task (which is similar to the Stroop test); and found that cocaine use impairs cognitive control functions (Sellaro et al., 2014). However, participants were required to abstain from any recreational drugs for only two days, thus the observed findings might be associated with the comedown effects. Furthermore, Colzato et al. (2007) compared the ability to inhibit behavioural responses in cocaine users (N=13) and a nonuser matched sample (N=13) while controlling for race, level of intelligence, gender distribution, age and alcohol consumption. The result revealed that cocaine users needed significantly more time than non-users to inhibit responses to stop signals. The lifetime cocaine consumption was positively correlated with the magnitude of the inhibitory deficit. However, this study also had a short abstinence period. Likewise, Hester and Garavan (2004) found that cocaine addicts (N=15) performed worse than nondrug-using controls (N=15) on response inhibition, using the Go/no-go task. However, positive urine samples from drug users suggest that they had used cocaine within the past 72 hr. In another study, the relationship between severity of

consumption of different drugs (e.g., cannabis, MDMA, and cocaine) and executive function performance was investigated in a sample of detoxified drug-dependent participants (N=38). Results indicated a differential impact of severity of cocaine abuse on an inhibitory control as the Stroop test detected the presence of slight or moderate cognitive inhibition impairments. However, the study did not have a control group (Verdejo-García et al., 2005). Hence, those findings could be due to pre-existing differences. Furthermore, a review, in which thirty-six articles on the effect of crack and/or cocaine use on inhibition were summarised, showed that the presence of inhibitory control deficits was reported in 90% of the studies reviewed (Czermainski et al., 2017).

Ecstasy and cannabis use has also been associated with inhibition deficits, but the findings are inconsistent. For example, some studies found that MDMA users performed more poorly than non-user controls while controlling for alcohol, sex and age (Croft et al., 2001; Piechatzek et al., 2009; Quednow et al., 2007). On the contrary, many other studies found that the inhibition process was unaffected by MDMA (Dafters, 2006; Fisk & Montgomery, 2009; Fox et al., 2002; Gouzoulis-Mayfrank et al., 2003; Thomasius et al., 2003; Wagner et al., 2013) or cannabis users (Crane et al., 2013; Lyons et al., 2004). In addition, a meta-analysis in which a total of 632 drug-using controls and 600 ecstasy polydrug users were compared on cognitive inhibition from 20 articles indicated there was no group difference in the performance of inhibitory control (Roberts et al., 2016a). Overall, the literature shows that type of drug is an important factor in whether participants displayed inhibition impairments, for instance, while cocaine users might be impaired in inhibition, addicts, in particular, MDMA and cannabis users might not be.

2.2.2. Working memory

As mentioned in Chapter 1, WM has four subcomponents; the central executive, the phonological loop, the visuospatial sketchpad, and the episodic buffer.

The phonological loop component of WM is measured via the digit span (forward and backward) test in which the ability to hold a sequence of numbers in memory is assessed. Madoz-Gúrpide et al. (2011) examined the association between working memory and three measures of severity of cocaine use: frequency of use, quantity used, and years of use. The performances of 24 severe and chronic cocaine users (fulfilled the criteria of DSM-IV for cocaine dependence) were compared with 27 non-drug user controls. All patients were assessed between 12 and 36 hours of cocaine (or other drugs) abstinence. Compared to control, chronic cocaine users performed worse on most measures of executive functions including the digit span test. While the quantity of cocaine use was linked with deficits in the forward digit span, years of cocaine use and frequency of cocaine were linked with deficits in the backward digit span. Another study with chronic drug users (e.g., heroin, cocaine, and marijuana) showed that chronic use of substances had a significant negative impact on the functioning of working memory (Soliman et al., 2013). However, in this study, only drug addicts were recruited. Furthermore, Frolli et al. (2021) investigated how the use of cannabis (chronic, occasional and absent use) affects WM in participants aged between 15 and 16. The result revealed that 46 chronic users of cannabis (at least 4 times a week for at least a year) scored significantly worse than 46 occasional users (about once every 2 weeks for at least 1 year) and 46 non-user controls, while there was no significant difference between occasional users and controls. Other studies with chronic MDMA users (total lifetime consumption of ecstasy tablets twice to more than 30 occasions; McCardle et al., 2004) or substance-dependent individuals (Verdejo-García & Pérez-García, 2007) found similar findings, suggesting that impairments in the phonological loop component of WM may be more pronounced in heavy/chronic users.

The central executive component of WM is measured via a verbal N-back paradigm in which participants are presented with a series of visual stimuli and asked to determine

which stimulus they had seen N screens prior to the present one. Sanvicente-Vieira et al. (2016) compared the N-back verbal task performance of young adult crack-cocaine dependent users (CRK; N=26), healthy older adults (HO; N=19), and healthy young adults (HC; N=32); and found that the CRK and HO groups performed worse than the HC and there were no differences between the HO and CRK groups. The authors associated such deficits with crack use and developmental ageing (Sanvicente-Vieira et al., 2016). However, all the participants in this study were dependent users. Similar findings were obtained in other studies with heavy or dependent users (Soliman et al., 2013; Wang et al., 2008). Furthermore, a couple of studies documented significant deficits in the central executive component of WM following acute cannabis intake (Ilan et al., 2004, 2005).

The visuospatial sketchpad component of WM is assessed via the computation span tasks in which participants need to remember the location or content of the previously shown objects (Gathercole et al., 1999). For example, Verdejo-García and Pérez-García (2007) recruited two groups of people: abstinent polydrug users and controls to compare their performances on the spatial task. Polydrug users scored significantly worse than controls. The study further shows the link between the severity of drug use and WM test performances as the greater severity of drug use was associated with the worst performances on WM tests. Moreover, Soliman et al. (2013) tested individuals with substance use disorder (SUD; N=128) and compared their scores with healthy individuals' scores on the spatial span task. The SUD group had significantly worse test scores. Regular marijuana use has also been linked to significant visuospatial processing declines (Lyons et al., 2004).

The fourth component of WM is the episodic buffer. The logical memory subtest of the Wechsler memory scale (Wechsler, 1945) is one of the tests of the episodic buffer functioning in which participants listen to two short stories and are then asked to retell them.

Parallel to other components of WM, chronic drug dependents performed worse than non-users (Soliman et al., 2013).

Even though it is hard to investigate the effects of a specific drug on WM as most drug users are poly-drug users, some studies attempted to compare certain drug users with other drug users to identify the particular effect of that specific drug. For example, many studies compared ecstasy poly drug users with non-ecstasy poly drug users and found that ecstasy users are impaired in WM, compared to other drug users (Fisk et al., 2004; Fox, Parrott, et al., 2001; Montgomery et al., 2007; Montgomery & Fisk, 2007; Wareing et al., 2000). Moreover, Colzato et al. (2009) compared cocaine polydrug users with non-cocaine poly drug users (33 men and 7 women) and found no differences in their performances of WM tasks. This suggests that WM impairment might be more common in ecstasy users. On the other hand, Bedi and Redman (2008) ran a cross-sectional cohort study to assess 48 cannabis polydrug users, 45 currently abstinent ecstasy polydrug users, and 40 non-users on various cognitive functions including working memory while controlling for potential confounds (e.g., mood, lifestyle). The three groups performed similarly, thus it was not possible to discriminate between them on the basis of their cognitive performance. Another study with cannabis users also found no differences between users and non-users on WM (Jager et al., 2006). To sum up, these findings demonstrate that WM deficits might be more common in heavy poly-drug users or/and ecstasy users. Further studies are needed to assess the effects of light drug use on WM while controlling for possible confounds, such as gender and age.

2.2.3. Cognitive Flexibility

Cognitive flexibility is the ability to switch from thinking about one concept to another which is often investigated using task-switching and set-shifting tasks, such as the Wisconsin Card Sorting Task (WCST) in which participants are asked to sort the cards by

colour, shape, or number without being told the correct sorting criterion. The task for participants is to deduce the correct matching criterion on the basis of feedback and to flexibly switch sorting rules whenever it has changed (Heaton, 1993). A family of other tasks that taps cognitive flexibility includes design fluency, verbal fluency and category (or semantic) fluency in which participants need to name as many category exemplars (e.g., animals) within one minute (Wysokiński et al., 2010).

A few studies indicate that acute intoxication of marijuana has disruptive impacts on cognitive flexibility (Weinstein et al., 2008). Some studies also show non-acute effects of cannabinoids on cognitive flexibility, for instance, a study assessed 18- 22-year-old college students, who were heavy (≥ 5 times/week) marijuana users or healthy controls. The marijuana group had a significantly lower score compared to the control group on cognitive flexibility and this was associated with greater past 30-day marijuana use (Lahanas & Cservenka, 2019). Furthermore, Fontes et al. (2011) examined individuals who started cannabis use before the age of 15 compared with those who started cannabis use after 15 years old and non-user controls in the WCST and found that the early-onset, but not the late-onset, individuals performed worse than controls. A couple of researchers suggest dose-related neurocognitive effects of marijuana use as heavy marijuana users (e.g., 78–117 joints/week or who had smoked marijuana a median of 29 days in the last 30 days) displayed significantly greater impairment than light users (e.g., 2–14 joints/week or who had smoked a median of 1 day in the last 30 days; Bolla et al., 2002; Pope & Yurgelun-Todd, 1996). In addition, a recent systematic review and meta-analysis by Figueiredo et al., (2020) indicates that there was a low cross-sectional link between cognitive flexibility impairments and chronic cannabis use and/or a cannabis dependency, with a small effect size of 0.33.

Several other studies have found a parallel pattern of impairments in chronic ecstasy users with lifetime use of 50 or more ecstasy tablets (Dafters, 2006), recreational cocaine

users (Colzato et al., 2009) or cocaine dependence (Alonso-Matias et al., 2019; Cunha et al., 2010; Madoz-Gúrpide et al., 2011; Woicik et al., 2009), and other substance-dependent individuals (e.g., heroin and methamphetamine; Hekmat et al., 2011; Salmani et al., 2020; Verdejo-García et al., 2006; Verdejo-García & Pérez-García, 2007). This contrasts with a number of studies that found no residual effects of cannabis (Curran et al., 2002; Hart et al., 2001; Selamoglu et al., 2021; Solowij et al., 2002) or ecstasy (Piechatzek et al., 2009) on cognitive flexibility. In summary, the findings on the effects of drugs use on cognitive flexibility are inconsistent while some studies found that drug use impair cognitive flexibility, in particular heavy drug use, others did not find this effects.

2.3. Neuroimaging and neurochemical studies

Neuroimaging and neurochemical studies provide some insights into the neuroanatomic changes responsible for these cognitive deficits summarised above, for example, Bosch et al. (2013) compared the performance of 19 chronic, but currently abstinent users of MDMA with the performance of 19 participants with no history of illegal drug use, employing a German version of the RAVLT. They also assessed regional cerebral brain glucose metabolism (rMRGlu) via PET scans. MDMA users showed significant impairment in verbal learning which was associated with decreased rMRGlu in the bilateral dorsolateral prefrontal and inferior parietal cortex, pons (at the level of raphe nuclei), right cerebellum, bilateral thalamus, right precuneus and right hippocampus (Bosch et al., 2013). Furthermore, poorer performance on the CVLT has been associated with a reduction in neocortical SERT binding (Semple et al., 1999) and reduced recall on the AVLT has been linked to an up-regulation of SERT density in the occipital cortex in MDMA users (Reneman et al., 2001). A meta-analysis of studies investigating SERTs in ecstasy users by Roberts et al. (2016b) revealed that ecstasy users displayed significant SERT reductions in 11 out of the 14 regions in the brain, including every neocortical (in particular in the occipital cortex) and limbic

region. Multiple reviews have supported the notion that recreational MDMA use leads to long-lasting reductions in neocortical serotonin signalling (Benningfield & Cowan, 2013; Biezonski & Meyer, 2011). The authors of those reviews suggest that the detected cognitive deficits are attributable to MDMA induced 5-HT impairments. Numerous imaging studies also indicate that there are decreases in DA D2 receptors and DA release due to drug abuse in various parts of the brain, including the OFC and DLPFC, which are associated with executive dysfunction (Volkow et al., 2004, 2009). Functional neuroimaging studies further show that drug abusers exhibit persistent functional brain abnormalities in prefrontal brain circuits, such as the OFC and the anterior cingulate gyrus (Bolla et al., 2004; Garavan & Hester, 2007; Jovanovski et al., 2005).

Levar et al. (2018) investigated the effect of cannabis use on the uncinate fasciculus (UF) and its association with memory performance in adolescents. The UF is a long-range white matter association tract that connects limbic regions to the frontal lobe (Olson et al., 2015) and has been associated with verbal memory (e.g., the retrieval of word; Papagno et al., 2011). Compared to non-users, cannabis users displayed worse memory performance, reduced fiber bundle length in the UF, and reduced cortical thickness of brain regions along the UF, such as the fusiform gyrus and entorhinal cortex. Several studies have also observed decreased whole brain volume (Wilson et al., 2000), in particular gray matter volume in the bilateral hippocampus (Ashtari et al., 2011) and the medial orbital PCF (Churchwell et al., 2010); and a smaller hippocampus (Batalla et al., 2013; Lorenzetti et al., 2014; Meier et al., 2022) in cannabis abusers.

Furthermore, chronic cocaine users displayed cerebral hypoperfusion (a reduced amount of blood flow) in the frontal, periventricular, and/or temporal-parietal areas which were associated with deficits in concentration, attention, word production, new learning, visual and verbal memory (Strickland et al., 1993). In addition, cocaine users displayed

reduced activity in both the anterior cingulate and medial prefrontal regions while performing executive function set-shifting (Bolla et al., 2004; Kübler et al., 2005) or inhibition tasks (Kaufman et al., 2003) in which they scored poorly.

Together, these studies provide ample evidence for structural and functional brain changes in substance users which may explain observed cognitive impairments.

2.4. Methodological considerations

As introduced in Chapter 1, the use of illegal drugs continues to pose a significant threat to global well-being. To reduce the use of illegal drugs and associated harms, it is vital to improve the understanding of the effects of those drugs on the brain and behaviours. As reviewed in this chapter, the evidence from past studies on the effects of drug use on retrospective memory and executive functions is rather inconclusive and suffer from methodological shortcomings (see Appendix A for a summary of those studies and Appendix B overview of their results with the quality assessment). Some researchers have found that illegal drug users performed worse than non-users on verbal learning (Rodgers, 2000; Schilt et al., 2007; Solowij et al., 2011), associative learning (Ardila et al., 1991; Croft et al., 2001), autobiographical memory (Mercuri et al., 2018; Oliveira et al., 2007; Pillersdorf & Scoboria, 2019), source memory (Cuttler et al., 2021; Fisk et al., 2014), false memory (Cuttler et al., 2021; Doss et al., 2020; Doss, Weafer, Gallo, & de Wit, 2018; Kloft et al., 2020; Riba et al., 2015), working memory (Frolli et al., 2021; Madoz-Gúrpide et al., 2011; Soliman et al., 2013; Verdejo-García & Pérez-García, 2007), cognitive inhibition (Croft et al., 2001; Hester & Garavan, 2004; Sellaro et al., 2014; Verdejo-García et al., 2005), and cognitive flexibility (Alonso-Matias et al., 2019; Dafters, 2006; Fisk & Montgomery, 2009; Fox, Parrott, et al., 2001; Hekmat et al., 2011). However, this contrasts with other studies where drug users were not impaired in working memory (Bedi & Redman, 2008; Jager et al., 2006), false memory (Kloft et al., 2019, 2022), cognitive inhibition (Dafters, 2006; Fox et al., 2002; Roberts et al.,

2016a), source memory (Morgan, Schafer, et al., 2010) or verbal learning (Kuypers et al., 2016).

A possible explanation for this discrepancy might be that several of those studies that examine the effects of illegal drug users on cognitive processes suffer from methodological challenges. First, most studies (Alonso-Matias et al., 2019; Basedow et al., 2021; Bossong et al., 2012; Colzato et al., 2007; Croft et al., 2001; Doss, Weafer, Gallo, & de Wit, 2018; Hester & Garavan, 2004; Kloft et al., 2022; McCardle et al., 2004; Oliveira et al., 2007; Quednow et al., 2007; Roberts et al., 2009; Rodgers, 2000; Sellaro et al., 2014) had small sample size (<100 participants) as it is difficult to recruit hard-to-reach drug using populations who may actively try to conceal their group identity (Duncan et al., 2003) due to fear of confrontation with legal authorities (Shaghaghi et al., 2011). Some studies recruited a large sample by using internet-based surveys (Dregan & Gulliford, 2012; Rodgers et al., 2001, 2003). However, there are likely a number of factors that influence the validity of data collected online. For instance, sampling bias where respondents who are more active online are systematically more likely to be selected in a sample than others (Bethlehem, 2010). Moreover, the physical disconnection from the investigator may increase the likelihood of careless answering (Hardré et al., 2012).

Second, they had a short abstinence period (Colzato et al., 2007; Croft et al., 2001; Dafters, 2006; Fisk et al., 2004; Madoz-Gúrpide et al., 2011; Mercuri et al., 2018; Quednow et al., 2007; Roberts et al., 2009; Solowij et al., 2011). It is important that participants who take part in a study are not under influence of any drug as acute effects can interfere with individuals' cognitive functions (Garavan et al., 2008). There are also comedown effects that occur when the effects of drugs wear off during which, the brain is readjusting the chemical imbalance. The symptoms of the immediate comedown of many drugs (e.g., insomnia, depression, irritability, agitation, anxiety) have been thought to be identical to the symptoms

of acute withdrawal (Davison & Parrott,1997; Gawin & Ellinwood, 1988; Greenough, 2021; McKetin et al., 2014) which begin within hours or days after last use of drugs and gradually go away. The length of time symptoms last depends on the specific drug used due to their pharmacokinetic profiles. For example, methamphetamine withdrawal symptoms last 3 to 7 days (McGregor et al., 2005), cannabis 5 days (Welch & Martin, 2003), amphetamine and cocaine 3-7 days (Miller & Gold, 1998; Wilkins et al., 2009). Therefore, ideally, it is recommended that participants should be drug-free for at least 7 days (Miller & Gold, 1998).

Third, while most studies controlled for age and gender or/and education (Doss, Weafer, Gallo, & de Wit, 2018; Fisk et al., 2004; Gouzoulis-Mayfrank et al., 2000, 2003; Hester & Garavan, 2004; Riba et al., 2015; Rodgers, 2000; Yip & Lee, 2005), they had neglected other potential confounds, such as alcohol use (Frolli et al., 2021; Quednow et al., 2007; Soliman et al., 2013), depression (Croft et al., 2001; Frolli et al., 2021; Quednow et al., 2007; Riba et al., 2015; Rodgers, 2000; Soliman et al., 2013), sleep quality (Croft et al., 2001; Gallagher et al., 2012; Gouzoulis-Mayfrank et al., 2000; Pillersdorf, & Scoboria, 2019; Quednow et al., 2007; Rodgers, 2000; Soliman et al., 2013), and intelligence quotient (Alonso-Matias et al., 2019; Hester & Garavan, 2004; Kuypers et al., 2016; Pillersdorf & Scoboria, 2019; Rodgers, 2000; Soliman et al., 2013) which are thought to have an impact on cognitive functions by data from several studies (Ballard et al., 2015; Kim et al., 2016; Mantua & Simonelli, 2019; Mohn et al., 2014; Rock et al., 2014). Some studies did not control for any confounding variables (Oliveira et al., 2007; Rouse & Bruno, 2011).

Fourth, most studies focused on adolescence (Basedow et al., 2021; Frolli et al., 2021; Goycolea et al., 2020; Oliveira et al., 2007; Solowij et al., 2011), and young adulthood (Colzato et al., 2009; Lyons et al., 2004; Montgomery, Fisk, Newcombe, et al., 2005; Montgomery & Fisk, 2007; Piechatzek et al., 2009; Rodgers, 2000; Sanvicente-Vieira et al.,

2016; Sellaro et al., 2014), resulting in a dearth of information about the possible consequences of adult illegal drug use for cognitive performance.

Fifth, commonly, student (Montgomery & Fisk, 2007; Lahanas & Cservenka, 2019) or patient populations (Cunha et al., 2010; Hekmat et al., 2011; Hester & Garavan, 2004; Madoz-Gúrpide et al., 2011; Sanvicente-Vieira et al., 2016; Soliman et al., 2013; Verdejo-García et al., 2006; Verdejo-García & Pérez-García, 2007; Woicik et al., 2009) were recruited who might not represent the general population, for example, a student sample only include individuals with similar age range and education background and a clinical population include individuals with mental disorders (e.g., addiction) that might directly affect the result of a study.

Sixth, most previous studies assessed regular drug users, for instance, ecstasy user who used ecstasy 10 or more times per month(Heffernan et al., 2001a); MDMA users who took MDMA at least 50 times over a period of at least 1 year (Quednow et al., 2007) cannabis users who used cannabis at least once a week over three years(Solowij et al., 2002) or drug addicts (Alonso-Matias et al., 2019; Ardila et al., 1991; Basedow et al., 2021; Hoffman et al., 2006; Madoz-Gúrpide et al., 2011; Sanvicente-Vieira et al., 2016; Soliman et al., 2013; Woicik et al., 2009; Woods et al., 2005). There is an implicit belief that using drugs is okay as long as you do it once in a while (Torregrossa et al., 2011). Hence, it is not clear whether light drug use has the same negative effects on cognitive functions.

Seventh, some studies used self-report questionnaires to assess cognitive functions (Fisk & Montgomery, 2008; Rodgers et al., 2001, 2003, 2006; Rodgers, 2000). Self-report information obtained from individuals with a history of illegal substance use may not be accurate as it relies on participants' abilities to recall their past memories correctly which might be impaired due to drug use (see section 2.1).

Lastly, drug naïve controls were absent in most studies (Basedow et al., 2021; Fisk et al., 2014; Fox et al., 2002; Fox, Toplis, et al., 2001; Gallagher et al., 2012; Hoffman et al., 2006; Kalechstein et al., 2007; Kumar et al., 2019; Roberts et al., 2009; Volkow et al., 2001; Woods et al., 2005), or there were no control groups (Bossong et al., 2012; Verdejo-García et al., 2005) which can be seen a weakness in study designs (Joy et al., 2005; Pithon, 2013).

Therefore, one of the aims of the current study is to explore the possible consequences of recreational drug use on executive functions and retrospective memory while taking the aforementioned methodological issues into consideration and fill the identified research gaps in the existing literature, such as the possible long-term effects of popular recreational drugs (e.g., cocaine, GHB) on false memory and source memory. This will be shown in Chapters 5 and 6 respectively after reviewing the literature (Chapter 3) and presenting a new study (Chapter 4) on the effects of drug use on prospective memory.

Chapter 3: Illegal Drug Use and Prospective Memory: A Systematic Review

This chapter summarises studies on illegal drug use and prospective memory. This chapter was published: Levent, A., & Davelaar, E. J. (2019). Illegal drug use and prospective memory: A systematic review. *Drug and alcohol dependence*, *204*, 107478. https://doi.org/10.1016/j.drugalcdep.2019.04.042

3.1. Abstract

Illegal drug use is proposed to interfere with neurobiological functioning by damaging the neurotransmitter communication systems that are believed to be responsible for cognitive abilities, including perception, attention, and memory. This review specifically examined effects of illegal drug use on PM – memory for future actions. Twenty-seven studies spanning 14 years were included in this review which were divided into two broad categories based on testing methods used: self-report and lab-based testing methods. The quality of the included studies was assessed across five categories: sample type, sample size, abstinence period, testing methods and control for confounding factors. The overall quality of evidence was good for six studies and moderate for sixteen studies and low for five studies. The results from the studies employing self-report were inconsistent as illegal drug users exhibited PM deficits in some studies, but not in others. However, the studies with lab-based testing methods demonstrated more consistent findings with illegal drug users scoring worse than non-users on various PM tests. There were also consistent findings on the link between the dosage of drug taken and level of PM deficit. Based on the literature, there is moderate evidence that illegal drug use impairs PM ability. It is recommended that further lab-based studies be conducted to assess dose-response effects on drug-specificity.

K**eywords:** Behavioural pharmacology, prospective memory, illegal drug use, cognition, neuropsychology, ecstasy, cocaine, cannabis.

3.2. Introduction

In the last 25 years, much research has demonstrated the negative consequences of a number of illicit substances, such as MDMA, cocaine and cannabis. As discussed in Chapter 1, these drugs affect the communication system of the brain by interfering with the natural circulation of neurotransmitters, such as DA, 5-HT, NE, Glu, and GABA that have been thought to be responsible for a wide range of processes, including perception, attention, memory, emotion, appetite, sleep, and more. As a result of illicit drug use, some biological and behavioural abnormalities have been observed in humans (see Chapter 2). For example, individuals who regularly use MDMA showed a reduction of cortical 5-hydroxytryptamine (5-HT) transporter binding compared to a non-user group (Semple et al., 1999). Furthermore, Volkow et al. (2009) demonstrated that cocaine and methamphetamine reduced dopamine release and dopamine D2 receptors in drug users. Behavioural consequences of illegal drugs use (e.g., MDMA, cocaine and more) are varied, including motor skill deficits (Klugman & Gruzelier, 2003), paranoia (Morton, 1999), tachypsychia (Atakan et al., 2012) and executive dysfunctions (Fox, Parrott, et al., 2001; Madoz-Gúrpide et al., 2011). Different types of memory are also influenced by illicit drug use. For instance, ecstasy users scored significantly lower on the verbal memory test compared to non-user controls (Schilt et al., 2007) and illegal poly-drug users had more difficulties in accessing semantic memory and autobiographical memory compared to non-users (Oliveira et al., 2007). Another type of memory that suggested to be negatively affected by illegal drug use is prospective memory (Heffernan, et al., 2001a).

Prospective memory (PM) is the ability to remember to carry out a particular behaviour at some future point in time which maybe in the short- or long-term (Henry et al., 2004). PM plays a very important role in everyday life as it governs one's ability to organise his or her time in an efficient and independent way. The failures of PM can be irritating (e.g.,

forgetting to buy bread on the way home from work) as well as life threatening (e.g., forgetting to take daily medications; Terrett et al. 2014). For example, Nelson et al., (2006) found that people who reported forgetting to take their blood pressure medication were more likely to have a heart attack or die than people who did remember to take their medication. It can also influence an individual's reputation and self-esteem, such that one might be perceived as being organised and conscientious or as being unorganised and unreliable (Walter & Meier, 2014). PM is a multi-phase, complex cognitive ability that includes the following characteristics (McDaniel & Einstein, 2007). There must be a deliberately formed goal or plan that should be performed in the future. The PM task must be combined with an ongoing activity that needs attentional resources. Therefore, an individual has to consciously interrupt the ongoing task to perform their aimed action. There are five stages of PM: the formation of intention, a temporarily extended interval during which the intention is not attended to, the detection of a cue that triggers retrieval of the intention, recall of the intention and, lastly, execution of the intention (Zogg et al., 2012). There are two forms of PM: time-based and event-based. Time-based PM involves remembering to perform a planned action at a particular future time point, for example, attending a lecture at 12 pm, taking medication at 8 pm or drinking milk at 11 pm. Event-based PM involves remembering to perform a planned action when a particular event occurs. For instance, taking medication after dinner or buying a loaf of bread when passing the bakery on the way home. Event-based tasks are usually considered less cognitively demanding than time-based tasks as it is mostly likely that external cues trigger intended actions. By contrast, time-based tasks require more self-initiation and monitoring, thus they are more demanding and more sensitive to memory deficits (Einstein et al., 1995; Sellen et al., 1997).

It is also worthy of note that PM relies on various cognitive processes, including executive functioning. Planning takes part in the formation and encoding of an intention

(Kliegel et al., 2002) and working memory is responsible for storing the postponed intention while carrying out the ongoing task (Marsh & Hicks, 1998). Furthermore, attentional monitoring of the external world is important to recognise the convenient time or event to start the PM action (Landsiedel et al., 2017). Lastly, inhibition control and cognitive flexibility are also essential for PM as one has to shift their attention away from the ongoing task to perform a planned intention (Kliegel et al., 2002).

The aim of this review was to examine research reporting the presence or absence of impairments in PM associated with the use of illicit drugs. The rationale for this review is two-fold. First, there is an increase in illegal drug use across the world. For example, according to the Crime Survey 2015/16, around 1 in 5 young adults aged 16 to 24 had taken an illicit drug in 2014 in England and Wales, which equates to around 1.1 million people (Home Office Statistical Bulletin, 2016). Globally, it is estimated that 1 in 20 adults, or a quarter of a billion people, aged 15-64 years, used at least one illicit drug in 2014 (United Nations Office on Drugs and Crime, 2016). Second, most studies on human memory have been retrospective in nature, referring to memory of words, people and events experienced or encountered in the past. While there is an increase in the number of research on PM, the research on the impact of illicit drug use on PM is lagging behind.

3.3. Methods

3.3.1. Identification of studies

A computer-based search involving Science Direct, PubMed, PMC and Birkbeck Library databases was conducted. The key conceptual terms used as search parameters were prospective memory, everyday memory, prospective memory questionnaire, prospective memory task, virtual reality prospective memory task, cognition, drug, drug abuse, recreational drug, illicit drug, illegal drug, MDMA, cocaine, cannabis, amphetamine, methamphetamine, ketamine, heroin, opioids, methadone, magic mushroom, LSD and

different combinations of these words. Furthermore, a backwards citation search was conducted (i.e., references in each of the journal articles retrieved were checked). There was no limitation on publication date.

3.3.2. Inclusion/exclusion criteria

The search was limited to English-language publications with human participants. Conference presentations, dissertations were excluded from the review. Studies had to report new findings, including replications, but those that examined participants under the influence of any drugs were also excluded.

3.3.3. Data Extraction

As Figure 3 shows, twenty-seven studies met the inclusion criteria. There were a number of cases where an article consisted of more than one study (Cuttler et al., 2012; Gallagher et al., 2014; Heffernan, et al., 2001b). In these cases, each study was assessed individually. Some studies used self-report PM tests as well as lab-based PM tasks and were reviewed twice, once under each appropriate subtitle.

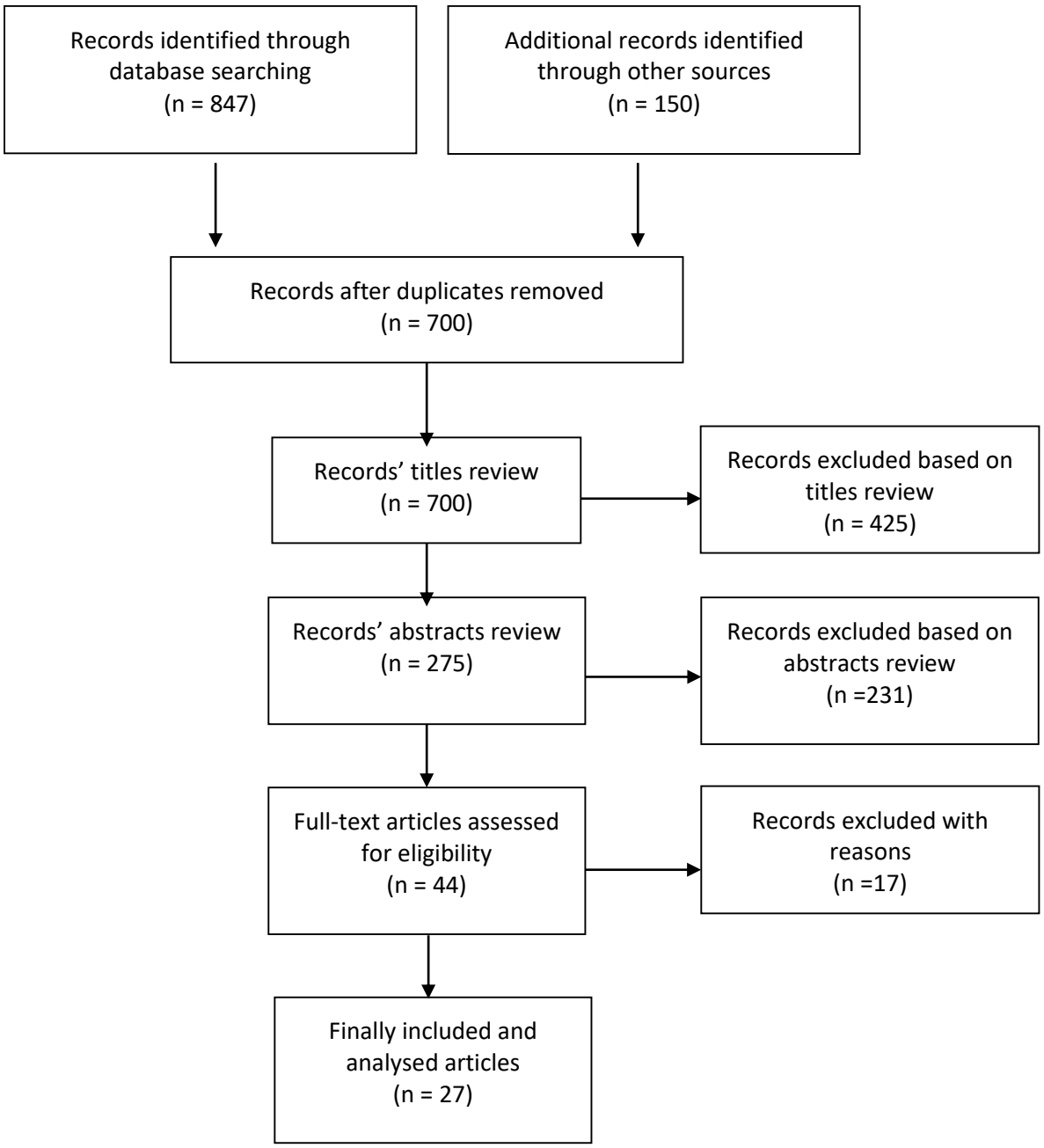

Figure 3. Systematic review search results and flow chart.

Most participants from the drug user groups were ecstasy/poly-drug users, since they reported taking a range of other recreational compounds (e.g., cannabis, cocaine, amphetamine) with the exception of the six studies in which participants were only cannabis users (Arana et al., 2011; Bartholomew et al., 2010; Cuttler et al., 2012; Fisk & Montgomery, 2008; McHale & Hunt, 2008; Montgomery et al., 2012). Furthermore, most studies compared drug users with non-users, with the exception of four studies (Hadjiefthyvoulou et al., 2011a; Montgomery et al., 2010; Zakzanis et al., 2003; Gallagher et al., 2014 study 1) in which ecstasy/poly-drug users were compared with no ecstasy poly-drug users (no drug naïve controls).

3.3.4. Systematic Evaluation

The included studies were assessed on the following categories: sample size, sample type, testing methods, abstinence period, control for potential confounds. Each category was defined as good, moderate or low based on the information that was supplied in the article. The overall quality of each study was determined based on the following standards: studies that had three and more categories defined as either good, moderate or low were classified as good, moderate or low quality of evidence respectively; and studies that had at least two categories defined as good and one category defined as moderate or one category defined as good and two categories defined as moderate were classified as moderate quality of evidence.

3.3.4.1. Population Representativeness

3.3.4.1.1. Sample type

There were three classifications "good," "moderate," and "low" in this subcategory. A sample from the general population was defined as good in population representativeness when it included individuals of different ages, educational level, economic status and geographical locations. A sample from the student population was defined as moderate in population representativeness as they include individuals with similar age range and

education background. A sample from the clinical population was defined as low in population representativeness as they include individuals with mental disorders that might directly affect the result of a study.

3.3.4.1.2 Sample size

There were three classifications "good," "moderate," and "low" in this subcategory. Good sample size was defined as 100+ participants; moderate sample size was defined as 50-100 participants; and low sample size was defined as 0-50 participants. It should be noted that a sample size depends on the nature of a research study and should be determined using power calculation. However, broadly speaking, small sample sizes undermine the internal and external validity of research (Faber & Fonseca, 2014). They decrease statistical stability and power. For instance, outliers can have a big impact on the confidence interval in a study with a small sample size as they cause a wider confidence interval with a larger margin of error, therefore, producing less precise results (Rosenblum, & Laan, 2009). On the contrary, large sample sizes produce confidence intervals that are often extremely small in width, producing estimates that are more accurate (Hazra, 2017). They also give greater statistical power (Suresh, & Chandrashekara, 2012).

3.3.4.2. Abstinence period

There were three classifications "good," "moderate," and "low" with 7+ days, 3-7 days and less than 3 days of drug abstinence respectively. Studies in which the abstinence period was not given were also defined as low. It is very important that participants who take part in a study are not under influence of any drug as acute effects can interfere with individuals' cognitive functions (Garavan et al., 2008). There are also comedown effects (e.g., insomnia, depression, irritability, agitation, anxiety) that occur when the effects of drugs wear off during which, the brain is readjusting the chemical imbalance. It lasts 3 to 7 days (McGregor et al., 2005; Miller & Gold, 1998; Welch & Martin, 2003; Wilkins et al.,

2009). Therefore, ideally, it is recommended that participants should be drug-free for at least 7 days (Miller & Gold, 1998).

3.3.4.3. Testing Methods

There were three classifications "good," "moderate," and "low" in this category. Good testing method was defined as both self-report and lab-based tests. Moderate testing method was defined as only lab-based tests. Low testing method was defined as only self-report tests. Self-report information obtained from individuals with a history of illegal substance use may not be accurate as it relies on participants' abilities to recall their past memories correctly which might be impaired due to drug use (Cuttler et al., 2012). By contrast, it is believed that lab-based tests are more objective and reliable as they offer real-world function testing through the use of a controlled setting (Montgomery et al., 2012).

3.3.4.4. Control for confounding factors

There were three classifications "good," "moderate," and "low" in this category. There are some factors that can contribute to PM performance, such as age (Henry et al., 2004), depression (Li et al., 2013), sleep quality (Grundgeiger et al., 2014), IQ (Uttl et al., 2013) and more. Therefore, studies that controlled for three or more of these factors were defined as good. Studies that controlled two of these factors were defined as moderate. Studies that controlled for only one factor or did not control for any potential confound at all or did not give any information about the controlling of confounding were defined as low.

3.4. Results

A summary of the twenty-seven studies included in the systematic review and overview of their results with the quality assessment are provided in Appendix C and D respectively. As Table 1 presents, of these, six studies met the requirements for good quality of evidence, sixteen studies met the requirements for moderate quality of evidence, and five studies met the requirement for low quality of evidence. This section consists of two parts on

the basis of testing methods of PM: self-report questionnaires and lab-based tasks; and each part is broken down into three subtitles: the types of PM test, the studies using a between-groups design and studies with a correlation design.

Table 1: Quality assessment of the 27 studies included in the systematic review. The studies are ordered by overall quality of evidence.

No	Reference	Sample type	Sample Size	Testing Methods	Control for confounds	Abstinence Period	Overall Quality of Evidence
1	Bartholomew et al., 2010	M	M	G	G	G	G
2	Gallagher et al., 2014 study 1	M	G	M	G	G	G
3	Gallagher et al., 2014 study 2	M	G	M	G	G	G
4	Hadjiefthyvoulou et al., 2011a	M	M	G	G	G	G
5	Hadjiefthyvoulou et al., 2011b	M	M	G	G	G	G
6	Cuttler et al., 2012 study 2	M	G	G	G	L	G
7	Weinborn et al., 2011a	G	M	G	M	M	M
8	Weinborn et al., 2011b	L	M	G	G	L	M
9	Bedi and Redman, 2008	G	G	M	M	L	M
10	Heffernan et al.,2001a	G	M	L	M	L	M
11	Heffernan et al., 2001b study 1	G	M	L	M	L	M
12	Heffernan et al., 2001b study 2	G	M	L	M	L	M
13	Zakzanis et al., 2003	M	L	M	G	G	M
14	Montgomery and Fisk, 2007	M	M	L	G	G	M
15	Montgomery et al., 2010	M	L	M	G	G	M
16	Montgomery et al., 2012	M	L	M	G	M	M
17	McHale and Hunt, 2008	G	M	M	M	L	M
18	Rendell et al., 2007	G	M	M	G	L	M
19	Rendell et al., 2009	L	L	M	G	G	M
20	Terrett et al., 2014	G	M	M	G	L	M
21	Rodgers et al., 2001	G	G	L	M	L	M
22	Rodgers et al., 2006	G	G	L	M	L	M
23	Rodgers et al., 2003	G	G	L	L	L	L
24	Arana et al., 2011	M	G	L	L	L	L
25	Fisk and Montgomery, 2008	G	L	L	G	L	L
26	Ciorciari and Marotte, 2011	G	G	L	L	L	L
27	Cuttler et al., 2012 study 1	M	G	L	L	L	L

G: Good, M: Moderate; L: Low

3.4.1 The studies with self-report PM questionnaires

3.4.1.1. The self-report PM questionnaires

Two types of self-report PM questionnaires were used in the studies; the Prospective Memory Questionnaire (PMQ; Hannon et al., 1995) and the Prospective and Retrospective

Memory Questionnaire (PRMQ; Piauilino et al., 2010). The PMQ is a self-reported measure of PM that provides measures of three aspects of PM (short-term habitual, long-term episodic and internally cued) on a 9-point Likert scale (Hannon et al., 1995). There are fourteen questions that assess short-term habitual PM, (e.g., "I forgot to lock the door when leaving my apartment or house"); fourteen items assess long-term episodic PM, (e.g., "I forgot to return books to the library by the due date"); and ten items assess internally cued PM, (e.g., "I forgot what I wanted to say in the middle of a sentence").

The PM subscale of the PRMQ is also another type of self-report PM questionnaire which contains 8 PM complaints; four environmentally cued (e.g., "How often do you forget to buy something you planned to buy, like a birthday card, even when you see the shop?") and four self-cued (e.g., "How often do you forget appointments if you are not prompted by someone else or by a reminder, such as a diary or a calendar?") PM complaints (Piauilino et al., 2010).

3.4.1.2. The studies using between groups design

There were twelve studies that used self-report questionnaires in order to examine perceived problems concerning PM (Bartholomew et al., 2010; Ciorciari & Marotte, 2011; Cuttler et al., 2012 study 2; Fisk & Montgomery, 2008; Hadjiefthyvoulou et al., 2011a, 2011b; Heffernan, et al., 2001a, 2001b; Montgomery & Fisk, 2007; Weinborn, et al., 2011a, 2011b)

As seen in Table 2, most studies with self-report testing methods had a moderate or above rating on the confounding control, sample type and size categories. In contrast, a low rating on the abstinence period category. The overall of quality of evidence was good for four studies, moderate for six studies and low for two studies.

Table 2: The studies with self-report testing methods.

	Confounding Control	<3	≥3AND<7	≥7	<3	≥3AND<7	≥7	<3	≥3AND<7	≥7
General Sample	≥ 3	15								
	2				10, 11, 12	7		21, 22		
	≤ 1							23, 26		
Student Sample	≥ 3						1, 4, 5, 14	6		
	2									
	≤ 1							24, 27		
Patient Sample	≥ 3				8					
	2									
	≤ 1									
		Abstinence Period **Sample Size <50**			Abstinence Period **50<Sample Size<100**			Abstinence Period **Sample Size >100**		

In Table 3, the findings of the nine studies that used the PMQ are summarised. There were also three studies employing the PRMQ: the first two studies (Hadjiefthyvoulou et al., 2011b; Weinborn et al., 2011b) showed that illicit drug users made significantly more complaints on Environmentally and Self-Cued PM compared to non-drug users. Whereas, the third study (Weinborn et al., 2011a) did not find significant differences between the groups on PM complaints.

Table 3: Overview of the findings of the nine studies employing the PMQ.

Reference	Short-Term PM Deficit	Long-Term PM Deficit	Internally Cued PM Deficit
Heffernan et al., 2001a	✓	✓	✓
Heffernan et al., 2001b, study 1	✓	✓	✓
Heffernan et al., 2001b, study 2	✓	✓	✗
Montgomery and Fisk, 2007	✗	✓	✓
Fisk and Montgomery, 2008	✓	✓	✓
Hadjiefthyvoulou et al., 2011a	✓	✗	✗
Bartholomew et al., 2010	✗	✗	✗
Ciorciari and Marotte, 2011	✗	✓	✗
Cuttler et al., 2012 study 2	✗	✗	✓

Keys: ✓= present, ✗= not present

In summary, the association between illegal drug use and PM deficits is not clear as some studies found PM deficits in drug user groups, but others did not. However, these findings should be treated with some caution for the following reasons: first, in the study by Bartholomew et al. (2010), data were not normally distributed in terms of age, alcohol or nicotine consumptions and therefore non-parametric Mann-Whitney U tests were performed. Second, Hadjiefthyvoulou et al. 2011a compared ecstasy/poly-drug users with no ecstasy poly-drug users, so there was no non-drug user group. Third, Cuttler et al. (2012) study 2 used the more conservative alpha level of .01 rather than .05 to control for inflation of Type I error while performing multiple tests. Fourth, overall, most studies had low ratings on abstinence periods and testing methods.

3.4.1.3. The studies using correlational designs

There were six studies that used the self-report PM questionnaires to examine the relationship between the frequency or/and level of drugs taken and severity of PM deficit (Arana et al., 2011; Ciorciari & Marotte, 2011; Cuttler et al., 2012; Rodgers et al., 2001, 2003, 2006).

As seen in Table 1, all studies were classified as good in the sample size category, but low in the testing method and abstinence period. Four studies included participants from the

general population and two studies from student population (Arana et al., 2011; Cuttler et al., 2012 study 1). There were four studies that did not control for any potential confound and two studies controlled only for two potential confounds (Rodgers et al., 2001, 2006). Overall, of the six studies, two were classified as being of moderate quality of evidence and four studies as having low quality of evidence.

Rodgers' et al.'s (2001) web-study included four groups: ecstasy and cannabis users, only ecstasy users, only cannabis users and non-users. This study showed that the level of cannabis use predicted more self-reported errors on the PMQ short term and internally cued scales. Whereas, the level of ecstasy use predicted more self-reported errors on the PMQ long-term scale and the number of errors made during the test.In another web-study by Rodgers et al. (2003), poly-drug users were tested and the result revealed that the level of ecstasy use, but not cannabis use, predicted worse score on the long-term scale of the PMQ and the number of errors made while completing the questionnaires. Rodgers et al. (2006) replicated and extended these findings with another web-based study in which ecstasy/poly-drug users were tested. These users were divided into groups based on the number of occasions they took ecstasy (e.g., group 1: users with 1-9 occasions ecstasy use; group 2: users with 10-99 occasions; and group 3: users with more than 100 occasions) and they found that there was significant relationship between the frequency of MDMA use and frequency of reporting a number of PM problems. Moreover, Arana et al. (2011) examined cannabis users who were divided into groups based on the level of cannabis use and what age they have started using cannabis. The result revealed that the earliest the year was negatively correlated with long term PM andthe higher estimated quantity of cannabis use was negatively correlated with internally cued PM. Cuttler et al., 2012 study 1 also carried out an online study in which cannabis users (users with a high risk, a moderate risk, a low risk and no risk of cannabis abuse and/or dependence) were assessed. In order to test the relationships

between cannabis consumption, problems with cannabis use, and self-reported PM failures, a series of correlation analyses were conducted. Significant correlations were detected between cannabis consumption and self-reported failures on the short-term internally-cued and long-term episodic subscales of the PMQ and the PM subscale of the PRMQ.

In contrast to these findings, Ciorciari and Marotte (2011) did not find any correlation between drug frequency and PM impairment after assessing MDMA users, MDMA-free cannabis users and controls who were naïve to illicit substance use.

Overall, the findings of five studies showed that there is a significant link between the frequency or/and level of drug taken and PM deficit with higher level of drug use being associated with poorer prospective memory.

3.4.2. The studies with lab-based PM tasks

3.4.2.1. Lab-based PM tasks

The lab-based PM tasks used in the reviewed research can be categorised into two groups: event-based and time-based. In event-based PM tasks, participants are requested to remember to carry out a task when cued by appropriate information; it could be short-term or long-term. For example, in the Pattern Recognition task, participants are asked to press the "/" key when two patterns appearing on the computer screen are the same or the "z" key when they are different. After each ½ minute period, the patterns increase in complexity and for each complexity level the computer holds a record of the number of correct responses. In order to save their scores, the participants are asked to remember to press the 'F1' key when the message "please wait a moment" appears on the computer screen at the end of each ½ minute period. This task is repeated three times and failure to press "F1" key is used to assess an event-based PM deficit (Hadjiefthyvoulou et al., 2011a; Gallagher et al., 2014 study 1). Another event-based PM task is the Belonging subscale of the Rivermead Behavioural Memory Test in which participants have to remember to ask for a belonging back at the end

of the experiment (McHale and Hunt, 2008). Regarding time-based PM tasks, participants are requested to remember to carry out a task at a certain point in time. For instance, in the Fatigue short-term PM test (Hadjiefthyvoulou et al., 2011a) participants are asked to indicate their fatigue level every 20 minutes throughout the experiment and in the Mail long-term PM test participants are asked to return a document via post a week or two later from the time of experiment (Gallagher et al., 2014 study 1).

There are also standardised tests, such as the Memory for Intentions Screen Test (MIST; Woods et al., 2008) and the Cambridge Prospective Memory Test (Wilson et al., 2004). In the former, participants are asked to complete a word-finder puzzle that serves as a distractor and carry out eight different PM tasks (time- and event-based), including four 2-min (short delay) and four 15-min (long delay) trials in 30 minutes. In the latter test, participants are asked to complete some distractor tasks (e.g., word-search) for a twenty-minute period while they need to remember to carry out the PM tasks (three time-based and three event-based).

Another popular task is the Jansari-Agnew-Akesson-Murphy (Jansari et al., 2004) test which is a virtual reality assessment where participants have to play the role of an assistant in an office setting. Their responsibilities include making the office ready for a meeting, turning on the coffee machine when the first person turns up for the meeting, noting the times of fire alarm, organising chairs and tables for a meeting etc. The JAAM task consists of eight constructs: planning, adaptive thinking, selection, creative thinking, prioritisation, together with action-based, event-based and time-based PM subscales.

Another virtual task that is used to measure PM is the Virtual Week task which is a board game where participants move around the board by rolling a dice (Rendell & Craik, 2000). The starting point is the time when people wake up and each circuit of the board represents a day. The participants are required to make choices and perform daily activities

for a virtual week (7 days) throughout the game. There are ten PM tasks for each virtual day: four regular (time- and event-based) where normal daily duties are undertaken; four irregular (time- and event-based) in which occasional tasks are undertaken; and two time-check tasks where participants are requested to stop playing the game and monitor actual time on the stop-clock.

Lastly, in a video-based PM task participants are given a list of 17 specific locations, such as "at Starbucks" and associated actions that are either questions to be answered, such as "what colour is the wall?" or tasks to be carried out at that location, such as "buy coffee." This is followed by the presentation of a 10-minute long video depicting a shopping area and concentrating on fronts of shops and passers-by that give cues about the location that are to be used to recall the previously shown location-action combinations (Bartholomew et al., 2010).

3.4.2.2. The studies using between groups design

Sixteen studies (Bartholomew et al., 2010; Bedi & Redman, 2008; Cuttler et al., 2012; Gallagher et al., 2014; Hadjiefthyvoulou et al., 2011a, 2011b; McHale & Hunt, 2008; Montgomery et al., 2010, 2012; Rendell et al., 2007, 2009; Terrett et al., 2014; Weinborn et al., 2011a, 2011b; Zakzanis et al., 2003) used lab-based tasks in order to examine participants' performance on PM.

Table 4 shows the results of the quality assessment of the sixteen studies. As seen, most studies had a good rating on the control confounding factors category. As a sample type and size, most studies were rated as moderate or below. Overall, of the sixteen studies, six studies were classified as being of good quality of evidence and ten studies as having moderate quality of evidence.

Table 4: The studies with lab-based testing methods.

		Abstinence Period **Sample Size <50**		Abstinence Period **50<Sample Size <100**			Abstinence Period **Sample Size >100**		
General Sample Confounding Control	≥3			18, 20					
	2			17	7		9		
	≤1								
Student Sample Confounding Control	≥3	16	13, 15			1, 4, 5	6		2, 3
	2								
	≤1								
Patient Sample Confounding Control	≥3		19	8					
	2								
	≤1	<3	≥3AND<7	≥7	<3	≥3AND<7	≥7	<3	≥3AND<7	≥7

In Table 5, the findings of the fifteen studies that assessed time- and event-based PM deficit are summarised. There was another study with a lab-based testing method that employed the video-based PM task to assess overall PM deficit. The result of this study also demonstrated that cannabis users performed significantly poorer than the controls on the video-based PM task (Bartholomew et al., 2010).

Table 5: The Overview of the findings of fifteen studies employing lab-based testing methods.

Reference	Event-based PM deficit	Time-based PM deficit
Zaknanis et al., 2003	✓	✓
McHale and Hunt, 2008	✗	✓
Terrett et al., 2014	✓	✓
Hadjiefthyvoulou et al., 2011a	✓	✓
Hadjiefthyvoulou et al., 2011b	✓	✓
Weinborn et al. 2011a	✓	✓
Weinborn et al. 2011b	✓	✓
Gallagher et al., 2014, study-1-	✓	✓
Gallagher et al., 2014, study-2-	✓	✓
Rendell et al., 2007	✓	✓
Rendell et al., 2009	✓	✓
Montgomery et al., 2010	✓	✗
Montgomery et al., 2012	✓	✓
Bedi and Redman, 2008	✗	✗
Cuttler et al., 2012 study 2	✗	✗

Keys: ✓= present, ✗= not present

Overall, most lab-based studies found either event-based or time-based PM deficits or both in illegal drug user groups, in particular MDMA/poly-drug users compared to non-user groups apart from two exceptions: Cuttler et al., (2012) study 2 and Bedi and Redman (2008) failed to find significant differences between illicit drug users and non-illicit drug users on time-based PM or event-based PM. However, as mentioned earlier, Cuttler et al. (2012) study 2 used an adjusted alpha level of .01 to control for inflation of Type I error. While less conservative alpha (e.g., .05) would have revealed a significant effect on the event-based PM.

Most studies did not differentiate between short- and long-term PM while testing either time- or event-based PM apart from four studies (McHale and Hunt, 2008; Hadjiefthyvoulou et al., 2011a; Gallagher et al., 2014, study 1, study 2). These four studies tested participants on short- and long-term time-based PM and found that poly-drug users were impaired in both types of time-based PM.

3.4.2.3. The studies using correlational designs

Three of the aforementioned studies with lab-based testing methods also looked into the relationship between the freguency or/and level of drug use and PM impairment (Hadjiefthyvoulou et al., 2011a; Gallagher et al., 2014 study 2; Montgomery et al., 2012).

As seen in Table 1, most studies were classed as "good" for control of potential and abstinence period and "moderate" for sample type and testing methods. In term of sample size, one study was classed as "good" (Gallagher et al., 2014, study 2), one study as "moderate" (Hadjiefthyvoulou et al., 2011a) and one study as "low" (Montgomery et al., 2012). The overall quality of evidence was good for two studies and moderate for one study.

Gallagher et al. (2014 study 2) tested ecstasy/poly-drug users, cannabis-only users, and nonusers of illicit drugs and found that poorer performance on the event-based and short-term time-based PM tasks were associated with higher long-term average typical dose of ecstasy. Montgomery et al. (2012) also reported this finding; the frequency of drug use was correlated with deficits in planning, time-based and event-based PM on JAAM after assessing twenty cannabis-only users and non-illicit drug users. Furthermore, Hadjiefthyvoulou et al. (2011a) tested drug users (ecstasy/poly-drug users and non-ecstasy drug users) and demonstrated that increased total lifetime use of various drugs were related to increased real world memory impairment. For example, there was a correlation between event-based PM score and life time use of cocaine, ecstasy or cannabis; and time-based PM score and life time use of cannabis or cocaine. Overall, the findings of three studies demonstrated that poorer PM performances were associated with a higher level of illegal drug use.

3.5. Discussion

The aim of this review was to assess studies reporting the presence or absence of PM deficits that are associated with the use of illicit drugs. PM, the ability to remember to do something in the future, is a crucial component for successful execution of countless

everyday tasks, including remembering to attend a meeting, paying the utility bill on time, buying bread on the way home. Multiple studies have demonstrated that PM errors account for more than half of all everyday memory problems (Schnitzspahn and Kliegel, 2009). Therefore, it is essential to keep track of the patterns of finding in this field in order to provide a comprehensive understanding of the potential impact of illicit drug use on PM.

The overall quality of evidence was good for six studies, moderate for sixteen studies and low for five studies. Most studies with self-report testing methods had a higher rating on the population representativeness categories (e.g., sample type and size) and lower rating on the abstinence period and confounding control categories compared to the studies with lab-based testing methods.

The studies employing self-report measures of PM, have shown mixed findings on the effect of illicit drug use on PM, but more evidence is in favour of illegal drugs being associated with time-based PM impairment (Heffernan et al., 2001a, 2001b study1, b study 2; Montgomery and Fisk, 2007; Fisk and Montgomery, 2008; Ciorciari and Marotte, 2011; Weinborn et al., 2011b), also some deficits in short-term (Heffernan et al., 2001a, 2001b study1, b study 2, Fisk and Montgomery, 2008; Hadjiefthyvoulou et al. 2011a) and internally cued PM (Heffernan et al., 2001a, 2001b study 1; Montgomery and Fisk, 2007; Fisk and Montgomery, 2008; Cuttler et al., 2012 study 2). However, these findings may not necessarily reflect pure PM deficit as the PMQ and PRMQ rely on self-reports and it has been noted that drug users may not be able to accurately recall their past memories. Cuttler et al. (2012) study 2 compared three groups (chronic cannabis users, experimenter cannabis users and non-users) on the lab-based and self-report tests and found only significant differences on the internally cued PM subscale. However, the deficit was eliminated after controlling for self-reported problems with retrospective memory and deficits on the RAVLT. Thus, it is possible that some of the impairments evident on the PMQ and PRMQ might be attributable

to other memory components rather than the PM itself. Moreover, as mentioned earlier, most studies with the self-report testing method that found significant PM impairment in drug user groups did not control or report the abstinence period, thus participants might have been in the comedown period during testing where the brain tries to readjust the chemical imbalance, hence the result might not reflect their real long-term cognitive abilities.

To overcome this problem, researchers have started using lab-based testing methods that are very close to everyday life settings (e.g., the Virtual Week). There are some memory components that are involved in lab-based PM tasks as well, for example, the Virtual Week task relies on associative learning component of memory (Montgomery, Fisk, Newcombe, et al., 2005). However, they were designed to primarily test PM unlike the self-report PM measures. These researchers have demonstrated consistent findings with illicit poly-drug users scoring worse than non-users on either event-based or time-based PM tasks or both (Zaknanis et al., 2003; McHale and Hunt, 2008; Terrett et al., 2014; Hadjiefthyvoulou et al., 2011a, 2011b; Weinborn et al. 2011a, 2011b; Gallagher et al., 2014 study 1, study 2; Rendell et al., 2007, 2009; Montgomery et al.,2010, 2012). Although many different types of PM tasks were used in these studies, the results were consistent in that they found that drug users exhibited partial or complete PM deficits. It is unlikely that these findings are due to individual differences (e.g., age, gender, education level, IQ etc.), as the groups were well matched on these factors.

The body of work summarised in the current review also provided consistent results on the link between the amount of illicit drug consumption and PM deficit (Rodgers et al., 2001, 2003, 2006; Arana et al., 2011; Cuttler et al., 2012 study 1; Hadjiefthyvoulou et al., 2011a; Gallagher et al., 2014, study 2; Montgomery et al., 2010) apart from one study (Ciorciari and Marrotte, 2011) that failed to find the link. However, it should be noted that there was inconsistency in recording the level of illicit drug use (e.g., duration of use, average

dose use, frequency of use, age at first use, total lifetime dose and usage etc.). Hence, it is hard to draw any firm conclusions based on a specific variable reflecting the level of drug use. There are findings that show that lifetime usage of both ecstasy and cannabis were related to either time-based or event-based PM measures or both indicating that as the lifetime usage goes up, the PM deficits increase in magnitude (Hadjiefthyvoulou et al., 2011a, 2011b; Montgomery et al., 2010, 2012; Rodgers et al., 2001; Arana, et al., 2011; Gallagher et al., 2014, study 2; Weinborn et al., 2011a). With regard to frequency of use, cocaine and ecstasy use were significantly correlated with several of the PM measures including time- and event-based or short- and long-term (Hadjiefthyvoulou et al., 2011a; Rendell et al., 2007; Zakzanis et al.,2003). The frequency of cannabis use was also significantly associated with the two time-based PM measures (Gallagher et al., 2014, study 2). Furthermore, early users of cannabis displayed more deficits with long term PM and performed worse compared to the control group in the internally-cued PM strategy use (Arana, et al., 2011). These indicators of the level of drug use may be correlated and moderated by the type and potency of the drug. Based on the available research it can be said that the frequency or/and level of drugs taken is one of the greatest predictors in magnitude of PM impairment.

The findings from the range of studies demonstrated that excessive drinking can lead to impairments in everyday PM (Heffernan, 2008). Therefore, it is crucial to control for alcohol use while assessing PM performance. Most studies reviewed here found no significant differences due to alcohol use between drug user and control groups (Weinborn et al., 2011a; Heffernan et al., 2001a; Hadjiefthyvoulou, et al., 2011b; Montgomery et al., 2012; Rendell et al., 2009; Bedi and Redman, 2008). However, in some studies the group of drug users consumed more alcohol than the control group (Montgomery et al., 2010; Arana, et al., 2011; Hadjiefthyvoulou et al.,2011a; Heffernan., 2001b, study 1 and 2; Montgomery and

Fisk, 2007; Gallagher et al., 2014, study -2; Bartholomew et al., 2010; and Fisk and Montgomery, 2008). After controlling for alcohol consumption, the illegal drug use-related differences in PM remained significant in these studies (Hadjiefthyvoulou et al.,2011a; Heffernan et al., 2001b, study 1 and 2; Montgomery and Fisk, 2007; Gallagher et al., 2014, study -2; Bartholomew et al., 2010; Fisk and Montgomery, 2008). Therefore, in these studies, alcohol use does not appear to have an effect on PM deficits over and above the effect due to drug use.

As mentioned in the introduction, PM relies on various cognitive processes, including executive functioning and working memory. Several studies have assessed the consistency between PM deficit and deficits in other memory and executive functions. For example, Rendel, et. al. (2009) demonstrated that methamphetamine-induced PM deficit co-occur with deficits in retrospective memory, as ex-methamphetamine users scored worse than controls on the RAVLT, Digit Span, Phonemic Verbal Fluency and Hayling Sentence Completion Test in addition to PM. However, the literature does not support the claim that drug use affects all cognitive functions equally. For example, Hadjiefthyvoulou, et al. (2011b) did not find any effect on the RAVLT with ecstacy/poly drug users, whereas PM was impaired. It turns out that some non-PM tasks, such as computation span task (Montgomery and Fisk, 2007) show drug-related deficits, while other tasks, such as stem completion (Zakzanis et. al., 2003) do not. This is even more striking when considering assessments of non-PM executive function, such as Random Letter Generation (Montgomery and Fisk, 2007), Behavioural Rating Inventory of Executive Function (BRIEF; Hadjiefthyvoulou, et al., 2011b), and even the Wisconsin Card Sorting Test (WCST, Arana, et al., 2011), all of which do not show drug-related deficits.

These results need to be interpreted with caution, however, as the reviewed literature on drug use and PM, did not use a standard battery of non-PM tasks. This necessarily means

that not enough data has been published to assess whether the drug-related PM deficits reflect a deficit on all cognitive functions or is specific to functions underlying PM function. Based on the inconsistencies in the effects of drugs on non-PM functions, there is some suggestion of cognitive specificity - some cognitive functions are specifically affected by drug use. It is acknowledged that in the limit, excessive drug use affects all cognitive functions. Therefore, the differential effect of drug use on PM and non-PM tasks may in part reflect the sensitivity of PM tasks to disruptions of cognitive sub-processes (e.g., recognising a PM trigger) and in part the drug type, drug dosage, and drug tolerance of participants in the studies in the current literature. To adjudicate among the possibilities, future work on the impact of drugs on PM need to include non-PM memory tasks as well as well-established tasks of executive functions, such as the WCST or Tower of London (Shallice, 1982).

Interestingly, all the studies reviewed in this paper found significant PM deficit at least one PM measure with one exception (Bedi and Redman, 2008), suggesting the possibility of publication bias. For example, as seen in Table 2, there is a gap in the research literature of studies with a small sample size. This could be due to those studies not finding significant effects and therefore not published or submitted for publication. Even though a publication bias is not impossible, most studies with a large sample size reported significant findings.

The pattern of results found in the current review support previous empirical studies in which it has been reported that illegal drug use was associated with a range of neurotoxic effects. For example, Ramaekers et al. (2009) directly assessed the pharmacological effect of MDMA on PM and brain activity in a double-blind, placebo-controlled, cross-over study. Twelve recreational MDMA users received MDMA 75 mg and placebo and performed a lab-based PM task during functional imaging. The result showed that a single dose of MDMA increased PM failures and that MDMA concentration in plasma was positively correlated to

number of prospective memory failures. Furthermore, ecstasy use has been linked to structural and functional damage to serotonergic cells in the frontal cortex of the brain that is believed to support PM (McCann et al., 2005; Urban et al., 2012). The medial temporal hippocampal structure is also linked to PM (Gordon, et al., 2011). Abnormalities in these brain regions were observed with different types of drug users, such as Cannabis users (Jager et al., 2007), cocaine users (Nestler, 2005) and ecstasy users (Kish et al.,2010).

The included studies examined mostly poly-drug users who consumed a combination of different drugs. Thus, it is hard to associate PM impairment with a particular type of drug type (e.g., sedative and stimulant) or a specific drug (e.g., MDMA and cocaine). However, in most studies, ecstasy poly-drug users scored significantly worse than non-ecstasy users (Hadjiefthyvoulou, et al., 2011b; Gallagher et al., 2014, study 1; Zakzanis et al., 2003; Montgomery et al., 2010) or non-drug users (Heffernan et al., 2001a, 2001b; Montgomery and Fisk, 2007; Rendell et al., 2007; Weinborn et al., 2011a; Hadjiefthyvoulou et al., 2011a) on PM measures, specifically on the long-term PM subscales (Gallagher et al., 2014, study 1, 2; Heffernan et al., 2001a, 2001b; Montgomery and Fisk, 2007; Weinborn et al., 2011a; Rodgers et al., 2001, 2003; and Ciorciari et al., 2011). Furthermore, as mentioned earlier, Ramaekers et al. (2009) demonstrated MDMA-specific toxicity on PM performance, therefore it can be argued that the use MDMA associated with PM impairment. There might also be a possible link between cannabis use and PM impairment as in multiple studies cannabis use was associated with PM impairments (Hadjiefthyvoulou, et al., 2011b; Montgomery et al., 2012; McHale et al., 2008; Gallagher et al., 2014, study 2; Cuttler et al., 2012 study 2; Arana et. al., 2011; Ciorciari et al., 2011), in particular with internally-cued PM deficits (Cuttler et al., 2012 study 1, 2; Arana et. al., 2011; Fisk and Montgomery, 2008; Montgomery and Fisk, 2007; and Rodgers et al., 2001). However, these results need to be interpreted with caution as some studies fail to find a significant difference between cannabis

user and non-user groups or a link between cannabis use and PM impairment. For example, in Gallagher et al., (2014, study 2) and Hadjiefthyvoulou, et al., (2011b) studies, there were no significant differences between cannabis-only users and non-users even though there were significant differences between MDMA polydrug users and non-users. Moreover, Ciorciari and Marotte (2011) did not find any correlation between drug frequency and PM impairment in MDMA-free cannabis users. In addition to this, a few studies controlled for cannabis use while assessing the possible consequences of MDMA use on PM. After controlling for cannabis use, the results remained significant which shows that cannabis is not an important mediator of PM deficits in MDMA polydrug users (Heffernan et al., 2001a, 2001b study 1, 2).

Taken together, these results suggest that cannabis and MDMA differentially affected aspects of PM. Ecstasy use was associated with the long-term PM impairments, which could be related to storage and retrieval difficulties. On the contrary, cannabis use was associated with reports of 'here-and-now' memory problems in the internally cued PM.

3.6. Strengths, limitations, and future directions

This review was based on an extensive search of electronic databases, study selection, data extraction, study categorisation and comprehensive quality of evidence assessments. However, as mentioned earlier, the review might be limited by publication bias, whereby studies with non-significant results are less likely to be published. The inclusion of only studies published in the English language might also be seen as a limitation of this review.

It is clear that further studies are needed to clarify the negative effect of illegal drug use on PM by employing lab-based testing methods rather than only employing self-report testing methods (as Cuttler et al., 2012 demonstrated people with a history of drug use had self-report problems with retrospective memory), recruiting a greater sample size, better control of potential confounds (as there are many factors that might affect PM performance),

recruiting a sample from the general population rather than the student or patient populations, requiring a longer abstinence period (at least a week), and using non-drug user participants as a control group. Future studies also should test particular drug users, such as only cannabis or MDMA users in order to understand the effects of a particular drug on PM. Moreover, in future studies, there should be consistency in recording the level of drug use. Lastly, most studies in this review were conducted by the same research group, therefore it is also necessary to carry out similar studies in different institutions and countries in order to maximise the generalisability of the findings.

3.7. Conclusion

To conclude, the present review intended to determine the impact of illicit drug use on PM, a crucial aspect of day-to-day cognitive functioning. The pattern of findings from studies with mostly moderate quality of evidence in this review suggests that PM is impaired in illegal drug users and should thus be included in the list of neuropsychological deficits resulting from illegal drug use.

Chapter 4: Recreational Drug Use and Prospective Memory

This chapter presents a study on recreational drug use and prospective memory. This chapter was published: Levent, A., & Davelaar, E. J. (2022). Recreational drug use and prospective memory. *Psychopharmacology*, *239*(3), 909–922. https://doi.org/10.1007/s00213-022-06081-0

4.1. Abstract

PM impairment in recreational drug users has been documented in recent years. However, most studies on the effects of drugs on PM contain several methodological challenges, such as small sample size (<100 participants), unrepresentative sample type (e.g., student or patient), short abstinence period (<7days), and lack of control of potential confounds (e.g., sleep, and IQ). The present study investigated the possible consequences of recreational drug use on prospective memory, using self-report and lab-based prospective memory measures while overcoming the methodological challenges. The sample was composed of 47 non-users (27 females, age range from 18 to 50+) and 53 drug-users (21 females, age range from 18 to 50+). Recreational drug users reported significantly more deficits in the Long-term Episodic, Short-term Habitual and Internally cued PM failures subscales of the Prospective Memory Questionnaire. However, these deficits were eliminated after controlling for covariates (e.g., age, sleep quality, general health, alcohol usage). Recreational drug users also performed worse than non-users in the Short-term, Long-term, Event-based and Time-based PM subscales of the Royal Prince Alfred Prospective Memory Test**.** These results remained significant after controlling for the covariates. Drug users demonstrated greater impairments on time-based and long-term PM tasks thought to be linked with executive functioning. Taken together, the present study provides further support

for recreational drug-related deficits in PM and highlights a dissociation between self-report and lab-based PM measures.

4.2. Introduction

As summarised in Chapter 3, the findings from past studies on the effects of drug use on PM rather inconclusive as PM deficits were detected in some studies (Fisk and Montgomery, 2008; Heffernan et al., 2001a, 2001b), especially those with lab-based measures (Hadjiefthyvoulou et al., 2011a, 2011b; Rendell et al., 2007, 2009; Terrett et al., 2014), but not in others (Bedi and Redman, 2008; Cuttler et al., 2012 study 2), in particular those with self-report measures (Bartholomew et al., 2010; Ciorciari and Marotte, 2011).

Chapter 3 also shows that most investigations on the effects of illegal drugs on PM contain several methodological challenges, for instance, small sample size(<100 participants) (Hadjiefthyvoulou et al., 2011a, 2011b; Montgomery et al., 2010; Rendell et al., 2007, 2009; Montgomery et al., 2012; Zakzanis et al., 2003); a short abstinence period (Heffernan et al., 2001a; McHale & Hunt, 2008; Rendell et al., 2007; Terrett et al., 2014); unrepresentative sample, such as students (Arana et al., 2011; Bartholomew et al., 2010; Gallagher et al., 2014; Hadjiefthyvoulou et al., 2011a; Montgomery & Fisk, 2007; Zakzanis et al., 2003) or patients (Rendell et al., 2009; Weinborn et al., 2011b); neglecting potential confounds, such as alcohol use (Kyriacou et al., 2021; Zamroziewicz et al., 2017), depression (Li et al., 2013), sleep quality (Grundgeiger et al., 2014), and IQ (Uttl et al., 2013). Furthermore, previous studies mostly assessed regular drug users (Heffernan et al., 2001a, 2001b; Terrett et al., 2014) or drug addicts (Rendell et al., 2009; Weinborn et al., 2011b).

Additionally, Chapter 3 indicates that most studies had poor testing methods as they used only self-report questionnaires to assess PM impairment (Fisk & Montgomery, 2008; Heffernan et al. 2001a, 2001b; Rodgers et al., 2001, 2003, 2006). Self-reported data from people who have used illegal substances in the past may not be accurate since it relies on participants' ability to recall past memories correctly, which may be damaged by drug use. For example, Cuttler et al. (2012) compared three groups (chronic cannabis users, occasional

users and non-users) on the lab-based and self-report tests and found only significant differences on the internally cued PM subscale. However, the effect disappeared after controlling for self-reported problems with retrospective memory and deficits on the RAVLT. Thus, it is possible that some of the impairments evident on the self-report PM measures (e.g., the PMQ and PRMQ) might be attributable to other memory components rather than the PM itself. By contrast, it is believed that lab-based tests are more objective and reliable as they offer real-world function testing through the use of a controlled setting (Montgomery et al., 2012).

This is consistent with findings from previous studies employing self-report measures of PM, where mixed findings of the effect of illegal drug use on PM have been reported, with some studies finding an effect (Hadjiefthyvoulou et al., 2011b; Heffernan et al., 2001a, 2001b; Fisk & Montgomery, 2008; Weinborn et al., 2011b), while other studies did not (Bartholomew et al. 2010; Ciorciari and Marotte 2011; Cuttler et al. 2012; Weinborn et al. 2011a). This contrasts with studies that employed lab-based testing methods reporting consistent findings with illegal poly-drug users scoring worse than non-users on either event-based or time-based PM tasks or both (Gallagher et al., 2014; Hadjiefthyvoulou et al., 2011a, 2011b; McHale & Hunt, 2008; Montgomery et al., 2010, 2012; Rendell et al., 2009, 2007; Terrett et al., 2014; Weinborn et al., 2011a, 2011b; Zakzanis et al., 2003).

Therefore, the aim of the present study is to assess the possible consequences of light or recreational drug use on PM while addressing the methodological challenges facing previous studies. As suggested in Chapter 3, both lab-based and self-report measures of PM were used and 100 participants were recruited from the general population. In addition, a comprehensive number of possible moderating variables including age, fluid intelligence, sleep quality, general health, level of education, alcohol and nicotine use were examined and where appropriate included as covariates in the statistical analyses. Drug users, were asked to

abstain from any recreational substance use for at least 7 days. It was hypothesised that despite the light drug use a negative impact on PM would be observed. It was also expected this effect to be observed using lab-based measures, but not necessarily using self-report questionnaires.

4.3. Methods

4.3.1. Participants

One hundred participants were recruited via advertising (e.g., posters, leaflets) and social media (e.g., Facebook). The sample consisted of 47 non-users (27 females, age range from 18 to 50+) and 53 drug-users (21 females, age range from 18 to 50+)[1]. Participants were classed as users if they currently use or had used in the past any recreational drugs. No drugs were excluded. All participants were native English speakers or were fluent in English. They were requested to abstain from any recreational substance use for at least 7 days and to abstain from alcohol consumption for at least 24 hours prior to the test session. None of the participants reported having had a history of neurological or psychiatric symptoms.

4.3.2. Design and Analysis

A quasi experimental design was used in this study. The independent variable was the recreational drug use status (users and non-users) and the dependence variables were the performances of the self-report and lab-based PM tests. SPSS was utilised to analyse the data. A chi-square test was used to determine the relationship between drug use status and background variables. Non-parametric tests (e.g., Mann Whitney U) were used as the variables were not normally distributed (all tests of normality ps < .05). In order to control for covariates, Quade's rank analysis of covariance (RANCOVA) was used (Quade, 1967), which has been shown to be robust and powerful when data is nonnormally distributed

[1]As participants were engaging with illegal activity, person-identifying information was not collected. Thus age brackets were used to instil an explicit sense of anonymity in participants.

(Conover & Iman, 1982). Family-wise error rates were mitigated using Holm-Bonferroni corrections.

4.3.3. Materials

Demographic information (e.g., age, gender and ethnicity) and current use of alcohol, nicotine and illegal drugs were obtained via background questionnaires.

The 12 items short form of Raven's Advanced Progressive Matrices was used to measure fluid intelligence in which participants were shown eight figures arranged in an incomplete 3x3 matrix and were required to infer the rules within each row and column in order to choose one of eight options that would complete the matrix (Arthur and Day 1994).

The General Health Questionnaire (GHQ; Goldberg & Hillier, 1979) was used to identify minor psychiatric disorders in the sample population. It assessed participants' current states and asked if that differed from their usual states. There were 12 items and each item was accompanied by four possible responses, typically being 'not at all', 'same as usual', 'rather more than usual' and 'much more than usual', scoring from 0 to 3, respectively. The total possible score on the GHQ 12 ranges from 0 to 36. The higher scores indicate greater health concerns. It has previously been observed that the GHQ is reliable and valid tool for measuring psychological distress (Guan & Han, 2019; Laranjeira, 2008; López-Castedo & Fernández, 2005; Winefield et al., 1989). In the present study, an explanatory factorial analysis using a principal component extraction methods and varimax rotation revealed three significant components, which accounted for 65.4% of the total variance. These results reflect those of Martin (1999) who also found that a three factor solution fits better than structures with one or two components previously identified. Furthermore, Cronbach's alpha coefficient is .88, which shows high internal consistency.

The Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) was used to investigate any group differences in sleep quality over the last month. The PSQI measures

seven areas, including sleep latency, sleep disturbances and sleep duration. Each component was scored on a 0-3 scale and an overall score was calculated by adding the seven component scores, which ranged from 0 to 21 where lower scores indicate a healthier sleep quality. Previously, the PSQI have showed good internal consistency, test-retest reproducibility, and a good validity (Backhaus et al., 2002; F. Fontes et al., 2017; Popević et al., 2018). In the current study, two components were extracted by using an explanatory factorial analysis. Those results resonate with other research that found the two-factor models of the PSQI to be reliable and consistent, compared to the unidimensional model (Dunleavy et al., 2019). Internal consistency was acceptable (Cronbach's $\alpha = 0.7$).

The PMQ (see Appendix E) is a self-report measure of PM which contains 52 items that assess short-term (ST) habitual PM (e.g., "I forgot to tip when I finished dinner at a restaurant"), long term (LT) episodic PM (e.g., "I missed appointments I had scheduled"), internally-cued PM (e.g., "I forgot what I came into a room to get"); and the use of memory aiding strategies (e.g., "I keep a calendar or appointment book in order to remember to do things"; Hannon et al., 1995). Responses in the three subtests range from 0 (no PM failures) to 4 (a great deal of PM failures) and in the use of memory aiding strategies scale range from 0 (never used) to 4 (a high number of strategies used). Hence, higher scores reflect more forgetting and strategies used. The PMQ has an excellent internal consistency (.92) and a good test-retest reliability (.88; Hannon et al. 1995; Blondelle et al., 2020). Furthermore, the PMQ subscales exhibited significant correlations with all of the reliable objective PM tests (Uttl & Kibreab, 2011).

Royal Prince Alfred Prospective Memory Test (RPA-ProMem) is a four-item behavioural measure of PM designed to be administered among other cognitive test batteries (Radford et al., 2011). It contains two event-based (EB) and two time-based (TB) PM tasks, to be completed either within the assessment session (ST) or up to a week following the

assessment session (LT). For EB PM tasks, participants were required to ask for the information sheet about the note-taking at the end of the experiment (ST) and to email to the researcher, saying how the weather was when they got home (LT), they were asked an estimated time of arrival to their home at the end of the testing session which was used to score their LT EB PM performance (e.g., whether they emailed on time or not). For TB PM tasks, they were instructed to tell the researcher at the end of the first 15 minutes of the experiment (ST) what they ate last on that day and to go to the given link one week after the session to answer the question (what is your favourite colour) they were asked at the end of the experiment (LT). The e-mail address of the researcher and link with the participation ID was printed on a card and given to participants at the end of the experiment. Each category was scored out of 3 points, giving a maximum total score of 12. For more details about test items and scoring criteria, see Appendix F. To achieve the maximum score for each item, participants needed to recall the task content correctly and either respond to the environmental cue or at the appropriate time. Lower points were given for responding in a partially correct manner (e.g., 2-5 minutes delay in response). The creators of the RPA-ProMem test reported a strong inter-rater reliability (.90; Radford et al. 2011) and a good alternate form of reliability (Rho = .71; Radford et al. 2011). It also proved to be sensitive enough to identify patients' PM impairments compared to healthy controls (Radford et al., 2011).

4.3.4. Procedure

The study consisted of two phases. In the first phase, participants were informed of the general purpose of the experiment and written informed consent was obtained. They were sent a link to complete an online survey that contained self-report questionnaires (e.g., the demographics questionnaires, PMQ, GHQ and PSQI). In the second phase, participants were in the testing lab, where they completed the RPA-ProMem as well as other tests to create the

temporal spacing needed for the RPA-ProMem. These "filler" tests were irrelevant cognitive tests to distract the participants from actively remembering the PM cues for the ST-EB and ST-TB tasks. For example, after receiving the ST task instructions, the participants would complete the IQ, Digit Span, Wisconsin Card Sorting Game, and Stop-It Signal tests (the results of those tests will be presented in Chapter 5). They would then go home and complete the long-term components of the RPA-ProMem. At the end of the study, participants were sent the debrief sheet, given £25 Amazon voucher, and drug education leaflets. The study was approved by the Ethics Committee of Birkbeck University, and was administered in accordance with the ethical guidelines of the British Psychological Society.

4.3.5. Level of Drug Use Classification

There is no single agreed upon set of criteria to identify heavy, moderate or light drug use in the scientific literature. For example, Fisk and Montgomery (2009) defined heavy ecstasy users who consumed 400 tablets in their lifetime (mean=149.69, SD=96.91) and light users who consumed less than 400 tablets mean: 1000.21, SD: 786.4). Whereas, Fox, Parrot, et al. (2001) defined low ecstasy users who consumed between 0 and 100 ecstasy tablets, medium users who consumed 100 and 500 tablets and high-intensity users who consumed 500+ tablets. Similar issues are present in studies with other substance users. For instance, Riba et al. (2015) defined heavy cannabis users who consumed cannabis daily for at least the last 2 years and occasional users who consumed cannabis on less than 50 occasions in their lifetime. Whereas Ong et al. (2021) and Vidot et al. (2017) classified light users who used cannabis less than 10 days in the past 30 days, moderate users who used cannabis 10–20 days in the past 30 days, and frequent users who used cannabis more than 20 days in the past 30 days.

Also, each drug has a different classification for level of drug use. For example, using ecstasy on 10 or more separate occasions in the last 90 days was classified as heavy use

(Sterk et al., 2007). Whereas, using cannabis at least five times a week was classified as heavy use (Lahanas & Cservenka, 2019). It can be a completely different classification for psychedelic drugs which are usually taken a few times in a lifetime.

In this study, most drug users were current polydrug users who mostly consumed cannabis, MDMA/ecstasy and cocaine. There were also ex-users (mainly ex-cannabis users). However, it should be noted that an ex-user of certain drugs is a current user of other drugs. For instance, five ex-cannabis users were current cocaine users (see Appendix O) and four ex-cannabis users were current ecstasy users (see Appendix N). Thus, the level of drug use classification was done based on the frequency of those three drug use. Participants who consumed cannabis, cocaine and/or MDMA/ecstasy weekly or more often (who reported that they used one of those drugs 1 or 2 times a week or 3 or more times a week) were classified as heavy users; participants who consumed any of those drugs (individually or together) 1 or 2 times a month were classified as moderate users; and participants who consumed any of those drugs 1 or 2 times a year or 1 or 2 times every three months were classified as light users.

4.4. Results

The demographic information of users and non-users together with alcohol/nicotine use, fluid intelligence, and health variables are presented in Table 6. Chi-square tests were used to assess the relationship between the background variables and drug use, for which some of the cells were combined as they had expected count less than 5. For example, for alcohol use, never and monthly or less; and 2 to 3 times a week and 4 or more times a week were combined. For age, 18-25 and 26-30 (e.g., 18-30), 31-35 and 36-40 (e.g., 31-40), 41-45, 46-50 and 50+ (e.g., 41-50+) were combined. For degree, secondary and college degrees; and masters and advanced/PhD degrees were combined. For ethnicity, participants were categorised as white and non-white and for nicotine use, they were classified as smoker and

non-smoker. Chi-square tests revealed that the two groups did not differ in age, gender, level of education or ethnicity. The groups were mainly between 26 and 45 years old, of white ethnic background and were educated to BSc or MSc level. There was a group difference with respect to alcohol and nicotine use, with drug users having a higher frequency of alcohol use ($\chi^2(2, N = 100) = 19.91, p < .001$) and more smokers ($\chi^2(1, N = 100) = 15.83, p < .01$) than non-users. Nicotine use was associated with cannabis use, with 76.7% of smokers and 35.7% of non-smokers using cannabis ($\chi^2(1, N = 100) = 14.11, p < .001$). Mann-Whitney U-tests also revealed that compared with non-users, drug users had significantly more problems with general health ($U = 850.5, p < .01$) and sleep quality ($U = 644.5, p < .001$). No group difference was apparent on intelligence ($p > .81$). As nicotine use was associated with cannabis use in particular, only alcohol consumption and the scores on the GHQ and PSQI were used as covariates. Given the age range of the individuals in this sample, age was also included in analyses as a covariate as it has been found that performance on PM tasks declines in older age (Henry et al., 2004; Ihle et al., 2013).

Table 6. Demographic information of users and non-users together with alcohol/nicotine use, fluid intelligence, and health variables.

		Drug user	Non-user	Total
N		53	47	100
Gender (M/F)		32/21	20/27	52/48
Age	18 – 25	5	4	9
	26 – 30	9	6	15
	31 – 35	11	15	26
	36 – 40	11	7	18
	41 – 45	11	7	18
	46 – 50	3	7	10
	50+	3	1	4
Ethnicity[a]	White	38	28	66
	Asian	4	11	15
	Black	5	5	10
	Mixed	3	3	6
	Other	3	0	3
Education level	Secondary	2	3	5
	College	7	8	15
	Bachelor	26	19	45
	Masters	14	15	29
	Advanced/PhD	4	2	6
Alcohol use* **	Never	2	14	16
	Monthly or less	9	13	22
	2 – 4/month	17	15	32
	2 – 3/Week	18	4	22
	>4/week	7	1	8
Nicotine use**	Never	28	42	70
	Several/month	8	2	10
	Several/week	6	2	8
	Once/day	4	0	4
	Several/day	7	1	8
RAPM	Median	10	11	11
GHQ**	Median	12	8	10
PSQI* **	Median	6	3	5

** $p < .01$, *** $p < .001$

[a] The following classification of ethnicity was used: Asian includes British-Asian, Black includes Black-British, African, and Caribbean. RAPM = Raven's Advanced Progressive Matrices, GHQ = General Health Questionnaire, PSQI = Pittsburgh Sleep Quality Index

As seen in Table 7, the most commonly used recreational drug was cannabis, followed by cocaine, MDMA and GHB. Most drug users were classified as light drug users.

Table 7. Drug use frequency for the drug user group.

	1	2	3	4	5	6	Total
Cannabis	14	16	10	3	2	3	48
Cocaine	4	9	11	10	2	1	37
MDMA or Ecstasy	6	11	13	6	0	0	36
GHB	3	9	5	1	0	0	18
Hallucinogenic	4	11	1	0	0	0	16
Ketamine	7	9	1	0	0	0	17
Methamphetamine	6	4	1	1	0	0	12
Mephedrone	4	4	2	1	0	0	11

1 = Ex-users; 2 = Very Rarely: 1 or 2 times a year; 3 = Rarely: 1 or 2 times every three months; 4 = Occasionally: 1 or 2 times a month; 5 = Frequently: 1 or 2 times a week; 6 = Very Frequently: 3 or more times a week.

Approximately 72% of all drug users reported polydrug use, see Figure 4 for the overview of drug use profiles with the number of participants for each profile.

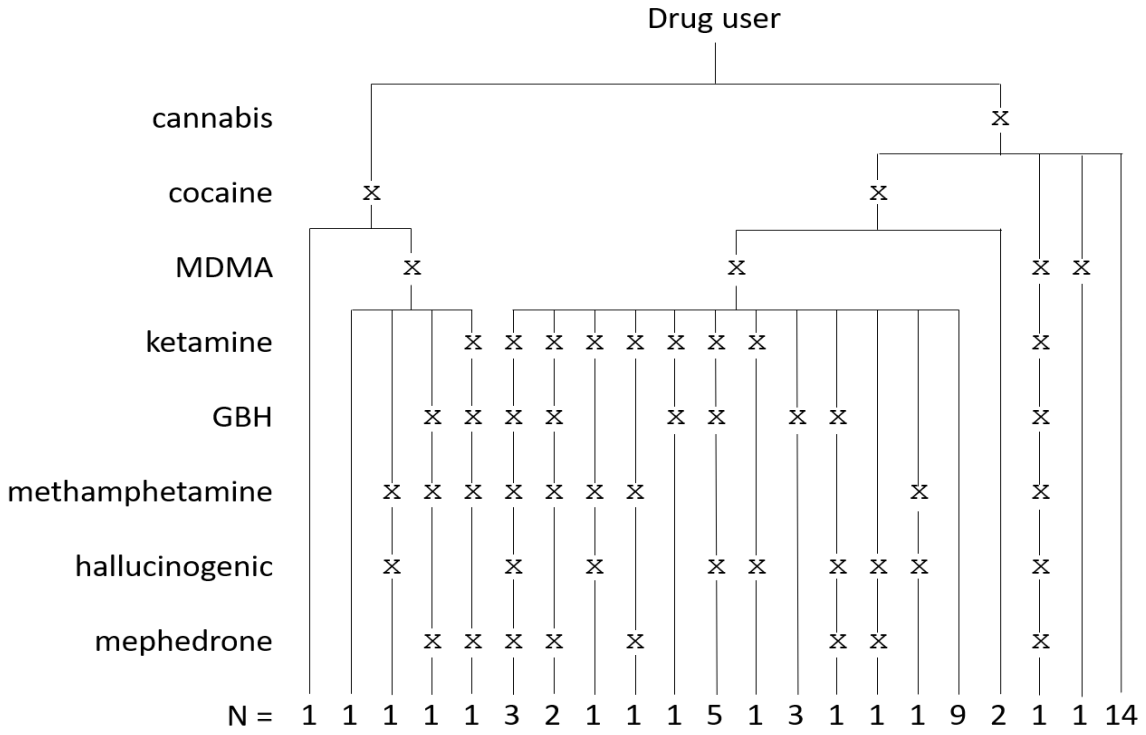

Figure 4. Overview of drug use profiles with the number of participants for each profile which provides a breakdown of the polydrug usage.

Table 8 and Table 9 show Spearman correlations between PM measures and the covariates. While the PMQ subscales were correlated with the two covariates, the RPA-

ProMem subscores did not, apart from a weak association between PSQI and long-term PM. One way ANOVAs were run to assess a relationship between PM measures and the other covariates (e.g., age and alcohol use), however, none of the relationships was significant.

Table 8. Spearman correlations between the PMQ subscales and the covariates.

	LT episodic PM failures	ST habitual PM failures	Internally cued PM failures	Use of memory aiding strategies
GHQ	.28**	.35***	.38***	.48***
PSQI	.37***	.25*	.38***	.31**

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

Table 9. Spearman correlations between the RPA-ProMem subscales and the covariates.

	ST PM	LT PM	EB PM	TB PM
GHQ	.03	-.16	-.03	-.12
PSQI	-.08	.27**	-.19†	-.19†

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

There were no correlations among the subscales of the PMQ and the RPA-ProMem (see Appendix G), apart from marginal correlations between the long-term PM failures and the long-term RPA-ProMem ($r_s(100) = -.181$, $p = .071$) and between the long-term PM failures and the time-based RPA-ProMem ($r_s(100) = -.184$, $p = .067$) in the whole sample. The GHQ and PSQI were moderately correlated ($r_s(100) = .40$, $p < .001$). See Appendix H for correlations among the PMQ subscales and see Appendix I for correlations among the RPA-ProMem subscales.

The profile of self-reported PM and lab-based test was compared between the drug user and non-user group (see Table 10). Mann-Whitney tests revealed that the groups differed on all subtests, apart for the use of memory aiding strategies. However, only the scores on the RPA-ProMem subscales remained significant after Holm-Bonferroni correction for multiple comparisons. When taking the covariates (sleep and general health) into consideration, the uncorrected scores for the PMQ subscales became non-significant, whereas the RPA-

ProMem subscales remained significant after correction. When alcohol use and age (with 3 categories) were included as covariates in the RANCOVA the same results were obtained.

Table 10. Comparison of PMQ and RPA-ProMem scores between drug users and non-users

	Drug user	Non-user	Mann-Whitney		RANCOVA	
	Mdn	Mdn	*U*	*p*	*F*	*p*
PMQ						
LT Epi	5	2	962	.049	0.100	.753
ST Hab	1	0	941	.026	1.384	.242
Int cued	4	2	955.5	.044	0.053	.818
AidPM	19	14	995.5	.084	0.095	.759
RPA-ProMem						
ST PM	4	6	1652	.003*	8.618	.004*
LT PM	3	6	1913.5	< .001*	11.652	.001*
EB PM	3	6	1744.5	< .001*	8.194	.005*
TB PM	3	5	1847.5	< .001*	11.575	.001*

* Significant after Holm-Bonferroni correction. LT Epi = Long-term episodic PM failures, ST Hab = Short-term habitual PM failures, Int cued = Internally cued PM failures, AidPM = use of memory aiding strategies. ST PM = short-term PM, LT PM = long-term PM, EB PM = event-based PM, TB PM = time-based PM. RANCOVA = ranked ANCOVA with GHQ, PSQI, age and alcohol as covariates.

The frequency of the given responses for each trial by the timing of the responses (e.g., on time, 2–5 mins delay or ahead of time etc.) by drug users vs. non-users in the RPA-ProMem test was summarised in Table 11. It is apparent that, in most subscales, drug users failed to give a response to the given tasks or perform the tasks on time.

The difference in accuracy is also apparent when the performance was scored across the four trial types (Mean_users=1.77, Median_users=2, Mean_non-users=2.91, Median_non-users=3, U =587, p <.001).

Table 11: The frequency of the given responses for each trial by the timing of the responses (e.g., on time, 2–5 mins delay or ahead of time etc.) by drug users vs. non-users in the RPA-ProMem test.

RPA-ProMem Test Items								
Part 1 (Short-term, Time-based)								
	Drug users (53)				**Non users (47)**			
	On time	Delay 2–5 mins	Delay >5 mins	Total	On time	Delay 2–5mins	Delay >5 mins	Total
Correct response	27	0	13	40	30	7	2	39
Incorrect response	2	3	0	5	5	0	1	6
Total	29	3	13	45	35	7	3	45
No Response				8				2
Part 2 (Short-term, Event-based)								
	On time	Delay 2–5 mins	Delay >5 mins	Total	On time	Delay 2–5mins	Delay >5 mins	Total
Correct response	33	2	0	35	40	0	1	41
Incorrect response	3	0	0	3	0	0	0	0
Total	36	2	0	38	40	0	1	41
No Response				15				6
Part 3 (Long-term, Event-based)								
	On time		Incorrect time	Total	On time		Incorrect time	Total
Correct response	23		5	28	39		0	39
Incorrect response	3		2	5	0		3	3
Total	26		7	33	39		3	42
No Response				20				5
Part 4 (Long-term, Time-based)								
	On time		Incorrect time	Total	On time		Incorrect time	Total
Correct response	11		9	20	31		1	32
Incorrect response	1		4	5	2		1	3
Total	12		13	25	33		2	35
No response				28				12

4.5. Discussion

PM, the ability to remember to carry out a particular behaviour at some future point in time, is a crucial cognitive ability for successful and independent everyday life (Hering et al., 2018). The self-report and lab-based PM measures were used to assess PM in recreational

light drug users.In the self-report PMQ measure, drug users reported more failures on LT episodic, ST habitual and internally cued PM. There was no group difference in the use of memory aiding strategies. These differences did not survive a conservative statistical correction and did not reach statistical significance when controlled for moderating variables, including sleep quality, age, alcohol usage and general health which also measured emotion well-being. This result is consistent with a previous study where anxiety and depression were confounded with self-reported memory complaints amongst ecstasy users, possibly due to the effects of mood-related negative self-appraisals (Bedi & Redman, 2008). Furthermore, self-reported PM measures were criticised for relying on the ability to remember past events at the time of recollection (e.g., episodic autobiographical memory) which has been thought to be impaired in drug users (Devin et al., 2015; Oliveira et al., 2007). For instance, as mentioned in the introduction of this chapter, Cuttler et al. (2012) found that the PM deficit became non-significant after controlling for self-reported problems with retrospective memory. Poorer quality of sleep in drug users may be mediated by the drugs interfering with the natural wake-sleep cycle (Gordon, 2019; Navarro-Martínez et al., 2020). However, it should be noted that drug users might not correctly report their sleep quality due to restropsective memory deficits. Thus, those findings should be interpreted with caution.

Recreational drug users also performed worse than non-users in all the subscales of the lab-based RPA-ProMem test, which remained significant after controlling for covariates and statistical correction. This supports previous findings showing an association between drug use and PM impairment on lab-based measures (Gallagher et al., 2014; Hadjiefthyvoulou et al., 2011a, 2011b; McHale & Hunt, 2008; Montgomery et al., 2010, 2012; Rendell et al., 2007, 2009; Terrett et al., 2014; Weinborn et al., 2011a, 2011b; Zakzanis et al., 2003).

There were no significant correlations between self-report and lab-based PM measures. Although surprising, this is in line with previous findings that show little or no overlap between lab-based and self-reported memory performance in drug user samples, for example, Moeller et al. (2016) assessed former cocaine abusers (n=14), active cocaine users (n=8) and healthy controls (n=13) on a visuo-perceptual accuracy task, using objective and self-report measures. A weaker link between self-reported confidence of performance and objective performance was found in active cocaine users. This result matches those observed in earlier studies (Bartholomew et al., 2010; Hadjiefthyvoulou et al., 2011a; Parvaz et al., 2016; Weinborn et al., 2011a).

The discrepancy between self-report and lab-based measures could be attributed to impaired metacognition in drug users (Goldstein, Craig, et al., 2009) which refers to awareness of one's own abilities (Hester et al., 2007). For instance, drug users rated their emotional and cognitive functioning as less impaired than do close informants (Verdejo-García & Pérez-García, 2008) and consistently demonstrated reduced awareness of errors (Hester et al., 2007, 2009). Moreover, individuals with cocaine use disorder reported a greater need for behaviour change than those without the disease, but they did not agree that they needed to change their drug usage (Moeller et al., 2020). Therefore, metacognitive deficits have the potential to contribute to the maintenance of drug use despite adverse consequences and well-intentioned plans to abstain.

EB tasks are measures of the retrospective component of PM (Raskin et al., 2011). Thus, the EB PM impairment is suggested to be related to the retrospective memory deficit such that the cue to the intention is not recognised and/or the associated intention not retrieved (Raskin, 2018). In multiple studies, drug users performed worse than non-users on retrospective memory measures (Cuttler et al., 2012; Devin et al., 2015; Oliveira et al., 2007). EB PM performances might also rely on the ability of associative learning. During the

formation of an intention, an associative link is made between the intention and the associated event related to this intention. Failure of forming this link might result in EB PM task failures. Deficits in associative learning were shown in ecstasy users (Montgomery, Fisk, Newcombe, et al., 2005). In a verbal paired associates task, participants were required to learn a list of word pairs and recall the second member of each pair after they were prompted with the first member. The result revealed that the ecstasy user group performed worse overall compared to the non-user group (Montgomery, Fisk, Newcombe, et al., 2005). Other studies employing associative learning tests also confirmed that ecstasy use may cause an impairment in associative learning (Fox et al., 2002; Gallagher et al., 2012).

Drug users failed to complete the given tasks on time in most subscales, compared to non-users which suggests that overall PM deficits could be due to lateness of remembering the intentions. Time perception, clock monitoring, attention shift and planning are important contributors to a TB PM task. Theoretically, time perception is based on an internal clock, also known as the biological clock in which a pacemaker continually emits pulses, with the number of pulses relating to a physical time interval recorded by an accumulator (Gibbon et al., 1984). At the molecular level, dopaminergic projections within the corticostriatal circuits play an important role in time perception (Petter et al., 2016) which have long been associated with drug use (Aston-Jones, 2015). For example, chronic cocaine use has been linked to a reduced functioning of Dopamine D2 receptors (Navarro et al., 2013; Volkow et al., 2009) in the anterior cingulate cortex (Goldstein, Alia-Klein, et al., 2009), the lateral PFC and the OFC (Goldstein & Volkow, 2011). Those changes in the dopaminergic system subsequently influence time perception. This matches well with findings showing that drug users exhibit impairment in time processing (Shahabifar & Movahedinia, 2016; Wittmann et al., 2007). However, further work is needed to assess whether the mechanism underlying time

perception is related to deficits in TB PM over short and long time intervals and for drugs other than cocaine.

There were greater deficits in the PM tasks (EB or TB) with longer ongoing task delay intervals in the drug user group, compared to shorter time delays. This might be related to executive functions underlying monitoring and maintenance of the cue-intention pairing over longer time delays. The TB PM tasks are strongly correlated with task measuring executive functioning (Groot et al., 2002). In addition, drug users have been shown to score worse than non-users on various executive functions tests (Fernández-Serrano et al., 2010; Heffernan et al., 2001a; Hester & Garavan, 2004; Montgomery, Fisk, Newcombe, et al., 2005; Sellaro et al., 2014).

An association between alcohol usage and PM was found in the current study which resonates with previous studies (Griffiths et al., 2012; Heffernan et al., 2010; Heffernan & O'Neill, 2012; Laloyaux et al., 2012; Marshall et al., 2016; Platt et al., 2016). It should be noted, however, that most participants in those studies were diagnosed with alcohol dependency (Griffiths et al., 2012; Laloyaux et al., 2012; Platt et al., 2016) or binge/heavy drinkers (Heffernan et al., 2010; Heffernan & O'Neill, 2012; Platt et al., 2016). Some of those studies also did not have a control sample and compared individuals with alcohol dependency against social drinkers (Griffiths et al., 2012) or binge drinkers against non-binge drinkers (Heffernan et al., 2010; Heffernan & O'Neill, 2012).

4.6. Limitations and future directions

Limitations of the current study are similar to those found in many studies of neurocognition among drug users (e.g., polysubstance use and use of self-report assessment to confirm an absence of substance use). Lifetime use of the individual drug was not measured for example, there were some ex-user of certain drugs, but no data was collected about how often they used to consume those drugs and how many year which might have had

an impact on the results. It is possible that the groups may differed on some variable other than recreational drug use. Some possibilities were excluded (e.g., IQ, general health, sleep quality, age), but some could not (e.g., nicotine use).

Even though 100 participants from general population were recruited, the sample was not as representative as it could be as the groups were mainly of white ethnic background, between 26 and 45 years old, and were educated to BSc or MSc level. This suggests that people from white background in that age range with higher education level were more likely to admit that they use recreational drugs than people from other backgrounds.

Furthermore, the lab-based PM measure had a relatively low number of PM trials. It has been found that PM tasks with few trials tend to have low levels of reliability (Kelemen et al., 2006)[2]. Therefore, future work should use additional test, such as Memory for Intentions Screen Test (Woods et al., 2008), Cambridge Prospective Memory Test (Wilson et al., 2004), the Jansari-Agnew-Akesson-Murphy Test (Jansari et al., 2004), or the Virtual Week Test (Rendell & Craik, 2000).

Participants were classed as users if they currently use recreational drugs or had used in the past. Although a drug use questionnaire confirmed that the drug user group were drug-free for at least a week and had not consumed alcohol in the 24 hours prior to the testing session, ideally using drug testing kits (urine or saliva) could be used to provide an objective assessment of compliance. Hence, it is not ruled out that the results found here are in part due to drug users not abstaining from drug use for the required duration.

The high level of polydrug use makes it difficult to tease apart the independent contributions of drug type on PM. In addition, smoking and cannabis usage have a high co-

[2] Cronbach's Alpha for the RPA-ProMem test was .60 in the current study when the responses for each trial were scored out of three points (3 points for the correct response on time) and .51 when classifying the responses for each trial to be either correct (correct response on time) or incorrect (other possible responses). It should be noted that each trial of the RPA-ProMem test measures a different component of PM and there is only a single trial for each component, therefore, Cronbach's Alpha might not present the true reliability of the test.

occurrence, cannabis being the most common drug consumed. This means that the results are not only difficult to be explained with reference to individual drug types, it is also dominated by one particular drug: cannabis. Although from a research perspective this is a limitation, from an ecological perspective, the finding of a general deficit on lab-based PM tasks can be generalised to the typical population with polydrug use and cannabis-dominance. More targeted research is needed to understand drug-specific contributions.

In this paper, the main focus was on overcoming several of the challenges in previous studies on the influence of recreational drug use and PM. This work adds to a growing body of literature by demonstrating a deficit measured on lab-based tasks, but not on self-report measures, when controlling for age, general health, sleep quality and alcohol usage, and overcoming the methodological challenges identified in the literature. Future research could expand the investigation by addressing other cognitive domains, investigating drug-specific contributions, and ascertain whether drug-induced cognitive deficits can be rehabilitated after drug cessation.

4.7. Conclusion

Consistent with the literature, drug users performed worse than non-users on self-report and lab-based PM measures, even there were few PM trials and light drug users who were highly educated. However, only the results of the lab-based measure remained significant after controlling for moderating variables. This finding calls into question the use of self-report in drug users and necessitates the use of objective measures that do not rely on retrospective memory. It has also important implications for developing drug education programs targeting the general population by highlighting how even light drug use can impair cognition to prevent people from starting to use drugs or encourage drug users to stop or reduce drug consumption.

Chapter 5: Recreational Drug Use and Executive Functions

5.1. Abstract

Recreational drug use is proposed to interfere with the neurobiological functioning of the brain by damaging the neurotransmitter communication systems that are believed to be responsible for executive functions. The previous studies that examined the effects of illegal drug use on executive functions are rather inconclusive and suffer from methodological shortcomings, such as small sample size (<100 participants), unrepresentative sample type (e.g., student or patient), short abstinence period (<7days), and lack of control of potential confounds (e.g., sleep and IQ). In this study, the possible consequences of recreational drug use on executive functions were investigated while trying to address the methodological challenges facing previous studies. The sample consisted of 100 subjects: 47 non-users (27 females, age range from 18 to 50+) and 53 drug users (21 females, age range from 18 to 50+). Participants were requested to fill in self-report questionnaires and perform lab-based cognitive tasks. Recreational drug users performed significantly worse than drug-naïve controls in the Verbal Fluency, and Digit Span tests. Most results remained significant after controlling for the covariates (e.g., general health, sleep routine, alcohol use and age). On the contrary, there were no significant differences between the groups in the Wisconsin Card Sorting and Stop-It tests. Taken together, recreational drug users displayed subtle executive dysfunction which might be associated with light recreational polydrug use.

5.2. Introduction

As discussed in Chapter 1, executive function or system is a set of mental abilities that are needed to organise, activate, integrate and manage other mental functions and behaviour. There are three core EFs (Lehto et al., 2003): working, cognitive flexibility and cognitive inhibition. The brain regions and neural pathways that are impacted by drug use have a lot in common with those that support executive functions (see 1.3. section). For example, cannabis (THC) activates endocannabinoids that act as retrograde messengers in the brain (Katona and Freund, 2012) and cause long-lasting reduction of neurotransmitter release including DA (Chevaleyre et al., 2006) which has been thought to be the main neurotransmitter of the executive system (Logue & Gould, 2014). Cocaine and MDMA use also impairs dopaminergic neuron activities in the brain, in particular the prefrontal cortex (Volkow et al.,1997, 2009; Ricaurte et al., 2002). Therefore, it has been proposed that drug usage may be linked to executive dysfunctions.

As reviewed in Chapter 2, the literature shows that drug users display various executive functioning impairments, but the evidence sometimes is not clear or/and quite conflicting. For example, Croft et al. (2001), Piechatzek et al. (2009) and Quednow et al. (2006) found that MDMA users performed more poorly than non-user controls on cognitive inhibition. On the contrary, many other studies found that the inhibition process is unaffected in MDMA users (e.g., Dafters, 2006; Fisk & Montgomery, 2009; Fox et al., 2002; Gouzoulis-Mayfrank et al., 2003; Wagner et al., 2013). It also appeared that specific drug users tend to exhibit particular forms of cognitive dysfunction. For instance, while cocaine use is linked to cognitive inhibition dysfunction (e.g., Colzato et al., 2007; Czermainski et al., 2017; Hester & Garavan, 2004; Sellaro et al., 2014; Verdejo-García et al., 2005), MDM/ecstasy use is associated with WM deficiencies (e.g., Fisk et al., 2004; Fox, Parrott, et al., 2001; Montgomery et al., 2007; Montgomery & Fisk, 2007; Verdejo-García et al., 2005; Wareing et al., 2000). It is unclear,

nevertheless, if the use of these drugs in combination has the same impact on those executive functions.

In addition, most previous studies assessed regular/heavy drug users (Heffernan et al., 2001; Quednow et al., 2007; Solowij et al., 2002) or drug addicts (Alonso-Matias et al., 2019; Hester & Garavan, 2004; Pace-Schott et al., 2008; Sanvicente-Vieira et al., 2016; Soliman et al., 2013; Verdejo-García et al., 2005) in which drug users performed worse than controls. However, it is not clear whether light recreational polydrug use leads to cognitive deficits as heavy/chronic use does.

Additionally, while the majority of earlier studies included individuals who used cannabis, MDMA and cocaine (either alone or jointly), there are limited studies with users of other recreational substances such as GHB and mephedrone. Therefore, it is unknown how those drugs influence cognitive functions when combined with other widely used recreational drugs.

Lastly, as discussed in Chapter 2, several of those studies that examined recreational drug users suffer from methodological challenges (see section 2.4 and Appendix A), for example, most studies had small sample sizes (Alonso-Matias et al., 2019; Croft et al., 2001; Hadjiefthyvoulou et al., 2011; McCardle et al., 2004; Montgomery & Fisk, 2007; Quednow et al., 2007), unrepresentative sample types (Hadjiefthyvoulou et al., 2011; Montgomery & Fisk, 2007; Balodis et al., 2010; von Geusau et al., 2004; Aharonovich et al., 2018; Hekmat et al., 2011; Hester & Garavan, 2004; Parolin et al., 2016; Soliman et al., 2013; Verdejo-García et al., 2006), short abstinence periods (Croft et al., 2001; Dafters, 2006; Fisk et al., 2004; Madoz-Gúrpide et al., 2011; Quednow et al., 2007; Roberts et al., 2009; Rodgers, 2000), and poor control of possible confounds (Alonso-Matias et al., 2019; Croft et al., 2001; Frolli et al., 2020; Gouzoulis-Mayfrank et al., 2000; Hester & Garavan, 2004; Quednow et al., 2007; Soliman et al., 2013)

Therefore, the present study sought to explore the possible consequences of light recreational drug use (e.g., MDMA, GHB) on executive functions, using lab-based measures while trying to overcome the methodological challenges facing previous studies. A hundred participants, aged between 18- 50+, were recruited from the general population (please note that those are the same participants who were recruited in Chapter 4) and drug users were asked to abstain from any recreational substance use for at least 7 days. A comprehensive number of possible moderating variables including age, ethnicity, fluid intelligence, sleep quality, general health, level of education, alcohol and nicotine use were examined and where appropriate included as covariates in the statistical analyses. It was hypothesised that light drug use would negatively impact executive functions.

Another aim of the current study was to understand what part of PM is compromised by addressing the different cognitive components of PM, such as cognitive flexibility and working memory. As summarised in the previous chapter, drug users were impaired in PM, but it was not clear what lead to such impairments. PM relies on various cognitive processes, including executive functions such as working memory (which is in charge of storing the postponed intention while carrying out the ongoing task; (Marsh & Hicks, 1998), attention (which is responsible to monitor the external world to detect PM cues (Landsiedel et al., 2017) and inhibitory control/cognitive flexibility (which is required to shift one's attention away from the ongoing task in order to perform a PM intention; Kliegel et al., 2002). By assessing drug users on those processes, it might be possible to understand why drug users exhibited PM impairments.

5.3. Methods

5.3.1. Participants

The sample consisted of 100 participants: 47 non-users (27 females, age range from 18 to 50+) and 53 drug users (21 females, age range from 18 to 50+). The participants were

recruited via advertising (e.g., posters, leaflets), using appropriate media (e.g., Facebook), the snowball technique (Solowij et al., 1992) and social networks. Participants were classed as users if they currently use or had used any recreational drugs in the past. No drugs were excluded. All participants were residing in London and spoke English as their native language or were fluent in English. All participants were requested to abstain from any recreational substance for at least 7 days and to abstain from alcohol consumption for at least 24 hours before the test session. The pre-study questionnaire showed that none of the participants had a history of neurological or psychiatric symptoms, including addiction.

5.3.2. Design

A quasi-experimental design was used in this study. The independent variable was the recreational drug use status (users and non-users) and the dependent variable was the performances of the cognitive tests.

5.3.3. Analysis

SPSS was utilised to analyse the data. Most data were not normally distributed, thus Mann Whitney U test (the nonparametric alternative to the independent t-test) was used. For significant results, Quade's rank analysis of covariance (RANCOVA) was employed (Quade, 1967) to control for covariates which has been shown to be robust and powerful when data is nonnormally distributed (Conover & Iman, 1982). Spearman's Rank-Order Correlation was used to assess correlations between the tests. Family-wise error rates were mitigated using Holm-Bonferroni corrections.

5.3.4. Materials

The characteristics of the sample population (e.g., gender, age, education level) and their current use of nicotine, alcohol, and recreational drugs were investigated via background questionnaires. Concerning recreational drug use, participants were asked a range of questions including how old were they the first time they used a recreational drug? how often

did they use each drug?; when did they last time use each drug? The RAPM, GHQ and PSQI were also used in this study (see section 4.3.3).

The Digit Span (DS) test was used to assess the ability to hold a sequence of numbers in short-term memory (Rosenthal et al., 2006). The DS subtest of the Wechsler Memory Scales-Revised (WMS-R; Wechsler, 1987) was used for this study in which participants were read out digit sequences that ranged from two to nine digits and asked to repeat them in the forward and then reverse order as presented. Two trials were presented at each increasing list length (maximum 9 digits for forward span and 8 digits for backward span) and the total number of lists reported correctly was combined across forward and backward span to generate an overall DS score. A higher score indicates better performance.

The Verbal Fluency Test (VFT; Wysokiński et al., 2010) was used to assess the ability to form and fluently say words compatible with given criteria. There were two parts in the test. In the first part, participants were asked to list as many animals (semantic category fluency) as they could in one minute. In the second part, the objective was to list as many words as they could in one-minute beginning with the letter "M" (initial letter fluency). Participants were informed that proper nouns (the name of people and places), repetitions and the same words with a different ending (e.g., run, runner and running) were not acceptable answers and were given examples of each. The total number of acceptable answers produced the verbal fluency score for each category. A higher score indicates better performance.

The WCST (Heaton, 1993) was used to assess the abstract reasoning ability and the ability to display flexibility (another component of executive function) in response to changing environmental contingencies. Participants were presented with a number of stimulus cards and asked to match the cards without being told how to match; however, at the end of each match, she or he was told whether a particular match is right or wrong. They could sort cards to match either colour (green, yellow, blue or red), form (stars, circles, triangles or crosses),

or the number of figures (one, two, three, four). During the test, when the criterion of 10 consecutive correct responses were reached, the sorting principle changed discreetly from colour to form or number of figures without participants being informed. The participants had to shift sets accordingly and sort cards following the new sorting principle. When a participant completed all six sorting categories or sorted all 128 cards, the test was ended. The following scores were generated: the correct responses, perseverative errors (i.e., the number of failures to shift in response to negative feedback which indicate set-shifting difficulties) and non-perseverative errors (the number of incorrect responses that do not match the perseverated-to criteria which shows lack of strategy for the correct matching and a propensity to give a chance), errors (the sum of perseveration and non-perseveration errors), failure to maintain (i.e., the set happens whenever a wrong response follows a consecutive series of correct matches), the total number of trials and categories completed. This instrument has shown good reliability and validity (Kopp et al., 2021; Miranda et al., 2020).

The Stop-It Test is a test to assess response inhibition (the ability to stop responses that are no longer appropriate which is one of the components of executive function) by using the stop-signal paradigm (Verbruggen et al., 2008). In the test, participants performed a shape judgment task (the primary task) in which they were asked to discriminate between a square and a circle by pressing a left key for a square and a right key for a circle as fast and accurately as possible. Occasionally, the primary task stimulus was followed by an auditory stop signal and participants were instructed to withhold their responses. Outcome measures cover the proportion of successful stops, reaction time on Go trials, and stop-signal reaction time.

5.3.5. Procedure

The study consisted of two phases. In the first phase, participants were sent a link before the testing session for the online survey that contained self-report questionnaires, such as the

GHQ and PSQI which took around an hour to complete, ideally on the day of the testing session or one day before. In the second phase, participants were asked to attend the testing session in which they performed lab-based tests, such as the Stop-It, Wisconsin Card Sorting test etc. This part of the study lasted around 2 hours. Participants were informed of the general purpose of the experiment and written informed consent was obtained. Participants were fully debriefed, paid £25 in-store vouchers, and given drug education leaflets. The study was approved by the Ethics Committee of Birkbeck University and was administered under the ethical guidelines of the British Psychological Society.

5.3.6. Level of Drug Use Classification

In this study, most drug users were current polydrug users who typically consumed cannabis, MDMA/ecstasy and cocaine (see Figure 4). Therefore, the level of drug use classification was done based on the frequency of those three drugs use. Participants who consumed cannabis, cocaine and/or MDMA/ecstasy weekly or more often (who reported that they used one of those drugs 1 or 2 times a week or 3 or more times a week) were classified as heavy users; participants who consumed any of those drugs (individually or together) 1 or 2 times a month were classified as moderate users; and participants who consumed any of those drugs 1 or 2 times a year or 1 or 2 times every three months were classified as light users. There were also ex-users (mainly ex-cannabis users). However, it should be noted that an ex-user of some drugs was a current user of other drugs. For instance, five ex-cannabis users were current cocaine users (see Appendix O) and four ex-cannabis users were current ecstasy users (see Appendix N).

5.4. Results

The demographic information of users and non-users are the same as in Chapter 4 (see section 4.4, Tables 6 and 7). As aforementioned, the most commonly used recreational drug

was cannabis, followed by cocaine, MDMA and GHB. Most drug users were classified as light drug users.

There were no correlations between cognitive tests and the general health and sleep quality covariates, apart from a few weak correlations (see Appendix J). However, those correlations did not remain significant after Holm-Bonferroni correction. One way ANOVAs were run to assess a relationship between cognitive measures and the other covariates (e.g., age and alcohol use). There were no significant association between cognitive tests and those covariates

As seen in Table 12, Mann-Whitney U tests revealed that drug users performed significantly worse than non-users only in the DS and VFT. Most results remained significant after statistically controlling for the covariates (e.g., sleep quality, general health, alcohol use and age).

Table 12: Mann-Whitney and RANCOVA tests' results for the executive functioning measures

	Drug User (53)		Non-Users (47)					
					Mann-Whitney		RANCOVA	
	M (SD)	*Mdn*	*M (SD)*	*Mdn*	*U*	*p*	*F*	*p*
The DS								
Forward	9.19(1.75)	9	9.65(2.18)	11	1002.5	.089		
Backwards	7.02(2.03)	7	8.13(2.37)	8	876.5	.010*	3.32	.071
Total score	16.19(3.13)	16	17.79(3.94)	19	867.5	.009*	4.37	.039*
The VFT								
Semantic category	21.94(6.72)	21	25.04(6.48)	24	896.5	.016*	9.79	.002**
Initial letter	13.60(5.25)	13	15.77(5.52)	15	943	.036*	5.34	.023*
Total score	35.55(10.59)	33	40.81(10.50)	41	890.5	.014*	9.95	.002**
The WCST								
Corrects	71.45(11.95)	67	68.85(7.78)	65	1057	.192		
Errors	24.08(17.57)	17	23.09(18.15)	16	1097	.305		
Perseverative errors	15.06(10.50)	11	13.98(10.56)	9	1059.5	.197		
Non-perseverative errors	9.19(10.03)	6	9.11(9.01)	5	1172.	.610		
Categories completed	5.47(1.19)	6	5.49(1.14)	6	1229.5	.874		
Total trials completed	95.11(21.30)	87	91.72(22.61)	82	1078.5	.247		
Failure to maintain	.51(.78)	0	.55(.97)	0	1218	.821		
Stop-it Test								
P(respond|signal)	.56(.15)	.50	.57(.16)	.51	1115.5	.678		
Stop-signal delay	251.9(153.9)	230.6	235.7(179.5)	183.9	1053.5	.388		
Stop-signal RT	446 (89.15)	442.8	445.1(84.7)	447.2	1165	.954		
Signal-respond RT	621.2(150.2)	624.2	612.9(154.4)	580.1	1085.5	.636		
No-signal RT	694.7(162.6)	697.9	681.7(174)	669.4	1125	.729		
No-signal HIT	89.4(22.5)	97.6	92.3(12.6)	97.6	1158.5	.916		
No-signal MISS	3.92(7.06)	.70	5.12(10.3)	.70	1157.5	.908		

*** $p < .001$, ** $p < .01$, * $p < .05$. RT: Reaction Time. Probability of reacting in Stop Signal Trials= P(response|signal)

5.5. Discussion

The present study assessed the possible consequences of light recreational polydrug use on executive functions, using lab-based measures while trying to overcome the methodological challenges facing previous studies. Light recreational polydrug users who were light users differed significantly from drug-naive controls in some measures, but not in others. For instance, drug users scored worse than non-users in the DS test which is a

measure of verbal short-term and working memory. A similar pattern of results was obtained in multiple studies in which polysubstance users remembered significantly fewer numbers than non-user matched samples (Frolli et al., 2021; Roberts et al., 2016a; Soliman et al., 2013). The digit span performance requires the following steps: (1) maintaining the first digits presented in memory, (2) constant monitoring for incoming items, and (3) frequent updating of obtained information when a new item is presented by attaching the newest item and removing the old item from the target series (Jahanshahi et al., 2008). It has been argued that the running DS test requires two independent systems of WM: the phonological loop (temporarily storing and rehearsing auditory information) and the central executive (monitoring the continuous incoming information and updating the obtained information). Therefore, these results suggest that recreational drug users are impaired in WM.

In recent years, there has been growing evidence that DA and WM are closely linked, in particular, its activities in the PFC (Cools et al., 2001; Klaus & Pennington, 2019; Puig et al., 2014; Sawaguchi & Goldman-Rakic, 1991; Surmeier, 2007). As discussed in the introductory chapter, most illegal drugs exert their effects by interacting with DA neurotransmitters, thus they tend to have DA dysfunction in the brain which might explain the observed poor DS test performance in this study.

When looking at each subtest, drug users recalled significantly fewer numbers than the controls in the DS Backward, but not in the DS forward subtest. Several theories have been taken to account for differences between DS forwards and backwards recall. While both forward and backwards recall use short-term phonological storage (i.e. short-term verbal memory), backwards recall also requires attention demanding transformation of the series of a digit, hence it measures executive and planning components of working memory (Ellingson et al., 2014) in addition to short-term memory (Alloway et al., 2006; Clair-Thompson & Allen, 2013). Backwards digit recall has also been consistently reported to be more sensitive

to the effects of brain dysfunction than forwards digit recall (Clair-Thompson & Allen, 2013). However, the result did not remain significant after controlling for the confounds which suggest general health, sleep quality, alcohol use and age mediated scoring on the Backward subtest. For example, one study assessed the effects of sleep on digit span and found that participants' digit span performance was significantly increased by just an additional hour of sleep (Sadeh et al., 2003). Increasing age (Bopp & Verhaeghen, 2005), anxiety (Darke, 1988) and alcohol use (Saults et al., 2007) have been also associated with poor digit span performance.

In line with the previous findings (Bhattachary & Powell, 2001; Croft et al., 2001; Montgomery, Fisk, Newcombe, et al., 2005; Reske et al., 2011), drug users produced fewer words based in both the category and letter fluency tasks than non-users in the present study. Those tasks assess both verbal ability (participants need to access their mental lexicon to retrieve words from their language) and executive control (Fisk & Sharp, 2004). However, it is not clear which component of EFs is most strongly associated with verbal fluency performance. While performing the task, participants must keep the given criteria and the earlier responses in WM and they must suppress repetition and irrelevant responses which is associated with cognitive inhibition. Furthermore, participants must switch from one category to the next one after successfully producing sets of relevant words which ability requires cognitive flexibility. While some scientists argue that verbal fluency performance reflects inhibition, working memory and effortful self-initiation (Henry & Crawford, 2004; Hirshorn & Thompson-Schill, 2006; Rende et al., 2002) others emphasise the importance of mental shifting ability (Abwender et al., 2001). Additionally, attention has been thought to be another component of the VFT (Amunts et al., 2020). Therefore, the observed verbal fluency deficits might be associated with executive dysfunction in drug users. It has been found that

the verbal fluency task acts as a sensitive screening tool to detect subtle executive deficits (McDonnell et al., 2020).

Though the category and letter fluency tasks are similar, the task demands differ in minor but significant ways. The initial letter fluency is strongly associated with executive ability (e.g., selective inhibition, selective attention, mental set shifting, self-monitoring and internal response generation) whereas category fluency is more related to semantic memory organisation (Crawford et al., 1998). Consistent with this view, it has been suggested that the overlapping, but not identical brain mechanisms are involved in the two tasks. Several neuroimaging and lesion studies have suggested that letter fluency is regulated predominantly by the frontal cortex, while category fluency is regulated primarily by the temporal cortex (Baldo et al., 2006, 2010; Gourovitch et al., 2000). The current findings suggest that drug use might be impaired in both the frontal and temporal cortex.

Drug users were also assessed on response inhibition, but there were no group differences. Previously published studies on the effect of drug use on cognitive inhibition are inconsistent. For instance, Hester and Garavan (2004) demonstrated that cocaine users find it difficult to inhibit their own actions in the GO-NOGO response inhibition task, compared to drug-naive controls. Drug users also performed worse on other response inhibition tasks; the Simon task (Sellaro et al., 2014), and the Stroop task (Croft et al., 2001). However, it should be noted that the sample size was small in both studies and drug users were instructed to abstain from recreational drug use for only two days, thus the observed deficits might be due to the comedown effects. On the contrary, some studies did not find any difference between drug users and non-users on various cognitive inhibition tests. For example, a meta-analysis in which a total of 632 controls and 600 ecstasy polydrug users were compared on cognitive inhibition from 20 articles indicated there was no between-group difference in the performance of inhibitory control (Roberts et al., 2016a). Noteworthy is the fact that those

studies that found cognitive inhibition deficits in drug users assessed regular drug users (Colzato et al., 2007) or drug addicts (Hester & Garavan, 2004). This suggests that the inhibition deficits might only appear in heavy/dependent drug users. This is in line with past research in which the moderate MDMA (22–50 lifetime episodes of use) users did not exhibit inhibition deficits while the heavy users (60–450 uses) showed significant impairment (Halpern et al., 2004). Moreover, a meta-analysis that integrated results from 97 studies that compared groups with heavy substance use or addiction-like behaviours with healthy controls on response inhibition, revealed that inhibitory deficits were apparent for heavy use/dependence on MDMA, methamphetamine and cocaine (Smith et al., 2014).

Another possible explanation could be that the Stop-it test might not be sensitive to detect cognitive inhibition impairments. For example, in a study by Morein-Zamir et al. (2015), 24 recreational cocaine users who used cocaine in relatively small amounts for at least 2 years without experiencing psychological or physiological symptoms of dependence and 32 non-user controls matched for gender, age, and IQ were assessed during the Functional Magnetic Resonance Imaging (fMRI) on a stop-signal task. The results revealed that recreational cocaine users did not significantly differ from non-users on any task performance. However, interestingly, recreational users showed increased activation in the brain's areas associated with response inhibition, such as the dmPFC and ACC, compared to controls. This increased recruitment may be associated with compensatory mechanisms to preserve cognitive control in recreational users. In other words, recreational drug users work harder to suppress prepotent responses, compared to controls. These findings suggest that drug users have reduced cortical efficiency, however, such impairment might not be detectable with behavioural tests. Similarly, in various other studies, drug users had greater brain activity compared to the controls while performing various cognitive tests, but their behavioural performance did not differ from controls (Becker et al., 2013; Watkins et al.,

2013). These results show that behavioural measurements are less sensitive to detect subtle/mild cognitive deficits than neuroimaging measurements (Morein-Zamir et al., 2015).

Moreover, most drug users in the current study had approximately 15 years of drug use experience, it is believed that prolonged drug use leads to neuroadaptation in the brain which might compensate for drug-induced impairments. This is in line with a study in which the negative effects of cannabis intoxication on attention were stronger in less experienced cannabis users than in those with more experience (Crean et al., 2011).

Likewise, the groups did not differ in the WCST which was used to assess abstract thinking, executive function and cognitive flexibility in particular (Kolakowsky-Hayner, 2011). This finding is contrary to previous studies which have revealed that polydrug users scored worse than nonusers on cognitive flexibility measures (Alonso-Matias et al., 2019; Dafters, 2006; Fisk & Montgomery, 2009; Fox, Parrot, et al., 2001; Hekmat et al., 2011). However, it should be mentioned that in cases where ecstasy/polydrug user groups were broken down into further subgroups e.g. 'light' (an estimated lifetime dose of less than 400 tablets (mean=149.69, SD=96.91)) and 'heavy' users (an estimated lifetime dose exceeding 400 tablets (mean: 1000.21, SD: 786.4; Fisk & Montgomery, 2009) or low (consumed between 0 and 100 ecstasy tablets.)/medium (100 and 500 tablets)/high-intensity (500+ tablets) users (Fox, Parrot, et al., 2001), only data from the heavy/high-intensity users were included in the analysis and data from light user groups were excluded. Furthermore, Alonso-Matias et al. (2019) assessed only drug-dependent individuals. In the current study, most users were very light users which might explain why they did not display cognitive flexibility impairments. This finding supports Halpern's et al. (2004) study in which although the heavy users showed significant impairment on many measures including WCST light drug users exhibited virtually no differences from non-users on any cognitive measures.

Similar to cognitive inhibition, cognitive flexibility dysfunctions might be absent in the current sample due to the sensitivity of the test or a compensatory mechanism that is associated with prolonged drug use.

Another aim of the current study was to understand the underlying factors of the observed PM deficits in drug users (see Chapter 4). As discussed in the introduction, PM relies on various cognitive processes, including executive functions. The current findings suggest that the PM impairments in Chapter 4 might stem from the observed executive function deficits in the current Chapter. A RANCOVA was run to assess the association between drug use and PM that was found in Chapter 4 while controlling for executive functions (see Appendix M). The data from non-users was used as normative data to calculate z-scores for cognitive measures in which there were significant group differences. All z scores belonging to those measures (i.e., the DS and VFT) were then averaged to create a new variable that represents overall executive functioning skills. RANCOVA revealed that the results remained significant after controlling for executive function, suggesting that executive functions had no impact on PM in the current sample. However, as drug users exhibited executive dysfunctions in some tests, but not in others, such a possibility, therefore, needs to be treated with a degree of caution.

Taken together, drug users performed worse than drug-naive controls on verbal fluency, and digit span, but not on cognitive flexibility and inhibition which might be associated with frequency of drug use in the current sample, as most drug users were classified as light users. It might be that cognitive flexibility and inhibition dysfunctions may only be apparent in heavy drug users/drug addicts (Halpern et al., 2004; Smith et al., 2014).

5.6. Limitations and future directions

The study had similar limitations as Chapter 4, such as polysubstance use, use of self-report assessment to confirm an absence of substance use, and no information on lifetime use

of the individual drug. Furthermore, it is possible that the groups may differ on some variables other than recreational drug use. Some possibilities were excluded (e.g., IQ, general health, sleep quality, age), but some could not (e.g., nicotine use). Therefore, future studies should control those variables, use drug testing kits (urine or saliva) to confirm abstinence and assess lifetime use of the individual drug. Additionally, some subtle/mild cognitive impairments in drug users are only noticeable in very sensitive tests or neuroimaging measures (Becker et al., 2013; Morein-Zamir et al., 2015; Watkins et al., 2013). Thus, in future, it is essential to combine methodologies such as neurocognitive assessments, and neuroimaging techniques to provide a more complete picture of the effects of drugs.

5.7. Conclusion

In this study, the focus was on overcoming several of the challenges in previous studies on the association between light recreational polydrug use and executive functions. Contrary to initial predictions, drug users only displayed subtle executive deficits which might be associated with light drug use.

Chapter 6: Recreational Drug Use and Retrospective Memory

6.1. Abstract

The neurotransmitter communication systems that are responsible for various memory processes have been thought to be damaged due to recreational drug use. The previous research that assessed the effects of illegal recreational drug use on memory processes are rather inconclusive and suffer from methodological shortcomings, such as small sample size (<100 participants), unrepresentative sample type (e.g., student or patient), short abstinence period (<7days), and lack of control of potential confounds (e.g., sleep and IQ). In this study, the possible consequences of recreational drug use on retrospective memory were investigated while trying to address the methodological challenges facing previous studies. The sample consisted of 100 subjects: 47 non-users (27 females, age range from 18 to 50+) and 53 drug-users (21 females, age range from 18 to 50+). Participants were requested to fill in self-report questionnaires and perform lab-based retrospective memory tasks. Recreational drug users performed significantly worse than drug-naïve controls in the California Verbal Learning and Autobiographical Memory tests. On the contrary, there were no significant differences between the groups in the Source Memory, False Memory and Verbal Paired Associates tests. Most results remained significant after controlling for the covariates (e.g., general health, sleep routine, alcohol use and age). Taken together, recreational drug use impairs verbal learning and autobiographical memory. Drug users tended to perform poorly on free recall, but normally on recognition tests which suggests that drug users were impaired at the retrieval level, not the encoding. Those impairments have the potential to contribute to the maintenance of drug use and increase the risk of becoming addicted to drugs.

6.2. Introduction

As summarised in Chapter 1, recreational drugs interfere with the way some neurotransmitters work. For example, the most consistent neurobiological consequence of cannabis use is decreased CB1 receptor numbers in the brain (Hoffman et al., 2021) which have been reported to mediate the release of glutamate (Lévénés et al., 1998) that plays a critical role in the synaptic plasticity (Padamsey & Emptage, 2014). Furthermore, it is well established that MDMA impairs serotoninergic neurotransmission (e.g., SERT reductions; Roberts et al., 2016b) that significantly contributes to memory formation (Brunelli et al., 1976). Therefore, various drugs use has been associated with cognitive impairments, including retrospective memory deficits. Retrospective memory is the ability to recall information about things that have already happened. There are various ways to assess retrospective memory, such as through verbal learning and false memory tests in which participants are asked to learn a list of words (learning phase) to recall those words in the testing phase after a break. Additionally, retrospective memory can be measured via autobiographical memory tests where participants are asked to recall personally experienced past events.

As reviewed in Chapter 2, the literature showed that drug users display various retrospective memory impairments, but the evidence sometimes is not clear or/and quite conflicting. For example, some studies found retrospective memory impairments in abstinent drug users (e.g., Basedow et al., 2021; McCardle et al., 2004; Quednow et al., 2007), but others did not (e.g., Kuypers et al., 2016; Kloft et al., 2019).

It also appeared that the long-term effects of certain drugs (such as those of cannabis and ketamine) on specific cognitive functions (e.g., false memory, source memory) have not received as much attention as their acute effects on those cognitive processes. For instance, numerous studies have been conducted on the short-term effects of drug use on false

memory, mostly in cannabis users (Cuttler et al., 2021; Doss et al., 2020; Doss, Weafer, Gallo, & de Wit, 2018; Kloft et al., 2021, 2022), whereas only a small number of studies have examined the long-term effects of cannabis use, which revealed inconsistent findings (Kloft et al., 2019; Riba et al., 2015). Similarly, most studies assessed only the acute effects of drug use on source memory (e.g., Cuttler et al., 2021; Morgan, Schafer, et al., 2010). The findings demonstrated that the acute use of ketamine or MDMA impairs retrospective memory (Morgan et al., 2004; Morgan, Muetzelfeldt, et al., 2010), but the findings for cannabis use were inconsistent as Cuttler et al. (2021) found that the acute use of cannabis impairs source memory, but Morgan, Schafer, et al. (2010) did not.

In addition, most previous studies assessed regular/heavy drug users (e.g., Gouzoulis-Mayfrank et al., 2000, 2003; Pillersdorf & Scoboria, 2019; Quednow et al., 2006; Rodgers, 2000; Rouse & Bruno, 2011) or drug addicts (Ardila et al., 1991; Basedow et al., 2021; Hoffman et al., 2006; Oliveira et al., 2007; Solowij et al., 2002; Volkow et al., 2001; Woicik et al., 2009;) in which drug users performed worse than controls. However, it is not clear whether light recretional polydrug use leads to cognitive deficits as heavy/chronic use does.

Additionally, while the majority of earlier studies included individuals who used cannabis, MDMA and cocaine (either alone or jointly), there are limited studies with users of other recreational substances such as GHB and mephedrone. Therefore, it is unknown how those drugs influence cognitive functions when combined with other widely used recreational drugs.

Lastly, as discussed in Chapter 2, several of those studies that examined recreational drug users suffer from methodological challenges (see section 2.4), for example, most studies had small sample sizes (e.g., Basedow et al., 2021; Croft et al., 2001; Doss et al., 2018; McCardle et al., 2004; Oliveira et al., 2007; Rodgers (2000)), unrepresentative sample types (e.g., Fox, Toplis, et al., 2001; Hoffman et al., 2006; Solowij et al., 2002; Volkow et al., 2001; Woicik et

al., 2009), short abstinence periods (e.g., Basedow et al., 2021; Croft et al., 2001; Gouzoulis-Mayfrank et al., 2003; Reske et al., 2010; Solowij et al., 2002, 2011; Wagner et al., 2015) and poor control of possible confounds Mercuri et al., 2018; Oliveira et al., 2007; Pillersdorf & Scoboria, 2019; Rouse & Bruno, 2011)

Therefore, the present study sought to explore the possible consequences of light recreational drug use (e.g., MDMA, GHB) on various retrospective memory, using lab-based measures while trying to overcome the methodological challenges facing previous studies and filling the identified research gaps in the existing literature. A hundred participants, aged between 18- 50+, were recruited from the general population (please note that those are the same participants who were recruited in Chapter 4) and drug users were asked to abstain from any recreational substance use for at least 7 days. A comprehensive number of possible moderating variables including age, ethnicity, fluid intelligence, sleep quality, general health, level of education, alcohol and nicotine use were examined and where appropriate included as covariates in the statistical analyses. It was hypothesised that light drug use would negatively impact retrospective memory.

Another aim of the current study was to understand what part of PM is compromised by addressing the different cognitive components of PM. As summarised in Chapter 2, drug users were impaired in PM, but it was not clear what lead to such impairments. PM relies on various cognitive processes, including retrospective memory (Einstein & McDaniel, 1990). By assessing drug users on various retrospective memory processes, it might be possible to understand why drug users exhibited PM impairments.

6.3. Methods

6.3.1. Participants

The sample consisted of 100 participants: 47 non-users (27 females, age range from 18 to 50+) and 53 drug-users (21 females, age range from 18 to 50+). The participants were

recruited via advertising (e.g., posters, leaflets), using appropriate media (e.g., Facebook), the snowball technique (Solowij et al., 1992) and social networks. Participants were classed as users if they currently use or had used in the past any recreational drugs. No drugs were excluded. All participants were residing in London and spoke English as their native language or were fluent in English. All participants were requested to abstain from any recreational substance for at least 7 days and to abstain from alcohol consumption for at least 24 hours before the test session. The pre-study questionnaire showed that none of the participants had a history of neurological or psychiatric symptoms, including addiction.

6.3.2. Design

A quasi-experimental design was used in this study. The independent variable was the recreational drug use status (users and non-users) and the dependent variable was the performances of the cognitive tests.

6.3.3. Analysis

SPSS was utilised to analyse the data. Most data were not normally distributed, thus Mann Whitney U test (the nonparametric alternative to the independent t-test) was used. For significant results, Quade's rank analysis of covariance (RANCOVA) was employed (Quade, 1967) to control for covariates which has been shown to be robust and powerful when data is nonnormally distributed (Conover & Iman, 1982). Spearman's Rank-Order Correlation was used to assess correlations between the tests. Family-wise error rates were mitigated using Holm-Bonferroni corrections.

6.3.4. Materials

The characteristics of the sample population (e.g., gender, age, education level) and their current use of nicotine, alcohol, and recreational drugs were investigated via background questionnaires. Concerning recreational drugs use, participants were asked a range of questions including how old were they the first time they used a recreational drug?; how

often did they use each drug?; when did they last time use each drug? The RAPM, GHQ and PSQI were also used in this study (see section 4.3.3).

The CVLT 3rd edition (CVLT3; Delis et al., 2017) was used for the assessment of learning and retrieval strategies. Participants were read a list of 16 target words (List A) by the experimenter at a rate of approximately one word per second. The words from List A were carefully selected for their frequency of use across multiple demographic variables and can be divided into four distinct semantic categories (animal, vegetable, ways of travelling and furniture), four words for each category. List A was learned across five trials, after which an interference list (List B) was read. There were also 16 words (4 words from each of four semantic categories) in List B. After the presentation of List B, free recall and cued recall of List A were tested. Participants then were engaged with non-verbal tests (e.g., the Wisconsin Card Sorting Test, see below) for 20-25 minutes. After the delay period, free and cued recall of List A words was examined. After the delayed recall trials, the yes/no recognition test that consisted of all 16 List A target words and 32 distractors, of which 16 are List B words and 16 are novel distractors, was conducted. For each word, participants were asked to say "yes" if that word was from List A or say "no" if it was not from List A. Some of the words from the CVLT3 were changed because they were used in other tests to avoid the learning effect. For example, the word "squirrel" was swapped with "leopard" and the word "cabbage" was swapped with "broccoli" in List A. Furthermore, the word "rose" was swapped with "rice" in the Yes/No Recognition subtest. The CVLT3 generates the following measures: immediate recall for trials 1-5, total delay (short and long) recall, total recall (including free and cued recall and recognition), repetition, intrusion (which shows the number of false recalls that is a recall of word that is not on the list), yes/no recognition hits, yes/no recognition false alarm, recall consistency (which shows whether participants recall the same words across consecutive presentations of a list) and learning slope (which measures the average number

of new words per trial a participant can acquire) across trials 1-5, recency, primacy and middle region recall for trial 1-5 and semantic (which measures whether participants recall the words from the same category consecutively) and serial clustering (which measures whether participants recall the words in the same order in which they were presented) for trials 1-5. All the raw scores were converted to scaled scores based on the participant's test age range, apart from repetitions and intrusions for each trial (e.g., trial 1 repetitions, and trial 1 intrusions). The scaled scores are derived from the 100 normative cases within each specific age band (Delis et al., 2017). For all the scaled scores, higher scores indicate better performance. It has been found that the CVLT3 has good validity (Siqveland et al., 2014) and reliability (Woods et al., 2006).

The Source Memory Test (Johnson et al., 1993) was used to measure source memory which is a representation of the origin of encoded information. Source memory may include contextual, perceptual, affective and other features that were presented when memory was acquired. For this experiment, 128 words (64 target items and 64 distractors) were selected from the MRC psycholinguistic database (http://websites.psychology.uwa.edu.au/school/MRCDatabase/uwa_mrc.htm). All words (one or two-syllable nouns) were between four and seven letters in length, had familiarity ratings between 500 and 700, and had concreteness ratings between 600 and 700. Each participant was shown the PowerPoint presentation in which the 64 target items were randomly placed either in List 1 or List 2 (32 words each); either at the top or bottom section of the screen (32 words for each condition). Prior to the presentation, participants were told that they would see lists of words and that their memory would be tested later in the experiment. The nature of the test was not specified. During the learning phase of the experiment, the 64 words were displayed one at a time in random order for 2.5 seconds on the computer screen. After the learning phase, they were asked to perform an unrelated filler task (e.g., digit span task) for 2-

3 min to erase the target items from short-term memory. In the testing phase, each participant was given the answer sheet in which randomly selected 32 words from the 64 target items and 32 words from the distractors were listed. For each of the 64 words, participants had to decide in the first step whether the word had been presented or not. In the case of a "presented" response, participants had to decide in the second step whether the word had appeared in the first list or the second list and in the third step whether the word had appeared at the upper section or the lower section of the computer screen. For each condition, two scores were calculated; the total number of hits, and false alarms. Overall scores across the source conditions (whether the word had appeared in the first list or the second list and whether the word had appeared at the upper section or the lower section of the computer screen; e.g., total source hit= list 1 hit + list 2 hit+ top hit + bottom hit). A higher score in the Hit subtests reflects better performance. Whereas, a higher score in the FA subtests reflects poorer performance.

The Verbal Paired Associates (VPA) subtest from the WMS-R (Wechsler, 1987) was used to assess memory for associated word pairs in which eight-word pairs (four easy/related, such as Rose-Flower; and four difficult/unrelated, such as Obey-Inch) were read out to participants and asked to provide the associated word when given the first word of the pair. This task was repeated across three trials. The total score was calculated by adding the number of correct recalls. A higher score indicates better performance.

The Autobiographical Memory Test (AMT; Williams & Broadbent, 1986) was used to assess the ability to retrieve specific memories from autobiographical memory. Participants were told 5 negative (e.g., clumsy, angry, hurt, lonely, and sorry) and 5 positive cue words (e.g., happy, successful, surprised, safe, and interested) in random order one by one and given 30 seconds to generate a specific memory that happened on a particular day at least three months ago (to avoid the recency effect) and briefly describe this memory in response to each cue

word. Three neutral, practice words (car, forest, and chair) were presented to participants first. All participants were asked to provide a specific memory for at least two of the three practice trials before completing the rest of the test. Participants' responses were taped-recorded and scored according to the criteria defined by Mark et al. (Mark et al., 1992) as specific or non-specific memories. Specific memories were defined as events that occurred at a particular place and time within the course of one day (e.g., "I broke my arm while I was playing football on 22nd June 2015"). Non-specific memories included extended memories (events that lasted for a longer period of time; e.g., "I enjoyed my weekend in Berlin"), categoric memories (events that happened repeatedly over a period of time; e.g., "Whenever I go for a bike ride"), non-memories (semantic associated; e.g., "I am a clumsy person"), and omissions (no response within the time limit; e.g., "I don't know"). Each response for the given word was labelled as omission, non-memory categoric memory, extended memory or specific memory and scored 0 to 4 respectively and the total score ranged from 0 to 40. A higher score indicates better performance.

The False Memory Test (Roediger & McDermott, 1995) was used in which participants were presented the 10 strongly related words (e.g., note sound, piano, sing, radio, band, melody, concert, instrument, orchestra) at a rate of one word every 2 seconds on the computer screen at the encoding phase. Participants were then presented with a list of words that consisted of 5 presented words (e.g., note, sing, sound, concert, orchestra), 4 unpresented words (e.g., beef, sink, train, door) and a non-presented critical target word (e.g., music) and asked to tick words they remember in the answer book (recognition phase). There were ten trials which were selected from the Roediger and McDermott (DRM) study (Roediger & McDermott, 1995) for this study. To avoid learning effects, some of the words from the DRM study were changed as they were used in another test. The subjective score was calculated based on the number of correct responses and false recognition (FR; e.g., lure).

6.3.5. Procedure

The study consisted of two phases. In the first phase, participants were sent a link before the testing session for the online survey that contained self-report questionnaires, such as the GHQ and PSQI which took around an hour to complete, ideally on the day of the testing session or one day before. In the second phase, participants were asked to attend the testing session in which they performed lab-based tests, such as the CVLT3 and AMT. This part of the study lasted around 2 hours. Participants were informed of the general purpose of the experiment and written informed consent was obtained. Participants were fully debriefed, paid £25 in-store vouchers, and given drug education leaflets. The study was approved by the Ethics Committee of Birkbeck University and was administered under the ethical guidelines of the British Psychological Society.

6.3.6. Level of Drug Use Classification

In this study, most drug users were current polydrug users who typically consumed cannabis, MDMA/ecstasy and cocaine (see Figure 4). Therefore, the level of drug use classification was done based on the frequency of those three drugs use. Participants who consumed cannabis, cocaine and/or MDMA/ecstasy weekly or more often (who reported that they used one of those drugs 1 or 2 times a week or 3 or more times a week) were classified as heavy users; participants who consumed any of those drugs (individually or together) 1 or 2 times a month were classified as moderate users; and participants who consumed any of those drugs 1 or 2 times a year or 1 or 2 times every three months were classified as light users. There were also ex-users (mainly ex-cannabis users). However, it should be noted that an ex-user of some drugs was a current user of other drugs. For instance, five ex-cannabis users were current cocaine users (see Appendix O) and four ex-cannabis users were current ecstasy users (see Appendix N).

6.4. Results

The demographic information of users and non-users are the same as in Chapter 4 (see section 4.4, Tables 6 and 7). As mentioned earlier, the most commonly used recreational drug was cannabis, followed by cocaine, MDMA and GHB. Most drug users were classified as light drug users.

There were no correlations between cognitive tests and the general health and sleep quality covariates, apart from a few weak correlations (see Appendix J). However, those correlations did not remain significant after Holm-Bonferroni correction. One way ANOVAs were run to assess a relationship between cognitive measures and the other covariates (e.g., age and alcohol use), however, only alcohol use was associated with autobiographical memory as 2 to 3 times a week alcohol users (M=5, SD= 1.98) scored worse than non-alcohol user (M=7.31, SD=2.7) in the AMT specific subtest (F (4, 95) = 3.56, p=.009). There were no associations between age and cognitive tests.

As seen in Table 13, Mann Whitney U tests revealed that drug users recalled significantly fewer words than non-users in most trials in the CVLT3. Numerous contrast scores were also calculated, such as List B correct vs. Trial 1 correct to assess vulnerability to proactive interference; short delay free recall correct vs. trial 5 correct and long delay free recall correct vs. trial 5 correct to examine vulnerability to retroactive interference and forgetting after a short delay and long delay respectively; short delay free recall correct vs. long delay free recall correct to measure forgetting after a long delay. However, the results revealed there was no proactive or retroactive interference.

Table 13: Mann-Whitney and RANCOVA tests' results for the CVLT

	Drug User (53)		Non-Users (47)					
					Mann-Whitney		RANCOVA	
	M (SD)	*Mdn*	*M (SD)*	*Mdn*	*U*	*p*	*F*	*p*
California Verbal Learning Test								
Trial 1 recall	9.70 (3.56)	10	11.40 (3.17)	13	853.50	.006**	5.07	.027*
Trial 2 recall	10.09 (3.35)	10	11.91 (2.41)	12	825.50	.003**	6.31	.014*
Trial 3 recall	9.85 (3.00)	10	11.47 (2.08)	12	804	.002**	7.29	.008**
Trial 4 recall	9.98 (2.89)	10	11.55 (2.25)	11	838.50	.005**	8.6	.004**
Trial 5 recall	9.91 (3.11)	10	11.85 (2.55)	12	793	.002**	8.42	.005**
List B recall	9.72 (2.72)	10	10.72 (2.46)	10	1065	.206		
Short-delay free recall	10.11 (3.04)	10	12.06 (2.31)	12	755.00	<.001***	7.88	.006**
Short-delay cued recall	9.66 (3.10)	10	10.81 (2.20)	10	957.00	.044*	4.91	.029*
Long-delay free recall	9.89 (3.14)	10	11.49 (2.18)	12	840.50	.005**	6.58	.012*
Long-delay cued recall	9.57 (3.10)	10	10.47 (2.08)	11	974.00	.058		
Total recall for list A trials 1-5	49.55(13.62)	49	58.26(10.21)	61	748	<.001***	9.45	.003**
Total delay recall	38.96(11.45)	39	45.83(8.88)	45	784.5	.001	7.65	.007**
Total recall	98.43(25.23)	95	113.63(17.5)	117	789.5	.002	7.95	.006**
Total repetitions	10.07(2.22)	10	10.51(2.38)	10	1122.5	.392		
Total intrusions	9.20(2.68)	9	10.57(2.98)	11	907	.018*	2.17	.144
Yes/no recognition hits	9.83(3.13)	9	11.02(2.62)	13	977	.045*	.821	.367
Yes/no recognition FA	9.71(2.71)	10	11.08(2.72)	13	830	.003*	4.38	.039*
Across trials 1-5 recall consistency	9.47(3.04)	9	11.17(2.25)	11	783	.001**	7.99	.006**
Total learning slope trials 1-5	9.54(3.27)	9	10.34(2.63)	10	1031	.136		
Primacy region recall for trial 1-5	9.90(2.24)	10	9.12(2.14)	10	1092.5	.285		
Middle region recall for trial 1-5	9.39(2.32)	9	10.40(2.05)	11	943.5	.035*	5.52	.021*
Recency region recall for trial 1-5	9.67(2.93)	9	9.74(2.43)	10	1229.5	.911		
Semantic clustering for list A trials 1-5	9.45(3.46)	9	9.72(3.46)	10	1192.5	.713		
Serial clustering for list A trials 1-5	9.84(3.45)	9	9.46(3.56)	9	1208	.794		

*** $p < .001$, ** $p < .01$, * $p < .05$. M: Mean, SD: Standard Deviation, Mdn: Median

Drug users also retrieved fewer specific memories from autobiographical memory and they were less likely to give a response, compared to non-users. On the contrary, drug users did not differ from non-users on other retrospective memory measures (see Table 14).

Table 14: Mann-Whitney and RANCOVA tests' results for other retrospective memory measures

	Drug User (53)		**Non-Users (47)**					
					Mann-Whitney		**RANCOVA**	
	M (SD)	***Mdn***	***M (SD)***	***Mdn***	***U***	***p***	***F***	***p***
The AMT								
Specific memories recall	5.21(1.94)	5	7.40(1.75)	7	494	<.001***	13.3	<.001***
Non-specific memories recall	3.13(1.47)	3	2.30(1.86)	2	837	.004**	3.81	.054
Extended memories recall	2.13(1.49)	2	1.55(1.19)	1	971.5	.053		
Categorical memories recall	0.45(0.61)	0	0.34(0.60)	0	1114	.276		
Non-memories recall	0.28(0.72)	0	0.21(0.51)	0	1237	.928		
Omission/no respond	1.66(1.50)	1	0.47(1.12)	0	581.5	<.001***	11.03	.001***
Memories recall for positive words	2.36(1.13)	2	3.47(1.25)	3	652.5	<.001***	8.34	.005***
Memories recall for negative words	2.94(1.26)	3	3.95(1.02)	4	670	<.001***	8.12	.005***
Overall score	29.21(6.24)	29	35.21(4.91)	36	525	<.001***	11.3	.001***
The VPA								
Hit	17.60(4.12)	18	19.21(3.18)	19	986	.072		
False Memory test								
Hit	.86(.11)	.90	.87(.12)	.90	1143	.477		
FA	.01(.05)	0	.00(.01)	0	1179	.299		
False recognition	.58(.29)	.60	.49(.30)	.50	1047	.168		
Source Memory test								
Present Hit	19.60(9.33) 62.3%	22	22.87(6.75) 71.5%	23.5	1008.5	.101		
Present FA	12.40(9.33)	10	9.13(6.75)	8.5	1008.5	.101		
List 1 Hit	7.34(3.11) 43.2%	7	8.17(3.61) 48.1%	8	1084.5	.264		
List 1 FA	9.66(3.11)	10	8.83(3.61)	9	1084.5	.264		
List 2 Hit	5.55(2.71) 37%	5.5	7.00(3.72) 46.7%	6.5	1005.5	.096		
List 2 FA	9.45(2.71)	9.5	8.00(3.72)	8.5	1005.5	.096		
Top Hit	6.98(3.21) 38.8%	7.5	7.98(3.83) 44.3%	8	1061	.201		

	Drug User (53)		Non-Users (47)					
					Mann-Whitney		RANCOVA	
	M (SD)	***Mdn***	***M (SD)***	***Mdn***	***U***	***p***	***F***	***p***
Top FA	11.02(3.21)	10.5	10.02(3.83)	10	1061	.201		
Bottom Hit	4.75(2.53) 33.9%	5	4.89(2.49) 34.9%	5	1211	.810		
Bottom FA	9.25(2.53)	9	9.11(2.49)	9	1211	.810		
Source Total hit	24.62 (9.51) 38.5%	25	28.04 (10.75) 43.8%	26	1046	.168		
Source Total FA	39.38 (9.51)	39	35.96 (10.75)	38	1046	.168		

*** $p < .001$, ** $p < .01$, * $p < .05$. FA: False Alarm, CR: Correct Rejection.

Most results remained significant after statistically controlling for the covariates (e.g., sleep quality, general health, alcohol use and age) with the exception of the CVLT3 total intrusion and yes/no recognition hits subtests, and the AMT non-specific. This suggests that general health, sleep quality, alcohol use and age might be mediating scoring on these subscales.

6.5. Discussion

The present study assessed the possible consequences of recreational drug use on cognitive functions, using lab-based measures while trying to overcome the methodological challenges facing previous studies as well as attempted to fill the identified research gaps. Recreational polydrug users who were light users differed significantly from drug-naive controls in some measures, but not in others. For instance, drug users did appear to recall less specific personal event memories than non-users in the AMT. They were also less likely to give a response. These findings are in line the literature (Mercuri et al., 2018; Oliveira et al., 2007; Pillersdorf & Scoboria, 2019). As reviewed in Chapter 2, most of those studies assessed regular and heavy drug users. The current study showed that even light recreational drug use can impair AM.

As discussed in Chapter 2, AM is the combination of episodic (personal memories of past events and experiences) and semantic memory (knowledge about the self; Willoughby et al., 2012). The episodic memory component, characterised as conscious mental time travel,

allows for past events to be recalled in rich detail, thus considered the defining feature of AM retrieval (Baddeley et al., 2001). The inability to recall specific memories, therefore, is associated with difficulties in accessing episodic autobiographic memory. Tulving (2002) views episodic memory as a distinct memory system from semantic memory, hence it has been argued that episodic and semantic autobiographical memory might be stored in separate yet interacting memory systems (Beike & Ransom, 2012). A meta-analysis of 24 functional imaging studies of AM showed that the medial and lateral temporal cortices, the medial and ventrolateral prefrontal cortices, the posterior cingulate cortex (PCC), the temporoparietal junction, and the cerebellum regions are consistently activated during AM tasks (Svoboda et al., 2006). These results are in line with those of two earlier reviews of AM (Conway et al., 2002; Maguire, 2001). The study further confirms overlapping, but different patterns of brain activity corresponding to semantic and episodic AM. For example, Levine et al. (2004) found that both semantic and episodic components of AM engaged the left anteromedial prefrontal cortex, but the episodic component did so to a higher degree. Furthermore, the episodic component of AM uniquely engaged the medial temporal, diencephalic, and posterior cingulate areas (Levine et al., 2004). This theory of distinct episodic and semantic systems ties well with findings from case studies in which patients with severe amnesia remain aware of general self-knowledge, but are unable to recall details of past events (Beike & Ransom, 2012). Those findings suggest that drug users might be impaired in certain regions of the brain, such as the anteromedial PFC and the medial temporal region which might be associated with poor AM. Those brain regions are also associated with PM which will be discussed in detail in Chapter 8 (Okuda et al., 1998).

A lack of specific autobiographical memory may result from general memory deficit, disturbing memories of adverse events and/or exposure to traumatic experiences. For example, Williams (1996 as cited in Valentino et al., 2009) hypothesised that children who

experience early trauma adopt the way they retrieve autobiographical memories as an affect-regulating strategy, thus they tend to recall general memories (non-specific) to avoid negative effects that are associated with painful specific memories. This is a phenomenon known as "mnemonic interlock" (Williams, 1996). In line with this hypothesis, parental abuse (Dalgleish et al., 2003; Valentino et al., 2009), childhood sexual abuse (Burnside et al., 2004; Henderson et al., 2002), cancer (Kangas et al., 2005), and burn injury (Stokes et al., 2004) have been associated with impaired autobiographical memory specificity.

Decades of research have found a strong connection between exposure to traumatic experiences and substance use/dependence (Khoury et al., 2010). There are possible explanations for such connection. For example, according to the self-medication hypothesis, people who are exposed to traumatic events use drugs in an attempt to handle or counteract their symptoms (Reed et al., 2007). The high-risk hypothesis argues that individuals who abuse drugs have higher rates of trauma as a result of their drug use (Windle, 1994). The susceptibility hypothesis emphasises that individuals who use drugs are more susceptible to developing post-traumatic stress disorder after exposure to trauma than individuals who do not use drugs (Chilcoat & Breslau, 1998) as they may be unable to effectively deal with negative emotions resulting from the traumatic experience (Stewart et al., 1998). Lastly, the shared vulnerability hypothesis indicates that both PTSD and drug abuse problems share risk factors, thus they might not be causally related when shared risk factors are considered (Stewart & Conrod, 2003). Among all those hypotheses, the self-medication hypothesis has the strongest evidence from previous studies (Haller & Chassin, 2014). In relation to the current study, drug users might have experienced trauma which might lead them to use drugs or vice versa, but consequently, both experiences have the potential to explain (in isolation or together) the observed AM impairments.

The self-memory system, proposed by Conway and Pleydell-Pearce (2000), offers an alternative explanation for the phenomenon of autobiographical memory specificity which may complement Williams' hypothesis (Conway & Pleydell-Pearce, 2000). In this model, three levels of specificity (e.g., event-specific, general events, and lifetime periods) are identified. In lifetime periods (the most general level), there is a thematic and chronological knowledge about shared features of a given period, for instance, 'college years'. General events (the intermediate level) are more specific and contain a sequence of associated events or single representations of repeated events (e.g., 'taking tests during college years'). Event-specific knowledge (ESK; the most specific level) refers to richer sensory-perceptual aspects of single events (vivid reminders of what occurred; the content of episodic memories), such as 'final exam in the last year of the college'. Those three domains are structured in a hierarchy and together form the overall life story of a person (Conway, 2005). Therefore, when a specific autobiographical memory is recalled, this hierarchical arrangement must be navigated. This model consists of the working self and long-term self. The working self is a temporary activation of present aims that limits the search for elements to be bound up in the memory system. The long-term self is formed from the conceptual self (abstract self-knowledge, such as beliefs, attitudes, and self-guides) and autobiographical knowledge base together (lifetime periods and general events). There are two main functions of the self-memory system: to ensure self-coherence (attempt to create a meaningful and integrated representation of one's self and one's life story that is matching with one's aims and ideals) and to preserve adaptive correspondence (the creation of a relatively precise record of continuous experience that can be utilised to guide goal attainment).

According to Conway and Pleydell-Pearce, the retrieval of autobiographical memories is controlled by a working-self and one of the main goals of this system is to avoid affective disturbance and therefore regulate affect. It is believed that when the searched memories are

not consistent with the working-self's goals, it leads to a failure to remember specific memories. This tendency (fail in attempts to remember specific memories) is known as overgeneral memory and most pronounced in clinical populations (including those with major depressive disorder, and posttraumatic stress disorder; Van Vreeswijk & De Wilde, 2004; Williams et al., 2007).

Williams et al. (2007) suggested another possible explanation for the reason why individuals may have difficulty in retrieving specific autobiographical memories. He believes that there are three systems that underlie the phenomenon of autobiographical memory specificity, alone or in combination. The first mechanism is functional avoidance which is based on Conway and Pleydell-Pearce's idea on the working self, if ESK is not associated with the current working self during encoding, it will not be linked to stored representations in the autobiographical knowledge base and hence will not be available for later recollection. The second mechanism is capture and rumination (having constant and repetitive thoughts which considered as a core feature of depression). When there is an overlap between one's long-term concerns and attitudes and the cue words used in the AMT, the memory is more likely to be overgeneral as the cue might represent current distress that gives rise to rumination. In order to avoid such effect, one recalls overgeneral memories. Alongside functional avoidance and capture/rumination, the third mechanism that may contribute to overgeneral memory is reduced executive capacity and control that limit s person's ability to remain focused on retrieval in the presence of distraction and inhibit interfering cognitive material (Williams et al., 2007). For instance, Guler and Mackovichova (2019) showed that people with higher levels of executive function skills, notably higher levels of cognitive flexibility and inhibitory control remembered much more specific memories than people with lower levels of executive function skills. Extensive studies on the effects of drug use on cognitive functions show that drug users are impaired in executive functions (see section 2.2).

Although those explanations have clear face validity as an account of reduced specific autobiographical memory recall, they appear unlikely to be a complete account. For instance, reduced specific autobiographical memory recall might also be associated with age-related changes in memory as older adults tend to recall less specific memories than younger adults (Piolino et al., 2002; St. Jacques & Levine, 2007).

AM has been thought to have three main functions: directive, social, and self-representative (Robinson & Swanson, 1990). The directive function works as a guide that uses previous experiences to solve current problems or direct a future action (Madore et al., 2016; Mar & Spreng, 2018; Williams et al., 2008). For instance, a study found that impaired AM has been associated with reduced social problem-solving effectiveness (Goddard et al., 1996). Personal experiences are encoded with the rewards and losses that are associated with them to create successful models of behaviour that can be used as a reference for future behaviours (Pillemer, 2003). The social or communicative function helps to build and maintain social bonds by providing material for people to converse about. Telling about ourselves and hearing about others increase the intimacy level in a relationship (Bluck et al., 2005). AM also serves a self-representative function by using personal memories for the development of personal identity and the continuity of the self. A coherent self-identity enables for evaluation of previous experiences which leads to self-insight and self-growth (Wilson & Ross, 2003). Williams et al., (2008) have proposed the fourth function; adaptive which helps to alter undesirable moods or maintain desirable moods by recalling positive personal experiences (Robinson & Swanson, 1990), hence it is important for emotional resilience (Williams et al., 2008). Consequently, impaired AM might result in deficits in these functions which, in turn, cause personal and social problems that may lead to drug use or contribute to the maintenance of drug use and, in some cases, the transition from recreational drug use to drug addiction.

Recreational drug users also performed worse than non-users on verbal learning measure. They recalled fewer words than non-users in immediate recall across five trials and long-delay free recall, short delay free and cued recall trials which reflects poor auditory and verbal learning skills (Delis et al., 2017). Drug users had inconsistent recall which indicates limited learning capacity (Delis et al., 2017) as they abandoned one learning strategy for another (e.g., trying to recall words from the recency region on one trial and the primacy region on the next). Inconsistent recall of words from trial to trial may also be associated with poor systematic retrieval strategies which might reflect an executive deficit (Hahn-Barma et al., 1998). Furthermore, drug users falsely recognised new items that are related to actually presented items as old much more often than non-users in the yes/no recognition FA subtest of the CVLT3. These findings broadly support the work of other studies in this area linking drug use with verbal learning deficits as drug users performed worse in various verbal learning measures (Basedow et al., 2021; Brown et al., 2010; McCardle et al., 2004; Quednow et al., 2007; Reske et al., 2010; Roberts et al., 2009). However, the current findings contradict Kuypers' et al. (2016) study in which MDMA users did not differ from non-users on verbal learning, but it should be noted that IQ was not controlled in this study. Previously, it has been found that there is a significant association between intelligence and memory (Mohn et al., 2014). For example, Rapport et al., (1997) found that participants with low-average IQ performed worse than those with average and high-average IQs on measures of learning and memory.

In contrast to free recall subtests of the CVLT, there were no group differences in the recognition subtests. Tulving (1983, as cited in Frankland et al., 2019) established a key conceptual division between accessibility versus availability of information in memory. According to this view, some types of memory failure might be associated with a lack of availability of relevant information which causes permanent loss of that information, whereas

other types of memory failure might be associated with temporary problems in accessibility, therefore such information usually can be retrieved with cues. The current findings suggest that drug users were impaired at the retrieval level, not at the encoding (Squire, 2009) as they were able to encode the words into memory (intact availability), but fail to recall them without assistance (impaired accessibility). These findings support Gouzoulis-Mayfrank's et al. (2000) and Woods' et al. (2005) studies in which drug users performed worse in recall tests (but not in recognition tests) and partially contradict Basedow's et al. (2021), Reske's et al.(2010), Quednow's et al.(2006), and Solowji's et al. (2011) studies in which drug users displayed both recall and recognition impairments. However, it should be noted that Basedow et al. (2021) assessed only drug addicts and other studies had a short abstinence period (Reske et al., 2010; Quednow et al., 2006; Solowji et al., 2011).

The poor performance on free recall, but not recognition may be associated with the partial encoding deficit. According to this hypothesis, individuals only encode fragmented representations of the target words into the memory system. When they are asked to recall, they might only produce a deficient amount of information (Delis et al., 2017).

The observed impairments might also stem from attention deficits which are common in drug users (Gould, 2010; Pope et al., 2001). Scientists appear to be in fairly good agreement on the role of attention in the encoding and retrieval of information as they believe that one of the most vital aspects of learning is staying on task (Lozito & Mulligan, 2006; Muzzio et al., 2009; Schmitter-Edgecombe, 1996; Wiegner & Donders, 1999). For example, Gardiner and Parkin (1990) asked participants to memorise a list of words while some of them simultaneously engaged in distractor tasks that divided their attention (the experimental group) and others did not (the control group). The results showed that participants' ability in the experimental condition to explicitly recall those words later was impaired, compared to controls, even though their ability to recognise the words is not affected (Gardiner & Parkin,

1990). These results imply that the current sample may have attentional problems, which may help to explain the verbal learning deficiencies that were observed.

While both neuropsychological and cognitive studies have revealed that the encoding and retrieval neural mechanisms overlap, there is evidence that some differences do exist among those mechanisms. A large body of functional imaging and lesion studies shows that the hippocampus and left PFC play a major role in the encoding of verbal memories (Alessio et al., 2004; Ariza et al., 2006; Bor et al., 2004; Karlsgodt et al., 2005; Wright et al., 2009). Whereas, the retrieval of verbal memories is predominantly under the control of the right PFC and, in some cases, the hippocampus (Greicius et al., 2003; Habib et al., 2003; Karlsgodt et al., 2005; Wright et al., 2009). The current results suggest that drug users might be impaired in the right prefrontal cortex, but not in the hippocampus as they were able to form new memories, but failed to access them.

Multiple imaging studies demonstrated that reduced verbal memory performance is associated with modulations of the serotonin system (Klöbl et al., 2021; Meneses & Liy-Salmeron, 2012; Reneman et al., 2001). For example, a study found that poor performance on the CVLT has been associated with a reduction in neocortical serotonin transporter sites (Semple et al., 1999). As explained in Chapter 2 (see section 2.3), the use of various drugs (e.g., MDMA) interferes with serotonin systems (Benningfield & Cowan, 2013; Biezonski & Meyer, 2011; Reneman et al., 2001; Roberts et al., 2016b), which could also account for the present findings.

Learning plays an important role in everyday functional tasks. Therefore, these findings on verbal learning could translate to impaired functioning in daily life, such as poorer educational outcomes. Indeed, lower educational attainment has been consistently associated with adolescent drug use (Bugbee et al., 2019; Fergusson et al., 2003; Fothergill & Ensminger, 2006; Jeynes, 2021; Kandel et al., 1986; Lynskey & Hall, 2000; Macleod et al.,

2004; Silins et al., 2015). For example, a longitudinal study was conducted to assess the relationship between levels of educational achievement and adolescence/young adulthood cannabis use. The data were collected over the course of 25-years from 1265 New Zealand children. The results demonstrated that increasing cannabis usage was associated with poor educational achievement (e.g., failure to enter university or obtain a degree). Such associated persisted after controlling for potential confounding factors such as gender, smoking, family socio-economic status, cognitive abilities, family functioning etc. (Fergusson et al., 2003). Furthermore, a systematic review of 48 longitudinal studies also supports these findings as fairly consistent associations were found between cannabis usage and lower educational achievement (Macleod et al., 2004). However, there is also possible that people who have memory deficits are more likely to use drug (this possibility will discussed in detail in Chapter 8).

It is now well established from a variety of studies that poor academic attainment in adolescence is associated with an increased risk of drug abuse and subsequent drug addiction (Fothergill et al., 2008; Gauffin et al., 2013; Hawkins et al., 1992; Henry et al., 2012; Kendler et al., 2018; Schulenberg et al., 1994). One of the possible explanations for such association is social role expectation. According to this view, people use drugs to deal with the disappointment and frustration of not meeting social role expectations (Fothergill et al., 2008). Furthermore, educational achievements are a strong determinant of later-life income (Gregg et al., 2010). People with educational underachievement might have low incomes (Annen & Tiemann, 2017) which, in turn, may lead to drug abuse. Indeed, some researchers found that drug abuse/dependence is pronounced in people with lower socioeconomic status (Reinherz et al., 2000), however, such association might be mediated by depression (Goodman & Huang, 2002).

Similar to the results from the recognition subtest of the CVLT, drug users did not differ from non-users on source memory which was assessed via a recognition test. Source memory, memory for certain contextual details of a stimulus, such as its colour, location, or temporal context in which the stimulus is encountered, can be important while going through daily life, for instance remembering where you last saw an object (e.g., key), so you can retrieve it when needed or remembering the contexts in which you previously experienced individuals you meet so you can react appropriately to them (Talk et al., 2017).

The source memory test has two subcomponents; item (discriminating between old and new items) and source memory (remembering the contextual, perceptual or other features of encoded information). Source memory tests are practically harder than item memory tests, as they require the retrieval of extra detail and the use of more complex decision processes (Guo et al., 2006). Even though item and source memory are considered two different concepts, there are interactions between them as item memory contributes to source memory and source memory influences item memory (Guo et al., 2021). Source memory is strongly dependent on the binding and retaining of all features in the encountered context during an encoding phase (Talk et al., 2017), for instance, different encoding conditions, such as the time available, motivational elements, the level of distraction and the integrity of attentional mechanisms lead to rich source information (Johnson et al., 1993). Thus source memory impairment has been associated with encoding impairment, rather than retrieval impairment (Glisky et al., 2001). Given that mild drug users in the current sample were unimpaired in encoding, it explains why they did not differ from non-users in this test.

While this finding supports Morgan, Schafer's, et al., 2010 study and contradicted other reviewed studies in Chapter 2 (Cuttler et al., 2012; Fisk et al., 2014; Morgan et al., 2004; Morgan, Muetzelfeldt, et al., 2010). However, the findings of those studies should be treated with caution due to their methodological challenges. For example, Fisk et al. (2014)

and Morgan et al., (2004) did not have drug naïve controls (e.g., ecstasy poly drug users were compared to non-ecstasy poly drug users or ketamine users were compared to non-ketamine user controls) and Morgan, Muetzelfeldt's, et al. (2010) did not control for education levels (the control groups had significantly higher years in education). The current findings also contradict Cuttler's et al., (2021) study in which only the acute effect of cannabis was assessed. Also, the study was conducted during an online Zoom meeting which might have affected the results.

Contrary to initial predictions, the groups did not differ on false memory (remembering something that did not happen or remembering it in a different way than how it actually happened; Shaw, 2020) as the number of correct recognition hits was similar in both groups and drug users did not demonstrate an increase in false memory rates for critical lures. In the current study, false memory was assessed using the DRM paradigm, participants study lists of words that are all semantically associated with a lure word that is not presented. On subsequent recognition tests, subjects typically display a high rate of false memory for the nonpresented lure word. One of the most used theoretical explanations of the DRM paradigm in the literature memory is the activation-monitoring theory. According to this theory, false memories are due to the activations of the lure's representation in semantic memory while studying a lure's associates during the learning phase (Roediger et al., 2001 as cited in Sergi et al., 2014). Thus, encoding plays an important role in the formation of false memory (Okado & Stark, 2005). As discussed earlier, recreational drug users in the current study did not display encoding deficits as they were able to recognise the words when they were given the cues. This might explain the current findings. Furthermore, a variety of investigators have demonstrated that different encoding manipulations can reduce the formation of false memories in the DRM (Hege & Dodson, 2004). For example, Smith & Hunt (1998) found that visual study presentation of associatively related lists improves performance and reduces

the formation of false memory, compared to auditory study presentation in both recall and recognition (Smith & Hunt, 1998). In the current study, the false memory test was delivered, using a PowerPoint presentation, it is possible that the visual presentation prevented the production of false memories. Moreover, false memories were assessed via a recognition test, it might be that false memories are more likely to be produced in free recall rather than recognition tests.

These findings contradict most studies reviewed in Chapter 2 (Cuttler et al., 2021; Doss et al., 2018; Kloft et al., 2020; Riba et al., 2015). However, it should be noted that in those studies only the effects of cannabis on false memory were investigated. In the current study, most drug users consume a combination of different drugs, such as MDMA and cocaine. It has been found that MDMA does not affect false memory (Kloft's et al., 2022). Furthermore, the majority of those studies investigated the acute effects of drugs on false memory, unlike the current study in which the possible long-term effects of drugs were examined. Therefore, together, these findings suggest that drugs cannabis use, in particular, might acutely influence false memory, but the effect disappears when the drug wears off. This is in line with a study in which the performance of cannabis-naïve controls, regular cannabis consumers who were sober and regular cannabis consumers were compared, but there were no group differences (Kloft et al., 2019).

Drug users also performed similarly to non-users in the VPA which is consistent with the results of the majority of recognition tests in the current study. In the VPA, participants were required to encode pairs of words and asked to recall the second member of each pair after they were prompted with the first member. Therefore, it assesses verbal associative learning which has been thought to be regulated by the hippocampus. For example, a wide range of imaging studies showed that hippocampal damage was significantly associated with

the impairments on the VPA tasks (Clark et al., 2018). Therefore, these findings further suggest that recreational drug users are not impaired in the hippocampus.

Another aim of the current study was to understand the underlying factors of the observed PM deficits in drug users (see Chapter 4). As discussed in the introduction, PM relies on various cognitive processes, including retrospective memory. The current findings suggest that the observed PM impairments in Chapter 4 might stem from retrospective memory deficits as drug users scored worse than non-users on some retrospective memory measures[3]. This hypothesis is in line with previous research (Cuttler et al., 2012).

Taken together, drug users performed worse than drug-naive controls on verbal learning and autobiographical memory, but not on verbal paired associative learning, source and false memory. The performance of drug users was worse in the short-term (e.g., the CVLT3 immediate recall for trials 1-5 subtest) and long-term retrospective memory measures (e.g., the CVLT3 delay recall subtests, autobiographical memory). They tended to perform poorly on free recall, but normally on recognition tests (e.g., the CVLT3 yes/no recognition, False Memory, Source Memory). This suggests that drug users were impaired at the retrieval level, not the encoding (Squire, 2009) as they were able to encode the words into memory, but fail to recall them without assistance. They also did appear to have more difficulties in accessing autobiographical memory which consists of memories about personal experiences that define self and support well-being (Vanderveren et al., 2017).

[3] A RANCOVA was run to assess the association between drug use and PM that was found in Chapter 4 while controlling for retrospective memory. The data from non-users was used as normative data to calculate z scores for cognitive measures in which there were significant group differences. All z scores belonging to retrospective memory measures (i.e., the CVLT and AMT) were then averaged to create a new variable that represents overall retrospective memory ability. The results revealed that the LT and total score subtests of the RPA-ProMem remained significant, but the ST, EB, and TB subtests did not, implying the involvement of retrospective memory in those forms of PM (see Appendix M).

6.6. Limitations and future directions

The study had similar limitations as Chapter 4, such as polysubstance use, use of self-report assessment to confirm an absence of substance use, no information on lifetime use of the individual drug. Furthermore, it is possible that the groups may differed on some variable other than recreational drug use. Some possibilities were excluded (e.g., IQ, general health, sleep quality, age), but some could not (e.g., nicotine use). Therefore, future studies should control those variables, use drug testing kits (urine or saliva) to confirm abstinence and assess lifetime use of the individual drug. Furthermore, it was evident that attention deficits may be the root cause of the majority of the cognitive problems found in drug users. However, very few researchers have looked into how drug use affects attention and those that have mainly used indirect methods like WM measurements to quantify attention (Ilan et al., 2005; Macleod et al., 2004; Sanvicente-Vieira et al., 2016; Soliman et al., 2013; Wang et al., 2008). Direct evaluation of attention, using appropriate instruments (possibly a combination of different measures) in drug users is crucial. Lastly, it was evident PM impairments are associated with various cognitive deficits. Further studies should be conducted to investigate the role of those cognitive processes in PM.

6.7. Conclusion

In this study, the focus was on overcoming several of the challenges in previous studies on the influence of recreational drug use and cognitive functions. This work adds to a growing body of literature by demonstrating that recreational drug use impair retrospective memory (retrieval, but not encoding). Future research could expand the investigation by addressing other cognitive domains, investigating drug-specific contributions, and ascertaining whether drug-induced cognitive deficits can be rehabilitated after drug cessation.

Chapter 7: Recreational Drug Use and Prospective Memory: A qualitative study

7.1. Abstract

Extensive research has been conducted to investigate the effects of illegal drug use on prospective memory (PM), however, the findings are rather inconclusive. While the studies with lab-based PM testing methods demonstrated consistent findings with drug users scoring worse than non-users on various PM tests, the studies employing self-report measures of PM, have shown mixed findings as illegal drug users exhibited PM deficits in some studies, but not in others. These findings show little or no overlap between lab-based and self-reported PM performance in drug users. Such discrepancy emphasizes the necessity of taking into account the subjective experience of drug users. The current study aimed to understand how drug users manage to remember and execute delayed intentions in everyday life from their point of view, whether they use any specific strategies to perform such intentions and the confounding factors that might have an impact on their PM performance. Therefore, it has the potential to unfold the discrepancy between self-report and lab-based PM measures in drug users. Seven drug users, aged between 29 to 41, were interviewed on different components of PM (i.e., short-term memory, long-term memory, attention, and cognitive shifting), using the explicitation interview technique. Theoretical thematic analysis was employed to analyse the data. Five major themes, each with their respective subthemes, emerged from the dataset, namely, the role of attention, time-related factors, retrieval strategies, self-evaluation and other factors in memory processes. The results revealed that retrospective memory, cues availability at the retrieval phase, time awareness, and attention play a crucial role in PM. Thus impairments in such domains could be associated with poor PM performance in drug users. The perceived significance of the intention (consequently motivation) is also an

important component of PM which determines whether a PM intention is remembered or not. The results further showed that drug users are impaired in metacognition which explains why there is a discrepancy between questionnaire and lab-based PM measures in drug users. Such impaired insight into behaviour may prevent drug users from effectively recognising adverse consequences of drug use. Thus, it can contribute to the transition from recreational drug use to addiction.

7.2. Introduction

Recreational drug use remains popular despite its detrimental consequences. As discussed in Chapter 2, drug-affected brain areas and neural processes overlap significantly with those that enable cognitive functions, such as memory, and executive functions (Gould, 2010). As a result, recreational drug use has been linked to a variety of cognitive impairments, including prospective memory (PM), as reviewed in Chapter 3 and shown in Chapter 4.

As described in Chapter 3, PM is a multi-phase, complex cognitive ability that consists of five phases:(1) the formation of intention, (2) a temporarily extended interval during which the intention is not attended to, (3) the detection of a cue that triggers retrieval of the intention, (4) recall of the intention and, lastly, (5) execution of the intention (Zogg et al., 2012). PM relies on various cognitive processes, including retrospective memory and executive functioning. For example, planning takes part in the formation and encoding of an intention as one should make an initial plan that specifies how to carry out PM tasks (Kliegel et al., 2002; Settle et al., 2017) and working memory is responsible for storing the postponed intention while carrying out the ongoing task (Marsh & Hicks, 1998). In addition, attentional monitoring of the external world is important to recognise the convenient time or event to start the PM action (Landsiedel et al., 2017). Inhibitory control and cognitive flexibility are also necessary for PM because performing a planned intention requires diverting attention from the current task (Kliegel et al., 2002). Lastly, retrospective memory is required for the maintenance of the action and retrieval of the context (i.e., what action needs to be performed and when; Einstein & McDaniel, 1990). Therefore, deficits in such cognitive functions have been associated with poor PM performance. For example, Hutten et al. (2018) found that divided attention performance was negatively correlated with PM performance; demonstrating that enhanced attention was somewhat associated with better PM performance.

Furthermore, a study demonstrated that the observed PM deficit was eliminated after controlling retrospective memory problems which suggests that retrospective memory impairment might lead to PM failures (Cuttler et al., 2012). Moreover, various other factors, such as the perceived significance of an intention (Walter & Meier, 2017), ageing (Henry et al., 2004; Koo et al., 2021), mental well-being (Harris & Cumming, 2003), and sleep (Leong et al., 2019) have been thought to have an impact on PM.

There are two major theories proposed to account for how people remember to execute intended actions: the preparatory attentional and memory (PAM) processes theory and the multiprocess theory. The PAM theory, proposed by Smith (2003), claims that both memory processes and preparatory attentional processes are involved in successful PM retrieval. An individual must engage in attentional processes to scan the environment (monitoring) for PM cues (either an event or time). Upon encountering PM cues, the individual initiates a retrospective recognition check to decide if any of the particular cues are linked with the opportunity to perform the intended action (Smith, 2003). The multiprocess theory of PM, proposed by Einstein and McDaniel (2005), argues that PM retrieval does not always require an active monitoring process, but can happen spontaneously under certain task conditions ("focal targets") without the allocation of cognitive resources. There are various mechanisms that have been proposed to explain how spontaneous retrieval happens, but the reflexive associative retrieval hypothesis is the most widely accepted. According to this hypothesis, when individuals encode a PM intention, they create an association between the target cue and the intended action. When the target cue occurs, the retrieval of the intended action is triggered by an automatic associative-memory system and brought back into conscious awareness (McDaniels & Einstein, 2000). Certain conditions affect the likelihood of these spontaneous retrievals, such as cue focality and salience, dividing attention, emphasis of task instructions etc. (Einstein et al., 2000; Harrison et al., 2014; Kliegel et al.,

2001). Therefore, the role of cognitive processes in PM discussed above depends on how people remember to execute intended actions. For instance, the role of attention will be more significant when an individual actively monitors the environment to detect a PM cue as the PAM processes theory suggests, compared to spontaneous retrievals where the involvement of attention is minimal.

As discussed in Chapters 3 and 4, the findings from previous studies on the effects of illegal drug use on PM are rather inconclusive. While the studies with lab-based PM testing methods demonstrated consistent findings with drug users scoring worse than non-users on various PM tests, the studies employing self-report measures of PM, have shown mixed findings as illegal drug users exhibited PM deficits in some studies, but not in others.

These findings are in line with previous studies that show little or no overlap between lab-based and questionnaire-based memory performance in drug users (Bartholomew et al., 2010; Hadjiefthyvoulou et al., 2011a; Parvaz et al., 2016; Weinborn, et al., 2011a). The discrepancy between the self-report and lab-based measures might be associated with issues of measuring PM using questionnaires. Researchers have identified two critical factors that might compromise the veracity questionnaire data: situational issues and cognitive issues (Brener et al., 2003). Cognitive issues address whether the participants comprehend the question and whether they have the knowledge or memory to answer it correctly. As drug users are impaired in retrospective memory and especially in recall (see Chapter 6), completing the questionnaire accurately will be challenging (Oliveira et al., 2007; Pillersdorf & Scoboria, 2019). Situational issues include the influence of characteristics of the external environment. Certain questions may havesocially desirable responses that aim to increase the presence of some socially desirable characteristics or decrease the presence of some socially undesirable characteristics, such as minimized reports of substance use harm (Brener et al., 2003; DeMaio, 1984; Groh et al., 2009; Zemore, 2012).These issues increase measurement

error and can explain the discrepancy between lab-based tests and questionnaires assessing PM ability.

The discrepancy between questionnaires and lab-based tests could also be attributed to impaired metacognition in drug users (Goldstein, Craig, et al., 2009) which refers to awareness of one's own abilities (Hester et al., 2007). For instance, drug users rated their emotional and cognitive functioning as less impaired than do close informants, such as parents, brothers/sisters and spouses (Verdejo-García & Pérez-García, 2008) and consistently demonstrated reduced awareness of errors (Hester et al., 2007, 2009). Therefore, the discrepancy might also be associated with a lack of insight into drug users' own cognitive abilities.

To understand the observed discrepancy between questionnaire-based data and lab-based test measures a deeper assessment of the subjective experience of drug users is needed. This would elucidate why drug users believe that they are not impaired in PM while displaying PM deficits in lab-based tasks. The aims of the present study were exploratory in nature, using a qualitative interview approach which allows the investigators to explore the subjective realities of participants' life experiences which can be hard to grasp by employing a quantitative research approach. Interviews provide a number of advantages, for instance, they involve a more direct interaction between the respondent and the researcher than questionnaires and lab-based tests which facilitates discussions and provide a richer context in which the answer is situated. Moreover, interviews enable the examiner to determine if the respondent comprehends the question (as discussed earlier, that is one of the limitations of questionnaire-based measures). Furthermore, unlike other research methods that demand a precise framework with zero deviation, the structures of interviews are fluid and open-ended; the examiner can follow up answers with additional questions to get underneath superficial

responses in order to gather more information. Such formats also allow the acquisition of new information that is not a priori anticipated.

In this study, the explicitation interview technique was used[4]. This technique, largely derived from the phenomenological approach by Edmund Husserl, was developed by Claire Petitmengin. It aims to allow interviewees to become conscious of their own cognitive mechanisms and to make them explicit (Petitmengin, 2006) by encouraging the participants to think of a specific episode and go into a state of evocation so that the episode can be described with precision and in great detail, hence it can be seen a form of guided retrospective introspection. In this way, insights into the process of performing an activity can be obtained by both the participant and researchers. Sensorial questions (e.g., just put yourself back into the situation and tell me precisely what happened) are used to aid the respondent in recalling a particular episode. The respondent is steered away from any generalizations (e.g., whenever I…) to maintain focus on the specific episode. Throughout the interview, the interviewer extracts the most relevant information from the interviewee's response and ask further questions on that particular information, which may involve echoing, specifying (e.g., what did you mean by that? Can you tell me more?) or clarifying (e.g., you said that…. did I understand correctly?). Petitmengin, (2006) describes six nonlinear phases in the interview process: (1) stabilising attention which is the key component of the explicitation interview that enables participants to focus on a past experience to recall the detail of such experience, including the detail that they did not notice before; (2) shifting the focus from "what" to "how" which facilitates remembering of various dimensions of the experience (e.g., visual, auditory etc.); (3) moving from a generic representation to a unique experience that is usually highly sensorial and contextualised; (4) accessing the past experience; (5) turning the attention to the different dimensions of the

[4] The researcher was trained to use the explicitation interview technique before running interviews.

experience; and (6) deepening the description of the experience to the level of precision required. Thus, the last two steps (5 and 6) require the verbalisation of broad descriptions of the lived experience's multilayered dimensions (Petitmengin, 2006). Those steps demonstrate that the explicitation interview technique places a high value on the first-person perspective (Bedin et al., 2019) and allows the investigators to dig deeply into the participants' experiences, offering rich contextual which can be used to answer the current research questions. This procedure was validated by Vermersch (1994, pp. 176-181 as cited in Urquhart et al., 2003).

To address the perceived cognitive abilities related to PM in drug users, the explicitation interview needs to explore the various components are PM mentioned above. Therefore, questions should be dedicated to STM, LTM, attention, and cognitive shifting, while probing further about PM-specific aspect of remembering and executing delayed intentions. These questions would need to be contextualised within the person's everyday life, which may bring up further insights into the interaction between drug use and PM.

The collected data were analysed with thematic analysis (TA) which is used to identify, analyse and interpret patterns of meaning (or "themes") within qualitative data (Braun & Clarke, 2006). There are two reasons why TA was used in the current study, but not other qualitative methods. First, TA is similar to quantitative analyses in which the data is also analysed to identify, describe and explain patterns, but on larger scales. Therefore, TA and quantitative analyses can be complementary to each other to provide more in-depth findings. Second, due to its theoretical freedom, TA offers a highly flexible approach that can be adjusted according to the need of a study (Braun & Clarke, 2006; Nowell et al., 2017).

It was hypothesised that the discrepancy between questionnaire- and lab-based measures of PM might reside in some of the cognitive components of PM. By assessing the

responses from the interviews, it would be possible to ascertain whether either measurement instrument is differentially sensitive to drug use and why. Furthermore, the obtained data via the questionnaire- and lab-based measures from the participants in Chapters 4 and 5 would be compared with the current data to examine whether they match or contradict. A disagreement between the results from the lab-based data and the results from the questionnaire-based data or the current data would suggest impaired metacognition.

7.3. Methods

7.3.1. Participants

The sample consisted of seven drug users (three females). There are no power analyses or computations that can be used to determine a sufficient sample size in qualitative research. However, it has been argued that theoretical saturation, which refers to the point in data collection when sampling more data will not lead to more information related to the study's questions, can be reached with six interviews (Isman et al., 2013a, b). Furthermore, Braun and Clarke (2013) recommend recruiting 6–10 participants for thematic analyses. The participants' age ranged from 29 to 41 years old (mean age= 36.29, SD=5.91). Five participants[5] took part in the study presented in Chapters 4 and 5 and gave consent to be contacted for future studies were recruited. The cognitive profile of those participants were presented in Table 15. The non-user group data from Chapters 4 and 5 were used as normative data to calculate z-scores for cognitive measures for those participants. Z scores below 1.0 SD indicate mild cognitive impairment (Albert et al., 2011). The other two were recruited via the snowball technique (Solowij et al., 1992). They all had white backgrounds

[5] The participants who had a higher discrepancy between the self-report and lab-based PM measures in Chapter 4 were contacted to take part in the study, but most of them rejected the invitation due to different reasons. Therefore, any participant who gave consent to be contacted for future studies in Chapter 4 was invited to participate the study without any restriction.

and a Bachelor's (N=4) or Master's degree (N=3). All subjects were residing in London and spoke English as their native language (N=3) or were fluent in English (N=4).

Table 15: Cognitive profile of five participants

Cognitive measures	Participant				
	P1	**P2**	**P3**	**P4**	**P5**
The PMQ					
Internally cued PM failures	-.87	-.11	-.11	-.11	.90
LT episodic PM failures	-.98	-.46	.31	-.20	-.98
ST habitual PM failures	-.63	-.63	.61	-.63	-.63
Use of memory aiding strategies	-.87	1.78	.56	-1.17	-1.38
Total score without the aids subtest	-1.01	-.40	.21	-.28	-.15
The RPA-ProMem					
Short-term	-.03	-1.32	-2.61	-1.96	-3.25
Long-term	-.89	-1.41	.16	-2.45	-1.41
Event-based	-1.63	-2.39	-2.39	-2.39	-2.39
Time-based	.24	-1.01	-1.01	-2.89	-2.89
Total score	-.70	-1.91	-1.51	-3.12	-3.12
The CVLT Total Recall Score	-.09	-.10	.36	.59	-2.32
The VFT Total Score	.57	-.57	-1.24	-1.90	-1.52
The DS Total Score	-.96	-.20	-.96	-.71	-1.22
The AMT Total Score	-.25	-2.49	-3.51	-.86	-.86

PMQ: Prospective Memory Questionnaire, RPA-ProMem: Royal Prince Alfred Prospective Memory Test, CVLT: California Verbal Learning Test, VFT: Verbal Fluency Test, DS: Digit Span, AMT: Autobiographical Memory Test.

As seen in Table 16, all the participants were polydrug users, mainly using cocaine and MDMA, apart from one participant who only used cannabis (i.e., P6). They also consumed alcohol. The study was granted ethics permission from Birkbeck, University of London.

Table 16. Drug profile of the participants

	Participant						
	P1	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**
Cannabis	2	2	4	3	0	5	4
Cocaine	3	4	4	3	4	0	3
MDMA or Ecstasy	3	3	4	3	2	0	4
GHB	3	0	2	2	2	0	2
Hallucinogenic	2	0	0	2	0	0	4
Ketamine	1	0	0	2	0	0	2
Methamphetamine	0	0	0	0	2	0	2
Mephedrone	0	0	0	0	3	0	0

0 = Non-user; 1 = Ex-user; 2 = Very Rarely: 1 or 2 times a year; 3 = Rarely: 1 or 2 times every three months; 4 = Occasionally: 1 or 2 times a month; 5 = Frequently: 1 or 2 times a week; 6 = Very Frequently: 3 or more times a week.

7.3.2. Design

A qualitative research design was employed. The participants were interviewed on different components of PM through semi-structured interviews, using the explicitation interviewing approach.

7.3.3. Materials

Demographic information (e.g., age, gender and ethnicity) and current use of alcohol and illegal drugs were obtained via background questionnaires. The participants were asked 15 questions on PM (see Appendix L). Questions 1-11 were about different components of PM. For instance, questions 1-6 were about retrospective memory, more specifically about short- and long-term memory (e.g., how would you rate your short-term memory from 1 to 10, with 10 being excellent? or have you noticed any change in your long-term memory after you started using drugs? If yes, can you describe a particular time when you noticed any changes and what those changes were?). Questions 7-11 were about executive functions: attention (e.g., can you give an example in which you had to pay attention to something while there was a distraction present?) and cognitive flexibility (e.g., how good are you at switching your focus from one thing to another?). Questions 12-15 were directly related to PM. Each question assessed different types of PM. For instance, question 12 was about short-term event-based PM (e.g., can you give me an example of a situation when you have to remember to do something in the next few hours or days after a particular event, such as buying bread when passing the store? The possible prompts were: did you remember to do it? If yes, how did you manage to remember? Did you use a reminder or it just pops into your mind or someone reminds you? If no, why? What did you make you forget to do it? What circumstances led you to forget?) and question 15 was about long-term time-based PM (e.g., can you give me an example of a situation when you have to remember to do something in

the next week, next month or next year at a particular time, such as sending birthday wishes to a friend on his/her birthday?).

7.3.4. Procedure

The study consisted of two phases. In the first phase, participants were informed of the general purpose of the study and electronically written informed consent was obtained. They were then sent a link to complete an online survey that contained the demographics questionnaires which lasted around 5 minutes to complete. In the second phase, participants were asked to attend a meeting over Zoom in which they were interviewed. The meeting was recorded with the subject's permission and lasted around an hour. The interviews were fully transcribed by the investigator during which all identifying details were removed. At the end of the session, participants were debriefed about the study and given drug education leaflets and a £10 Amazon voucher for compensation for their time. All the interviews were conducted by the researcher.

7.3.5. Analysis

The data were analysed with TA. The analysis was completed in accordance with Braun and Clarke's recommendations (2006). First, the interview transcripts were read several times to familiarise with the data. During this stage, some early, rough notes were taken. Second, patterns within the data were identified that addressed specific research questions in a theoretical or top-down way. For example, any word or phrase that was somehow associated with the frameworks of PM was highlighted, such as any detail about attention or retrospective memory. Those patterns were then coded and extracted from the original data. Coding condensed large amounts of data into small chunks of meaning that helped to organise the data in a systematic way. Next, the initial codes were checked whether they match the data extracts. If so, they were collated into potential themes, assembling all information pertinent to each possible theme that appeared to say something particular about

the research questions. In this stage, as many themes as possible were generated and then reorganised according to their relationships with the data extracts and other themes. When necessary, themes were merged or discarded due to overlapping contexts or insufficient data to support them. The main theme needed at least five participants' involvement to emerge. These identified themes were further divided into subthemes when one notable specific element exists underneath the umbrella of a theme. A subtheme needed at least three participants' involvements to be formed. In the final stage, each theme and subtheme was defined (e.g., identify the essence of what each theme and subtheme is about). All the coding processes and analyses were conducted by the researcher.

7.4. The results

The participants reported various factors that have an impact on their retrospective and prospective memory abilities. As seen in Figure 5, five main themes, each with their respective subthemes, emerged from those factors.

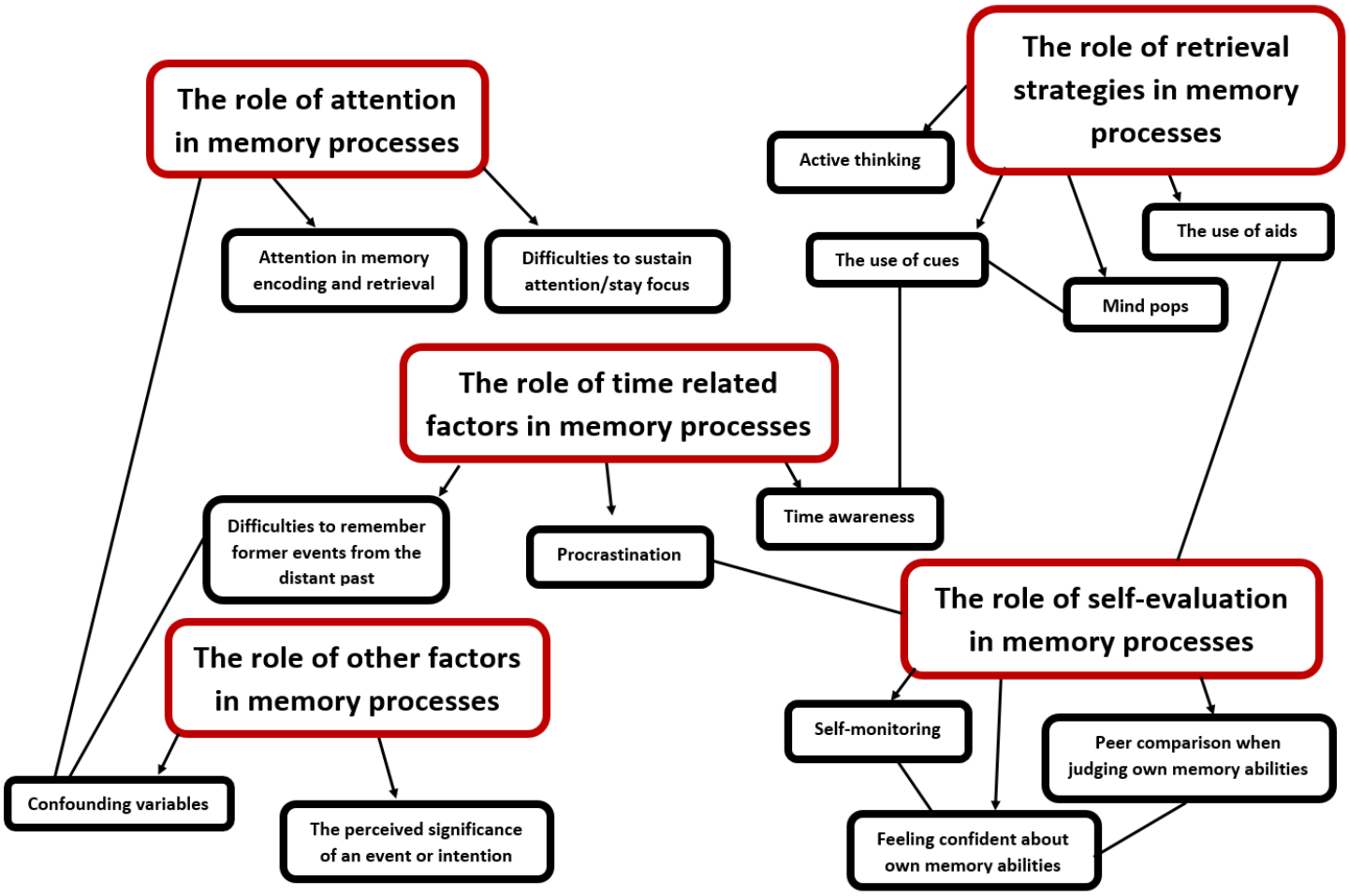

Figure 5: Thematic map, showing the themes and subthemes and the relationship among them.

Table 17 shows the prevalence of participants within each theme and subtheme. The main themes are the role of attention in memory processes, the role of time-related factors in memory processes, the role of retrieval strategies in memory processes, the role of self-evaluation in memory processes, and the role of other factors in memory processes. While each of these concepts is treated independently, there are a number of ways in which they interact and/or overlap. For instance, there is a strong association between retrieval strategies and self-evaluation as one uses a particular retrieval strategy based on their cognitive abilities.

Table 17: Prevalence of participants within each theme and subtheme table

Themes	Subthemes	Subject	No. of subjects	Sample %
The role of attention in memory processes	Attention in memory encoding and retrieval	P1,P2, P3, P4, P5, P6, P7	7	100
	Difficulties to sustain attention/stay focus	P1,P3, P4, P5, P6, P7	6	86
The role of time related factors in memory processes	Difficulties to remember former events from the distant past	P1, P2, P3, P4	4	57
	Time awareness	P1, P3, P4, P5, P7	5	71
	Tendency to postpone an activity	P1, P2, P4, P7	4	57
The role of retrieval strategies in memory processes	Active thinking	P1. P4, P6 P7,	4	57
	Mind pops	P1, P3, P6	3	43
	The use of cues	P1, P2, P3, P4, P5, P6	6	86
	The use of aids	P1, P2, P3, P4, P5, P6, P7	7	100
The role of self-evaluation in memory processes	Feeling confident about memory abilities	P1, P3, P4, P5, P7	5	71
	Peer comparison when judging own memory abilities	P3, P4, P5, P7	4	57
	Self-monitoring	P1, P2, P3, P4, P5, P6, P7	7	100
The role of other factors in memory processes	The perceived significance of an event or intention	P1, P2, P3, P4, P5, P6, P7	7	100
	Confounding variables	P1, P2, P3, P4, P5, P6, P7	7	100

7.4.1. Theme 1: The role of attention in memory processes

The participants indicated that attention, which is a cognitive function to engage with surroundings to process particular information while tuning out other details, is one of the main factors that contributes to their memory abilities. The theme has two subthemes: the role of attention in encoding and retrieval, and difficulties to sustain attention/stay focus.

7.4.1.1. Subtheme 1: Attention in memory encoding and retrieval

There are many forms of interaction between memory and attention. For example, when taking into account that memory has a limited capacity, it is understandable for the brain to be selective about what it lets in. Choosing to recall a certain memory, on the other hand, is a decision about how to use limited attention resources. Thus, memory encoding and remembering rely on attention abilities. In line with such notion, all the participants indicated

that attention plays a significant role in the encoding and retrieval of memories. For example, four participants associated their inability to make new memories with poor attention. As seen below, P3 demonstrated that he could not remember the names of films because he believed that he does not pay attention to the names of the films when he watches those films.

P3: The films, for example, I hardly remember. The film that I watched while ago. But if you tell me like this film, maybe I won't recognise it by the name. Also because many times I don't specially pay attention.

Three participants emphasised the role of concentration (maintaining attention for a certain amount of time) in memory recall. They believed that if they concentrate, they are able to recall the stored memories. For instance, the following participant showed that she can recall stored memory that happened two days ago if she spends some time to think about it. This is in line with the data from Chapter 5 where this particular participant performed below the normal range in the AMT as she failed to access a specific autobiographical memory in the given time (30 secs; see Table 15).

P4: I don't know why I'm thinking, but I'm like, what did I have for breakfast? And I find myself I can't remember by what I had. Or I can't remember what I did two days ago. I mean, I do remember, but I just need to spend some time to think about it…. I really need to spend some time to think about what I did…

P6 indicated that it might take a long time to bring a memory to consciousness, but she eventually remembers what she wants to remember.

P6: I think there is still things that I can't remember. I mean, I need to force myself….. You know, as I said, like, if it's not very important, I have to really sit down and focus and remember it which might take, you know, hours sometimes like remembering the situation or what I was saying, what I was talking, what I was wearing or like whatever. …. Not always, but most of the time. Yes, so I mean, if I actually dig in, they then come back…

Overall, this subtheme showed that attention plays an important role in memory processes, thus attention deficiencies may be linked to poor memory performance.

7.4.1.2. Subtheme 2: Difficulties to sustain attention/stay focus

Sustained attention, a cognitive process that enables the maintenance of attention on specific stimuli over extended periods of time, is a fundamental component of many everyday behaviours, for example, reading a book, playing tennis or attending a lecture as one needs to stay focus to perform those tasks. Six participants stated that they struggle to sustain attention while performing a task which might affect the outcomes of such task. For example, P6 demonstrated that she has attention problems as she cannot pay attention or stay focus when needed.

P6: I have a problem with concentration and stuff, so I can't focus…. I can't pay attention to be honest, it's I'm finding very difficult. Even these days, I'm actually trying myself to understand what's happening. Why is that? Why I can't focus?...

It was evident that the participants' attention span (the time spent focusing on an activity before becoming distracted) is mediated by interest and/or motivation. For example, the following participants demonstrated that when they are interested or motivated, they are able to sustain their attention to perform a task. On the contrary, when they are not interested or motivated, they find it difficult to pay attention or sustain it.

P5: My attention span is short, when I do something, like I want to do another thing at the same time. But that's usually happens when I'm not that concentrated or motivated.

P7: So something that I'm interested in, I'm very good at paying attention. Like I would remember everything. If something that I'm not interested in, it's really difficult for me to pay attention, so anything can distract me.

Six participants reported that they got easily distracted and they believed that it has a negative impact on their memory abilities and behaviours. For instance, P4 indicated that she gets easily distracted due to workloads which lead to forgetting. In Chapter 5, attention was indirectly measured via the DS and VFT in which P4 scored below the normal range (see Table 15). Thus, the findings in Chapter 5 are in line with the current results.

P4: I feel like my brain gets distracted easily. So if I'm busy with work if I'm running one place to another, I think my brain is distracted, thus I do not remember...

Those distractions were usually different thoughts/overthinking. As seen below, P1 and P5 disclosed that their mind keeps shifting away when performing a task which might have a negative impact on task performance. They seemed to have no control on those distractive thoughts.

P1: If my mind is too busy if I have a problem let's say it's just a generic example like I'm talking to a friend I need to pay attention to my friends but like I have a serious problem or issue with my work in my mind or let's say I had an argument with my partner is bothering me so my mind constantly actually recalling the problem is in my mind, so I don't pay the attention.

P5: Usually different thought distracts me most when I try to focus on something. My mind is all over the places.

P7 associated the observed memory impairment (i.e., forgetting) with overthinking which might be mediated by stress levels.

P7: I would say overthinking distract me most, like overthinking about other stuff. Today, for example, I woke up and I like slept really well. And last night was lovely and like everything was perfect. And I have a job interview. So I'm like really in a good mood. And I had coffee and like I'm getting ready and this and that. And suddenly I realised like, I'm stressing myself because I'm thinking about next month college, about this, about that's like no, just like, you know, focus on this first. You're going for this. And tonight you're meeting your friend, it's a good day. Like next week, next month will come, no need to think about that yet. So that's what I would say.

In summary, it was clear that drug users find it difficult to sustain their attention when performing a task, thus they get easily distracted, mostly by different thoughts/overthinking which might lead to poor task performance.

7.4.2. Theme 2: The role of time-related factors in memory processes

This theme emerged from time-related factors that somehow affect memory processes, such as the time interval (either short or long), or time awareness. Under this theme, there

were three subcategories, namely, difficulties to remember former events from the distant past (long time interval), the time awareness, and tendency to postpone an activity.

7.4.2.1. Subtheme 1: Difficulties to remember former events from the distant past

It appeared that amount of time between the occurrence of an event and the attempt to remember that event plays an important role in remembering the event. Longer interval makes it hard to recall a memory. For instance, four participants indicated that they were less able to remember events that happened a while ago. In other words, they struggled to recall long-term memories. This accords with the findings in Chapter 5 where those drug users performed below normal range in the AMT (see Table 15). As seen below, P4 indicated that she could not remember the detail of the film she watched or the book she read a while ago.

P4: If I watched the movie 10 years ago, I can't remember the details. Or I read the book, I do remember some bits, but I don't remember how it was ending, what was happening, so I need to re-watch the film!

Another participant confirmed that longer intervals make it harder to remember past memories.

P3: the longer the time the harder it is to remember.

It was indicated that memory fades when it is not used. For instance, the following participant demonstrated that she forgets the password that she uses to log in to the work computer or the print code (six digits) that she uses to print documents after a six-week summer holiday. In accordance with the present results, this finding supports evidence from previous observations in Chapter 5 where P2 scored above the normal range in the ST-PM, but below in the LT-PM (see Table 15).

P2: When I had that six-week summer holiday, the passwords and the print code that I use at school go, I cannot remember them. If I'm not using it, like, you know, several times in the week, then it

would go, so yeah, I have a problem after I had a holiday and then I go back to school, and I try and use those passwords and pins.

This subtheme showed that longer intervals between the occurrence of an event and the attempt to remember the event might lead to memory impairments (i.e., forgetting).

7.4.2.2. Subtheme 2: Time awareness

Time awareness, the ability to perceive the passage of time, is another factor that has an impact on memory abilities, particularly on the remembering of planned actions. This subtheme is also associated with the use of cues subtheme because dates act as a cue and trigger the retrieval of PM intentions which was discussed in more detail under the role of retrieval strategies in memory processes subtheme. Five participants reported that time awareness facilitates their PM abilities, resulting in successful PM retrieval. For instance, P7 showed that if he is aware of time (e.g., knowing which day is), he is more likely to remember to perform planned actions.

P7: So, I usually pay my rent like the last day of the month, at night. And like, last month I paid the rent at evening in Berlin. When I was partying, I was like I remembered. Okay, let's pay it… I guess I monitor dates because I'm on a vacation and I'm very aware of the days. And it's like, okay, yeah, I needed to do this so it was in my head… Not actively all the time, but when I see the dates like ahh it's this date. So it's time for rent. So, you know, it's not like I'm always thinking about it, but when you see like, it's the 30th or 31st or whatever. Like, okay, it's the time…

P3 demonstrated that when he has many upcoming events in the following days, he has a better perception of time which helps him to remember to execute planned intentions on time.

P3:... I don't always know exactly what day it is. For example, if I don't have many events on that week I do not know which day it is. ..... If there are three events in that week I have to do, one on 7th and one on 9th and the other thing on the 10th so I will have a better perception what day it is. So I know I'm closer to the 10 and on 10th I have to do that thing it's easier to remember that……

As seen below, P5 talked about the acute effects of drug use on his time awareness and how they might lead to forgetting, even for very important events. The following quotation demonstrated that the participant loses track of time and consequently time awareness while intoxicated, therefore, he fails to execute PM intentions (e.g., doctor appointment or brother's birthday). The findings in Chapter 5 support this finding as the participant scored much below the normal range in the TM-PM, compared to his performance in the EB-PM (see Table 15).

P5: …when I was all over the place and using lots of drugs, I missed my appointments, for example, I remember that... I was high when it happened. I was just like, in bed, and, like, totally out of time. I couldn't remember… Even it was important for me to do, but could not remember……I even forget my brother's birthday, because the dates were not reminding me anything when I was high.

Four participants reported that they have a special mechanism that monitors the time subconsciously and reminds them what they need to do before its due date. It seemed that such mechanism increases time awareness which, in turn, increases the success rate of PM retrieval. For example, the quotation below demonstrated that the mechanism occasionally reminds P1 a future intention, but the frequency of such reminder goes up in closer time to the event which helps him to execute the intention on time. However, those participants (i.e., P1, P3, P4 and P5) failed to complete the given PM tasks in Chapter 4 as they scored much below the normal range (see Table 15), implying that the mechanism that they rely on does not work.

P1: ….for example, let's say I have something next month on the first of September. Sometimes it doesn't come to my mind two days before, you know it starts coming now, for example, like next week, it comes to my mind. Okay, you know what, first September I'm going to do this following week is getting closer and here's something on first September, so it's always there. So there is some reminder mechanism in my mind, it reminds me occasionally.

Another participant indicated that such mechanism makes necessary arrangements for her (e.g., organising her time) to execute a future intention.

P4: When I do shopping, like I have things to return and they have the 30-day return period. And I don't exactly remember like if I bought it on the eighth of January but I am aware of the time so I know it has been one week, if it has already been a week or if it has been like three days or it has been like two weeks. So like if the time passes if it is three weeks or four weeks if I still didn't return it I start to worry and I go and check the receipt to see which day exactly I bought it but other than that I know that I have one month so during that period I try to organise my schedule and take it back to the shop. I know that is like a biological timing like that you know it. I know it when it is. I don't to put any reminders I don't know when I bought it. But somehow my brain just organises the time for me.

This subtheme demonstrated that time awareness could influence memory abilities. It appeared that participants with poor time awareness might fail to execute planned intention.

7.4.2.3. Subtheme 3: Tendency to postpone an activity

Tendency to postpone an activity, also known as procrastination, refers to the act of unnecessarily and willingly postponing to execute a task despite knowing that it might lead to negative consequences, such as forgetting. Four participants indicated that they tend to postpone executing planned intentions. For example, P7 indicated that when he does not want to do something he keeps postponing.

P7: Something that I don't want to do but I have to do, I will without realizing push it and push it and push it away. You know.

The following participant demonstrated that she feels confident that she would remember to execute an intended action later, that is why she tends to postpone. However, she finds herself forgetting the task later on. In accordance with the present results, P4 scored much below the normal range in the RPA-ProMem test, suggesting moderate to severe PM impairments. Whereas the same participant scored close to the normal range in the PMQ in Chapter 4 (see Table 15).

P4: I just remembered like, I always forget to call my friends, like, I'm thinking it is a friend's birthday and I am saying to myself, Okay, I'll call him now, then I am thinking maybe I should call him later as he might be working. I decide to call him one hour later. I feel like I still will remember to do it later on, but then at the end of the day, I find myself totally forgetting about it.

P2 seemed to be aware that procrastination might lead to forgetting, thus she tries to do things as soon as they come up to avoid forgetting.

P2: So like, I have it with my daughter's child care account, I need to renew, I just do it straightaway. Like my bills, as soon as I get the email, oh, you need to renew your information, or you need to pay this. I do it straightaway, like, kind of have to do something like that straightaway. Otherwise, then it lasts for a week and it hasn't been done and then it's over the day or whatever. So for me, when I had reminders to pay or fill out information or do things like that, I just try and do it as soon as possible…I just think for me, if I don't do it straight away, then I am in danger of forgetting to do it completely... If I don't do it straightaway, then it's much more difficult for me to remember to do it.

This subtheme showed that drug users tended to postpone executing intended actions which put them at high risk of forgetting such intentions, thus might impair PM.

7.4.3. Theme 3: The role of retrieval strategies in memory processes

A wide range of retrieval strategies (the process of getting information out of memory storage to consciousness) was reported. Those strategies were used to create four subthemes; mind pops, active thinking, the use of cues and the use of aids. Those strategies help participants to remember both retrospective and prospective memories. While most participants use all of those strategies, some only use certain strategies. This theme is associated with the self-evaluation theme as one decides to employ a retrieval strategy based on known own abilities.

7.4.3.1. Subtheme 1: Active thinking

Active thinking, one of the PM retrieval strategies, was reported. Four participants indicated that they actively think about planned actions and execute them at the appropriate

moment without the help of any aid. For instance, P1 demonstrated that when he has an appointment he keeps thinking about that appointment to keep it in mind and when it is time, he remembers to attend the appointment. However, the data from the RPA-ProMem test in Chapter 4 showed that this participant's PM performance was below the normal range (see Table 15), indicating that the strategy may have been ineffective.

P1: I have two appointments on coming Tuesday (3 days after the interview). For example, it was in my mind today before we had this discussion with you. Probably tomorrow or Sunday, I will think about it like I don't stop thinking and Tuesday I wake up and I remember that I have two appointments. Everything's in my mind. So it's just thinking, thinking, thinking and on Tuesday I don't miss it.

It appeared that the participants allocate their cognitive resources to future intentions to keep them in their minds. For example, P4 revealed that he remembers to pay her credit every end of the month because she keeps such intention in his mind all the time. However, she displayed mild to severe PM impairments in the lab-based measure, suggesting the discrepancy between how she perceives her PM and how it actually is. In line with this notion, as discussed above P4 also exhibited a discrepancy between the questionnaire-based and lab-based PM measures, as she scored much below the normal range in the the RPA-ProMem, but close to the normal range in the PMQ.

P4: I know like I mean, every end of the month I have my credit card payment. So I just keep in mind that I need to pay. I always keep them in my back of my mind, so I do remember those things.

This subtheme indicated that active thinking helps some participants to remember to execute intended actions. However, the data from the lab-based PM measure in Chapter 4 suggests that it might not always work.

7.4.3.2. Subtheme 2: Mind pops

Mind pop was another reported PM retrieval strategy which is a sudden and involuntary appearance of memory into the mind which helps to remember to execute planned actions on time. This subtheme is linked to the use of cues subtheme as mind pops might be triggered by cues. For example, the following participant indicated that he relies on those mind pops to remember to execute PM tasks.

P1: It just pops in my mind. it's like, also, like, how do you say my personality I'm a kind of men of habits, you know, I have my daily routines, because I know when I'm going to take my medicine, I know, for example, whenever I am going to bed or to do certain things. So it's all set in my mind. So usually I don't have this problem with remembering to do planned actions, unless I want to ignore them.

Mind pops might be triggered by different factors, such as time of day which might be associated with the PM intention when forming that intention. For example, the following participant demonstrated that time of day triggers mind pops which remind him of a planned action. As seen in Table 15, the PM performance of this participant in the lab-based measures is below the normal range, implying that mind pops that he relies on do not always work.

P3: We booked this meeting. I didn't put it on the calendar or reminder. I think it just popped my mind earlier. If it was like, oh, it's close to four? Because I have that thing…

Mind pops were used as a PM retrieval strategy that some participants rely on when performing future plans. However, the data from Chapter 4 showed that they might not always work.

7.4.3.3. Subtheme 3: The use of cues

Another reported retrieval strategy was the use of cues. Retrieval cues are stimuli that help individuals remember retrospective and prospective memories. They can be present in the environment, such as sights and smells and they can also be internal, such as feelings or

physical states. For instance, the following participant indicated that he associates a name with visual stimuli which helps him to remember the name later.

P3: Names is one that I tend to forget very easily. Unless it's like repeated a few times I get to say. If it's associated with something visual, I think it's easier to remember.

Another participant said that he associates past experiences with feelings which strengthen such memories and make them easy to be recalled.

P5: If it's like a birthday, or if it's like, a meeting with a friend, or maybe visiting a friend abroad, those types of things. I can relate those experience with feelings. Usually, let's say if I go abroad, you know, you feel different so I can correlate between being there and excitement, you can put together those two things and then yeah, it makes those things memorable.

It was apparent that most participants struggled to access the stored memories without the help of cues. For instance, the following participant indicated that she could not remember the important detail of the book she read a while ago. However, as soon as she read over the book, she remembered those points as the cues from the book helped her to recover those memories.

P2: When I'm rereading this novel, at the moment, there's so much and I just did the same task at the beginning of September. And there was so much, I did remember the main kind of salient points, but there was so much detail that I hadn't remembered. However, when I read over it, it comes back to me, you know. So it's not like I've forgotten it at all.

Regarding PM, four participants reported that cues help them to remember to carry out planned intentions. For example, the following participant revealed that being in a specific place (i.e., tube station) reminds her to execute an intended action (i.e., checking her travel history). She confirmed that being in the tube station triggers the memory of the planned intention.

P4: When I go to tube for example, like, every time that reminds me that I need to check my travel history to see if I have any missing touch or anything, so using the tube triggers this. So I don't remember this before using the tube.

They also stated that they deliberately use such cues as a reminder of PM tasks. As seen below, P2 demonstrated that she places a visual cue (i.e., medication) in a specific place at home that she visits very often (i.e., the kitchen) to remind her that she needs to execute an intended action (i.e., giving medication to her daughter).

P2: When I had to give medication to my daughter a couple of weeks ago, I would just place the medication out on the side in the kitchen so that every time I go into the kitchen to have a glass of water or make a cup of tea, the medications they're on the side which remind me that I need to give her medication. So kind of visual clues help me.

This subtheme showed that the use of cues plays a key role in the retrieval of retrospective and prospective memories. It was evident that drug users struggled to access those memories without cues.

7.4.3.4. Subtheme 4: The use of aids

All the participants said that they use or/and rely on various aids (e.g., calendar, to do list, and alarm) to remember future plans. This subtheme is associated with the perceived importance of an event or intention subtheme as one decides to put a reminder for the intention if such intention is important to him or her. Popular aids are calendar, to do list, and alarms as well as emails/posts/texts from companies or government organisations. As seen below, P2 indicated that she uses a to-do list (a list of tasks she wants to complete or things that she wants to do) on her phone and checks at least once a day to make sure she keeps on track of her plans.

P2: I have a to do list in my phone, so I constant check to find what I have to do…I probably look at that maybe once per day. So just make sure I keep on track of things.

The following participant argued that he remembers to execute planned actions, but he uses aids as a backup.

P3: I remember without the reminders, but I always have the reminders as a backup.

As seen below, P1 highlighted that he gets a reminder for certain things from the companies via post, email or text. Thus, he relies on those reminders to remember future intentions.

P1: Nowadays most things, you don't really have to remember because you get reminder, you know what I mean? You either receive a post, email or SMS. So I don't know like if it's a memory issue, but I don't have to remember so many things. when you need to do MRT check, you usually get reminder by car insurance company. So the thing is, I don't really have to memorise some part of these things. Like they just remind them and you do it.

Four participants displayed overreliance (excessive dependence on something or someone) on technological aids. For instance, the following participant (P4) felt like she does not need to memorise any future intentions because her phone does remind her of everything she needs to do, so she heavily relies on her phone.

P4: We have mobile devices; I don't need to keep that information in my mind...It is my phone that is helping me to remember things…I feel like I'm not using the long term memory because that I don't really need it. I mean, there are some tools which helped me to eliminate that skill. Like, I'm using my phone instead of using my brain…

Another participant also confirmed that he does not need to memorise future intentions as he gets reminders.

P1: Nowadays most things, you don't really have to remember because you get reminder, so I don't have to remember so many things.

Three participants exhibited overreliance on other people, such as their partner or mother. For example, P1 said that his partner is really at good keeping track of things, that is why he feels that he does not need to keep track of future plans.

P1: I am also a bit lucky because I live with a partner. He likes to put everything in writing in his calendar. So even if I don't want to remember so he's there to remind me everything's.

P2 demonstrated that she relies on her mother to remind her when she needs a babysitter, so she can make relevant arrangements.

P2: My mom often reminds me, she'll say, oh, you know, I know you've got half term you need to come to remind me what the dates are if you want me look after your daughter.

In summary, this subtheme showed that drug users use various aids to keep track of their future plans. Most of them displayed overreliance on those aids.

7.4.4. Theme 4: The role of self-evaluation in memory processes

Self-evaluation (the ability to examine yourself) theme was identified based on the participants' comments on their awareness of their memory abilities. Self-evaluation helps people to understand their weaknesses and strengths which influences how they use their cognitive resources for a given task. If a person feels fairly confident (that might be due to previous experiences or knowledge) about performing a task (which might be perceived easy), he or she will allocate fewer cognitive resources to that task. In other words, they would put less effort to execute such task. Also, the allocation of cognitive resources to one task limits the resources available for other tasks. Therefore, self-evaluation influences the allocation of cognitive resources which, in turn, affects memory abilities. There are three subthemes: feeling confident about own memory abilities confidence, peer comparison when judging own memory abilities, and self-monitoring.

7.4.4.1. Subtheme 1: Feeling confident about own memory abilities

Five participants appeared to be very confident (a broad sense of subjective belief and trust in one's own ability) about their memory abilities. For instance, the following participant

indicated that he remembers many details, including smells from past events, even from his childhood.

P7: My memory is really good. I have like really good memory I remember a lot of like details and things and like smells and like when I was in situations like from my childhood, I do have a great memory.

P1 revealed that he does not use any aids to remember any future intentions because he believes that he has a really good memory. He argued that he is 99% efficient about remembering future intentions. However, it was not the case as he performed below the normal range in the lab-based PM measure in Chapter 4 (see Table 15).

P1: But I will be honest, I am not the person who uses the calendar a lot. For the short term plans and memories I keep them in my mind. This is my habit. And so far, the I'm 99% efficient about it. Like if I had a meeting tomorrow, I know what I'm what day for example, like I know which day and what time I'm going to have meetings next week. It's all in my mind. I usually don't write if it is short term.

It was evident that three participants overestimated their abilities, they hence were not able to complete the task that they thought they would. For instance, the following participants demonstrated that they try to do too many things at once which impairs their memory.

P4: It is just like I'm trying to do couple of things in a short time. In those time I feel I find myself forgetting more stuff.

P6: My mind is too busy with everything. Like I'm just trying to do or think too much at once. I mean, I just want to do everything. I know that I cannot but I'm still trying to do like, you know, putting too much pressure on myself. And I think too much and that keeps my mind busy. And that's probably why I forget things.

In summary, this subtheme showed that drug users display overconfidence about their memory abilities which might have an impact on the allocation of cognitive resources. Drug users appeared to overestimate their abilities as they fail to complete planned tasks probably due to limited cognitive resources.

7.4.4.2. Subtheme 2: Peer comparison when judging own memory abilities

Four participants evaluated their memory abilities in comparison with others which might lead to overconfidence, resulting in poor cognitive resource allocation that might be associated with poor memory abilities. They believed they have a good memory, just because it is better than their friends' memory. For example, the following participant talked about a trip that he took with a friend 20 years ago. While he remembered a lot of details from a trip, his friend cannot remember those details. He used such example to verify that he has a good memory (above average). However, in Chapter 4, this participant failed to recall specific autobiographical memories in the given time, thus scored much below the normal range in the AMT, suggesting poor long-term memory (see Table 15).

P3: But sometimes, I tend to remember details from a long time ago that other people don't remember. So in that sense, I would say that my long term memory is above average… like the other day I was talking to a friend we did a trip 20 years ago and I remember a lot of things she didn't remember.

Another participant believed that he has good memory because his friend gave him positive feedback about his memory abilities.

P7: I was lately in Berlin with my best friend who I haven't seen in like five years. And we're talking about like us as teenagers and this and that. And he's like, I love this about you, you remember everything but I don't remember any of that. It was weird for me because like this is such a memorable time in my life. So, I remember very well, yeah.

This subtheme demonstrated that drug users compare their memory abilities to people around them when judging how good their memory abilities are. Such comparison might lead to misleading conclusions about own memory abilities which sequentially may cause poor allocation of cognitive resources that might be linked to reduced memory performance.

7.4.4.3. Subtheme 5: Self-monitoring

This subtheme emerged from the participants' comments on the effects of drug use on their memory abilities as they need to self-monitor to notice a change if there is any. The notice of a change might help individuals adjust the way they allocate their cognitive resources to a task therefore may affect retrospective and prospective memory abilities. For instance, if one recognises that she or he has very poor short-term memory, the person will try to compensate for such impairment by using different strategies to keep information in mind for a short period of time, such as repeating information in the head or taking notes when being given information (e.g., phone number). Four participants reported short-term effects of drug use on their cognitive functions. They reported that drug use impairs their cognitive functions, including attention and memory. For example, the following participant stated that when intoxicated he cannot perform daily routines and has poor attention.

P5: if I'm on a substance or something I don't even take my medication, I don't eat sometimes, I don't even remember eating or like you don't take given the medication, whatever you're supposed to take. Literally, you're like, you're not doing what you're supposed to do, detaching yourself from the reality. So your focus is not there if I'm on a substance.

The same participant also reported that he had a blackout (a temporary loss of consciousness) when intoxicated. During the blackout, he failed to encode what happened (failure to form new memories), thus he cannot remember anything. It seemed to happen when mixing alcohol with illegal recreational drugs.

P5: When I have alcohol or other substance, especially with alcohol, it makes me more, you know, I feel like more silly and I am asking stupid questions as well, I have realised that. kind of I feel like stupid. So I realise like, how can I not remember this?...simple questions like, I cannot find my wallet or earpods. Where did I leave them? I can't remember like, basically that memory is gone or sometimes it can be what they call it the blackout. Especially when I am drinking. I feel like I don't remember what happened. And I don't remember how I took the Uber, I don't remember how I went home. So that's a little bit scary.

Three participants reported the sub-acute effects of drugs on their cognitive functions which occur when drugs slowly wear off the body and usually last 3-7 days. The participants exhibited cognitive problems during those days. For example, P1 demonstrated that after using drugs at weekend, he struggles to pay attention to tasks in the following days.

P1: ...I had the weekend out with my friends and I drunk and took drugs, always the next working day, you know, you have the withdrawal, you know, calm down effect and everything. If I had to go to the work, you know, it's impossible to pay attention you just want to finish the day and have a rest.

As seen below, another participant also reported poor attention which seemed to be the most obvious acute and sub-acute effect of drug use in the current sample.

P3: I think the day after using drugs, definitely. Because you're less focused on things you tend to pay less attention. Overall you like letting past those days!

It appeared that the sub-acute effects of drugs last a couple of days. For example, the following participant revealed that her attention span gets worse in the following couple of days of drug use.

P2: I guess immediately afterwards if you're talking about the next couple of days. Yeah. attention span does go it does wane slightly. I guess I just wouldn't feel so kind of calm and peaceful, you know, ease so that might make me more winded, not annoyed but more restless, I suppose.

As seen above, drug users reported various cognitive impairments while intoxicated and in the following couple of days after using drugs. However, almost all the participants (apart from P6) believed that drugs did not have negative long-term effects on their cognitive functions. For example, P7 demonstrated he had never experienced negative side effects of drugs.

P7:... I don't have negative side effects of drugs. Never.

Three participants including P1 assumed that there might be some changes in their cognitive abilities due to drug users, but they had not noticed.

P1: Maybe there is an issue but I haven't realised something extraordinary

The other three participants noticed some long-term changes in their cognitive abilities, but were not sure whether they were due to drug use or something else. For example, the following participant acknowledged that there are some negative changes in his long-term memory, but did not associate them with drug use.

P7: I would say my long-term memory is slightly worst, not as good, but I don't know if it's related to drugs or something else…

P4 also realised some changes in her memory abilities, but associated them with having a busy lifestyle.

P4: I do notice some memory changes, but I don't think it is related to drugs that I am using. I'm relating it to maybe to the cycle of my life like I am rushing, running and like me being not calm down or everything. it is just like I'm trying to do couple of things in a short time. In those time I feel I find myself forgetting more stuff but I don't relate that to drug use.

In summary, this subtheme demonstrated that drug users observed short-term negative effects of drug use on their cognitive abilities. However, they did not notice any long-term effects. As discussed earlier, awareness of own abilities might facilitate both retrospective and prospective memory abilities as it determines the allocation of cognitive resources to a task. Thus, not being aware of cognitive changes might result in poor allocation of cognitive resources, consequently memory impairments.

7.4.5. Theme 5: The role of other factors in memory processes

Those are other factors that have an impact on memory processes, but do not fall under other themes. There are two subthemes: The role of the perceived significance of an event or intention in memory processes and confounding variables.

7.4.5.1. Subtheme 1: The perceived significance of an event or intention

The perceived significance of an event plays an important role in remembering that event. This subtheme is also associated with the attention theme because people pay attention to things that are important to them. All the participants reported that if the event is important to them, they remember it. For instance, as seen below, P6 demonstrated that she remembers every detail of the special days, such as a wedding party because those events are very important to her. On the contrary, she said she does not remember much of other events that are not important to her.

P6: It still depends on what it is. Because things that are not very important to me, I don't really remember. But, you know, if it's very special days, I still remember everything, like the conversations I had, like what I was wearing, and who were there, and how much I enjoyed myself, or how sad I was, and (little pause) yeah, these kind of things. I mean, I do remember. Even I can go back all the way to my childhood. You know, for example, wedding party is that I've gone with family, and stuff like that. Or, you know, meeting family members, these kind of things.

P2 also confirmed that she remembers important events.

P2: I think events that are important to me I can remember.

The importance of memory seemed to be based on subjective valuing. Two participants determine the importance of memory based on its functionality in real life. If it is useful for future use, they tend to store and remember it. For instance, the following subject indicated that she does not store useless information/details which is why she does not remember some stored memories.

P4: It depends on the importance of the subject. Like if the information is not going to be good use for my future, I don't keep that information in my mind, I think. But yeah, I can still remember that, I think, but not in too much details.

While the other two participants determined the importance of memory based on its emotional consequences (either positive or negative). If memory causes strong emotion, it is

more likely to be remembered. For example, P3 reported that the feelings associated with an event determine whether he remembers the event or not.

P3: I think it depends how much they experience was meaningful to you in a positive or negative way I guess for the feelings that if it caused you at that time I think also it's going to impact if you remember it or not... For example, my rental agreement ends on the 19th. I know exactly when it is because it's a very important event, right! it is critical…

Four participants reported that they tended to remember their family members' and close friends' birthdays without any aid as those people are important to them. As seen below, P7 showed that he remembers only his partner and best friends' birthdays because they are very important to him. Apart from those individuals, he does not remember the birthday of anybody else.

P7: For example, my partner's birthday. I do remember that and I don't have it in my diary. You know, it's something I would remember but a friend's birthday, I literally just forget, I love my friend, I just don't know, I just literally forget. Unless it's someone like really important, like my best friend or my boyfriend. That I would remember. Something else I would forget to be honest.

Regarding PM, five participants indicated that if the intention is important to them, they tend to remember to execute it. For example, the following subject indicated that he remembers to take his medication on time because such medication is important for his health.

P5: For example, if I need to take antidepressants at midnight, I always take them, I never forget. I guess if it's important for me then I never forget them. When it's about my health or something or when it's about work, or when it's about school or university then It is more important, thus I remember to do them more. Or it can be like for example, after my breakfast I take the vitamins, I never forget them either.

Another factor that influenced remembering planned actions was their consequences. If their consequences are costly or/and serious, they are likely to be remembered. For instance, the following participants demonstrated they usually remember future intentions that involve

money (e.g., paying a credit card), specifically when the cost is high when missing a payment.

P6: If it was very important or if costed me so much I would remember it. It did not cost me too much so I guess that is why I was more relax about it. So, it depends how important it and its consequence.

P7: If it's bills or something, you know, formal things like money I don't forget that.

This theme demonstrated that the perceived importance, which depends on subjective valuing, of an event or intention plays a key role in the retrieval of both retrospective and prospective memories. Drug users seemed to remember events or intentions that are important to them.

7.4.5.2. Subtheme 5: Confounding variables

All the participants reported some confounding factors that might affect their memory abilities. Four participants considered the age factor when they comment on their memory abilities. For example, P2 revealed that she becomes more forgetful due to ageing as well as due to having a child.

P2: I feel like there are some changes but it is hard to say whether it is due to drug users. Sometimes you think it is because you getting old, maybe it's having a child. But yeah, I guess become more forgetful. I suppose.

Another participant indicated that the way his brain works is changing due to ageing and lack of stimulus (activities that keep the brain active) in his life. He believed that it works slower.

P3: there is the age factor. And therefore I definitely feel like my brain works a little bit slower but also less fresh. I blame like stimulus and age for that as well.

Three subjects indicated that life demands might also affect their memory abilities. For instance, P4 demonstrated that she becomes forgetful due to workload.

P4: If I'm busy with work if I'm running one place to another, I think my brain is distracted, thus I do not remember or I remember to do but I do not do it.

Three participants mentioned anxiety which was thought to have a negative impact on memory. For instance, the following participant associated her poor attention span with anxiety.

P6: But sometimes it depends actually, on my mood. It's because I have a condition like anxiety, and I have a problem with concentration and stuff, so I can't focus. And those affects my short term memory as well.

Sleep was another confounding factor. Three participants reported that if they did not get enough sleep after using drugs, they displayed poor cognitive functions. For instance, P4 indicated that she feels negative effects of drugs (i.e., slowing down the brain processes) when she does not get enough sleep after using drugs. This suggests that when she gets enough sleep she does not any negative effects.

P4: But if I don't sleep well, I might feel the effects of the stuff that I did because like they are slowing down my brain process I feel like. It's not the only the brain but I don't have that energy to do something so I just want to lie down and watch something which doesn't need my brain processes.

This subtheme showed there are various factors that affect drug users' cognitive functions. For instance, most participants reported that their memory abilities get worse with ageing. Therefore, these confounding factors should be taken into account when assessing drug users.

7.5. Discussion

The present study sought to explore how drug users manage to remember and execute delayed intentions in everyday life from their point of view to unfold the discrepancy between self-report and objective measures in drug users, using the explicitation interview technique. The data were analysed via TA. Five major themes, each with their respective

subthemes, were identified from the dataset, namely, the role of attention, time-related factors, retrieval strategies, self-evaluation and other factors in memory processes.

The participants demonstrated that attention plays a key role in memory processes, including encoding and retrieval. They reported that if they pay attention to what they do, they have a better memory of that event. Their attention span was usually mediated by interest or/and motivation. It was apparent that most participants struggle to maintain attention, thus they get easily distracted. As mentioned earlier, attention involves in different phases of PM, such as the formation of intention, the detection of PM cue (attentional monitoring), the retrieval of intention, and the switching between tasks to execute intention (Brewer, 2011), thus the observed attentional control deficits in drug users might explain the poor PM performance in Chapter 4. Attention impairment in drug users was also evident in Chapter 5 as drug users performed worse than non-users in the DS and the VFT which are considered indirect measures of attention (Amunts et al., 2020; Coalson et al., 2010). Furthermore, there were weak, but significant correlations (corrected for multiple comparisons) between the VFT and the lab-based PM measure in drug users (Appendix K-2), but not in non-users (Appendix K-3). Together, these results support the notion that drug users are impaired in attention which might have led to poor PM performance. In line with these findings, attention has been shown to be associated with PM performance in previous research (Hutten et al., 2018; Robey et al., 2014; Wang et al., 2011). For example, Hutten et al. (2018) found that divided attention performance was negatively correlated with prospective memory performance; demonstrating that enhanced attention was somewhat associated with better prospective memory performance.

Almost all the participants (N=6) reported that they get easily distracted by mostly other thoughts/overthinking and have no control over those thoughts. The inability to suppress task-irrelevant cognitive processing has been associated with poor cognitive inhibition (i.e.,

attentional inhibition; Howard et al., 2014) which has been commonly observed in drug users, in particular, cocaine users (Colzato et al., 2007; Hester & Garavan, 2004; Sellaro et al., 2014; for review, see Smith et al., 2014). Poor cognitive inhibition has been linked to progressive (Tarter et al., 1999; Zucker et al., 2011) and compulsive drug use (Everitt & Robbins, 2005; Heitzeg et al., 2010; Koob & Volkow, 2010), thus may contribute to the transition from recreational drug use and drug addiction (Poulton & Hester, 2020).

Another theme was the role of time-related factors in memory processes. The current findings showed that the participants were less able to remember events that happened a while ago. The findings suggested that drug users might have difficulties to access long term memories which may partially explain why drug users scored significantly worse in the long-term PM tasks (M= 3.96, SD= 1.97), compared to the short-term PM tasks (M=2.68, SD=2.17; T =205, Z=-3.26, p=.001) in Chapter 4. A past study also showed that drug users performed comparably to the control groups (high-risk alcohol users and healthy nonusers) on short-delay PM trials, but were impaired on long-delay PM trials, in particular for time-based PM tasks (Weinborn et al., 2011a).

The participants reported that time awareness facilitates remembering to execute planned actions. They demonstrated that if they are aware of time (e.g., knowing which day is), they are more likely to remember to perform planned actions. They also talked about an unconscious mechanism that reminds them of future intentions before their due dates. However, it was evident in Chapter 4, that this mechanism does not always work and thus can lead to PM failures. Theoretically, time awareness is associated with the internal clock in which a pacemaker continually emits pulses, with the number of pulses relating to a physical time interval recorded by an accumulator (Gibbon et al., 1984). At the molecular level, dopaminergic projections within the corticostriatal circuits play an important role in time perception (Petter et al., 2016), for instance, the administration of dopaminergic agonists is

consistently linked to time passing faster than normal, while the administration of dopaminergic antagonists is consistently linked to time passing slower than normal (Meck, 1996; Ogden & Faulkner, 2022). Therefore, changes in dopamine levels alter the way the brain processes time (Meck, 1996). It is well established that most recreational drugs interfere with DA transmission in the brain (Aston-Jones, 2015, see section 1.4). In the current sample, most drug users used cocaine which for example has been linked to a reduced functioning of Dopamine D2 receptors (Navarro et al., 2013; Volkow et al., 2009) in the anterior cingulate cortex (Goldstein, Alia-Klein, et al., 2009), the lateral PFC and the OFC (Goldstein & Volkow, 2011). Time perception is consequently impacted by such modifications to the dopaminergic system. This matches well with previous findings showing that drug users exhibit impairment in time processing (Shahabifar & Movahedinia, 2016; Wittmann et al., 2007). It comes as no surprise that many regular users of GHB, which has a significant effect on the dopaminergic system (van Noorden et al., 2016), experience multiple GHB-related accidental overdoses (Degenhardt et al., 2003; Raposo Pereira et al., 2019). For example, a survey among GHB users showed that 66% of 42 users experienced accidental overdose once or multiple times during GHB use (Miotto et al., 2001). A cross-sectional study of 76 Australian GHB users revealed similar findings: 40 of the participants (53%) had overdosed on GHB, and a third had done so more than three times (Degenhardt and Darke Sh Dillon, 2003). GHB has been cited in several emergency department (ED) case studies as one of the main causes of drug overdoses and drug-related ED presentations (Dietze et al., 2008; Galicia et al., 2011; Zvosec et al., 2010). GHB/GBL-related health issues accounted for 66.5% of all patrons in need of medical attention for drug usage in a prominent nightclub in Central London in 2007 (Wood et al., 2009). GHB use is linked to a high risk of overdose (Abanades et al., 2007, 2006; Miotto et al., 2001) due to the narrow dose margin between the overdose and desired effects (Busardò & Jones, 2015). Thus, accurate timing of doses is critical (it is

advised to wait at least two hours before taking another dose (Various authors ACMD & Campbell, 2020) and a short interval between dosing can cause overdoses. It is possible that when intoxicated, GHB users might be impaired in time perception (e.g., time passing more quickly than normal) and might take another dose without an appropriate interval, resulting in accidental overdose. Such deficit in time perception might also contribute to the progression from recreational drug use to addiction as a speeding up of time might lead to greater amounts of drug consumption during a period of drug intake as drug users may feel that the interval between doses is longer than it actually is, resulting in more frequent use which, in turn, increase the likelihood of drug addiction due to a high amount of drug consumption.

The tendency to postpone an activity was another subtheme under the role of time-related factors in memory processes theme. It was indicated that when intended tasks are delayed, they are more likely to be forgotten. While majority of the participants preferred to delay task execution despite potential negative consequences (e.g., forgetting) some participants preferred to complete PM tasks without procrastination. This phenomenon is known as pre-crastination which is the tendency to complete a task as soon as it comes up to reduce cognitive load, in particular those associated with PM (Rosenbaum et al., 2014). Data from several studies suggest that there is an association between procrastination behaviour and the number of PM failures (Altgassen et al., 2019; Zuber et al., 2021). For instance, Zuber et al (2021) found that people who have a tendency to postpone activities for longer periods of time are less likely to execute PM tasks on time, confirming the effect of procrastination on PM. This is coherent with past PM models, which propose when the retention interval gets longer, PM performance decreases (Einstein et al., 2000; Kliegel et al., 2002).

There is a link between procrastination and poor self-control/self-discipline (Ariely & Wertenbroch, 2002; Ramzi & Saed, 2019) which is associated with poor executive functions,

in particular cognitive inhibition dysfunction (Barutchu et al., 2013) that has the potential to contribute to the transition from recreational drug use to drug addiction (Zilverstand et al., 2018).

The procrastination behaviours could also be associated with participants' metacognition. Individuals need to accurately monitor their behaviour (e.g., reflecting on "if I carry on at this pace, will complete on time?") to have a correct judgement of metacognition (e.g., knowing that "I have a tendency to procrastinate tasks for too long") which determines whether and which control tactics to use (see monitor-control circle; Nelson, 1990). Procrastinators tend to inaccurately assess their own procrastination and use inappropriate control approaches, which, in turn, might lead to PM impairments (Rummel & Meiser, 2013).

The questionnaire-based data obtained from five participants in Chapters 4 and 5 did not match with the lab-based data, which also suggests impaired metacognition in drug users. While those individuals scored close to the normal range in the questionnaire-based PM measure, they performed much below the normal range in the lab-based PM measure (see Table 15). For instance, P4 reported no PM issues in the PMQ, but displayed severe PM impairments in the RPA-ProMem. Additionally, there were discrepancies between the lab-based data and the current data. For example, P4 indicated that she is good at remembering to execute PM intentions in the current study while the lab-based PM measure revealed otherwise (see Table 15). Furthermore, P3 indicated that he has good memory because he remembers the details of an event from a long time ago in the current study. However, he displayed severe AM deficits in Chapter 5 (see Table 15). The observed discrepancies between the data demonstrate metacognitive impairments in drug users which, in turn, can lead to PM failures due to unawareness of PM deficits and subsequently poor allocation of cognitive resources. A recent review supported the notion that there is a link between metacognitive problems and PM failures (Kuhlmann, 2019). This idea ties well with previous

studies wherein drug users exhibited a dysfunctional metacognition ability (unrealistic representation; Balconi et al., 2014; Goldstein, Craig, et al., 2009; Moeller et al., 2016, 2020; Verdejo-García & Pérez-García, 2008). Furthermore, the loss of insight (unawareness of illness), which is a component of metacognition, has been linked to the inability to detect or adjust performance following errors (Lysaker et al., 1998). Hester et al. (2007) found that active cocaine abusers consistently demonstrated reduced awareness of errors which is linked with a diminished neural response to errors, predominantly in the anterior cingulate cortex thought critical to error processing. Cannabis users also exhibited significantly poorer awareness of errors than a matched control sample (Hester et al., 2009). Error detection is an important element of adaptive human behaviour which enables a person to learn to be efficient and reflexive to the environment (Buckley et al., 2016). Poor error detection in drug users could be expressed as diminished concern regarding behavioural outcomes, possibly resulting in increased drug use and subsequently drug addiction.

The role of retrieval strategies in memory processes was another major theme with four subthemes. The participants had different strategies to retrieve a PM intention. While some of them reported that they rely on mind pops (spontaneous retrieval), others indicated that they actively think about delayed intentions and execute them at a suitable time. These strategies reflect the previous frameworks of PM. The active thinking strategy ties well with the PAM theory (Smith, 2003) as one must engage attentional processes to scan the environment for PM cues thus he or she has to allocate his/her cognitive resources to the PM task. Whereas, mind pops support the multiprocess theory (McDaniels & Einstein, 2000) as PM retrieval does not always require an active monitoring process; it might occur spontaneously under specific task settings without the need for cognitive resources to be allocated.

The use of cues was another retrieval strategy. All the participants indicated that cues help them to remember to execute planned intentions. These findings explained significant correlations after the correction for multiple comparisons between the VPA (a measure of associative learning) and the RPA-ProMem in drug users, for instance, the VPA was strongly associated with the ST-PM subtest (r_s= .50, p<.001; see Appendix K-2) in drug users, but not in non-users (r_s=.25, p>.05; see Appendix K-3), emphasising the role of associative learning and cue availability in a successful PM retrieval in drug users.

Most participants displayed strong dependency on cues during retrieval as it was apparent that they struggled to access the stored memories without the help of cues which suggests that drug users can encode information, but are unable to access it without aids. This accords with the earlier observations which showed drug users performed worse than non-users in recall tests (e.g., the free recall subtest of the CVLT), but their performances were similar on recognition tests (e.g., the recognition subtest of the CVLT, source memory and false memory; see Chapter 5) as participants were able to recognise the words when presented. In the CVLT, drug users also required more repetitions in order to learn the list of the words which has been associated more with impairments in retrieval or/and storage than capacity per se (Fox, Toplis, et al., 2001). Those findings support evidence from previous studies in which drug users scored worse than controls on recall tests, but they performed at similar levels in recognition tests (Gouzoulis-Mayfrank et al., 2000; Woods et al., 2005). These results further propose that drug users are impaired at the retrieval level, not at the encoding as they are able to encode information into memory, but fail to recall it without assistance. Therefore, cues availability at the retrieval phase represents possibly the most important factor that regulates memory accessibility and corresponding success at retrieval in drug users.

All the participants reported that they use various aids (e.g., calendar, do list, alarm or others) to remember future intentions. Most of them displayed overreliance (excessive dependence) on technological aids or others. Thus, they might put in less effort to sustain an intention if they rely on external tools and resources which, in turn, might lead to PM failures. For example, D'Angelo et al. (2012) conducted two experiments in which participants were requested to complete or collaborate during a PM task. The results revealed that there was a decrease in PM performance when subjects collaborated. This is also known as the social loafing effect (Latané et al., 1979). When another person shares the same intention, an individual might allocate less processing resources to remembering the intention as he/she believes that the person who shares the same intention will fulfil it. In relation to the previous study (Chapter 4), if drug users did not use any aids to remember to execute the given long-term PM tasks even though they were allowed, this might explain why they failed to complete those tasks as they heavily rely on external aids for future intentions. It should be noted that the decision to use an aid for a future intention is mediated by the perceived significance of such intention.

Another major theme was self-evaluation with three subthemes. Drug users seemed to be very confident about their overall memory abilities, however, it was evident that they overestimated their abilities as they frequently failed to complete a task that they thought they would be able to complete. Similar findings were obtained in a previous study where methamphetamine users had a significant tendency to overestimate their performance in the judgment of the learning paradigm (Liu et al., 2022). This might be associated with poor metacognition (Le Berre et al., 2010, 2016; Liu et al., 2022) which might lead to PM failures (Kuhlmann, 2019). For example, a study examined subjects' ability to remember PM intentions in a task in which they were allowed to set external reminders. Usually, individuals decide whether they need to set up reminders based on how good they think their memory is,

regardless of how good their memory objectively is. It was found that participants set reminders based on their metacognition; more precisely, how confident they felt in their memory performance which, in turn, mediates PM performance (Boldt & Gilbert, 2019).

When the participants were asked to rate their memory abilities, they tended to compare themselves to their friends and rated accordingly. However, such comparison could be misleading because drug users might be hanging out with people alike, hence having a better memory than their friends does not necessarily mean having a good memory or being above average. Such comparisons may also contribute to metacognitive impairment which is associated with the maintenance of drug use despite adverse consequences (Bahramnejad et al., 2012; Moeller et al., 2016).

Most participants noticed short-term effects of drug use on their cognitive functions which seemed to last a couple of days. In accordance with previous studies (Doss, Weafer, Gallo, & Wit, 2018; Dumont et al., 2008), the participants reported negative short-term effects, such as poor attention and impaired memory (e.g., blackout). In terms of long-term effects of drug use, most participants did not report any effects or they noticed some changes in their cognitive abilities but were not sure whether they were due to drug use or other factors such as ageing or workloads. However, various drug users performed worse than non-users on a wide range of cognitive tests in multiple cross sectional (Alonso-Matias et al., 2019; Basedow et al., 2021; Cohen & Weinstein, 2018; Dafters, 2006) and longitudinal studies (Auer et al., 2016; de Win et al., 2008; Schilt et al., 2007), suggesting that drug use has long term effects on cognitive functions. The current findings might be associated with poor metacognition as those adverse consequences might have gone unnoticed by users.

The role of other factors in memory processes was the last theme which consists of two factors that did not fall under other themes. The perceived significance of a future

intention, which is based on goals, values, desires and anticipated consequences, plays a key role in remembering to execute such intention. The participants tended to remember future indentions that are important to them, such as their partner's birthday. These findings broadly support the work of other studies in which it was found that the perceived importance of an intention can enhance the PM performance by manipulating task attractiveness (Aberle et al., 2010; Kliegel et al., 2010; Somerville et al., 1983), providing a reward (Jeong & Cranney, 2009; Krishnan & Shapiro, 1999; Meacham & Singer, 1977), importance instructions (Kliegel et al., 2001, 2004; Loft et al., 2008; Loft & Yeo, 2007; Smith & Bayen, 2004) or social motives (Brandimonte et al., 2010; Cicogna & Nigro, 1998; Kvavilashvili, 1987; Penningroth et al., 2011; Walter & Meier, 2017). Individuals tend to try harder to remember PM tasks that are important to them (Krishnan & Shapiro, 1999). These findings might explain the discrepancy observed in Chapters 3 and 4 between questionnaire and lab-based PM measures in drug users. The importance of the PM tasks in those studies might not be motivational enough for drug users, which might be why they did not complete such tasks. Even though a reward (an amazon voucher) was offered for taking part in Chapter 4, they still failed to complete the PM tasks. However, it should be noted that participants knew that they would receive the voucher regardless of the completion of PM tasks, thus they might not consider it as a reward related to the PM tasks.

Participants reported various confounding factors that have a negative impact on their memory abilities, including PM. In line with previous studies (Harris & Cumming, 2003; Henry et al., 2004; Koo et al., 2021; Matos, Santos, et al., 2020; Meier & Zimmermann, 2015), ageing, anxiety, sleep, workload and other life demands were thought to affect PM. For example, a study by Diekelmann et al. (2013) showed that sleep after the formation of an intention improves PM performance (also see for a review Leong et al., 2019).

7.6. Strengths, limitations and future directions

This study investigated PM in a group of recreational drug users, using a qualitative approach which allowed the exploration of subjective realities of drug users' life experiences associated with PM to address the discrepancy between questionnaire and lab-based PM measures.

There are possible limitations to the current study which should be acknowledged. First, the study relies on the participants' abilities to recall past experiences which were found to be impaired in drug users as Chapter 5 and previous evidence shows (Mercuri et al., 2018; Oliveira et al., 2007; Pillersdorf & Scoboria, 2019). This was mitigated by the use of the explicitation interview technique. However, its success depends on the ability of the interviewee to re-live the experience guided by the interviewer. In addition, the interviews were conducted online due to COVID-19 restrictions. Some participants may not have been comfortable being "on-camera" in particular when talking about illegal activity. This could have affected participants' responses. Moreovere, all the coding processes and analyses were conducted only by the researcher. Furthermore, data on abstinence period was not collected, thus participants might had been intoxicated during the interview, thus, their abilities to recall past experience might had been impaired.

In future studies, when possible, interviews should be conducted in-person to create a safe and comfortable environment which may facilitate discussions. In addition, they should avoid using only questionnaire-measures which rely heavily on metacognitive and retrospective memory abilities when studying drug users. Instead, they should employ both self-report and lab-based measures to study different aspects of the same topic to gain deeper understanding, Moreover, participants should be required to abstain from any recreational substance use for interview. To increase reliability of the data coding (O'Connor, & Joffe, 2020), another researcher should get involved in the coding processes and consistency between the coders

should be measured. Lastly, future studies should control for the perceived significance of used PM tasks when examining PM.

7.7. Conclusion

In summary, the present study sought to understand how drug users manage to remember and execute delayed intentions in everyday life from their point of view, whether they use any specific strategies to perform such intentions and the confounding factors that might have an impact on their PM performance in order to unfold the discrepancy between self-report and lab-based PM measures in drug users. The results revealed that retrospective memory, cues availability at the retrieval phase, time awareness, and attention play a crucial role in PM. Thus impairments in such domains could be associated with poor PM performance in drug users. The perceived significance of the intention (consequently motivation) is also an important component of PM which determines whether a PM intention is remembered or not. The results further showed that drug users are impaired in metacognition which explains why there is a discrepancy between questionnaire and lab-based PM measures in drug users. Such impaired insight into behaviour may prevent drug users from effectively recognising adverse consequences of drug use.

Chapter 8: General Discussion

In this chapter, the findings from different chapters will briefly be summarised and discussed in light of the existing literature and interpreted the combined results and their possible implications. The chapter ends with a reflection on strengths and limitations of the current study, future directions, and conclusions.

Recreational drugs are substances that are used for pleasure without medical justification. As Chapter 1 demonstrated, the use of illicit drugs is increasing globally (Public Health England, 2020; United Nations Office on Drugs and Crime, 2021). Chapter 1 further showed that those recreational drugs have an impact on a wide range of neurotransmitter systems which play a crucial role in cognitive processes. Therefore, various cognitive impairments have been associated with drug use (Gould, 2010). To reduce the use of illegal drugs and associated harms, it is vital to improve the understanding of the effects of those drugs on the brain and behaviours. As summarised in Chapter 2 and 3, previous research on the impact of illegal recreational drug use on cognitive functioning has been inconclusive and faced various methodological challenges, such as small sample size, unrepresentative sample type, short abstinence period, and lack of control of potential confounds. Therefore, this particular PhD project sought to explore the possible consequences of recreational drug use on cognitive processes, PM in particular while addressing the methodological challenges facing previous studies. A mixed methods approach was used in order to answer the current research questions which allowed the researchers to seek a more comprehensive view of the research landscape by examining participants from many angles and using different research lenses.

The study consisted of three interrelated studies. In the first study, a wide range of cognitive functions were assessed in drug user and drug naïve participants, using

questionnaire- and lab-based measures (Chapters 4, 5 and 6). In the second study (Chapter 7), a group of drug users were interviewed on different components of prospective memory to unfold the discrepancy observed between questionnaire- and lab-based PM measures in the first study. In the last study, the sub-acute and chronic effects of recreational drug use on memory and executive functions were investigated. However, due to COVID 19, the last study was not completed (see Appendix P for a rough draft of the manuscript, including the initial findings).

8.1. The effects of recreational drug use on prospective memory

One of the main aims of the current study was to investigate the effects of recreational drug use on PM. A systematic review of twenty-seven previous studies on the effects of illegal drug use on PM (see Chapter 3) revealed inconsistent findings, while drug users were impaired in lab-based measures (Gallagher et al., 2014; Hadjiefthyvoulou et al., 2011a, 2011b; McHale & Hunt, 2008; Montgomery et al., 2010, 2012; Rendell et al., 2009, 2007; Terrett et al., 2014; Weinborn et al., 2011a, 2011b; Zakzanis et al., 2003), they scored similarly to non-users in most self-report measures (e.g., Bartholomew et al. 2010; Ciorciari and Marotte 2011; Cuttler et al. 2012; Weinborn et al. 2011a).

Chapter 3 further showed that most investigations on the effects of illegal drugs on PM contain several challenges, such as small sample sizes (e.g., Hadjiefthyvoulou et al., 2011a, 2011b; Montgomery et al., 2010; Rendell et al., 2007, 2009; Zakzanis et al., 2003), unrepresentative sample types (e.g., Arana et al., 2011; Bartholomew et al., 2010; Gallagher et al., 2014; Montgomery & Fisk, 2007; Weinborn et al., 2011b; Zakzanis et al., 2003). Furthermore, most studies had a short abstinence period (e.g., Heffernan et al., 2001a; McHale & Hunt, 2008; Rendell et al., 2007; Terrett et al., 2014) which can interfere with participants' cognitive functions (Garavan et al., 2008). Indeed, drug users indicated that they suffered from the negative sub-acute effects of drugs (e.g., poor attention) in the following

days of drug intake in Chapter 7 (see section 6.3.4.3). Moreover, most studies failed to control for potential confounds, such as depression and sleep (e.g., Heffernan et al., 2001a, 2001b; McHale & Hunt, 2008; Rodgers et al., 2001, 2006; Weinborn et al., 2011b) which are thought to influence PM (Grundgeiger et al., 2014; Li et al., 2013). Indeed, in Chapter 7 drug users reported that those factors affect their cognitive functions (see section 7.3.5.2). Lastly, previous studies assessed regular drug users (Heffernan et al., 2001a, 2001b; Terrett et al., 2014) or drug addicts (Rendell et al., 2009; Weinborn et al., 2011b). Hence, it was not clear whether light recreational polydrug use has the same negative effects on PM.

Chapter 4 addressed those methodological challenges and revealed similar findings with drug users exhibiting PM impairments in the lab-based measure, suggesting that even light drug use impairs PM. On the contrary, drug users did not differ from non-users in the questionnaire-based PM measure after controlling for the confounding factors. Such discrepancy between self-report and lab-based assessments underscored the importance of considering drug users' subjective experiences in order to understand why they believe they are not impaired in PM while lab-based measures show PM deficiencies. In Chapter 7, seven drug users were interviewed on different components of PM (i.e., short-term memory, long-term memory, attention, and cognitive shifting), using the explicitation interview technique to unfold the observed discrepancy. TA was employed to analyse the data. The findings showed that various factors have an impact on PM. For instance, most participants reported that they struggle to maintain attention while performing a task, thus they get easily distracted. They also reported long-term memory deficits and poor time awareness. Such cognitive impairments could explain the observed poor PM performance in Chapter 4 in drug users. Furthermore, most participants displayed strong dependency on cues while performing a PM task, thus the availability of cues at retrieval determines whether a PM intention is remembered or not in drug users. Likewise, drug users exhibited overreliance on

technological aids and/or others. Hence, they might put in less effort to sustain an intention if they rely on external tools and resources which, in turn, may lead to PM failures. The perceived significance of the intention also plays an important role in PM. The significance of the PM tasks used in Chapter 4 may have not been motivational enough for drug users, which could be why they performed poorly in those tasks.

The findings also revealed that drug users may have reduced metacognition as they overestimated their abilities and tended to postpone PM intentions despite knowing that it may lead to forgetting. This, the reduced metacognition, could explain why self-report and lab-based PM measurements in drug users differ.

As discussed in Chapter 7, there are two major theories that explain PM: the PAM processes theory and the multiprocess theory. The PAM theory suggests active monitoring is the key component of successful PM retrieval, thus PM relies on top-down attentional processes (also known as conceptually-driven processes) which involve frequent repetition of the intention and monitoring for signs that indicate it is time to carry out the intention. Therefore, the use of top-down processes for PM tasks comes at a cost in the ongoing task as two tasks compete for resource capacity. The PAM theory has been supported by multiple studies, for instance, Smith run a study in which a group of participants were assessed on a PM task (e.g., press the F1 key when specific target words are present) while performing an ongoing lexical decision task (LDT) which measures how quickly individuals classify a group of letters as a real word or not. Results demonstrated that subjects were significantly slower making lexical decisions when a PM task was present, compared to when performing the ongoing task alone (Smith, 2003). More recently, Rummel et al. (2017) claimed that individuals perform poorly in ongoing tasks when PM tasks are present and they also engage in less off-task thinking than they would otherwise. They argued that people's attention usually drifts away while performing a task from the task at hand to unrelated thoughts

(TUTs) which is also known as mind wandering (Smallwood & Schooler, 2015). However, when holding a future intention, individuals try to think more about the current task at hand (PM intention and ongoing task), thus consciously or subconsciously reducing their engagement in TUTs (Rummel et al., 2017). They support their hypothesis by a study in which participants were periodically asked to report on their thoughts during PM or control tasks. It was observed that TUTs rates decreased when subjects executed an ongoing task while holding a PM intention versus carrying out the ongoing task alone (Rummel et al., 2017). The findings from Chapter 7 partially supports the PAM theory as some of the participants reported that they actively think about future intentions and execute them at an appropriate time. The data further support the hypothesis that impaired PM in drug users may be caused by attention dysfunction as the majority of the participants reported that they got easily distracted by irrelevant thoughts while performing a task (see section 6.3.1.2). This implies that they are not able to stop TUTs while performing a PM task that might interfere with their task performance, resulting in reduced performance. Disengagement from TUTs seems to be under some degree of executive functioning as people with stronger executive functions tend to mind wander less during the given tasks than do those with poor executive functions (Kane et al., 2016; Unsworth & McMillan, 2014). Thus, these results also suggest that drug users may be impaired in executive functions.

By contrast, the multiprocess view (MPV) proposes that PM retrieval can be triggered automatically under certain task conditions (such as whether or not the cues are more distant from ongoing activities “nonfocal cues” or in the centre of ongoing activities “focal cues”) without the allocation of cognitive resource, thus it is mediated by bottom-up processing (also known as data-driven processing) and comes at no cost in the ongoing task. Focal PM targets are those for which there is great overlap between the processes needed for the ongoing task and the processes needed to detect the PM target. For instance, with an ongoing LDT, a focal

target would be to press a key in the occurrence of a particular word (e.g., rake). In this example, the processing needed for lexical decision directly assists the processes essential to recognise if it is a specific word, thus PM retrieval can occur spontaneously. Whereas, nonfocal targets are those for which there is little overlap between those processes. For instance, with the ongoing LDT, a nonfocal PM target would be to press a key in the occurrence of a specific colour (e.g., red) as determining whether a group of letters is a word does not require processing colour (Einstein & McDaniel, 2005). Hence, it has been assumed that PM remembering relies on capacity-consuming attentional resources being dedicated to the PM task. Overall, cue focality has a key impact on whether or not individuals adopt a monitoring approach. The multiprocess theory has also been supported by the findings from Chapter 7 as the majority of participants indicated that they have mind pops which help them to remember to execute future intentions.

One of the most widely accepted mechanisms that explain how spontaneous retrieval happens is the reflexive associative retrieval hypothesis whose view posits that after an intention is stored in long-term memory, the retrieval of the intention is triggered by an automatic associative-memory system. However, such mechanism is mediated by various factors, such as the perceived importance of an intention, cue focality, and attention (Einstein et al., 2000; Harrison et al., 2014; Kliegel et al., 2001). It was evident that those factors have an impact on drug users' PM performance in Chapter 7 as well.

Most theory-based PM investigators tend to isolate whether subjects relied on monitoring (top-down processes) versus spontaneous retrieval (bottom-up processes). PM errors are frequently attributed to failures in top-down processes, such as poor effort or a lack of sufficient commitment; however, PM researchers acknowledge that even the most intelligent and conscientious people can forget to carry out very important delayed intentions (Dismukes, 2012; Loft, 2014). As a result, theories that rely entirely on top-down

mechanisms are unlikely to adequately explain PM. Shelton and Scullin (2017) criticise this "either/or" isolation approach and believe that it is misleading because it ignores the variety of daily PM challenges in the real world and offer the dynamic multiprocess framework (DMPV) which predominantly claims that spontaneous retrieval and monitoring are interconnected processes (Scullin et al., 2013) that are fluidly moderated by individual difference and environmental factors (Gilbert et al., 2013). Recent evidence from studies with behavioural and neurobiological measures has provided empirical support for the DMPV. For example, Scullin et al. (2010) run a study in which individuals were given multiple ongoing task contexts without instructions on which context the PM target would present. The results revealed that monitoring was absent in the 50 trials preceding the first presence of the PM target, but some of the subjects were able to spontaneously retrieve their intention. Subsequently, participants engaged in monitoring for the rest of the ongoing task context in which a second PM target appeared later on. They then disengaged monitoring at the end of that context as if they were restarting (Scullin et al., 2010). These results showed that participants use different retrieval strategies at different stages of the task, rather than using the same strategy throughout the task. Studies with neuroimaging (McDaniel et al., 2013) and eye-tracking (Shelton & Christopher, 2016) methods also support the DMPV. The findings in Chapter 7 also accord with the DMPV as some participants indicated that they rely on active monitoring as well as mind pops while performing a PM task.

Metacognitive processes may be a crucial mediator in the effect of context on PM dynamics. For instance, if an individual is aware that a retrieval cue will act as a strong reminder, then the individual should engage in monitoring less because that cue can initiate spontaneous retrieval. Alternatively, if an individual is aware that cue is weak or no external cue then the individual should engage in monitoring more because spontaneous retrieval will be ineffective. For instance, Lourenço et al., (2015) run a study in which participants were

given a strong or weak retrieval cue at the encoding phase, and then during the testing phase altered expectations for some of the participants by showing a weak retrieval cue. Those who expected the PM task to be easy (strong retrieval cue) displayed minimal or no monitoring. Whereas, participants who were presented with the weak retrieval cue engaged in monitoring more, probably due to noticing the unlikelihood of spontaneous retrieval happening. Hence, metacognitive processes during both encoding and testing phases influence the interaction between monitoring and spontaneous retrieval (Lourenço & Maylor, 2014) which in turn affects PM performance. Another study showed that attention–allocation strategies of PM heavily rely on metacognitive expectations about PM task demands (Rummel & Meiser, 2013).

These findings support the notion that drug-induced PM impairments observed in Chapters 3, 4 and 7 might be linked to metacognitive dysfunctions. It was evident that drug users are impaired in metacognitive as they tend to overestimate their cognitive skills (see section 7.3.4.1) and prefer to delay task execution despite potential negative consequences (e.g., forgetting; see section 7.3.2.3). Such impairments in metacognition might be associated with the poor allocation of cognitive resources as discussed above which, in turn, may lead to PM failures. Indeed, Kuhlmann (2019) proposes that PM performance is mediated by metacognitive control as one allocates his/her cognitive resources to a task based on the difficulty of that task. The poor allocation of cognitive resources was also evident in Chapter 6 where drug users displayed retrieval impairments while encoding was intact, suggesting that drug users' cognitive resources may have been allocated in an unbalanced way.

Another factor that affects PM dynamics is individual differences. It has been found that subjects with high working memory capacity scored better on a PM task with weak retrieval cue, compared to participants with low capacity even though the cost for the ongoing task was similar across groups (Brewer et al., 2010). The possible explanation by the

DMPV for such results is that subjects with high WM capacity effectively engaged monitoring at appropriate times and disengaged monitoring when the cues were less likely to appear. Another study showed that there is a positive correlation between PM and planning skills (Lourenço et al., 2015). These studies established that individuals can flexibly shift between a top-down and bottom-up approach to fulfil future intentions based on those individual difference factors (Shelton & Scullin, 2017).

Those findings reflect the previous frameworks of PM as it has been argued that PM relies on various cognitive processes, such as retrospective memory (Cuttler et al., 2012; Einstein & McDaniel, 1990; Hutten et al., 2018; Kliegel et al., 2002; Landsiedel et al., 2017; Marsh & Hicks, 1998; Settle et al., 2017). Therefore, impairments in such domains might be associated with PM failures. In line with the notion, there were significant correlations between some retrospective memory measures and the RPA-ProMem (see Appendix K). However, it should be noted that only strong correlations remained significant after the Holm-Bonferroni correction. The findings from RANCOVA in which an association between drug use and PM was assessed while controlling for retrospective memory support this notion as the results for some of the RPA-ProMem subtests were no longer significant (see Appendix M). Such hypothesis is in line with previous research (Cuttler et al., 2012).

The perceived significance of an intention is another important element of PM. In Chapter 7, participants indicated that they tend to remember important future intentions if they are important to them. In line with this finding, several studies show that the perceived importance of an intention plays a significant role in remembering and executing it. As aforementioned, the importance of an intention can be based on values, goals, desires, or anticipated consequences (Kvavilashvili & Ellis, 1996). For example, in an early study, a group of scientists used rewards as a way to increase importance. Participants were asked to send a letter to the researcher on eight different days over a period of two months. Some of

the participants were told that they would receive money for each letter they send on time and a chance to win a lottery if they return the letter regardless of their due dates (experimental condition). Whereas, no such promise was made for other participants (control condition). The results revealed that the former subjects were more likely to return the letters on time. The results further showed that more of those participants reported having used aids (external reminders) to remember the task. Thus, receiving a reward increased the importance of the task which, in turn, improved the PM performance (Meacham & Singer, 1977), also see other studies (Jeong & Cranney, 2009; Krishnan & Shapiro, 1999) for similar replications. The PM tasks used in Chapters 3 and 4 might not have been motivational enough for drug users, that could be why they might have failed to complete them. These results highlight the need to account for the perceived significance of the given PM tasks while assessing PM.

Cognitively demanding ongoing tasks have been also thought to influence PM performance. For example, Harrison et al. (2014) conducted a couple of studies to assess the effect of on-going tasks on PM performance. They found that while performing a moderately demanding divided-attention task (i.e., a digit detection task) had no impact on PM, performing a more challenging divided-attention task (i.e., random number generation) reduced PM performance (Harrison et al., 2014). Furthermore, Marsh and Hicks (1998) found that PM performance is impaired in conditions, in which WM load is high (Marsh & Hicks, 1998). Moreover, a systematic review of forty articles published between 1995 and 2020 on the role of ongoing task demand in PM revealed that people are likely to forget to execute a delayed intention while engaging in resource-demanding tasks (Matos, Pereira, et al., 2020). As discussed in Chapters 4 and 5, lab-based PM tasks were administered among other cognitive test batteries. Some of those tests can be considered to be cognitively demanding, therefore they might have interfered with PM, resulting in poor performance. However, it should be noted that all the participants (drug users and non-users) were tested under the

same condition, but only drug users displayed PM deficits. This finding suggests that drug users may have fewer cognitive resources than non-users while performing a cognitive task (Gould, 2010; Potvin et al., 2014; Verdejo-Garcia et al., 2019).

Although PM requires numerous different cognitive functions and presumably different neural networks, the particular contributions of executive functions and the prefrontal systems are most apparent (Anderson et al., 2017), hence the prefrontal lobes have been considered to be the neural basis of PM. Three sources of evidence are available to support this. First, neural activities in the prefrontal lobes while performing PM tasks. Two, PM impairments observed in people with frontal lobe lesions. Third, correlations between performance of PM and executive function tests which have been thought to control by the prefrontal lobes.

The first supporting evidence for the involvement of the prefrontal lobes in PM comes from Okuda et al. (1998) and Burgess et al. (2001). Those studies measured changes in regional cerebral blood flow (rCBF) while performing PM tasks, using PET and reported rCBF increase in the anterior prefrontal cortex (aPFC; Brodmann's area 10) when individuals held a PM intention during an ongoing task and when they had to respond to PM cues in those tasks (Burgess et al., 2001; Okuda et al., 1998). More specifically, it has been typically observed that when a PM task was embedded in the ongoing task, there is a significant rCBF increase in lateral aPFC and a decrease in medial aPFC, as compared to the ongoing task alone (Burgess et al., 2011 for a review). This pattern of findings has been observed in many subsequent studies using different types of PM tasks (e.g., event-based and time-based and), responses (e.g., manual versus oral response), materials (e.g., verbal and non-verbal,) and techniques (e.g., fMRI; den Ouden et al., 2005; Gilbert et al., 2009; Oksanen et al., 2014; Okuda et al., 2007).

In addition, other brain structures have been associated with PM, for instance, the PCC has been thought to play a key role in the encoding phase of PM (Cona et al., 2015). The activation of the insular regions has been associated with the retrieval phase of PM (Cona et al., 2015). Furthermore, the activation of the left parahippocampal has been observed while performing PM tasks, suggesting that this region plays an important role in the processes of novelty detection which is vital for checking the PM targets (Okuda et al., 1998) as well as encoding and remembering of PM intentions (Beck et al., 2014; Burgess et al., 2002; Gordon et al., 2011).

Supporting the notion that the prefrontal lobes are the neural basis of PM, numerous studies confirmed that patients with lesions in the aPFC exhibited impaired PM performance (Burgess, 2000; Burgess et al., 2003; Martins & Damasceno, 2008; Shallice & Burgess, 1991; Twamley et al., 2008; Uretzky & Gilboa, 2010).

As discussed in Chapter 2, drug use is associated with various abnormalities in the brain, specifically in the PFC (Bolla et al., 2004; Kaufman et al., 2003; Strickland et al., 1993; Zilverstand et al., 2018). For instance, cocaine users displayed reduced activity in both the anterior cingulate and medial prefrontal regions while carrying out executive function set-shifting test in which they performed poorly (Kübler et al., 2005). Furthermore, occasional users of amphetamine and MDMA underwent structural brain imaging and were followed up at 12 months and 24 months after the first assessment (Study 1, n = 38; Study 2, n = 28). The results revealed that subjects in both studies who subsequently increased amphetamine-type stimulants use displayed smaller medial prefrontal cortex volumes (Becker et al., 2015; also see Daumann et al., 2011; Ersche et al., 2011; Gu et al., 2010). Therefore, the observed PM deficits in Chapters 3, 4 and 7 in drug users could be associated with abnormalities in these brain regions.

As discussed in various chapters, PM is one of the most crucial cognitive processes for day-to-day functioning. While impairments in PM might interfere with those daily activities, they can also cause serious other consequences, such as forgetting to take one's heart medication, a pilot forgetting to make the necessary adjustment to take-off or land or a doctor forgetting to remove a tool before closing an incision. In fact, a study found that 50–70 per cent of everyday memory issues are associated with PM (Kvavilashvili et al., 2001). Another study demonstrated that people have 13 to 31 PM thoughts per hour (Gardner & Ascoli, 2015). Zogg et al., (2012) showed that PM plays a key role in the treatment of several health conditions, such as HIV/AIDS and diabetes after a review of emerging literature. Woods et al. (2009) also found that individuals who performed poorly in PM tasks were approximately six times more likely to forget to take their daily HIV suppression medication, compared to individuals who performed well in PM tasks. When such medication is not taken, HIV starts multiplying rapidly, that will have a significant negative impact on one's health and increase the risk of transmission (Cook et al., 2019).

PM also play a key role in social interaction, for example, one who consistently forgets to execute PM tasks (e.g., missing a meeting) in social contexts is likely to struggle to sustain positive personal and professional relationships with others. When compared to retrospective memory failures, PM failures are typically viewed more negatively. For instance, if one forgets to attend a meeting with a work friend, he or she might be seen as uncaring or irresponsible. Indeed, a study by Walter and Meier (2014) revealed that PM failures can influence one's self-esteem and reputation as an individual who always remembers to execute PM intentions may be viewed as organised and conscientious, while an individual who fails to remember those intentions might be perceived as disorganised and unreliable. Such social perception could have an impact on career development as people who are perceived as unorganised might find it difficult to find a job which, in turn, may

increase the risk of using drugs and drug addiction. For instance, a review on the prevalence of drug use among the employed and unemployed, the effects of drug abuse on unemployment and vice versa. It was found that drug consumption was more prevalent among the unemployed and problematic drug use increased the probability of unemployment and decreases the likelihood of finding and holding down a job (Henkel, 2011), therefore it consecutively might contribute to the transition from recreational drug use to drug addiction.

8.2. The effects of recreational drug use on retrospective memory and executive functions

Another aim of the current study was to examine whether recreational drug use has an impact on retrospective memory. As reviewed in Chapter 2, drug users display various retrospective memory impairments, but the evidence sometimes is not clear or/and quite conflicting, according to the literature. For example, the literature shows that drug users, in particular, stimulant users displayed retrospective deficits in some studies (e.g., Basedow et al., 2021; Quednow et al., 2007; Riba et al., 2015), but not in others (e.g., Kloft et al., 2019; Kuypers et al., 2016). The literature further shows that previous studies faced several methodological challenges, such as small sample sizes (e.g., Basedow et al., 2021; Fox, Toplis, et al., 2001; Kumar et al., 2019; Quednow et al., 2006; Rodgers, 2000), short abstinence periods (e.g., Quednow et al., 2006; Reske et al., 2010 Solowji et al., 2011), poor confound controls (e.g., Gouzoulis-Mayfrank et al., 2000; Rouse & Bruno, 2011), or unrepresentative sample types (e.g., Hoffman et al., 2006; Solowji et al., 2011; Woods et al., 2005).

In Chapter 6, those methodological challenges were addressed and mainly polydrug users were recruited. The findings were in line with the reviewed literature on verbal memory as drug users performed poorly in most subtests of the CVLT, suggesting that recreational light polydrug use is associated with poor auditory and verbal learning skills. Interestingly,

recreational drug users did not differ from non-users in the recognition subtest of the CVLT. Likewise, there were no group differences in other recognition tests, such as the VPA, false memory and source memory. These findings suggest that drug users are impaired at the retrieval level, not at the encoding (Squire, 2009) as they are able to encode the words into memory, but fail to recall them without assistance. These findings could also be associated with the partial encoding deficit as drug users may only encode fragmented representations of the target words into the memory system and produce a deficient amount of information when they are asked to recall, but are able to distinguish between the presented and distractive words in the recognition tests (Delis et al., 2017). The attention problems seen in drug users may potentially contribute to the observed impairments. In Chapter 5 drug users performed worse than non-users in the DS and VFT which indirectly examined attention. In Chapter 7, it was found that six drug users reported that they got easily distracted while performing a task, suggesting poor attention abilities (see section 7.3.1.2). These findings are in line with previous studies in which drug users displayed impaired attention (Gardiner and Parkin, 1990; Gould, 2010; Pope et al., 2001).

The observed retrospective impairments could also be potentially linked to metacognitive deficits. As discussed in Chapter 6, metacognition plays a key role in the allocation of cognitive resources; one will devote fewer cognitive resources to a task if they feel somewhat confident about completing it or vice versa. As Chapter 7 showed drug users were impaired in metacognition as they tend to delay task execution despite potential negative consequences and overestimate their cognitive abilities. The discrepancy between questionnaire-based and lab-based PM measures in drug users that was observed in Chapters 3, and 4 also can be seen as metacognitive dysfunctions (see Table 15). This accords with previous observations, which showed that drug users are impaired metacognition (Balconi et al., 2014; Buckley et al., 2016; Goldstein, Craig, et al., 2009; Hester et al., 2007, 2009; Lysaker et al., 1998;

Moeller et al., 2016, 2020; Verdejo-García & Pérez-García, 2008). Thus, drug users may have misallocated their cognitive resources during the CVLT, which could explain why they performed worse. Drug users' retrieval but not encoding deficiencies in Chapter 6 also showed inefficient use of cognitive resources, as some cognitive domains (i.e., retrieval) are under-resourced.

AM was also assessed in the current sample. The literature review in Chapter 2 (see section 2.1.4) showed that a wide range of drug users are impaired in AM. However, those studies suffered from various methodological challenges, for instance, they failed to control for potential confounds, such as sleep and IQ (Oliveira et al., 2007; Pillersdorf & Scoboria, 2019) or age (Mercuri et al., 2018). They also had a small sample size (Doss, Weafer, Gallo, & Wit, 2018; Oliveira et al., 2007). Furthermore, most of them recruited regular/chronic drug users or drug addicts (Oliveira et al., 2007; Pillersdorf & Scoboria, 2019). In the current study, those methodological challenges were addressed and light drug users were recruited. The results were in line with the previous studies. Therefore, it can be argued that even light drug use is sufficient for AM weaknesses to be present.

As discussed in Chapter 6, a lack of specific autobiographical memory may result from various factors such as disturbing memories of adverse events and/or exposure to traumatic experiences (Burnside et al., 2004; Dalgleish et al., 2003; Henderson et al., 2002; Kangas et al., 2005; Valentino et al., 2009; Van Vreeswijk & De Wilde, 2004; Williams et al., 2007).

Furthermore, AM impairment may stem from general memory issues. The findings from other chapters are also in line with this notion. For example, drug users exhibited retrieval deficits in Chapter 6 due to which they might have failed to access specific autobiographical memories. Moreover, in Chapter 7, drug users indicated that they struggle to access long-term memories. Chapter 4 also showed long-term memory deficits in drug users as drug users

scored significantly worse in the LT PM task, compared to the ST-PM task[6]. There was no significant difference between the performances of those two tasks in non-users.

These results may also be related to executive functions as poor executive function skills are associated with AM impairments (Guler & Mackovichova, 2019; Williams et al., 2007). In Chapter 5, drug users performed worse in two executive functioning measures (i.e., the DS and VFT). Chapter 7 also showed that drug users are impaired in executive functions. Therefore, executive dysfunctions may be linked to the observed AM impairments.

Additionally, the relationship between AM impairment and drug use may partly be explained by attention issues. Chapters 5, 6 and 7 showed that drug users are impaired in attention. For instance, in Chapter 7, four drug users reported that they struggle to access long-term memory and they associated such impairments with attention issues as they indicated that if they concentrate, they are able to recall the stored memories, but it might take a long time. In Chapter 6, drug users were given 30 seconds to recall a specific memory. The given time may not have been enough for drug users to concentrate to generate a specific memory. Taken together, the obervsed AM impairment might be due to attention dysfuntion.

The effects of recreational drug use on executive functions were also investigated. As discussed in Chapter 2 (see section 2.2), the findings in the existing literature are mixed. While some studies found that drug users were impaired in WM (e.g., McCardle et al., 2004; Sanvicente-Vieira et al., 2016; Soliman et al., 2013), cognitive flexibility (e.g., Colzato et al., 2009; Figueiredo et al., 2020; Lahanas & Cservenka, 2019) and cognitive inhibition (e.g., Colzato et al., 2007; Croft et al., 2001; Piechatzek et al., 2009; Sellaro et al., 2014), others could not find a link between drug use and executive dysfunctions (e.g., Crane et al., 2013; Hart et al., 2001; Jager et al., 2006; Piechatzek et al., 2009; Roberts et al., 2016a; Wagner et

[6]Mann-Whitney test revealed that drug users scored significantly worse in the LT PM task (M= 3.96, SD= 1.97), compared to the ST-PM task (M=2.68, SD=2.17; T =205, Z=-3.26, p=.001).

al., 2013). Those mixed findings might be due to their methodological issues as outlined in Chapter 2 (see section 2.4), such as small sample size (e.g., Colzato et al., 2007; Hester & Garavan, 2004; Sellaro et al., 2014), short abstinence periods (e.g., Colzato et al., 2007; Hester & Garavan, 2004). It was also clear that there is a dose-related association between executive dysfunctions and drug use. For example, cognitive flexibility dysfunctions were more pronounced in heavy drug users (e.g., Bolla et al., 2002; Dafters, 2006; Lahanas & Cservenka, 2019) or in addicts (e.g., Cunha et al., 2010; Hekmat et al., 2011; Salmani et al., 2020; Woicik et al., 2009).

According to Chapter 5, polydrug users had diminished executive functions in some tests, but not in others. For instance, drug users scored worse than non-users in the DS and VFT which have been thought to be sensitive to detect subtle/mild executive dysfunctions (McDonnell et al., 2020; Muangpaisan et al., 2010). On the contrary, there were no significant differences between drug users and non-users on the WCST and Stop-it test.

There are several possible explanations for these results. First, recreational drug users might have subtle/mild cognitive impairments that cannot be detected with the used tests (Becker et al., 2013; Morein-Zamir et al., 2015; Watkins et al., 2013). In Chapter 7, it was evident that drug users are impaired in various executive functions, such as they indicated that they cannot control distractive thoughts while performing a task, suggesting poor cognitive inhibition. Second, executive dysfunctions may only be present in heavy drug users or addicts as the literature suggests. Third, prolonged drug use (the current sample had approximately 15 years of drug use experience) may have led to neuroadaptation in the brain which might have compensated for drug-induced impairments (Crean et al., 2011).

8.3. The causality between drug use and cognitive impairments

While the current study established a link between cognitive impairments and recreational drug use, as with all cross-sectional designs it cannot determine whether

recreational drug use causes cognitive impairments or the other way around as cognitive deficits present prior to first drug use can act as a risk factor for drug use initiation. At the same time, drug use can directly lead to cognitive dysfunctions even in people without pre-existing dysfunctions. For example, impulsive behaviours (the tendency to behave without thinking) and sensation-seeking personalities (a personality trait defined as the seeking of varied, complex, intense and novel experiences and sensations while willing to take legal, social, physical, and financial risks) have been associated with lower 5-HT and DA functions (Dalley & Roiser, 2012; Netter et al., 1996). People with these types of personalities or behaviours are more likely to participate in substance use (Boly et al., 2013). Therefore, the extent to which the observed impairments in drug users result from substance use rather than pre-existing characteristics is unclear. There are two potential research designs that can be used to improve the understanding of the effects of recreational drug use on cognitive functions: (1) longitudinal and (2) animal studies. In a longitudinal study, participants are followed for a long period of time, ideally from the first time they use a drug, to assess cognitive changes that might be due to drug use while avoiding individual differences. For example, Auer and his colleagues (2016) run a longitudinal study to investigate the association between cognitive performance and cumulative lifetime exposure to marijuana use in middle age. They recruited 5115 black and white men and women aged 18 to 30 years who were assessed in 1986. Of the 3385 participants reassessed after 25 years in 2011. Among those, 2852 (84.3%) stated past marijuana use, but only 392 (11.6%) continued to consume marijuana into middle age. Current use of marijuana and cumulative lifetime exposure were associated with worse verbal memory (e.g., RAVLT). Furthermore, a prospective cohort study by Schilt et al. (2007) has indicated that ecstasy use is linked with a decrease in verbal memory. There were no significant differences in the verbal memory test performance between persistent ecstasy-naïve controls and future ecstasy users at the initial

examination. However, at follow-up, the ecstasy user group performed poorly on immediate and delayed verbal recall and recognition compared to the control group (Schilt et al., 2007).

Animal studies can also be used to address the consequences of drug exposure on cognitive functions. In those studies, animals are administered substances under controlled conditions in the laboratory, avoiding the confounds of pre-existing differences, poly-drug use, length and amounts of drug use thus, they provide comprehensive information on the neurochemical and neurotoxic effects of recreational drugs (Liu et al., 2008; Porter et al., 2011). For instance, in a study rhesus monkeys with a cocaine self-administration history (~5 years; n=5; mean 1395 mg/kg cumulative cocaine consumption) and age-matched controls (n=4) were used to test multiple cognitive domains associated with cocaine-related deficits. Monkeys were assessed in morning sessions and given food or self-administered cocaine in afternoon sessions. During cognitive tasks, PET and 18F-fluorodeoxyglucose were utilised to assess cerebral metabolic rates of glucose utilisation (MRglu). Cocaine-experienced monkeys performed poorer on multi-dimensional discriminations and reversal learning relative to cocaine-naive monkeys. Cognitive impairments were related to differences in glucose utilization as the controls but not cocaine-experienced monkeys exhibited greater MRglu during a multi-dimensional discrimination task in the hippocampus, caudate nucleus, anterior and posterior cingulate which are associated with memory, attention, error-detection, and reward (Gould et al., 2012). Moroever, George et al. (2008) examined whether a history of controlled vs escalated cocaine intake is linked with particular working memory deficits and long-lasting changes of the OFC and dmPFC in rats. Working memory deficits were observed after a history of chronic and escalated cocaine consumption (6 hours per session), but not after repeated limited access (1 hour per session) to cocaine (0.5 mg/kg per injection). Working memory impairments were correlated with a decreased density of neurons and oligodendrocytes (a type of large glial cell) in the dorsomedial prefrontal cortex (dmPFC) and

the OFC (George et al., 2008; also see Cadoni et al., 2017; García-Pardo et al., 2015; Jentsch et al., 2002; Karuppagounder et al., 2014; S. Liu et al., 2008; Moyano et al., 2004; Mustafa et al., 2020; Schoenbaum et al., 2004)

In summary, the findings from longitudinal and animal studies are in line with the current study, supporting the notion that exposure to various drugs can lead to abnormalities in critical cognitive domains, including verbal learning which have been associated with the dysfunction of PFC and neural activities.

8.4. Transition from recreational drug use and addiction

Substance addiction does not happen overnight, but takes years to develop. Most people start using drugs recreationally and this type of use might not be considered harmful since drugs are only consumed casually, one to four times a month (Torregrossa et al., 2011). According to American Psychiatric Association, drug addiction or dependence is a chronically relapsing mental disorder that is characterised by impaired control (i.e., intention to stop using but not being able), social problems (e.g., neglecting relationships and responsibilities), risky use (continued use despite negative consequences) and physical dependence (developing tolerance and having withdrawal symptoms; Hasin et al., 2013).

There are two main theoretical frameworks (i.e., individual-centred and drug-centred theories) have been proposed to explain the transition from recreational drug use to addiction. Drug-centred theories (based on experimental research) include all views which argue that the main cause of addiction is using a drug repeatedly as the brain's structure and chemical composition change. Hence, specific drug-induced psychopharmacological changes are observed, such as sensitisation, tolerance, and withdrawal or drug-induced cognitive changes in decision making, impulsivity, and conditioning (Piazza & Deroche-Gamonet, 2013). One of the drug-centred theories suggests that drug addiction is a learned behaviour. According to the theory, substance use begins by learning that the drug is rewarding due to its strong

psychoactive effects (positive reinforcing effects). This learning process is mediated by the pharmacological actions of drugs on various neurotransmitter systems, in particular DA. For instance, when a new event happens a DA signal is produced from the midbrain to both the ventral and dorsal striatum that enables learning about this new event (Jay, 2003; Schultz, 2010). As discussed in Chapter 1, most drugs (e.g., cocaine, and MDMA) increase DA levels in the brain, (Kalant, 2001; Torregrossa & Kalivas, 2008; Woolverton & Johnson, 1992). Thus, they create artificial learning signals that are of greater duration and magnitude compared to what is observed in response to natural events. Drug use also increases glutamate transmission (McFarland et al., 2003; Nichols, 2004) which plays an important role in learning and memory processes as well as in prefrontal cortical control over decision making and impulsivity (Stefani et al., 2003). Therefore, the boosted learning about a substance positive experience increases the likelihood to use the drug again. Also, over time, some cues in the environment (e.g., alcohol use, clubbing) become associated with illegal substance use through regular repetition (associative learning) until the cues alone are enough to trigger the desire for the drug (habit formation). Habits usually form when goal-directed behaviours become independent of the goal through constant repetition. While drugs boost normal learning systems involved in seeking rewards, they may weaken cognitive control (Hester & Garavan 2004; Sellaro et al., 2014; Verdejo Garcia et al., 2005) as discussed in Chapter 2 (see section 2.2.1), thus may result in compulsive drug use/drug addiction.

At the same time, sustained drug-taking despite harmful consequences proposes drug addicts might also be characterised by aberrant learning such that rewarding outcomes affect their behaviours more than punishing outcomes (Poulton & Hester, 2020). A commentary view by Poulton and Hester (2020) indicates that decreases and increases in DA in midbrain areas, also mediate learning from feedback (as well as reinforcement learning as discussed above). More specifically, unpredicted rewards (which are unexpected based on past

experience) provoke more DA release, compared to expected/predicted rewards (which are expected based on past experience) that elicit no response beyond baseline firing (Schultz, 2007). Thus decreases and increases in DA are respectively negatively and positively reinforcing which drive adaptive behaviour: activities that result in a reward are more likely to be repeated, whereas activities that result in less reward than expected are more likely to be avoided (Baker et al., 2011, 2013; Frank & Claus, 2006). This view further indicates that the ability to learn from both positive and negative feedback may be associated with DA receptor availability, in particular D2 (Baker et al., 2013). For example, Klein et al. (2007) assessed the learning preferences of participants with low D2 receptor expression in midbrain areas, using a probabilistic learning task (examining the propensity to learn from positive versus negative outcomes). The results revealed that individuals with low D2 receptors were less able to learn to avoid negative outcomes compared to controls. The results further indicated that individuals with low D2 receptors were significantly more likely to learn from positive feedback compared to negative feedback while controls exhibited no significant preference for learning from positive feedback compared to negative feedback. The authors linked low D2 receptor availability to attenuated learning from negative feedback and increased sensitivity to positive feedback (Klein et al., 2007). As discussed in Chapter 1, the number of receptors on the postsynaptic neuron can change based on the number of neurotransmitters they deal with. When there is an excessive amount of neurotransmitters, receptors are taken out of the membrane and recycled into the cell to decrease the neuron's sensitivity to the message (i.e., down-regulation). Multiple studies show that drug users have fewer D2 receptors due to down-regulation after excessive sustained drug use which leads to a high amount of DA in the brain. This may explain why drug addicts display increased sensitivity to the rewards of drug use, but are insensitive to the negative consequences such of behaviour. It has been also noted that nondependent individuals with a genetical

predisposition for impulsivity may also have a poor capacity to learn from negative feedback, but a greater ability for learning from positive feedback (Klein et al., 2007). In multiple studies, drug-dependent participants consistently performed poorly on various gambling tasks (the Iowa gambling task) where they failed to learn from negative feedback (Dom et al., 2005; Fridberg et al., 2010; Grant et al., 2000). In line with those findings, animal studies revealed similar results (Economidou et al., 2009).

On the contrary, individual-centred theories (based on observations in humans,) argue that drug use is necessary, but not enough condition to develop addiction. Instead, they propose that drug addiction results from a pathological reaction to the drug that is produced in some people by individual vulnerabilities, such as genetic factors, developmental factors, environmental factors and interaction between those factors (Ducci & Goldman, 2012; Ersche et al., 2020; Le Moal, 2009; Piazza & Deroche-Gamonet, 2013; Uhl et al., 2008). For instance, there is a strong association between psychiatric disorders (e.g., social phobia and bipolar disorder in adults, and anxiety, depression, and oppositional defiant disorders in children) and the subsequent development of drug dependence (Chan et al., 2008; Sheidow et al., 2012; Sterling et al., 2010). One study revealed estimated risks ranging from 44 % to 86% (Merikangas & Avenevoli, 2000). Furthermore, as discussed above low D2 receptor availability has been considered a risk factor for substance addiction (Noble, 2003). Moreover, parental substance use disorder (children of parents with drug addictions at particular risk of drug abuse; Hoffmann & Cerbone, 2002), a negative upbringing (Fuchshuber & Unterrainer, 2020; Gabrielli et al., 2016; Kobulsky, 2017), high impulsivity traits (Guttmannova et al., 2019), other addictions (Chuang et al., 2017), individual's perceptions and attitudes (youths with low or no perceived risk of using cannabis had a higher risk of abuse; Nawi et al., 2021; Schleimer et al., 2019), stress (Sinha, 2008; Torres-Berrio et al., 2018), ADHD (Harstad et al., 2014; Wilens et al., 2011), age of first drug use

(early drug use dramatically raises the risk of drug addiction; Jordan & Andersen, 2017) are other risk factors. Many animal studies support the notion that individual vulnerabilities contribute to the transition from recreational drug use to addiction (Piazza & Deroche-Gamonet, 2013).

In addition, cognitive impairments observed in the current study can be considered as a risk factor, such as verbal learning impairment has been associated with poor academic achievement (Kastner et al., 2001) which, in turn, leads to an increased risk of drug abuse and subsequent drug addiction (Kendler et al., 2018; King et al., 2006). Moreover, weakness in WM has been associated with acting-without-thinking which was a significant predictor of SUD (Khurana et al., 2017). Metacognitive impairments also have the potential to contribute to the transition from recreational drug use to addiction despite adverse consequences of drug use which might be gone unnoticed by users (Hester et al., 2009; Poulton & Hester, 2020). Furthermore, impaired AM has been considered a risk factor to develop addiction (Müller, 2013). Lastly, impaired time perception can potentially contribute to the transition the progression from recreational drug use to addiction as discussed in Chapter 5, most drugs including GHB appear to make time speed up which may lead to greater amounts of drug consumption during a period of drug intake as drug users may feel that interval between doses is longer than it actually is, resulting in more frequent use, subsequently a high amount of drug consumption.

In line with the risk factors above, various factors have been thought to protect individuals from developing addiction, known as addiction resilience. Those protective factors can be external resources and internal strengths that interact with harms to influence the chances of negative outcomes for people (Fergus & Zimmerman, 2005). Generally considered internal traits and characteristics internal protective factors include: self-control (Fadardi et al., 2010; Hills et al., 2016), intellectual ability (Rosenblum et al., 2005), locus of

control (Ismail et al., 2021) , optimism/hopefulness (Hills et al., 2016; Levey et al., 2016), self-efficacy (Brothers, 2016; Fadardi et al., 2010), self-respect/self-worth (Tozer et al., 2015), self-esteem (Currie et al., 2013; Levey et al., 2016), personal skills (e.g., problem solving, coping, help seeking, social; Hills et al., 2016; Tyler et al., 2014; Wong, 2008), and spirituality/religiosity (Currie et al., 2013; Ostaszewski & Zimmerman, 2006). Attitudes about drug use (e.g., fear of negative consequences of drug use, such as health problems) can also be considered as an internal factor (Andreas et al., 2016; Davis & Spillman, 2011; Gilliard-Matthews et al., 2016).

Moving beyond internal protective factors, many studies in the field of drug use consider external factors for resilience. There are three broad levels: school, community and family. Commonly explored external factors at the family level are: parental monitoring (Andreas et al., 2016; Becerra & Castillo, 2011), family bonding (e.g., closeness and cultural ties; Davis & Spillman, 2011; Ostaszewski & Zimmerman, 2006), family management (e.g., setting boundaries, rewarding or punishing accordingly; Davis & Spillman, 2011; Marsiglia et al., 2002), family and partner support (Stajduhar et al., 2009; Tozer et al., 2015). One study found that social roles involving family formation significantly reduced substance use, in particular, when individuals were engaged or married or/and when they were or their partner was pregnant (Staff et al., 2010).

At the community level community researchers look at: supportive relationships with friends or community members (Amandru et al., 2014; Brothers, 2016; Stajduhar et al., 2009), engagement with social activities (sense of belonging, commitment, caregiving) (Draper et al., 2015), participation in spiritual/religious activities (Ostaszewski & Zimmerman, 2006), and community supports by the government (e.g., social services or housing; Stajduhar et al., 2009). Finally, at the school level school involvement in curricular and extra-curricular activities engagement (Levey et al., 2016; Stajduhar et al., 2009), a

positive school environment (Marsiglia et al., 2002), positive relationship with teachers and peers (Davis & Spillman, 2011; Ostaszewski & Zimmerman, 2006) have been considered. After reviewing a total of 77 studies on resilience, Rudzinski et al. (2017) proposed that social support is a main external factor for resilience across all three aforementioned levels (Rudzinski et al., 2017).

In summary, drug-centred theories argue that the main cause of addiction is using a drug repeatedly as the brain's structure and chemical composition change. Whereas, individual-centred theories argue that drug addiction results from a pathological response to the substance that is caused in some individuals by individual vulnerabilities (e.g., genetic factors, environmental factors). While psychiatric disorders, high impulsivity traits, other factors listed above might put recreational drug users at higher risk to develop addiction, external resources (e.g., parental monitoring and community support) and internal strengths (e.g., intellectual ability and self-esteem) can protect them from such escalation.

8.5. Prevention vs. harm reduction strategies

Prevention strategies aim to prevent the use of illicit drugs, for example, there are several different criminal offences which restrict the use of harmful substances. Getting caught while carrying illegal drugs even for personal use, could result in a fine or prison time. However, the effectiveness of prevention strategies is called into question as the prevalence of drug use steadily goes up around the world (see Chapter 1), suggesting the necessity of a shift from prevention strategies to harm reduction strategies. In contrast to prevention strategies, harm reduction strategies aim to reduce drug-related harms without the requirement to abstain from drug use. Harm-reduction strategies do not replace prevention strategies. They are a useful complementary approach to prevention strategies. The principal feature of harm reduction is accepting that some people will use illicit drugs despite even

harsh preventative measures, thus, harm reduction strategies emphasise practical based goals rather than ideologically as prevention strategies do. The essence of the idea is to reduce the negative effects of drug use where people feel unwilling or incapable to stop using illicit drugs. Harm reduction has a long and successful history, for example, needle exchange programmes in the UK, which allow injecting drug users to obtain clean and unused hypodermic needles at no cost, have been found to be effective in reducing HIV transmission (Fernandes et al., 2017).

Another implemented harm reduction strategy is a drug safety testing service where drug users submit a sample of their substances for analysis and receive information about what the substances contain, and the way they can reduce those substances' harms if used. The findings from a wide range of studies on the effectiveness of those measures are promising. For instance, Ward (2015, 2016 as cited in Measham, 2019) found a 95% reduction in drug-related hospital admissions compared with the previous year after such a drug testing service was introduced at a festival (i.e., Secret Garden Party). Those drug-checking services also have the following benefits: accessing hard-to-reach populations, creating opportunities for dialogue between drug users and healthcare consultants about health and harm, facilitating onward referral to local substances services, monitoring trends in drug markets and drug use; launching regional, national, and global early warning systems for dangerous substances (Brunt et al., 2017; Giné et al., 2017; F. Measham & Turnbull, 2021).

There are various other harm reduction strategies, for instance, police-led harm reduction strategies. In the UK, instead of arresting, prosecuting or formally cautioning individuals for minor drug possession offences, police offer to divert those individuals to assessments and/or specific assistance like drug education, harm reduction, or treatment (Ozcubukcu & Towl, 2022). Moreover, educating individuals on how to stay safe when

consuming recreational drugs is also used as a harm-reduction strategy. Empowering individuals to make wise decisions that will maximise their health is one of the crucial components of harm reduction. Such information on drugs can be delivered through workshops, talks, campaigns, and online materials. The information offered should be accurate (covering both the positive and negative consequences of recreational drugs), useful (providing advice on how to stay safe when using drugs), non-judgmental (accepting the different motives of using drugs), and supported by evidence (not scaremongering; Ozcubukcu & Towl, 2022).

8.6. Polydrug use among drug users

In the current sample, most drug users reported polydrug use (using more than one drug; see Figure 4). Combined use of numerous substances is a common behaviour pattern among drug users, for instance, a study assessed 400 drug users aged 18-29-year-old between 2004-2006 and found that 91.7 per cent of the participants had engaged in polydrug use. Most of them tended to combine ecstasy and cocaine (Grov et al., 2009). In many cases, drug users use two or more drugs in combination to achieve a specific effect, such as the mixture of cocaine (stimulant) and ketamine (also known as Calvin Klein) produces powerful euphoric highs along with a hallucinogenic feeling (Gold et al., 2020) or enhance the effects of another drug, such as mixing MDMA with GHB; the mixture gives a high that is more strong and perceived as more enjoyable than using one of the drugs alone (Teter & Guthrie, 2001; Uys & Niesink, 2005). In some cases, an additional drug is used to compensate for the negative effects of the main drug, for instance, MDMA or cocaine (both drugs increase wakefulness) users smoke cannabis (improve sleep) to be able to sleep after drug intake (Gonçalves & Nappo, 2015). Drug availability is also associated with polydrug use as drug users can easily access other drugs (Ives & Ghelani, 2006).

The use of a combination of two or more drugs has been thought to be more harmful than the use of a single drug (Gouzoulis-Mayfrank & Daumann, 2006; Soliman et al., 2013), for example, when ketamine is taken with cocaine it enhances the toxic effects of cocaine (Hayase et al., 2006), thus such mixture can put extra pressure on the heart and lead to life-threatening conditions (Abdel-Rahman & Ismail, 2000; Gold et al., 2020). Furthermore, polydrug use might also lead metabolic cross-tolerance where the chronic use of one drug reduces the pharmacological effect of a second drug (Stark, 2016). As the drug is metabolised more quickly due to tolerance one need to use more of it to reach the desired effect which might increase the likelihood of drug addiction due to a high amount of drug consumption.

The examination of how drugs affect the brain and behaviours is also complicated by polydrug use. As discussed in Chapter 1, recreational drugs exert their effects by interacting with different neural mechanisms, thus polydrug use makes it harder to track the effects of a particular drug (Gouzoulis-Mayfrank & Daumann, 2006). Some studies attempted to investigate the specific effects of a certain drug by different research methods. For instance, Schilt et al. (2007) recruited ecstasy users with minimal exposure to other drugs to assess the effects of ecstasy use on cognition. Furthermore, McCardle et al. (2004) compared the performance of 17 participants with a history of MDMA polydrug use to the performance of 15 non-MDMA polydrug users. However, those methods have little power to exclude the polydrug use effects. Alternatively, statistical regression models can be used to investigate the separate and joint effects of those drugs, while taking the frequency of each drug use into account. However, given that drug users frequently use multiple drugs, more research should be done to determine how different drug combinations (e.g., MDMA and GHB) affect the brain and behaviours.

8.7. Adolescent substance use

As summarised in the introduction chapter, recreational drug use is more common among younger people as approximately one in five young people aged 16 to 24 years have used drugs at least once in 2019 in the UK alone. Cannabis is the most common illegal recreational drug used by youths (Public Health England, 2020). In a study from 2020, 44% of university students reported having used cannabis in the previous year, up significantly from 38% in 2015 (Johnston et al., 2022). The popularity of drug use, cannabis use in particular, among younger people might be associated with a low perception of risk. For instance, the World Drug Report 2021 indicates that the percentage of young people who perceive cannabis as harmful has dropped by 40 per cent, even though cannabis products have almost quadrupled in strength over the period 1995–2019. The prevalence of cannabis use is anticipated to go up following recent legalisation of recreational use in many countries and the introduction of a legal cannabis sector (Johnston et al., 2015). For example, a report from the 2014 Monitoring the Future Survey funded by the National Institute of Drug Abuse showed that states in US that have legalised cannabis, 40 per cent of secondary school seniors had consumed cannabis, compared with 26 per cent in states where cannabis use is not legal (Johnston et al., 2015). Another study assessed postlegalization changes in cannabis use and found that current marijuana users statistically increased their use, probably due to a climate that is supportive of cannabis use (Barker & Moreno, 2021). The report further shows that only 16.4 per cent of secondary school seniors thought that cannabis smoking is risky (Johnston et al., 2015). However, scientific evidence including the current evidence has showed various harms caused by cannabis use. Such disconnect between public perception and real risks might further increase cannabis use among young generations.

A wide range of studies showed that adolescents are at higher risk of suffering harmful effects of drug use. For example, a study found that adult cannabis abusers who

started using before the age of 17, but not abusers who started using after the age of 17, had significantly more impairments in verbal learning, verbal fluency, and executive functioning compared to non-using controls (Pope et al., 2003). Another study found that despite fairly brief cannabis usage (an average 2.4 years), adolescent users exhibited similar cognitive impairments relative to their age-matched counterparts (adult users with 24 years use). These results demonstrated that bigger adverse effects of cannabis use on the developing brain (Solowij et al., 2011). One of the explanations for such harmful effects of drug use in adolescents is that teen's brain is undergoing significant development until approximately 25 years of age (Jordan & Andersen, 2017; Paus, 2005; Schepis et al., 2008; Schneider, 2008), and interfere with these processes may manifest in observed cognitive impairments. These results tie well with findings of neuroimaging studies in which it is apparent that the brain structure and function are impaired in adolescent cannabis using-samples which might explain the observed cognitive dysfunctions (Arnone et al., 2008; Ashtari et al., 2009; Mata et al., 2010). For example, compared to later onset users, early 24 onset (before age 17) cannabis users tended to have smaller whole brain volumes, lower grey matter and higher white matter (Wilson et al., 2000). Those impairments might make young people more vulnerable to drug addiction as the brain, in particular, the PFC (which is responsible most emotional and cognitive functions, including decision making, and cognitive inhibition) is still maturing between ages 10 and 25, thus the use of drugs might interrupt such development and increases the risk of becoming drug addicted (Jordan & Andersen, 2017; Salmanzadeh et al., 2020; Winters & Arria, 2011).

According to several studies, young cannabis users are more likely to use more harmful drugs (e.g., cocaine) and develop addiction later in life (Secades-Villa et al., 2015). For instance, a study investigated the impact of cannabis use patterns on the probability of initiation with other illegal drugs in 29,393 teenagers and found that compared to non-users,

the risk for other drug use was 21 times higher among cannabis experimenters and 124 times higher among daily cannabis users (Mayet et al., 2012). Another study found that rates of subsequent or other illegal drug use were 100 times higher amongst adolescent (weekly) cannabis users than non-user controls (Fergusson et al., 2006).

In the current study, it was found that recreational drug use, including cannabis impairs various memory processes (e.g., PM, AM and verbal learning) which play an important role in daily functioning as well as in psychological well-being. For adolescents, these deficiencies might be more detrimental. For instance, verbal learning is a key component of academic achievement, thus impaired verbal learning might lead to poor academic performance. As discussed earlier, poor academic attainment in adolescence is associated with an increased risk of drug addiction (Fothergill et al., 2008; Gauffin et al., 2013; Hawkins et al., 1992; Henry et al., 2012; Kendler et al., 2018; Schulenberg et al., 1994). Moreover, poor school performance has been linked to an increase in social and behavioural problems (Kremer et al., 2016) which might also put adolescents at higher risk of developing addiction later in life. Therefore, these findings emphasise an urgent need to use effective interventions to prevent or reduce substance use among adolescents.

8.8. Challenges to studying illegal recreational drug users

As discussed in various chapters, there are many challenges to studying illicit drug users. For example, it is difficult to recruit hard-to-reach drug-using populations who may actively try to conceal their group identity (Duncan et al., 2003) due to fear of confrontation with legal authorities (Shaghaghi et al., 2011). To increase study participation, researchers should protect the anonymity of participants and the confidentiality of the information that they provide. However, the ability of the researcher to sustain confidentiality is usually limited by law as courts in some countries (e.g., the U.K.) may order researchers to provide study information to law enforcement (Hall & Fry, 2004). The researcher–participant

relationship should be privileged as an attorney–client or physician–patient relationship, thus, it should be provided with the same protections for absolute confidentiality (Stone, 2002). For instance, in the United States, researchers can obtain a Certificate of Confidentiality from the National Institutes of Health to ensure the privacy of study participants. Other countries should also provide such protection to promote studies on drug use. Such an approach might also help researchers to recruit participants from diverse minority communities. In the current study, most participants had white ethnic backgrounds (72%). However, it has been found that drug use prevalence is highest among those from non-white ethnic backgrounds, such as mixed race (Beddoes et al., 2010). This suggests that people from non-white ethnic background are less likely to admit that they use recreational drugs than people from white backgrounds, perhaps due to racial bias within the criminal justice system that leads to racially disproportionate drug arrests. According to a report black Asian and minority, ethnic people were 240% more likely to be sent to prison than white offenders in drug-related offences (Lammy, 2017).

Most drug use studies have been conducted in industrialized nations that have significant societal funds to devote to those studies, such as the United Kingdom and the United States. Therefore, theories about drug use have been developed from Western models (Ryan et al., 2019). In order to view drug use through multiple lenses and get a better understanding of it, future studies should be conducted in non-western countries. The current study was conducted in the UK; hence its results can only be inferred from the UK population who tend to be well-educated. According to the current report, an estimated 83% of adults aged 19-64 have a National Qualifications Framework (NQF) level 2 (e.g. GCSE grade 9-4/A*-C, National 5 grade A-C) or above; an estimated 66% with NQF level 3 (e.g. A Level, T Level, Highers) or above; and an estimated 47% at level 4 (e.g. higher apprenticeship) or above across the UK (National Statistics, 2022). It has been well established that cognitive

function is positively correlated with the number of years of formal education completed by individuals (Lövdén et al., 2020), thus such drug use in other countries, particularly in developing countries where citizens tend to be less educated (Hossain & Hickey, 2019), might have a different impact on users- possibly worse (Ritchie & Roser, 2019) due to lack of the infrastructure, public health and treatment support in those countries (Salwan & Katz, 2014).

Most studies on the effects of drug on cognition used cross-sectional study design that involves looking at data from a sample at one particular time point. There is no prospective or retrospective follow-up. Therefore, it is difficult to make a causal inference between drug use and cognitive functions due to pre-existing characteristics. As discussed earlier, cognitive deficits present prior to first drug use can act as a risk factor for drug use initiation (Boly et al., 2013). A longitudinal study design can be used to avoid pre-existing characteristics where participants are repeatedly observed over a period of time to detect changes in the characteristics of the target population.

There is inconsistency in recording the level of illicit drug use (e.g., duration of use, average dose use, frequency of use, age at first use, total lifetime dose and usage etc.). Hence, it is hard to draw any firm conclusions based on a specific variable reflecting the level of drug use. Moreover, as aforementioned (see 4.3.5), there is no single agreed-upon set of criteria to identify heavy, moderate or light drug use in the scientific literature. While a certain amount of drug use (such as 400 ecstasy tablets used in lifetime) can be classified as heavy use in one study (Fisk and Montgomery, 2009) and moderate use in another study (Fox, Parrot, et al., 2001). Also, each drug has a different classification for level of its use. For example, using ecstasy on 10 or more separate occasions in the last 90 days was classified as heavy use (Sterk et al., 2007). Whereas, using cannabis at least five times a week was classified as heavy use (Lahanas & Cservenka, 2019). It can be a completely different

classification for psychedelic drugs which are usually taken a few times in a lifetime. Therefore, those points should be taken into consideration while classifying drug users. First, it is important to record drug use in a consistent way- ideally, precise amount of drug use as units should be recorded. A precise classification of the degree of drug use for each drug should also be established.

The full picture of the polydrug use phenomenon appears to be missing in the current literature. The term 'polydrug use' is used to describe the use of more than one illegal drug by an individual (Font-Mayolas & Calvo, 2022). However, there are two types of polydrug use: concurrent polydrug use (use of more than one substance on different occasions) and simultaneous polydrug use (use of more than one substance on the same occasion, or at the same time; Baggio et al., 2014). Despite the absence of comprehensive data on the subject, the available information indicates simultaneous polydrug use poses greater health risk than concurrent polydrug use (Baggio et al., 2014; Earleywine & Newcomb, 1997; McCabe et al., 2006), perhaps due to pharmacokinetic drug-drug interactions in the brain which occur when a drug alters the pharmacokinetic properties (e.g., absorption, distribution, metabolism, and elimination) of a coadministered drug (Abbott et al., 2020). It has been also found that illicit substances may have a significant influence on medications used to treat health conditions (Lindsey et al., 2012). Hence, it is important to distinguish between concurrent and simultaneous polydrug use and employ comparable measures in parameters for the frequency, magnitude and combination of drugs involved in polydrug use. The used of medication should also be investigated and included in analyses.

It has been well established that participants display various cognitive impairments while intoxicated (see Chapter 2). Thus, studies that investigate the long-term effects of drug use on cognition make sure that participants are not under influence of any drugs during testing- ideally drug testing kits (urine or saliva) should be used to provide an objective

assessment of compliance. The comedown effects should also be considered. As reviewed in Chapters 2, 3 and 4, the comedown effects were not taken into account while testing participants in most studies on drug use. As discussed in Chapter 3, the comedown effects occur when the effects of drugs wear off during which the brain is readjusting the chemical imbalance. It was also evident in Chapter 7 where drug users reported the negative comedown effects on their cognitive functions after using drugs. Those symptoms begin within hours or days after the last use of drugs and gradually go away. The length of time symptoms last depends on the specific drug used due to their pharmacokinetic profiles. For example, methamphetamine withdrawal symptoms have been thought to last 3 to 7 days (McGregor et al., 2005), cannabis 5 days (Welch & Martin, 2003), amphetamine and cocaine 3-7 days (Miller & Gold, 1998; Wilkins et al., 2009). Therefore, future studies should require participants to stop using illegal drugs at least 7 days prior to testing.

8.9. Strengths, limitations and future directions

In the current study, the effects of light recreational polydrug use on a wide range of cognitive functions were investigated while addressing methodological challenges (e.g., small sample size, a short abstinence period, poor control of cofounding factors) that were presented in the existing literature.

A mixed research methods approach was used in the current study which enabled the investigators to seek a more panoramic sight of research landscape; studying the topic from different perspectives and through different research lenses. On the one hand, the quantitative component allowed the investigators to gain a broad picture of the possible effects of recreational drug use on cognitive functions, using self-report and lab-based measures. On the other hand, the qualitative component allowed the researcher to understand why such effects were observed from drug users' point of view. Therefore, the present study has been one of

the first attempts to thoroughly examine the effects of recreational drug use on cognitive functions, PM in particular.

This study also provides a comprehensive assessment of PM which is one of the most important cognitive functions in everyday life. The different components of PM were assessed, using qualitative and quantitative research methods to understand its underlying mechanising.

In the current study, it was also evident that using a quantitative approach to research does not adequately reflect the full range of how using recreational drugs affects cognitive functions. More research should employ mixed research methods to further understand how drug use affects users' cognitive functioning, perhaps exploring metacognition more thoroughly which appears to have a significant role in a number of cognitive processes as well as in drug use.

Furthermore, in the current study, only time- and event-based PM forms were assessed. However, it has been argued there are more forms of PM, such as activity-based PM which involves performing a planned intention at the end of an event or at a specific point during a sequence of events (e.g., turning off the iron after ironing; Yang et al., 2019). Moreover, additional distinctions within both time- and event-based PM have been made such as Kvavilashvili and Ellis (1996) separated time-based PM intentions into two kinds: pulse, to be performed at a particular time (e.g., at 8 pm), and step, to be performed during a broader time period (between 3pm-8pm; (Brandimonte et al., 1996). There is also mixed prospective memory that has both event and time cues (Gan et al., 2021). Further studies are needed to assess the effects of drug use on those forms of PM.

Due to the high level of polydrug use in the current sample, it is challenging to distinguish between the independent effects of different drug types on cognitive functioning. However, given that polydrug use is very common in drug users (Gold et al., 2020; Grov et

al., 2009; Teter & Guthrie, 2001; Uys & Niesink, 2005), more research should be conducted to investigate the effects of polydrug use on cognitive functions. Furthermore, the impact of widely used combinations of drugs (e.g., cocaine and cannabis) on cognitive functioning should be the subject of further research, possibly by recruiting drug users who regularly combine those drugs and those who do not to investigate differences in their cognitive profiles or using statistical regression models to investigate the separate and joint effects of those drugs, while taking frequency of use into account.

8.10. Conclusion

The current study investigated the potential effects of light recreational polydrug use on various cognitive processes, PM in particular while addressing methodological challenges that were presented in the existing literature. It has been reaffirmed the harm that light drug use causes to PM. The observed PM impairments have been associated with retrospective memory deficits, reduced attention, metacognition dysfunctions, poor time awareness, diminished executive functions and cues availability at retrieval. Moreover, a discrepancy between questionnaire-based and lab-based PM measures in drug users has been identified which presents a methodological challenge for future studies in the area. The study has uncovered the cognitive factors (i.e., metacognition and motivation) that explain the observed discrepancy between the questionnaire-based and lab-based PM measures in drug users. It appears that drug use has not been taken into consideration when PM theories have been developed. This study has reaffirmed the detrimental impact of drug use on PM, therefore, future PM research should control for drug use. The study has further showed that recreational drug use leads to verbal learning deficits which have been associated with retrieval impairments, poor attention and metacognition. Recreational drug users also exhibit impaired AM which may result from disturbing memories of adverse events, general memory issues, reduced attention and executive dysfunctions. The study has also revealed that light

drug users are impaired in specific cognitive processes (recall, but not recognition). The pattern of the findings has implied that drug users have retrieval impairments. Lastly, the study has shown that light drug use leads to subtle executive dysfunctions which can be detected with sensitive measures.

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Appendixes

Appendix A: Summary of the studies reviewed in Chapter 2.

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
Verbal learning						
Rodgers (2000)	Group 1:15 regular ecstasy users- an average of 20 times over a 5-year period (mean age:31, 8 females. Group 2-15 regular cannabis users-average 4 days per week over an 11-year period (mean age 30 years, 8 females). Group 3-15 drug naïve controls (mean age 32, 8 females)	General population	Ecstasy Cannabis LSD Amphetamine Cocaine	Reaction Time Tasks The Wechsler Memory Scale Cognitive Failures Questionnaire	Education Socioeconomic Status	>1 month
Solowij et al. (2011)	52 cannabis users who used cannabis at least twice/month for at least the past 6 month (mean age 19, 21 females), 67 alcohol users (mean age 18, 32 females), and 62 controls (mean age 18, 44 females)	Student/ young population	Cannabis Ecstasy Amphetamines Cocaine Hallucinogenic Mushrooms	Rey Auditory Verbal Learning Test	Age, Education, Premorbid Verbal and Numerical Ability Anxiety Depression Gender	12 hrs
Solowij et al. (2002)	51 Short-term cannabis dependents (mean age: 29, 15 females), 51 long-term users(mean age: 42, 12 females) and 33 nonuser controls (mean age: 25. 11 females)	Patient population	Cannabis, Cocaine, Amphetamines Hallucinogens	Various tests including The Rey Auditory Verbal Learning Test, Wisconsin Card Sorting Game, Stroop Test	Sex, Education, IQ, Age	12 hrs
Gouzoulis-Mayfrank et al., 2000	28 ecstasy regular users-use over 6 months or longer with a minimum frequency of twice a month within the past 2 years or use of ecstasy on at least 25 occasions during the past 2 years (mean age:23, 12 females) 28 healthy persons who had never taken ecstasy (mean age:24, 13 females) 28 persons who had never taken ecstasy and were matched for cannabis use with the ecstasy user group, (mean age:23, 11 females)	General population	Ecstasy Cannabis	Attention Tests (e.g., Selective Visual Attention, Divided Attention), Memory Span And Working Memory Tests (e.g.,., Digit Span, Corsi Block Tapping Test), Verbal Learning And Memory Test	Sex Distribution, Age, And Educational Level, General Knowledge Score	>7+ days
Reske et al. (2010)	154 non-dependent users of cocaine, prescription amphetamines and/or	Student population	Cannabis Ecstasy Cocaine	California Verbal Learning test	Age Education Verbal IQ	Not given

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
	methylphenidate (at least three uses over the past six month) (mean age 21, 61 females)and 48 comparison subjects (mean age 21, 26 females)		Amphetamine			
McCardle et al. (2004)	17 MDMA users-total lifetime consumption of ecstasy tablets twice to more than 30 occasions (mean age=21, 4 male) and 15 controls who did not use MDMA (mean age=22, 2 females)	Young population	Cannabis Cocaine Amphetamine	The Rey Auditory Verbal Learning Test Digit Span The Trail Making Test, and more	Age, Gender, Level Of Education IQ	>7+ days
Kumar et al., (2019	Cocaine users (n = 17) were required to report that they had used cocaine around 3.5 yrs (mean age 36, 4 females) Control participants (n = 17) were non-cocaine users (<10 reported lifetime exposures to cocaine, none within the last year)(mean age: 34, 7 females)	General population	Cocaine Cannabis	The List-Learning and Figure Copy Tasks Executive, Attention and Motor Tasks Acquired Equivalence Task	Depression Age Sex Race Education Level	Not given
Woicik et al. (2009)	64 cocaine-addicted subjects and 64 non-dependent subjects	Patient population	Cannabis, Cocaine	Oral Word Association Task, Trail Making Test, The Wisconsin Card Sorting Test, Stroop Task, California Verbal Learning Test And More	Gender, Race, Verbal And Non-Verbal Intelligence Socioeconomic Status, Age, And Education	72 hrs
Fox, Toplis, et al., 2001	14 Short-term ecstasy users (consumed the drug for 5 years or less, mean age:29, 10 females), long-term ecstasy users (consumed the drug for 8 years or more, mean age:27, 7 females) and 14 polydrug controls (mean age: 30, 3 females)	General population	Cannabis Cocaine Amphetamine LSD Opiates	The Auditory Verbal Learning Task	Age Gender Pre-Morbid Verbal IQ Cannabis, Cocaine, LSD And Mushroom Use	Ecstasy-2 weeks Cannabis-24 hrs
Gouzoulis-Mayfrank et al. (2003)	30 heavy ecstasy users (lifetime dose > or =80 ecstasy tablets; mean age:25, 9 females), 30 moderate users (lifetime dose <80	General population	Ecstasy Amphetamine Cannabis LSD	Digit Span Backwards 2-Back, Verbal Learning Test	General Knowledge Sex Level Of Education,	Most drugs-7 days Cannabis-24 hrs

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
	ecstasy tablets; mean age: 24, 9 females) and 30 nonusers (mean age: 25, 9 females)				Age	
Quednow et al., 2006	19 male chronic MDMA users(least 50 times over a period of at least 1 year, mean age:24), 19 male chronic cannabis users(mean age:25); and 19 drug-naive controls (mean age:23)	General population	Cannabis MDMA Cocaine Amphetamine Hallucinogens	The Rey Auditory Verbal Learning Test	Age Verbal IQ Year of Education Cannabis	3 days
Rouse & Bruno, 2011	15 regular ecstasy users, 17 only cannabis users, 20 regular ecstasy and cannabis users and 17 drug naïve participants	General population	Cannabis MDMA	Verbal Learning Test	Not Given	Not given
Yip & Lee, 2005	100 ecstasy users (mean age:28) and 100 non-users (mean age:28	General population	Ecstasy	Digit Span Verbal Learning Test Stroop Test Symbol Digit Modalities Test Verbal Fluency and more	Age, Education	not given, but average abstinence was 2 months
Basedow et al., 2021	18 users with methamphetamine use disorder (MUD, mean age 16, 8 females), 18 adolescents with other substance use disorders (SUDs, mean age:16, 8 females), 18 controls without SUDs (mean age 16, 8 females).	Young population	Cannabis MDMA Amphetamine Methamphetamine	Verbal Learning And Memory Task The Alertness Go/Nogo Subtests Of The Test Of Attentional Performance	Depression Age, And Gender, Alcohol Tobacco Cannabis MDMA Amphetamine	24–72 hrs
Hoffman et al., 2006	41 MA-dependent individuals (mean age: 38, 10 female) and 41 controls participated (mean age: 35, 11 females)	Patient population	Methamphetamine	Rey Auditory–Verbal Learning Test, Trail making Test, Grooved Pegboard, Stroop Wisconsin Card Sorting Test and more	Age, And Gender, Years Of Education	2 weeks
Volkow et al., 2001	15 methamphetamine dependence-average methamphetamine use involved at least 0.5 g/day, at least 5 days per week, for at least 2 years. (mean age=32,	Patient population	Methamphetamine	The Symbol Digit Modalities Test, The Trail Making Test, Stroop	Age IQ	2 weeks

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
	9 females) and 18 healthy volunteers (mean age: 31, 6 females)			Interference Test, The Rey Auditory Verbal Learning Test		
Woods et al., 2005	71 non-MA-using (mean age:36, 29 females) controls (MA–) and 87 individuals diagnosed as MA dependent (MA+ ;Mean age: 38; 27 females)	Patient population	Methamphetamine	The Hopkins Verbal Learning Test	Age, Education, Sex, Ethnicity, And Estimated Premorbid Verbal Intelligence	5 days
Kuypers et al. (2016)	65 polydrug ecstasy-users (mean age: 22, 25 females) and 65 drug-naïve participants (mean age: 22, 25 females)	Young population	Ecstasy Amphetamine Cannabis Cocaine LSD Mushrooms Ketamine GHB	The Word Learning Task	Sleep, Age And Gender	Intoxicated
Reneman et al., 2001	22 MDMA users (mean age:26, 11 females), 16 Ex-MDMA users (mean age: 25, 8 females), 13 Control subjects (mean age:25, 6 females)	General population	Mdma Cannabis Amphetamine Cocaine LSD Mushrooms	The Rey Auditory Verbal Learning Test	IQ Age Sex	3 weeks
Thomasius et al. (2003)	30 current ecstasy users (mean age:25, 15 female) and 31 ex-ecstasy users (mean age: 24, 15 female), 29 polydrug users (mean age: 24, 14 female and 30 drug-naive control (mean age:23, 15 female)	General population	Ecstasy Amphetamine Cannabis LSD	Gonogo, Divided Attention, The Trail-Making-Test The Wisconsin Card Sorting Test, The Rivermead Behavioral Memory Test	Gender Age, Level Of Education IQ	6 days
Thomasius et al. (2006)	11 current ecstasy users (mean age: 24, 4 females), 10 ex-ecstasy users (mean age: 26, 5 females), 11 polydrug (but not MDMA; mean age:25, 5 females) and 15 drug-naive controls (mean age:22, 7 females)	General population	Ecstasy Cannabis Amphetamine Cocaine LSD	The Rivermead Behavioural Memory Test The Auditory Verbal Learning Test	Gender, Age, Level Of Education, IQ	6 days

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
Associative learning						
Croft et al. (2001)	11 MDMA/cannabis users (mean age: 26, 6 females), 18 cannabis users (mean age: 27, 4 females), 31 drug-naive controls (mean age: 24, 17 females)	General population	Cannabis MDMA Cocaine Speed	Warrington Recognition Tests Associative Learning Tests Digit Span Verbal Fluency Stroop Test and more	Age IQ Education	2 days
Ardila et al., 1991	37 crack cocaine abusers (Mean age: 29, 14 females)	Patient population	Cocaine	Wechsler Memory Scale, Verbal Fluency, Wisconsin Card Sorting Test Associative Learning Test	N/A	30 days
Wagner et al., 2015	149 subjects were assessed at baseline. 96 subjects were assessed (mean age: 23, 33 females years), at the second follow-up assessment: 31 of these were non-users(mean age: 23, 9 females), 55 moderate-users (mean age: 22, 21 females), and 10 heavy-users (mean age:27, 3 females (0 pills, 1–49 pills, 50 or more pills respectively)	Student population	Cannabis MDMA Cocaine Hallucinogens Amphetamine	The Rey Auditory Verbal Learning Test Visual Paired Association Learning Task. Classical Paired Associates Learning Task. The Stroop Task, Digit Span, Trail Making Test	Age IQ Alcohol Use Cannabis Use Level of Nutrition, Sleep Patterns, Feelings of Subjective Well-Being,	Cannabis and MDMA-24 hours Other drugs-7 days
Fox et al., 2002	20 ecstasy polydrug users (Mean age: 27, 10 females) 20 non ecstasy polydrug users (Mean age: 28, 8 females)	General population	Ecstasy Cannabis Amphetamine Cocaine LSD Psilocybin Mushrooms	Verbal Fluency, Spatial Working Memory, Paired Associates Learning, Go/No Go, Tower Of London Test, and more	Age IQ, Amphetamine, Cocaine LSD Use	2 weeks
Gallagher et al., 2012	44 ecstasy users, (mean age: 22.50) and 48 non-users (mean age: 20.96)	Student population	Ecstasy Cannabis Cocaine Ketamine	Associative Learning Test	IQ Year of Education	Ecstasy- 10 days

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
					Alcohol Use Nicotine Use	Other illicit drugs- 24 hrs
Montgomery, Fisk, & Newcombe, 2005).	62 non-ecstasy users (mean age:21, 44 females) and 35 ecstasy users (mean age: 22, 15 female)	Student population	Ecstasy Cannabis Amphetamine Cocaine	Associative Learning Test	Age, Years Of Education, Fluid Intelligence Premorbid Intelligence Sleep, Health	Ecstasy- 7 days Other illicit drugs- 24 hrs
Wagner et al. (2013)	At baseline 149 subjects At follow up, 109 subjects (mean age: 23, 37 females) 23 MDMA users (mean age:26, 9 females) 43 Non MDMA cannabis users (mean age:23, 15 females)	General population	Cannabis Ecstasy Cocaine Amphetamine Hallucinogens	Verbal Learning Test Figural Visual Recognition Test Trail-Making Test Digit Span Stroop Task Digit Symbol Test	Age, General Intelligenc Cannabis Use, Alcohol Use, Cigarette Use, Medical Treatment, Sleep Wellbeing	Cannabis- 24 hrs Other illicit drugs- 7 days
Bossong et al., 2012).	13 healthy volunteers(having used cannabis at least four times but at most once a week in the year) (mean age:22)	General population	Cannabis	Pictorial Memory Task (Associative Memory Test), Consisting Of Separate Encoding And Recall Conditions.	N/A	Intoxicated
False memory						
Doss et al., 2020	24 healthy volunteers (Mean age: 23, 12 females;) with some cannabis experience (4-100 lifetime uses)	Student population	Cannabis	Mnemonic Similarity Task	N/A	Intoxicated
Kloft et al. (2020).	64 healthy, occasional cannabis users (mean age: 23, 32 female)	General population	Cannabis	Deese-Roediger–Mcdermott Paradigm Associative Word Lists	N/A	Intoxicated

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
Cuttler et al., (2021)	80 cannabis users (mean age: 24, 35 females), with 20 assigned to each of the four groups- (1) sober (2) high-potency fower (≥20% THC) without CBD, (3) high-potency fower with CBD, (4) high-potency concentrates (≥60% THC) with CBD	General population	Cannabis	Source Memory Test, Deese-Roediger–Mcdermott False Memory Paradigm Temporal Order Memory Test, Various Decision Making Tests	Age Verbal IQ Body Mass Index	Intoxicated
Doss, Weafer, Gallo, & de Wit, (2018)	23 healthy young adults (mean age:23, 12 females) with some experience using cannabis (4–100 lifetime occasions)	Young population	Cannabis	Negative, Neutral, And Positive Pictures (Emotional Memory Task) And Lists Of Semantically Related Words (False Memory Task).	N/A	They were assessed when intoxicated and 48 hrs later
Riba et al. (2015)	16 heavy cannabis users (daily use for at least the last 2 years; mean age: 38, 10 females), 14 occasional users (<50 occasions of cannabis use in their lifetime, mean age: 36, 10 females).	General population	Cannabis	A Modified Version Of The Deese/Roediger-Mcdermott Paradigm	Gender, Age, Years In Education, Verbal Intelligence IQ	4 weeks
Kloft et al. (2019)	53 cannabis users acutely intoxicated (mean age:22, 6 females), 53 sober but regular cannabis users (mean age:21, 8 females), and 53 controls (a lifetime cannabis use of ≤ 10 occasions. mean age:23, 33 females)	General population	Cannabis	The Deese/Roediger-Mcdermott Paradigm	Level Of Education Age, Sex, Native Language, Psychiatric Disorder	Cannabis-Intoxicated, Other drugs- 24 hrs
Kloft et al., 2022	61 healthy participants with previous MDMA experience (lifetime use 3–60 occasions, mean age: 23, 28 female)	General population	Mdma Cannabis Cocaine Cocaine LSD Mushrooms	The Deese/Roediger-Mcdermott Paradigm, Misinformation Paradigm	N/A	Intoxicated
Autobiographical Memory						
Oliveira et al. (2007)	25 drug users diagnosed as having alcohol and/or drug abuse or addiction age range 11 to 17, no females) 25	Patient population	Cannabis Cocaine, Hallucinogens,	Autobiographical Memory Questionnaire,	Age	Not given

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
	controls (age range:11 to 17, no females)		Benzodiazepine	Semantic Memory Questionnaire		
Pillersdorf and Scoboria (2019)	47 cannabis users and 52 non-user controls (mean age: 21, 71 females)	Student population	Cannabis	Sentence Completion For Events From The Past, Fading Affect Bias Protocol, Autobiographical Memory	Depression, Anxiety, And Alcohol Use	Not being under influenced of any drugs
Mercuri et al., 2018)	57 Cannabis-naïve controls (mean age: 21) 23 Recreational- cannabis users(mean age: 21) 34 Regular cannabis users(at least three times per week, mean age: 25)	General population	Cannabis	The Hayling Sentence Completion Test, The Trail Making Test, Verbal Fluency, Autobiographical Interview	IQ, Anxiety And Depression Scale	24 hrs
Doss, Weafer, Gallo, & Wit, (2018).	20 Placebo participants (mean age: 24, 10 females), 20 MDMA at encoding participants (mean age: 25, 10 females), 20 MDMA at retrieval participants(mean age: 23, 10 females)	General population	Cannabis, MDMA, Hallucinogen	Cued Recollection And Recognition Memory Tests	Gender Age Education	Cannabis- 72 hrs, Other illicit drugs- 48 hrs
Source memory						
Fisk et al. (2014)	62 ecstasy/polydrug users (mean age: 22, 25 women) and 75 non ecstasy using controls (mean age: 21, 48 women)	Student population	Ecstasy Cannabis Cocaine	Source Memory Task	Gender Alcohol Nicotine IQ	Cannabis- 24hrs Other illicit drugs-7 days
Morgan et al. (2004)	20 poly-drug controls (mean age 23, 7 females) and 20 ketamine users (mean age: 23, 9 females)	General population	Ketamine Ecstasy Cannabis Cocaine, Amphetamine LSD/Hallucinogens	Source Memory Task,	Age, Education Level, Pre-Morbid IQ, Lifetime Prevalence of Drug Use	Intoxicated and 3 days later
Morgan, Muetzelfeldt, et al. (2010).	25 frequent ketamine users (mean age:26, 10 females), 27 infrequent(mean age:28, 5 females), 24 abstinent ketamine users(mean age:27, 8 females), 23 polydrug (mean age:31, 7 females),	General population	Ketamine Ecstasy Cannabis Cocaine,	Pattern Recognition Memory Spatial Working Memory Stockings Of Cambridge	Age, Gender, IQ	Intoxicated

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
	and 20 non-drug-user(mean age:25, 7 females),			Source Memory Task Prose Recall Subtest Of The Rivermead Behavioural Memory Test Verbal Fluency		
Cuttler et al., (2021)	80 cannabis users (mean age: 24, 35 females), with 20 assigned to each of the four groups- (1) sober (2) high-potency fower (≥20% THC) without CBD, (3) high-potency fower with CBD, (4) high-potency concentrates (≥60% THC) with CBD	General population	Cannabis	Prospective Memory Tests. Source Memory Test, Deese-Roediger–Mcdermott False Memory Paradigm Temporal Order Memory Test, Under/Overconfidence Test, Various Decision Making Tests	Age Verbal IQ Body Mass Index	Intoxicated
Ilan et al., (2004)	10 casual cannabis smokers (smoking cannabis between once a month and once a week over the last year; mean age=27, 5 Females)	General population	Cannabis	A Spatial N-Back Task, Episodic Memory Test-Word List Learning Task (Mainly Source Memory)	N/A	Intoxicated
Morgan, Schafer, et al. (2010).	134 Cannabis users (mean age: 21, 36 females) who used cannabis 13.8 days per month.	General population	Cannabis	Prose Recall Verbal Fluency Source Memory Test	N/A	Intoxicated and 5 days later
Executive Function- Cognitive inhibition						
Sellaro et al. (2014)	17 recreational cocaine polydrug users (a monthly consumption (1–4 g) for a minimum of 2 years; mean age: 24, 3 females), 17 cocaine-free controls (mean age: 24, 5 females)	Young population	Cocaine Cannabis, And MDMA	The Simon Task	Age, Sex, Alcohol Consumption, And Intelligence	2 days
Colzato et al. (2007)	13 cocaine users (a monthly consumption (1 to 4 gram) for a minimum of two years; mean age: 29, 2 females) and	General population	Cocaine Cannabis, And MDMA	The Stop-Signal Task	Race, Level Of Intelligence, Gender	2 days

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
	13 nonusers (mean age: 29, 2 females				Distributio n, Age And Alcohol Consumpti on	
Hester and Garavan (2004)	15 nondrug-using subjects (mean age: 31, 8 females) and 15 active cocaine users (using an average of five times per week (range, 1-7) for the past 14 years; mean age:40, 6 females)	Patient population	Cocaine Cannabis	GO-NOGO Inhibition Task	Educational Attainment	3 days
Verdejo-García et al. (2005)	38 drug-dependent participants (Mean age:31, 6 females).	Patient population	Cocaine Cannabis Heroin MDMA	Stroop, Test of Cognitive Flexibility, Digit Span	N/A	2 weeks
Croft et al. (2001)	11 MDMA/cannabis users (mean age: 26, 6 females), 18 cannabis users (mean age: 27, 4 females), 31 drug-naive controls (mean age: 24, 17 females)	General population	Cannabis MDMA Cocaine Speed	Warrington Recognition Memory Tests Associative Learning Tests Digit Span Verbal Fluency Stroop Test Coughlan List and Design Learning	Age IQ Education	2 days
Piechatzek et al. (2009)	84 subjects (mean age: 25, 103 females)	Young population	Cannabis MDMA	Stroop Test, Verbal Fluency, Digit Span Visual Span, Cambridge Neuropsychol ogical Tests, Stockings Of Cambridge, Spatial Working Memory	N/A	7 days
Quednow et al. (2007).	19 male heavy MDMA users (least 50 times over a period of at least 1 year, mean age:24), 19 male chronic cannabis users (mean age:25); and 19 drug-naive controls (mean age:23)	General population	Cannabis MDMA Cocaine Amphetami ne Hallucinog ens	Matching Familiar Figures Test Go/No-Go Task Gambling Task (Gt)	Age Verbal IQ Year Of Education	3 days

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
Dafters, 2006;	33 ecstasy and cannabis users(lifetime use of 50 times or more; mean age: 23, 6 females), 17 subjects who had used cannabis (>50 times) but not ecstasy (<50 times; mean age: 23, 4 females) and 18 subjects who had used neither drug (mean age: 23, 8 females)	Student population	Ecstasy Cannabis Cocaine, Amphetamine LSD Heroin	The Stroop Task The Keep Track Task	None	Cannabis-48 hrs, Other drugs-5 days
Fisk & Montgomery, 2009	14 heavy ecstasy users (estimated lifetime dose exceeding 400 tablets; mean age 22.86; 5 females),39 light ecstasy users (mean age:21; 20 females) and 28 non-user controls (mean age: 21; 21 females)	General population	Ecstasy Cannabis Cocaine,	Letter Span Spatial Span Updating Random Letter Generation (Inhibition Process Measures)	Alcohol Use IQ Years In Education	Ecstasy-7 days, Other illicit drugs-24 hrs
Fox et al., 2002	20 ecstasy polydrug users (Mean age: 27, 10 females) 20 non ecstasy polydrug users (Mean age: 28, 8 females)	General population	Ecstasy Cannabis Amphetamine Cocaine LSD Psilocybin Mushrooms	Verbal Fluency, Spatial Working Memory, Paired Associates Learning, Attentional Shift, Go/No Go, Tower Of London Test, Decision-Making Task	Age IQ, Amphetamine, Cocaine And LSD Use	2 weeks
Gouzoulis-Mayfrank et al. (2003)	30 heavy ecstasy users (lifetime dose > or =80 ecstasy tablets; mean age:25, 9 females), 30 moderate users (lifetime dose <80 ecstasy tablets; mean age: 24, 9 females) and 30 nonusers (mean age: 25, 9 females)	General population	Ecstasy Amphetamine Cannabis LSD	Digit Span Backwards 2-Back, Verbal Learning Test	General Knowledge Sex Education, Age	Cannabis-24 hrs Other illicit drugs-7 days
Thomasius et al. (2003)	30 current ecstasy users (mean age:25, 15 female) and 31 ex-ecstasy users (mean age: 24, 15 female), 29 polydrug users (mean age: 24, 14 female and 30 drug-naive control (mean age:23, 15 female)	General population	Ecstasy Amphetamine Cannabis LSD	Gonogo, Divided Attention, The Trail-Making-Test The Wisconsin Card Sorting Rivermead Behavioral Memory Test	Gender Age, Level of Education IQ	6 days

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
Wagner et al. (2013). No significant difference	At baseline 149 subjects At follow up, 109 subjects (mean age: 23, 37 females) 23 MDMA users (mean age:26, 9 females) 43 Non MDMA cannabis users (mean age:23, 15 females)	General population	Cannabis Ecstasy Cocaine Amphetamine Hallucinogens	Verbal Learning Test Figural Visual Recognition Test Trail-Making Test Digit Span Stroop Task Digit Symbol Test	Age, General Intelligence Cannabis Alcohol Cigarette Medical Treatment, Sleep Wellbeing	Cannabis-24 hrs Other illicit drugs-7 days
Crane et al., (2013)	69 cannabis users (mean age: 21, 25 females)	Young population	Cannabis And Other Drugs	Verbal Episodic Memory The Iowa Gambling Task (Inhibitory Control),	N/A	<24 hrs
Lyons et al. (2004)	54 monozygotic male twin pairs, discordant for regular marijuana use in which neither twin used any other illicit drug regularly (mean age: 46)	General population	Cannabis	Wisconsin Card Sorting Test Stroop Test, Trail Making Test, Rey–Osterrieth Complex Figure Test, Wechsler Memory Scale, California Verbal Learning Test Etc.	Education Level, Marriage Status, Alcohol Use, Nicotine Use	1 year
Executive Function-Working memory						
Madoz-Gúrpide et al. (2011)	24 cocaine addicts (mean age: 36, 6 females) 27 non drug user controls (mean age: 33,)	Patient population	Cannabis Ecstasy Cocaine Benzodiazepines.	Digit Span The Wisconsin Card Sorting Test The Trail Making, The Behavioral Assessment of the Dysexecutive Syndrome	Gender, Age, And Years Of Schooling.	12-36 hrs

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
Soliman et al. (2013)	28 drug dependents aged 38.48 ± 4.75 years and 36 controls aged 37.61 ± 3.75 years.	Patient population	Cannabis Heroin Cocaine Other Drugs	Digit Span A Verbal Two-Back Paradigm, The Spot-The-Word, The Block Span Forward, The Spatial Span Task, The Logical Memory, Visual Cross-Modal Task,	Education Levels, Socioeconomic Backgrounds, IQ	10 days
Frolli et al. (2021)	100 chronic cannabis users(at least 4 times a week for at least a year; mean age 15, 40 females), 100 occasional cannabis users (about once every 2 weeks for at least 1 year; mean age:15.5; 30 females), 100 non user controls (mean age; 15.3; 35 female)	Student population	Cannabis	Wechsler Intelligence Scale For Various tests, including Tower of London test	Age	Not given
McCardle et al. (2004)	17 MDMA users-total lifetime consumption of ecstasy tablets twice to more than 30 occasions (mean age=21, 4 male) and 15 controls who did not use MDMA (mean age=22, 2 females)	Young population	Cannabis Cocaine Amphetamine	The Rey Auditory Verbal Learning Test Digit Span, The Trail Making Test, and more	Age, Gender, Level Of Education Or IQ	>7+days
Verdejo-García and Pérez-García (2007)	81 substance-dependents (mean age :30, 5 females) and 37 controls (mean age:33, 2 females)	Patient population	Cannabis MDMA Cocaine Amphetamine Heroin	Verbal Fluency Wechsler Adult Intelligence Scale, Including Digit Span, Stroop Test Category Test (Flexibility), IowaGambling	Age, Years of Education, And Premorbid IQ	15 days
Sanvicente-Vieira et al. (2016)	26 young female crack-cocaine dependent users (CRK; mean age: 28), 19 healthy female older adults (HO; mean age: 70), and 32 healthy female young adults (HC; mean age: 28)	Patient population	Crack-Cocaine	Verbal N-Back Task	Years of Formal Education, Individual Income, Antidepressants	24 hrs

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
Wang et al. (2008)	28 abstinent male heroin abusers (mean age: 31) and 25 male controls (mean age: 32)	Patient population	Heroin	N-Back Task And Backward Digit Spa	Age, Education Level And Gender	55 days
Ilan et al., (2004)	10 casual cannabis smokers (smoking cannabis between once a month and once a week over the last year; mean age=27, 5 Females)	General population	Cannabis	A Spatial N-Back Task, Episodic Memory Test-Word List Learning Task (Mainly Source Memory)	N/A	Intoxicated
Ilan et al., (2005)	23 healthy cannabis users (11 women): placebo (no active cannabinoids), or cigarettes containing THC with low or high levels of cannabichromene (CBC) and low or high levels of cannabidiol (CBD)	General population	Cannabis	Working Memory And Episodic Memory Test	N/A	Intoxicated
Lyons et al. (2004)	54 monozygotic male twin pairs, discordant for regular marijuana use in which neither twin used any other illicit drug regularly (mean age: 46)	General population	Cannabis	Wisconsin Card Sorting Test Stroop Test, Trail Making Test, Wechsler Memory Scale, California Verbal Learning Test Etc.	Education Level, Marriage Status, Alcohol Use, Nicotine Use	1 year
Fisk et al., 2004	44 Ecstasy users (mean estimated total lifetime use 343 tablets; mean age: 22,) and 59 non-users	Student population	Cannabis MDMA Cocaine Amphetamine	Random Letter Generation, Computation Span	Education Level Age, IQ Cannabis	Ecstasy-7 days, Other illicit drugs-24 hrs
Fox, Parrott, et al., 2001	45 currently abstinent ecstasy polydrug users (use of ecstasy and cannabis o10 times, mean age: 23, 21 females), 48 cannabis polydrug users (use of cannabis o10 times, mean age: 22, 22 females) and 40 legal drug users (mean age: 23, 19 females)	General population	Cannabis MDMA Cocaine Amphetamine LSD Ketamine Mushrooms	The Rey Auditory Verbal Learning Test Prospective Memory Tests Executive Function Measures,	Age, IQ, Gender,	Cannabis-24 hrs Other illicit drugs-10 days

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
Montgomery et al., 2007	104 ecstasy users(mean age: 22) and 103 non ecstasy polydrug users(mean age:21)	Student population	Ecstasy/MDMA Cannabis Cocaine Amphetamine	Computation Span Test, Consonant Updating, Paired Associate Learning, Word Fluency.	Age, IQ Sleep	Not given
Montgomery & Fisk, 2007;	43 Ecstasy/polydrug users (mean age: 22, 19 females) 51 Non ecstasy polydrug users (mean age:22, 34 females)	General population	Ecstasy/MDMA Cannabis Cocaine Amphetamine	The Everyday Memory Questionnaire, Prospective Memory Computation Span Random Letter Generation	Sleep Alcohol Use Age Gender IQ Education Heath	Ecstasy-7 days, Other illicit drugs-24 hrs
Wareing et al. (2000)	42 current MDMA users (mean age:22, 20 female), 17 previous users (mean age:26, 8 female)and 31 non-users (mean age: 23, 19 female)	Student population	Ecstasy/ MDMA Cannabis Cocaine Amphetamine Mushrooms	The Reading And Computation Span, Digit Span, Word Span	Years Of Education, IQ And Word And Digit Span Scores, Alcohol And Cannabis	Ecstasy-7 days, Other illicit drugs-24 hrs
Colzato et al. (2009)	20 recreational cocaine polydrug users (a monthly consumption (1–4 g) for at least 1 year; mean age: 24, 4 females) and 20 cocaine-free poly drug user controls(mean age:23, 3 females)	Young population	Ecstasy/ MDMA Cannabis Cocaine Amphetamine GHB Mushrooms	Wisconsin Card Sorting Test, Reasoning-Based Intelligence Test, Dots–Triangles Task	Ethnicity, Age, Sex, IQ, Alcohol Consumption	2 weeks
Bedi and Redman (2008)	45 Ecstasy polydrug user (use of ecstasy and cannabis >10 times, mean age: 23, 21 females) 48 Cannabis polydrug users (use of cannabis >10 times; mean age:22, 22 females) 40 Legal drug users (use of cannabis <5 times; mean age:23, 19 females)	General population	Cannabis Ecstasy Amphetamine Cocaine LSD Magic Mushrooms Ketamine	Prospective Memory Test	Age Gender IQ Sleep Mood	24 hrs
Jager et al. (2006).	10 frequently cannabis users (lifetime use, range 675–5,400 joints; mean age: 23, 3 females), 10 non-using healthy control subjects (mean age: 23, 3 females)	General population	Cannabis	Verbal Working Memory And Visuo-Auditory Selective Attention	Age, Gender Or Estimated IQ	7 days

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
Executive Function- Cognitive Flexibility						
Curran et al. (2002)	15 healthy male occasional cannabis users (mean age: 24).	General population	Cannabis	Baddeley Reasoning Task, Choice Reaction Time Task, Verbal Fluency, Gibson Spiral Maze, Perceptual Priming Task, Prose Recall	N/A	Participants were assessed pre and 1, 2, 4, 6, 8, 24 and 48 hr post-drug.
Weinstein et al. (2008)	14 regular cannabis users (mean age: 27, 4 females)	Student population	Cannabis	The Virtual Maze Task The Gambling Task Wisconsin Card Sorting Task	N/A	Intoxicated
Lahanas & Cservenka, 2019)	28 frequent marijuana users (MJ+; ≥ 5 times/week for the past year and reported ≤ 15 lifetime uses combined across any illicit substance other than MJ; mean age: 20, 9 females) and 33 healthy controls (HC: mean age:19, 15 females)	Student population	Cannabis Ecstasy Amphetamine Cocaine Hallucinogens	Modified Wisconsin Card Sorting Test, Timeline Follow back	Sex, Race, And Socioeconomic Status	12 hrs
Fontes et al. (2011)	104 chronic cannabis users (49 early-onset users and 55 late-onset users) and 44 controls- aged 18 to 55 years	Patient population	Cannabis	Stroop Test, Wisconsin Card Sorting Test, Frontal Assessment Battery, Vocabulary And Block Design	Age, IQ, Education Level	4 days
Bolla et al., 2002	7 Light cannabis users (10 joints/week; mean age:25, 2 females) 8 Moderate cannabis users (42 joint/week; mean age:22, 1 females) 7 heavy cannabis users (93 joint/week; mean age:21, 0 females)	General population	Cannabis	Verbal Fluency, The Wechsler Memory Scales, Rey Auditory Verbal Learning Test, Paired Associate Learning Test, The Wisconsin Card Sorting Test etc.	IQ Ethnicity Age, Alcohol	28 days

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
Pope & Yurgelun-Todd, 1996	65 heavy cannabis users and 64 light users	Student population	Cannabis	Abstraction Ability, Sustained Attention, Verbal Fluency, Verbal learning	IQ, Alcohol, Other Substances	19 hrs
Dafters, 2006;	33 ecstasy and cannabis users(lifetime use of 50 times or more; mean age: 23, 6 females), 17 subjects who had used cannabis (>50 times) but not ecstasy (<50 times; mean age: 23, 4 females) and 18 subjects who had used neither drug (mean age: 23, 8 females)	Student population	Ecstasy Cannabis Cocaine, Amphetamine LSD Heroin	The Stroop Task The Keep Track Task	None	Cannabis-48 hrs, Other drugs -5 days
Colzato et al. (2009)	20 recreational cocaine polydrug users (a monthly consumption (1–4 g) for at least 1 year; mean age: 24, 4 females) and 20 cocaine-free poly drug user controls(mean age:23, 3 females)	Young population	Ecstasy/ MDMA Cannabis Cocaine Amphetamine GHB Mushrooms	Wisconsin Card Sorting Test, Reasoning-Based Intelligence Test, Dots–Triangles Task	Ethnicity, Age, Sex, IQ, Alcohol Consumption	2 weeks
Alonso-Matias et al., 2019;	19 healthy male control individuals (mean age:30) and 41 male cocaine-dependent (mean age:32)-inhaled cocaine users (CDP-I) and crack cocaine users (CDP-C)	Patient population	Cocaine	Berg's Card Sorting Test, Flanker Task, Go/No-Go, Digit Span, Letter And Numbers, Tower Of London, Iowa Gambling	Age, Sex And Handedness.	10 days
Cunha et al., 2010	62 male cocaine dependents (mean age:27) 32 healthy male volunteer (mean age: 27)	Patient population	Cannabis Cocaine	Frontal Assessment Battery, Wisconsin Card Sorting Test, Digit Span, Stroop	Age, Education Economic Level Ethnicity,	2 weeks
Madoz-Gúrpide et al. (2011)	24 cocaine addicts (mean age: 36, 6 females) 27 non drug user controls (mean age: 33,)	Patient population	Cannabis Ecstasy Cocaine Benzodiazepines.	Digit Span The Wisconsin Card Sorting Test The Trail Making (TM)	Gender, Age, Years of Schooling.	12-36 hrs

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
Woicik et al. (2009)	64 cocaine-addicted subjects and 64 non dependent subjects	Patient population	Cannabis, Cocaine	Trail Making Test, The Wisconsin Card Sorting Test, Stroop Task, California Verbal Learning Test And More	Gender, Race, Verbal and Non-Verbal Intelligence Socioeconomic Status, Age, Education	72 hrs
Hekmat et al. (2011)	155 male drug addicts (mean age:29), 130 non-addict subjects (mean age:30)	Patient population	Opium Heroin Methamphetamine	Stroop Colour Word Test, Symbol Digit Modalities Test, Color Trail Making Test	Gender, Age, Education and Socio-Economic Status.	14 days
Salmani et al. (2020)	20 young male addicts and 30 male students in pre-university grade(age ranges between 16 and 2)	Patient population	Various Drugs	Wisconsin Card Sorting Test, Stroop Color-Word Test And The Wechsler Digit Span Subscale	Gender And Education	Not given
Verdejo-García et al. (2006)	35 substance-dependent individuals (SDI, mean age: 36, 21 females) and 36 healthy controls (mean age 38, 22 females)	Patient population	Cannabis, Cocaine Methamphetamine And Others	The Frontal Systems Behavioral Scale, Go0No Go Task, N-Back Task, Wisconsin Card Sorting	Age, Gender, Alcohol Use	15 days
Verdejo-García and Pérez-García (2007)	81 substance-dependents (mean age :30, 5 females) and 37 controls (mean age:33, 2 females)	Patient population	Cannabis MDMA Cocaine Amphetamine Heroin	Verbal Fluency Digit Span, Stroop Test Category Test (Flexibility), Cognitive Bias Task, Iowa Gambling Task etc.	Age, Years of Education, And Premorbid IQ	15 days
Hart et al. (2001)	18 healthy research volunteers (mean age:25, 8 females), averaging 24 marijuana cigarettes per week, smoked a single marijuana cigarette (0%, 1.8%, or 3.9% THC),	General population	Cannabis MDMA Cocaine LSD	Various Cognitive Measures, Including Cognitive Flexibility, Memory, Attention Etc.	N/A	Intoxicated
Selamoglu et al. (2021)	39 young adult daily cannabis addicts (mean age:	Patient population	Cannabis	Delayed Matching To	Sex	24 hrs

Study by	Sample Details	Sample type	Used Drugs	Test Batteries	Controlled Confounds	Abstinence period
	23, 13 females), 20 healthy controls (mean age: 24, 8 females)			Sample, Paired Associates Learning (PAL), Spatial Working Memory, Cambridge Gamble Task, Intra-Extra Dimensional Set Shift	IQ, Age, Lifetime Drug use, Smoking Status And Alcohol	
Solowij et al. (2002)	51 Short-term cannabis dependents (mean age: 29, 15 females), 51 long-term users(mean age: 42, 12 females) and 33 nonuser controls (mean age: 25. 11 females)	Patient population	Cannabis, Cocaine, Amphetamines, Hallucinogens	Attention tests, The Rey Auditory Verbal Learning Test, Wisconsin Card Sorting Game, Stroop	Sex, Education, IQ, Age	12 hrs
Piechatzek et al. (2009)	84 subjects (mean age: 25, 103 females)	Young population	Cannabis MDMA	Stroop Test, Verbal Fluency, Digit Span Spatial Working Memory etc.	N/A	7 days

Appendix B: Quality assessment of the studies summarised in Chapter 2.

The included studies were assessed on the following categories: sample size, sample type, abstinence period, and control for potential confounds. Each category was defined as good, moderate or low based on the information that was supplied in the article (see 3.3.4 for more detail).

	Sample size	**Sample type**	**Control of confound**	**Abstinence period**	**Significant Finding**
Verbal Learning					
Rodgers (2000)	L	G	G	G	✓
Solowij et al. (2011)	L	M	G	L	✓
Solowij et al. (2002)	G	L	G	L	✓
Gouzoulis-Mayfrank et al., 2000	M	G	G	G	✓
Reske et al. (2010)	G	M	G	L	✓
McCardle et al. (2004)	L	M	G	G	✓
Kumar et al., (2019	L	G	G	L	✓
Woicik et al. (2009)	G	L	G	M	✓
Fox, Toplis, et al., 2001	L	G	G	L	✓
Gouzoulis-Mayfrank et al. (2003)	M	G	G	L	✓
Quednow et al., 2006	M	G	G	M	✓
Rouse & Bruno, 2011	M	G	L	L	✓
Yip & Lee, 2005	G	G	M	G	✓
Basedow et al., 2021	M	M	G	L	✓
Hoffman et al., 2006	M	L	G	G	✓
Volkow et al., 2001	L	L	M	G	✓
Woods et al., 2005	G	L	G	M	✓
Kuypers et al. (2016)	M	M	G	N/A	✗
Reneman et al., 2001	M	G	G	G	✓
Thomasius et al. (2003)	G	G	G	M	✓
Thomasius et al. (2006)	L	G	G	M	✓
Associative Learning					
Croft et al. (2001)	M	G	G	L	✓
Ardila et al., 1991	L	L	N/A	G	✓
Wagner et al., 2015	G	M	G	L	✓
Fox et al., 2002	L	G	G	G	✓
Gallagher et al., 2012	M	M	G	L	✓
Montgomery, Fisk, & Newcombe,	M	M	G	L	✓
Wagner et al. (2013)	G	G	G	L	✓
Bossong et al., 2012).	L	G	N/A	N/A	✗
False memory					
Doss et al., 2020	L	M	N/A	N/A	✓
Kloft et al. (2020).	M	G	N/A	N/A	✓
Cuttler et al., (2021)	M	G	G	N/A	✓
Doss, Weafer, Gallo, & de Wit,	L	M	N/A	N/A	✓
Riba et al. (2015)	L	G	G	G	✓
Kloft et al. (2019)	G	G	G	N/A	✗
Kloft et al., 2022	M	G	N/A	N/A	✗
Autobiographical Memory					

	Sample size	Sample type	Control of confound	Abstinence period	Significant Finding
Oliveira et al. (2007)	M	L	L	L	✓
Pillersdorf and Scoboria (2019)	M	M	L	L	✓
Mercuri et al., (2018)	H	G	G	L	✓
Doss, Weafer, Gallo, & Wit, (2018).	M	G	G	L	✓
Fisk et al. (2014)	G	M	G	L	✓
Morgan et al. (2004)	L	G	G	N/A	✓
Morgan, Muetzelfeldt, et al. (2010).	G	G	G	N/A	✓
Cuttler et al., (2021)	M	G	G	N/A	✓
Ilan et al., (2004)	L	G	N/A	N/A	✓
Morgan, Schafer, et al. (2010).	G	G	N/A	N/A	✗
Executive Function- Cognitive inhibition					
Sellaro et al. (2014)	L	M	G	L	✓
Colzato et al. (2007)	L	G	G	L	✓
Hester and Garavan (2004)	L	L	L	M	✓
Verdejo-García et al. (2005)	L	L	N/A	G	✓
Croft et al. (2001)	M	G	G	L	✓
Piechatzek et al. (2009)	M	M	N/A	G	✓
Quednow et al. (2007).	M	G	G	M	✓
Dafters, 2006;	M	M	L	L	✗
Fisk & Montgomery, 2009	M	G	L	L	✗
Fox et al., 2002	L	G	G	G	✗
Gouzoulis-Mayfrank et al. (2003)	M	G	G	L	✗
Thomasius et al. (2003)	G	G	G	M	✗
Wagner et al. (2013).	G	G	G	M	✗
Crane et al., (2013)	M	M	N/A	L	✗
Lyons et al. (2004)	M	G	G	G	✗
Executive Function- Working memory					
Madoz-Gúrpide et al. (2011)	M	L	G	L	✓
Soliman et al. (2013)	M	L	G	G	✓
Frolli et al. (2021)	G	M	L	L	✓
McCardle et al. (2004)	L	M	G	G	✓
Verdejo-García and Pérez-García	G	L	G	G	✓
Sanvicente-Vieira et al. (2016)	M	L	G	L	✓
Wang et al. (2008)	M	L	G	G	✓
Ilan et al., (2004)	L	G	N/A	N/A	✓
Ilan et al., (2005)	L	G	N/A	N/A	✓
Lyons et al. (2004)	G	G	G	G	✓
Fisk et al., 2004	G	M	G	L	✓
Fox, Parrott, et al., 2001	G	G	G	L	✓
Montgomery et al., 2007	G	M	G	L	✓
Montgomery & Fisk, 2007;	M	H	G	L	✓
Wareing et al. (2000)	M	M	G	L	✓
Colzato et al. (2009)	L	M	G	G	✗
Bedi and Redman (2008)	G	G	G	L	✗
Executive Function- Cognitive flexibility					
Jager et al. (2006).	L	G	G	G	✗

	Sample size	Sample type	Control of confound	Abstinence period	Significant Finding
Weinstein et al. (2008)	L	M	N/A	N/A	✓
Lahanas & Cservenka, 2019)	M	M	G	L	✓
Fontes et al. (2011)	H	L	G	M	✓
Bolla et al., 2002	L	G	G	G	✓
Pope & Yurgelun-Todd, 1996	G	M	G	L	✓
Dafters, 2006;	M	M	L	L	✓
Colzato et al. (2009)	L	M	G	G	✓
Alonso-Matias et al., 2019;	M	L	G	G	✓
Cunha et al., 2010	M	L	G	G	✓
Madoz-Gúrpide et al. (2011)	M	L	G	L	✓
Woicik et al. (2009)	G	L	G	M	✓
Hekmat et al. (2011)	G	L	G	G	✓
Salmani et al. (2020)	M	L	M	L	✓
Verdejo-García et al. (2006)	M	L	G	G	✓
Verdejo-García and Pérez-García	G	L	G	G	✓
Curran et al. (2002)	L	G	N/A	N/A	✗
Hart et al. (2001)	L	G	N/A	N/A	✗
Selamoglu et al. (2021)	M	L	G	L	✗
Solowij et al. (2002)	G	L	G	L	✗
Piechatzek et al. (2009)	M	M	N/A	G	✗

Population Representative: Sample type: General Population= Good(G); Student/Young Population= Moderate (M); and Patient Population= Low (L) **and Sample size:** Sample size >100=Good(G); Sample size > 50 and <100 =Moderate (M); and Sample size<50= Low(L)
Abstinence period: Abstinence Period ≥7 days= Good(G); Abstinence Period< 7 days and ≤3 days=Moderate (M); and Abstinence Period <3 days or Abstinence period was not given = Low (L)
Control for Confounding Factors: Controlling for three or more confounding factors= Good (G); Controlling for two confounding factors= Moderate (M); and Controlling for only a factor or not at all or no information about it = Low (L).
N/A: Not applicable (due to research design)
✓: Present, ✗: Not present

Appendix C: Summary of the 27 studies identified in this systematic review.

Authors, Year and Country and the finding* **(t^+, t^-, r^+, r^-)**	**Sample Details: Number of participant (gender distribution, Mean age (Standard Deviation or Range)) for each group**	**Combination of drugs taken**	**Test Batteries**	**Statistical controls for potential confounds**	**Abstinence period**
Hadjiefthyvoulou et al., 2011a, UK r^+, t^+	42 ecstasy/ polydrug users (14 males, Mean age: 21.67 (SD 3.61)) 31 non-users (5 males, Mean age:21.03(SD 3.25))	Ecstasy Amphetamine Cannabis Cocaine	PMQ Lab-based PM tasks	IQ Age Education	14 days
Weinborn et al., 2011a, Australia t^+	31 Ecstasy/polydrug users (12 males, Mean age: 21.4 (SD 3.3)) 21 High risk alcohol users (9 males, Mean age: 19.5 (SD 2.1)). 31 Health adults (12 male, Mean age: 19.7 (SD 1.6))	Cannabis, Cocaine Ecstasy	MIST(Lab-based) and PRMQ	Sleep Age	3 days
Heffernan et al., 2001a, UK^{t+}	30 Regular ecstasy/polydrug users (Mean age: 24.3 (range 18-43)) 31 non users (Mean age: 24.8 (range 19-37))	Cannabis Cocaine Ecstasy	PMQ	Age Gender	Not given
Heffernan et al., 2001b, study -1-, UK^{t+}	46 Regular ecstasy/polydrug users (28males, Mean age: 24.6 (range 18-43)) 46 Controls (17 males, Mean age: 26.1 (range 18-40))	Cannabis Cocaine Ecstasy	PMQ	Age Number of strategies used to remember	1 day
Heffernan et al., 2001b, study-2-, UK^{t+}	30 Ecstasy/ polydrug users (17 males, Mean age:23.9 (range 19-40)) 37 Controls (10 males, Mean age: 25.5 (range 19-50))	Cannabis Cocaine Ecstasy	PMQ	Age Number of strategies used To remember	1 day
Rodgers et al., 2001, UK r^+	155 Ecstasy and Cannabis Users 46 Ecstasy users only 108 Cannabis Users only 225 Non-users Overall 193 males, the modal age group 21-25	Ecstasy Cannabis	PMQ	Age Gender	Not given
Rodgers et al., 2003, UK. r^+	199 Ecstasy/polydrugs users 172 Only Cannabis users 309 Non-users Overall 298 males, the modal age 21-25	MDMA Cannabis Cocaine Amphetamine Magic mushroom LSD	PMQ	Gender	Not given
Montgomery and Fisk, 2007, UK. t^+	43 Ecstasy/polydrug users (24 males, Mean age: 21.56(SD 1.68)) 51 Non-users(17 males, Mean age:21.51(SD 1.70))	MDMA Cannabis Cocaine Amphetamine	PMQ	Sleep Alcohol use Age Gender IQ Education Heath RLG	7 days

Hadjiefthyvoulou, et al., 2011b, UK. $^{t+}$	29 Ecstasy/polydrug users (17 males, Mean age: 21.17(SD 1.79)) 12 Cannabis Users (5 males, Mean age: 21.92(SD 1.56)) 18 Non users (2 males, Mean age: 20.44(SD 2.28))	MDMA Cannabis Cocaine Ketamine Poppers LSD Amphetamine Magic Mushroom	CAMPROMPT (Lab-based)	Age Gender IQ Education Nicotine use Alcohol use	7 days
Montgomery et al., 2010, UK. $^{t+}$	23 Ecstasy polydrug users (13 males, Mean age: 23.22(SD 4.56)) 26 Non-ecstasy polydrug users (9 males, Mean age: 21.92 (SD 2.27))	Ecstasy Cannabis Cocaine	JAAM (Lab-based)	Age Sleep IQ	7 days
Arana, et al., 2011, Spain. $^{r+}$	113 Cannabis users (19 males, Mean age: 19.85(SD 2.21))	Cannabis Valium	PMQ Lab-based PM tasks	Not given	Not given
McHale et al., 2008, UK. $^{r+, t+}$	18 Cannabis users (10 males, Mean age: 21.6(SD 1.1)) 20 Non-drug using controls (10 males, Mean age: 21.4(SD 1.6)) 20 Tobacco smokers(10 males, Mean age: 21.4(SD 1.6))	Cannabis	Lab-based PM tasks	Alcohol use	1 day
Montgomery et al., 2012, UK. $^{r+, t+}$	20 Cannabis users (13 males, Mean age:21 (range 18-25)) 20 non-illicit users (7 males, Mean age: 20 (range 18-25))	Cannabis	JAAM (Lab-based)	IQ Alcohol use Mood Age	5 days
Weinborn, et al., 2011b Australia. $^{t+}$	53 individuals with substance use disorder (SUD) (30 males, Mean age: 39.9(SD 11.8)) 44 Heathy Adults(HA) (18 males, Mean age: 42.1(SD 14.2))	Cannabis Amphetamine Heroin	PMQ MIST (Lab-based)	Age Sex Ethnic Identity	Not being under influence of any drug during testing
Ciorciari et al., 2011, Australia. $^{r-, t+}$	25 MDMA/ polydrug users (13 males, Mean age: 27.28(SD 6.30)) 37 Cannabis only users (9 males, Mean age: 27.70 (SD 7.65)) 43 Controls (12 males, Mean age: 27.72(SD 11.20))	Cannabis MDMA Methampheta mine Cocaine LSD Magic Mushroom	PMQ	Not given	Not being under influence of any drug during testing
Rendell et al., 2009, Australia. $^{t+}$	20 ex-Methamphetamine Users (12 males, Mean age: 27.50(SD 5.21)) 20 Controls (12 males, Mean age: 28.20 (SD 5.00))	Cannabis Cocaine Methampheta mine	Virtual Week: A computerised version (Lab-based)	Age Gender Education IQ Depression Anxiety Heath Sleep	3 months

Rendell et al., 2007, Australia. [t+]	27 MDMA users (14 males, Mean age:21.3 (SD 1.96)) 34 controls (15 males, Mean age: 20.6 (SD 1.40))	MDMA Cannabis	Virtual Week: A Computerised version (Lab-based)	Age Education Vocabulary Health	2 days
Terrett et al., 2014, Australia. [t+]	26 opiate users (18 males, Mean age:31(SD 7.46)) 39 controls (17 males, Mean age: 39.47 (SD 7.94))	Heroin Methadone Cannabis	Virtual Week: A Computerised version (Lab-based)	Gender IQ Education	5 hours
Zakzanis et al.,2003, Canada. [t+]	15 MDMA/ polydrug users (12 males, Mean age:24.1 (SD 5.6)) 17 Polydrug no MDMA Controls (14 males, Mean age:23.4(SD 2.0))	Cannabis MDMA Opiates Amphetamine Cocaine LSD Magic Mushroom	Lab-Based PM tasks: Belonging Appointment Message	Education Gender Age	14 days
Gallagher et al., 2014, study -1-, UK. [t+]	65 Ecstasy/polydrug users (38 males, Mean age: 21.91(SD 2.40)) 85 non ecstasy/polydrug users (31 males, Mean age:20.89 (SD 2.38))	Cannabis MDMA Cocaine	Lab-based PM tasks: Pattern Recognition Fatigue Mail	Education Gender IQ Alcohol use Nicotine Use	7 days
Gallagher et al., 2014, study -2- UK. [r+, t+]	103 Ecstasy/polydrug users (51 males, Mean age:21.85(SD 2.98)) 38 Cannabis only users (17 males, Mean age: 21.47(SD 3.00)) 65 nonusers of illicit drugs (17 males, Mean age: 20.64(SD 2.23))	Cannabis MDMA Cocaine	Lab-based PM: Pattern Recognition Fatigue Mail	Education Gender IQ Alcohol use Nicotine Use	7 days
Bartholomew et al., 2010, UK. [t+]	45 Cannabis Users (20 males, Mean age:19 (SD 5)) 45 Non-users (17 males, Mean age:19 (SD 3))	Cannabis	PMQ Video-based task (Lab-based)	Depression Anxiety Alcohol use Nicotine use	10 days
Rodgers et al., 2006, UK. [r+]	209 Ecstasy/ polydrug users (124 males, the modal age 16-20)	MDMA Cocaine Cannabis Amphetamine	PMQ	Gender Age	Not being under influence of any drug during testing
Cuttler et al.,2012, Study 1, Canada. [r+]	805 Participants (291 males, Mean age: 20.44 (SD 2.34)) of those 376 cannabis users	Cannabis	PMQ	Not given	Not being under influence of any drug during testing

Cuttler et. al..,2012, Study 2, Canada. $^{t+}$	178 Participants (54 males, Mean age: 20.31(SD 2.62)), 48 non-users (who had never used cannabis), 48 experimenters (who had used cannabis five or fewer times in their lives), and 48 chronic users (who had used cannabis at least three times a week for one year)	Cannabis	PMQ Lab-based PM tests: the Fruit, Reminder and Call in	Education Level Gender IQ	Not being under influence of any drug during testing
Fisk and Montgomery, 2008, UK, $^{t+}$	27 Cannabis users (Mean age: 21) 20 Non-users (Mean age:21)	Cannabis	PMQ	IQ Reading Alcohol use Nicotine use	2 days
Bedi and Redman, 2008, USA. $^{t-}$	45 Ecstasy polydrug user 48 Cannabis polydrug users 40 Legal drug users	Cannabis Ecstasy Amphetamine Cocaine LSD Magic Mushrooms Ketamine	Lab-based tasks: Reminder and Belonging test	Age Gender IQ Sleep Mood	1 day

***** $^{t+}$ Significant PM deficit in at least one PM measure**,** $^{t-}$ no group effect on PM

***** $^{r+}$ Significant correlation between at least one PM measure and drugs dosage**,** $^{r-}$ no correlation

Appendix D: Overview of the Findings of 27 Studies with Quality Assessment.

Appendix D1:Studies Employing self-report testing methods						
Reference	**Sample type**	**Sample Size**	**Testing Methods**	**Control for confounds**	**Abstinence Period**	**Overall quality of the study**
Significant Short-term PM deficit						
Heffernan et al., 2001a	G	M	L	M	L	M
Heffernan et al., 2001b study 1	G	M	L	M	L	M
Heffernan et al., 2001b study 2	G	M	L	M	L	M
Fisk and Montgomery, 2008	G	L	L	G	L	L
Hadjiefthyvoulou et al., 2011a	M	M	G	G	G	G
Non-significant Short-term PM deficit						
Montgomery and Fisk, 2007	M	M	L	G	G	M
Bartholomew et al., 2010	M	M	G	G	G	G
Ciorciari and Marotte, 2011	G	G	L	L	L	L
Cuttler et al., 2012 study 2	M	G	G	G	L	G
Significant Long-term PM deficit						
Heffernan et al., 2001a	G	M	L	M	L	M
Heffernan et al., 2001b study 1	G	M	L	M	L	M
Heffernan et al., 2001b study 2	G	M	L	M	L	M
Montgomery and Fisk, 2007	M	M	L	G	G	M
Fisk and Montgomery, 2008	G	L	L	G	L	L
Ciorciari and Marotte, 2011	G	G	L	L	L	L
Non-significant Long-term PM deficit						
Hadjiefthyvoulou et al., 2011a	M	M	G	G	G	G
Bartholomew et al., 2010	M	M	G	G	G	G
Cuttler et al., 2012 study 2	M	G	G	G	L	G
Significant Internally Cued PM Deficit						
Heffernan et al., 2001a	G	M	L	M	L	M
Heffernan et al., 2001b study 1	G	M	L	M	L	M
Montgomery and Fisk, 2007	M	M	L	G	G	M
Fisk and Montgomery, 2008	G	L	L	G	L	L
Cuttler et al., 2012 study 2	M	G	G	G	L	G
Non-significant Internally Cued PM Deficit						
Heffernan et al., 2001b study 2	G	M	L	M	L	M
Hadjiefthyvoulou et al., 2011a	M	M	G	G	G	G
Bartholomew et al., 2010	M	M	G	G	G	G
Ciorciari and Marotte, 2011	G	G	L	L	L	L
Significant Environmentally and Self-Cued PM Complaints						
Weinborn et al., 2011b	L	M	G	G	L	M
Hadjiefthyvoulou et al., 2011b	M	M	G	G	G	G
Non-significant Environmentally and Self-Cued PM Complaint						
Weinborn et al., 2011a	G	M	G	M	M	M
Significant relationship between drug usage and level of PM deficit						
Rodgers et al., 2001	G	G	L	M	L	M
Rodgers et al., 2006	G	G	L	M	L	M
Rodgers et al., 2003	G	G	L	L	L	L
Arana et al., 2011	M	G	L	L	L	L
Cuttler et al., 2012 study 1	M	G	L	L	L	L
Non relationship between drug usage and level of PM deficit						
Ciorciari and Marotte, 2011	G	G	L	L	L	L
Appendix D2: Studies employing lab-based testing methods						

Reference	Sample type	Sample Size	Testing Methods	Control for confounds	Abstinence Period	Overall quality of the study
Significant Event-based PM deficit						
Zakzanis et al., 2003	M	L	M	G	G	M
Terrett et al., 2014	G	M	M	G	L	M
Hadjiefthyvoulou et al., 2011a	M	M	G	G	G	G
Hadjiefthyvoulou et al., 2011b	M	M	G	G	G	G
Weinborn et al., 2011a	G	M	G	M	M	M
Weinborn et al., 2011b	L	M	G	G	L	M
Gallagher et al., 2014 study 1	M	G	M	G	G	G
Gallagher et al., 2014 study 2	M	G	M	G	G	G
Rendell et al., 2007	G	M	M	G	L	M
Rendell et al., 2009	L	L	M	G	G	M
Montgomery et al., 2010	M	L	M	G	G	M
Montgomery et al., 2012	M	L	M	G	M	M
Non-significant Event-based PM deficit						
McHale and Hunt, 2008	G	M	M	M	L	M
Bedi and Redman, 2008	G	G	M	M	L	M
Cuttler et al., 2012 study 2	M	G	G	G	L	G
Significant Time-based PM deficit						
Zakzanis et al., 2003	M	L	M	G	G	M
McHale and Hunt, 2008	G	M	M	M	L	M
Terrett et al., 2014	G	M	M	G	L	M
Hadjiefthyvoulou et al., 2011a	M	M	G	G	G	G
Hadjiefthyvoulou et al., 2011b	M	M	G	G	G	G
Weinborn et al., 2011a	G	M	G	M	M	M
Weinborn et al., 2011b	L	M	G	G	L	M
Gallagher et al., 2014 study 1	M	G	M	G	G	G
Gallagher et al., 2014 study 2	M	G	M	G	G	G
Rendell et al., 2007	G	M	M	G	L	M
Rendell et al., 2009	L	L	M	G	G	M
Montgomery et al., 2012	M	L	M	G	M	M
Non-significant Time-based PM deficit						
Montgomery et al., 2010	M	M	M	G	G	M
Bedi and Redman, 2008	G	G	M	M	L	M
Cuttler et al., 2012 study 2	M	G	G	G	L	G
Significant Overall PM Deficit						
Bartholomew et al., 2010	M	M	G	G	G	G
Significant relationship between drug usage and level of PM deficit						
Hadjiefthyvoulou et al., 2011a	M	M	G	G	G	G
Montgomery et al., 2010	M	L	M	G	G	M
Gallagher et al., 2014 study 2	M	G	M	G	G	G

Population Representative: Sample type: General Population= Good(G); Student Population= Moderate (M); and Patient Population= Low (L) **and Sample size:** Sample size >100=Good(G); Sample size > 50 and <100 =Moderate (M); and Sample size<50= Low(L)

Abstinence period: Abstinence Period ≥7 days= Good(G); Abstinence Period< 7 days and ≤3 days=Moderate (M); and Abstinence Period <3 days or Abstinence period was not given = Low (L)

Testing Methods: Self-report + Lab-based tests= Good (G); Lab-based tests=Moderate(M); and Self-report tests=Low(L)

Control for Confounding Factors: Controlling for three or more confounding factors= Good (G); Controlling for two confounding factors= Moderate (M); and Controlling for only a factor or not at all or no information about it = Low (L).

Appendix E: The Prospective Memory Questionnaire (PMQ)

1. I missed appointments I had scheduled.
   0) Never
   1) One - three times a month
   2) Four to six times a month
   3) Seven times a month or more

2. I forgot to follow a change in my usual routine.
   0) Never
   1) One - three times a month
   2) Four to six times a month
   3) Seven times a month or more

3. I forgot to send a card for a birthday or anniversary.
   0) Never
   1) One to Three times a year
   2) Four to six times a year
   3) Seven times a year or more

4. I forgot to make an important phone call
   0) Never
   1) Once a week
   2) Twice a week
   3) Three or Four times a week
   4) More than 4 times a week

5. I told someone something that I did not mean to tell.
   0) Never
   1) One - three times a month
   2) Four to six times a month
   3) Seven times a month or more

6. I forgot to return something I borrowed.
   0) Never
   1) One - three times a month
   2) Four to six times a month
   3) Seven times a month or more

7. I forgot to pick up items I needed when shopping.
   0) Never
   1) Once a week
   2) Twice a week
   3) Three or four times a week
   4) More than 4 times a week

8. I forgot to meet a friend on time.
   0) Never
   1) Once a week
   2) Twice a week
   3) Three or four times a week
   4) More than 4 times a week

9. I forgot to pass on a message to someone.
   0) Never
   1) Once a week
   2) Twice a week
   3) Three or four times a week
   4) More than 4 times a week

10. I forgot to run an errand I meant to do.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

11. I forgot to return a phone call.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

12. I forgot to make an appointment I needed to make (e.g. doctor or dentist)
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

13. I forgot to write an important letter.
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

14. I forgot to return books to the library by the due date.
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

15. I forgot to tip when I finished dinner at a restaurant
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

16. I forgot to turn my alarm clock off when I got up in the morning.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

17. I forgot to lock the door when leaving my apartment or house
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

18. I forgot to take my keys out of my car before locking the doors.
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

19. I forgot to button or zip some part of my clothing as I was dressing
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

20. I forgot to pay the bill when finishing a meal at a restaurant.
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

21. I forgot to put a stamp on a letter before mailing it.
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

22. I forgot to comb my hair in the morning.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

23. I forgot to put on deodorant after showering or bathing.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

24. I forgot to flush the toilet.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

25. I forgot to get the food shopping out of the car when I got home from the supermarket.
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

26. I forgot to lock up my house, bike, or car.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

27. I forgot to shower or bath.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

28. I forgot to cash or deposit my paycheck before my account ran out of money
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

29. I forgot what I wanted to say in the middle of a sentence.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

30. I forgot to say something important I had in mind at the beginning of a conversation.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

31. I forgot what I came into a room to get.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

32. I started to do something, and then forgot what it was I wanted to do.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

33. I forgot to bring something I meant to take with me when leaving the house.
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

34. I got part way through a chore and forgot to finish it
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

35. I was driving and temporarily forgot where I was going.
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

36. I dialled someone on the phone and forgot who I had called by the time they answered.
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

37. I started writing a note or letter and forgot what I wanted to say.
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

38. I started to write a cheque and forgot who I was to pay it to.
    0) Never
    1) Once - Twice a month
    2) Three - Four times a month
    3) More than four times a month

39. I make lists of things I need to do
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

40. I write myself reminder notes.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

41. I make a list whenever I go shopping for food.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

42. I plan my daily schedule in advance so I will not forget things.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

43. I repeat things I need to do several times to myself in order to remember.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

44. I use external reminders like tying a string around my finger to help me remember to do things.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

45. I rehearse things in my mind so I will not forget to do them.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

46. I place things I need to take with me by the door so I will not forget them.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

47. I make Post-It (sticky notes) reminders and place them in obvious places
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

48. I create mental pictures to help me remember to do something.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

49. I put things in piles so I know which ones to do first and which can wait.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

50. I lay in bed at night and think of things I need to do the next day so I won't forget to do them
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

51. I try to do things at a regular time so I will remember to do them.
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

52. I keep a calendar or appointment book in order to remember to do things
    0) Never
    1) Once a week
    2) Twice a week
    3) Three or four times a week
    4) More than 4 times a week

Appendix F: Royal Prince Alfred Prospective Memory Test (RPA-ProMem): Test items and scoring criteria

RPA-ProMem TEST ITEMS	SCORING FOR ALL TEST ITEMS	
Part 1 (Short-term, Time-based)	**Part 1 (Short-term, Time-based)**	
In 15 minutes time I would like you to stop what we are doing and tell me the last thing you had to eat	Correct response, up to 2 minutes delay (or ahead of time)	3
	Correct response, 2–5 minutes delay (or ahead of time)	2
	Incorrect response, up to 2 minutes delay (or ahead of time)	2
	Correct response, >5 minutes delay (or ahead of time) Incorrect response, >2 minutes delay (or ahead of time)	1
	No response volunteered at any stage during session	0
		0
Part 2 (Short-term, Event-based)	**Part 2 (Short-term, Event-based)**	
At the end of our session today, I would like you to ask me for an information sheet on notetaking strategies	Correct response, up to 2 minutes delay	3
	Incorrect response, up to 2 minutes delay	2
	Correct response, 2-5 minutes delay	2
	Correct response, >5 minutes delay (or ahead of time)	1
	Incorrect response, > 2 minutes delay (or ahead of time)	0
	No response	0
Part 3 (Long-term, Event-based)	**Part 3 (Long-term, Event-based)**	
When you arrive home today, I want you to email me*, telling me what the weather is like	Emails at correct time*, gives correct message	3
	Emails at correct time, gives incorrect message	2
	Emails at incorrect time, gives correct message	2
	Emails at incorrect time, gives incorrect message	1
** participants were asked an estimated time of arrival to their home*	Does not email (up to 2 days) **allow 2 hour margin of error from expected time*	0
Part 4 (Long-term, Time-based)	**Part 3 (Long-term, Time-based)**	
Go to the given link* one week after the session to answer the question (what is your favourite colour) they were asked at the end of the experiment. ** the e-mail address of the researcher and link with the participation ID is printed on a card and given to participants at the end of the session*	The link was visited on correct day and correct information was given	3
	The link was visited, incorrect day, correct information	2
	The link was visited, correct day, incorrect information	2
	The link was visited, incorrect day, incorrect information	1
	The link was not visited (up to 2 weeks)	0

Appendix G: Spearman correlations between the RPA-ProMem and PMQ subscales

1) Spearman correlations between the RPA-ProMem and PMQ subscales in the whole sample

	the RPA-ProMem			
	ST-PM	**LT-PM**	**EB-PM**	**TB-PM**
The PMQ				
LT Epi	-.081	-.181	-.092	-.184
ST Hab	-.060	-.127	-.128	-.069
Int cued	-.027	-.030	-.012	-.040
AidPM	.025	-.084	-.033	-.006

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). LT Epi = Long-term episodic PM failures, ST Hab = Short-term habitual PM failures, Int cued = Internally cued PM failures, AidPM = use of memory aiding strategies. ST PM = short-term PM, LT PM = long-term PM, EB PM = event-based PM, TB PM = time-based PM

2) Spearman correlations between the RPA-ProMem and PMQ subscales in drug users

	the RPA-ProMem			
	ST-PM	**LT-PM**	**EB-PM**	**TB-PM**
The PMQ				
LT Epi	.096	-.195	-.078	-.033
ST Hab	.151	-.025	.007	.100
Int cued	.132	-.057	.045	-.008
AidPM	.122	-.143	-.043	.054

3) Spearman correlations between the RPA-ProMem and PMQ subscales in non-users

	the RPA-ProMem			
	ST-PM	**LT-PM**	**EB-PM**	**TB-PM**
The PMQ				
LT Epi	-.176	-.008	.109	-.163
ST Hab	-.183	-.043	-.100	-.035
Int cued	-.084	.188	.167	.097
AidPM	.015	.124	.146	.134

Appendix H: Spearman correlations among the PMQ subscales

1) Spearman correlations among the PMQ subscales in the whole sample

	LT episodic PM failures	ST habitual PM failures	Internally cued PM failures	Use of memory aiding strategies
ST habitual PM failures	.58***	-	-	-
Internally cued PM failures	.67***	.51***	-	-
Use of memory aiding strategies	.43***	.28**	.49***	-

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

2) Spearman correlations among the PMQ subscales in drug users

	LT episodic PM failures	ST habitual PM failures	Internally cued PM failures	Use of memory aiding strategies
ST habitual PM failures	.56***	-	-	-
Internally cued PM failures	.59***	.55***	-	-
Use of memory aiding strategies	.42***	.30*	.43***	-

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

3) Spearman correlations among the PMQ subscales in non-users

	LT episodic PM failures	ST habitual PM failures	Internally cued PM failures	Use of memory aiding strategies
ST habitual PM failures	.55***	-	-	-
Internally cued PM failures	.74***	.43**	-	-
Use of memory aiding strategies	.35*	.16	.53***	-

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

Appendix I: Spearman correlations among the RPA-ProMem subscales

1) Spearman correlations among the RPA-ProMem subscales in the whole sample

	ST PM	LT PM	EB PM	TB PM
LT PM	.29**	-	-	-
EB PM	.58***	.72***	-	-
TB PM	.65***	.77**	.51***	-

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

2) Spearman correlations among the RPA-ProMem subscales in drug users

	ST PM	LT PM	EB PM	TB PM
LT PM	.34*	-	-	-
EB PM	.62***	.76***	-	-
TB PM	.71***	.62***	.40**	-

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

3) Spearman correlations among the RPA-ProMem subscales in non-users

	ST PM	LT PM	EB PM	TB PM
LT PM	-.06	-	-	-
EB PM	.41**	.57***	-	-
TB PM	.49***	.70***	.43**	-

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

Appendix J: Spearman correlations between cognitive tests and two covariates

	GHQ	PSQI
The VFT		
Semantic Category	.006	.023
Initial Letter	-.124	-.056
Total	-.073	.009
The VPA		
Hit	.011	-.079
The DS		
Forward	.058	.070
Backward	-.043	-.153
Total	-.015	-.066
The CVLT3		
Trials 1 to 5 recall	-.024	-.125
Short delay score	-.024	-.202*
Long delay score	-.027	-.130
Overall Delay Recall	-.018	-.140
Total Recall	-.027	-.129
Intrusions	-.161	-.130
Repetitions	.073	-.029
Yes/no recognition hits	-.187	-.191
Yes/no recognition FA	-.164	-.079
Semantic Clustering	-.028	-.063
Serial Clustering	.145	.190
Learning slope	.116	-.031
Recall consistency	-.077	-.046
Recall from primacy region	.006	.019
Recall from middle region	-.014	.011
Recall from recency region	-.147	-.079
The AMT		
Specific memories recall	-.216*	-.204*
Non-specific memories recall	.095	.073
Extended Memories recall	.227*	-.027
Categorical Memories Recall	-.073	.028
Non-memories recall	-.233*	-.102
Omission/No respond	.222*	.195
Memories recall for positive words	-.149	-.215*
Memories recall for negative words	-.166	-.101
Overall score	-.180	-.198*
False Memory test		
Hits	-.066	-.151
False Alarm	-.035	.045
False Memory	.060	-.065
The WCST		
Correct	.087	.163
Errors	-.029	-.005
Perseverative Errors	.015	.031
Non Perseverative Errors	-.024	-.013
Categories	.121	.115
Total trials	-.003	.022
Fail to maintain	.022	.147

Source Memory test		
Present Hit	-.016	-.013
Present FA	.016	.013
Total Source Hit	.098	-.187
Total Source FA	-.098	.187
Stop-it test		
P(respond|signal)	.184	.101
Stop-signal delay	-.202*	-.107
Stop-signal RT	-.084	-.086
Signal-respond RT	-.255*	-.198
No-signal RT	-.249*	-.157
No-signal HIT	.179	.019
No-signal MISS	-.301**	-.112

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

Appendix K: Spearman correlations between PM measures and other cognitive tests

1) Spearman correlations between PM measures and other cognitive tests in the whole sample

	the RPA-ProMem					The PMQ			
	ST-PM	**LT-PM**	**EB-PM**	**TB-PM**	**Total-PM**	**LT Epi**	**ST Hab**	**Int cued**	**Aid PM**
The VFT									
Semantic category	.186	.319**	.221*	.309**	.316**	-.142	-.134	-.007	.059
Initial letter	.256*	.292**	.214*	.349**	.330**	-.049	-.117	-.033	-.006
Total score	.240*	.349**	.248*	.369**	.363**	-.114	-.150	-.013	.033
The VPA									
Hit	.400**	.145	.216*	.269**	.297**	-.129	-.146	-.116	-.058
The DS									
Forward	.200*	.071	.143	.147	.175	-.064	-.073	.086	.234*
Backward	.389**	.278**	.340**	.321**	.396**	-.116	-.27**	-.040	-.045
Total score	.365**	.235*	.311**	.301**	.367**	-.107	-.213*	.029	.104
The CVLT3									
Trials 1 to 5 recall	.401**	.462**	.415**	.498**	.529**	-.186	-.153	-.137	-.056
Overall delay recall	.329**	.472**	.396**	.449**	.489**	-.228*	-.133	-.137	-.082
Total recall	.355**	.484**	.400**	.490**	.515**	-.212*	-.130	-.118	-.058
Total intrusions	.206*	.283**	.196	.325**	.329**	-.264**	-.224*	-.057	-.142
Total repetitions	-.057	.095	-.141	.170	.031	.046	.034	.081	.081
Yes/no recognition hit	.187	.377**	.362**	.277**	.356**	-.243*	-.209*	-.106	-.190
Yes/no recognition FA	.205*	.358**	.226*	.376**	.360**	-.256*	-.287**	-.159	-.162
Semantic clustering	.179	.129	.160	.150	.181	-.240*	-.186	-.147	-.009
Serial clustering	.036	-.048	.014	.008	.003	.056	-.094	.111	.180
Learning slope	-.063	.146	.237*	-.078	.078	-.059	-.030	-.135	-.087
Recall consistency	.295**	.309**	.277**	.333**	.362**	-.084	-.095	-.050	-.047
Primacy region recall	-.095	.015	-.009	.002	-.006	.017	-.087	.055	.091
Middle region recall	.224*	.290**	.163	.340**	.305**	-.076	.004	-.024	-.073
Recency region recall	-.036	-.154	-.045	-.174	-.133	-.005	.017	-.016	-.103
The AMT									
Specific memories recall	.299**	.394**	.317**	.442**	.421**	-.142	-.109	-.128	-.101
Non-specific memories recall	-.217*	-.291**	-.158	-.365**	-.298**	-.057	-.020	.016	-.034
Extended memories recall	-.096	-.230*	-.154	-.216*	-.208*	-.097	-.066	-.018	.035
Categorical memories recall	-.239*	-.008	-.054	-.158	-.120	-.034	-.087	-.050	.002
Non-memories recall	-.085	-.043	-.021	-.099	-.059	.014	-.086	.051	-.121
Omission/no respond	-.312**	-.316**	-.306**	-.357**	-.376**	.256*	.167	.141	.178
Memories recall for positive words	.220*	.293**	.258**	.305**	.312**	-.032	-.070	.016	-.091

	the RPA-ProMem					The PMQ			
	ST-PM	**LT-PM**	**EB-PM**	**TB-PM**	**Total-PM**	**LT Epi**	**ST Hab**	**Int cued**	**Aid PM**
Memories recall for negative words	.300**	.320**	.266**	.400**	.367**	-.156	-.074	-.193	-.034
Overall score	.343**	.350**	.308**	.428**	.413**	-.189	-.115	-.132	-.113
False Memory test									
Hits	.192	.219*	.181	.275**	.249*	-.057	.075	-.152	-.128
False alarm	.013	-.209*	-.166	-.144	-.173	-.037	-.047	-.127	-.147
False memory recall	-.145	-.144	-.071	-.212*	-.177	.005	.009	-.067	.044
The WCST									
Correct	-.135	-.216*	-.184	-.186	-.213*	-.063	-.006	.003	.139
Errors	-.281**	-.227*	-.202*	-.293**	-.294**	.076	.103	.120	.081
Perseverative errors	-.245*	-.239*	-.224*	-.255*	-.277**	.128	.156	.208*	.111
Non perseverative errors	-.275**	-.115	-.090	-.269**	-.226*	-.045	.020	.026	-.025
Categories completed	.166	.157	.150	.186	.185	-.131	-.120	-.204*	-.094
Total trials completed	-.288**	-.236*	-.205*	-.316**	-.309**	.064	.074	.139	.118
Fail to maintain	-.054	-.272**	-.115	-.263**	-.218*	.145	.055	.106	.182
Source Memory test									
Present Hit	.410**	.129	.232*	.268**	.287**	.053	-.145	-.025	.010
Present FA	-.410**	-.129	-.232*	-.268**	-.287**	-.053	.145	.025	-.010
Total source Hit	.145	.158	.166	.132	.176	-.142	-.174	-.155	-.011
Total source FA	-.145	-.158	-.166	-.132	-.176	.142	.174	.155	.011
Stop-it Test									
P(respond|signal)	.105	-.221*	-.009	-.173	-.112	.133	.148	.167	.220*
Stop-signal delay	-.126	.135	-.042	.094	.032	-.073	-.142	-.131	-.221*
Stop-signal RT	-.025	-.093	-.172	-.020	-.076	-.192	.008	-.123	-.080
Signal-respond RT	-.184	.033	-.164	.019	-.064	-.205*	-.135	-.202*	-.27**
No-signal RT	-.156	.079	-.141	.076	-.015	-.179	-.149	-.204*	-.245*
No-signal HIT	-.007	.128	.038	.118	.093	-.040	-.126	.006	.208*
No-signal MISS	-.038	-.061	-.083	-.041	-.067	-.110	-.111	-.182	-.31**

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). LT Epi = Long-term episodic PM failures, ST Hab = Short-term habitual PM failures, Int cued = Internally cued PM failures, AidPM = use of memory aiding strategies. ST PM = short-term PM, LT PM = long-term PM, EB PM = event-based PM, TB PM = time-based PM

2) Spearman correlations between PM measures and other cognitive tests in drug users

	the RPA-ProMem					The PMQ			
	ST-PM	**LT-PM**	**EB-PM**	**TB-PM**	**Total-PM**	**LT Epi**	**ST Hab**	**Int cued**	**Aid PM**
The VFT									
Semantic category	.170	.292*	.223	.209	.273*	-.152	-.085	.069	.173
Initial letter	.216	.221	.166	.280*	.254	.004	-.034	-.026	.037
Total score	.220	.293*	.234	.274*	.304*	-.094	-.074	.037	.129
The VPA									
Hit	.470**	.117	.291*	.278*	.353*	-.047	-.048	.019	-.008
The DS									
Forward	.103	.051	.119	.084	.116	-.066	-.044	.081	.272*
Backward	.249	.209	.200	.210	.256	-.090	-.136	-.060	-.044
Total score	.220	.194	.227	.194	.255	-.112	-.135	.007	.112
The CVLT3									
Trials 1 to 5 recall	.378**	.423**	.411**	.412**	.505**	-.171	-.119	-.079	.034
Overall delay recall	.271	.480**	.415**	.333*	.476**	-.239	-.077	-.076	-.078
Total recall	.317*	.491**	.429**	.400**	.516**	-.252	-.133	-.131	-.023
Total intrusions	.098	.209	.175	.134	.214	-.312	-.216	-.143	-.190
Total repetitions	-.212	-.191	-.357**	-.015	-.243	.232	.176	.198	.175
Yes/no recognition hit	.239	.358**	.401**	.211	.389**	-.314**	-.222	-.046	-.201
Yes/no recognition FA	.179	.336*	.340*	.223	.367**	-.198	-.269	-.129	-.175
Semantic clustering	.185	.238	.259	.153	.261	-.199	-.160	-.016	-.126
Serial clustering	.062	.025	.057	.110	.074	-.056	-.291*	-.148	.218
Learning slope	-.110	.335**	.309*	-.057	.152	-.131	-.045	-.086	-.017
Recall consistency	.308*	.217	.250	.241	.321*	-.085	.025	.040	.033
Primacy region recall	-.124	-.173	-.117	-.144	-.184	.169	.024	.120	.123
Middle region recall	.220	.254	.223	.246	.301*	.029	.043	.197	-.046
Recency region recall	.040	-.068	-.012	-.052	-.040	-.145	-.028	-.212	-.104
The AMT									
Specific memories recall	.252	.135	.161	.312*	.249	-.105	-.098	.014	.025
Non-specific memories recall	-.198	-.163	-.108	-.303*	-.226	-.207	-.240	-.103	-.087
Extended memories recall	-.087	-.211	-.168	-.166	-.197	-.116	-.150	-.068	.064
Categorical memories recall	-.226	-.002	-.025	-.202	-.128	-.131	-.218	-.206	-.191
Non-memories recall	-.180	.012	-.021	-.169	-.102	-.101	-.176	-.066	-.201
Omission/no respond	-.252	-.048	-.128	-.207	-.172	.265	.260	.007	.001
Memories recall for positive words	.026	.059	.018	.091	.046	-.063	-.139	.075	-.045
Memories recall for negative words	.424**	.113	.218	.406**	.336*	-.041	.075	.052	.203

	the RPA-ProMem					The PMQ			
	ST-PM	**LT-PM**	**EB-PM**	**TB-PM**	**Total-PM**	**LT Epi**	**ST Hab**	**Int cued**	**Aid PM**
Overall score	.318*	.063	.117	.317*	.225	-.170	-.146	.046	.061
False Memory test									
Hits	.237	.340*	.251	.380**	.365**	.018	.224	-.072	.048
False alarm	.131	-.269	-.093	-.087	-.113	.073	-.027	-.088	-.105
False memory recall	-.174	-.330*	-.239	-.263	-.311*	.069	.072	-.151	.212
The WCST									
Correct	-.080	-.236	-.170	-.171	-.187	-.149	-.053	-.071	-.013
Errors	-.256	-.338*	-.279*	-.325*	-.358**	-.058	.124	.024	-.049
Perseverative errors	-.185	-.445**	-.338**	-.301*	-.383**	.027	.194	.201	.041
Non perseverative errors	-.295*	-.070	-.078	-.273*	-.199	-.195	.039	-.092	-.190
Categories completed	.258	.244	.288*	.231	.312*	-.156	-.199	-.248	-.084
Total trials completed	-.294*	-.347*	-.292*	-.360**	-.385**	-.054	.070	.084	-.002
Fail to maintain	-.029	-.330*	-.130	-.267	-.233	.181	.139	.195	.110
Source Memory test									
Present Hit	.442**	.168	.294*	.324*	.366*	.144	-.072	-.009	.005
Present FA	-.442**	-.168	-.294*	-.324*	-.366*	-.144	.072	.009	-.005
Total source Hit	-.021	.221	.201	.026	.139	-.040	-.088	-.030	-.007
Total source FA	.021	-.221	-.201	-.026	-.139	.040	.088	.030	.007
Stop-it Test									
P(respond|signal)	.326*	-.149	.109	.043	.083	.235	.148	.309*	.270
Stop-signal delay	-.228	.217	-.022	.040	.012	-.141	-.178	-.158	-.235
Stop-signal RT	-.166	-.197	-.210	-.185	-.229	-.083	.048	-.193	-.130
Signal-respond RT	-.380**	.104	-.125	-.134	-.147	-.361**	-.195	-.225	-.301*
No-signal RT	-.341*	.063	-.172	-.091	-.156	-.314*	-.250	-.313*	-.317*
No-signal HIT	-.150	.145	.006	.034	.015	.026	-.176	-.103	.240
No-signal MISS	-.022	-.093	-.088	-.056	-.077	-.160	-.192	-.140	-.395**

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). LT Epi = Long-term episodic PM failures, ST Hab = Short-term habitual PM failures, Int cued = Internally cued PM failures, AidPM = use of memory aiding strategies. ST PM = short-term PM, LT PM = long-term PM, EB PM = event-based PM, TB PM = time-based PM

3) Spearman correlations between PM measures and other cognitive tests in non-users

	the RPA-ProMem					The PMQ			
	ST-PM	**LT-PM**	**EB-PM**	**TB-PM**	**Total-PM**	**LT Epi**	**ST Hab**	**Int cued**	**Aid PM**
The VFT									
Semantic category	.071	.093	.036	.225	.183	-.027	-.062	.005	.016
Initial letter	.116	.175	.061	.214	.219	-.035	-.145	.046	.065
Total score	.099	.166	.058	.269	.236	-.053	-.127	.017	.028
The VPA									
Hit	.247	.054	-.032	.118	.145	-.138	-.186	-.202	-.024
The DS									
Forward	.300*	-.072	.073	.148	.181	.060	-.016	.220	.336*
Backward	.397**	.139	.356*	.237	.366*	-.048	-.332*	.052	.066
Total score	.382**	.078	.265	.247	.340*	-.014	-.249	.126	.206
The CVLT3									
Trials 1 to 5 recall	.225	.340*	.206	.331*	.364*	-.023	-.027	-.115	-.015
Overall delay recall	.162	.298*	.156	.284	.268	-.081	-.089	-.137	.000
Total recall	.141	.348*	.130	.310*	.298*	-.050	-.016	-.073	-.026
Total intrusions	.162	.089	-.007	.195	.157	-.136	-.146	.073	-.025
Total repetitions	.109	.243	.045	.316*	.262	-.115	-.091	.009	-.002
Yes/no recognition hit	.049	.335*	.233	.198	.227	-.037	-.069	-.102	-.049
Yes/no recognition FA	.095	.210	-.150	.305*	.157	-.221	-.190	-.090	-.015
Semantic clustering	.077	.015	-.004	.102	.116	-.293*	-.246	-.270	.073
Serial clustering	.065	-.144	-.039	-.117	-.090	.157	.117	.340*	.175
Learning slope	-.118	-.258	-.075	-.262	-.215	.105	.085	-.157	-.162
Recall consistency	.006	.180	.022	.131	.138	.079	-.076	-.034	-.113
Primacy region recall	.032	.360**	.223	.313*	.337*	-.236	-.294*	-.063	.038
Middle region recall	.135	.196	-.090	.290*	.187	-.068	.094	-.182	-.052
Recency region recall	-.180	-.305*	-.121	-.368*	-.333*	.154	.063	.228	-.104
The AMT									
Specific memories recall	.027	.238	.090	.249	.177	.033	.096	-.094	-.152
Non-specific memories recall	-.070	-.152	.041	-.216	-.121	-.043	.046	.064	-.002
Extended memories recall	.065	-.107	.037	-.110	-.031	-.156	-.040	-.007	-.037
Categorical memories recall	-.248	.073	-.009	-.088	-.061	.046	.036	.127	.302*
Non-memories recall	.050	-.064	-.049	-.041	-.016	.148	.042	.189	-.020
Omission/no respond	-.157	-.142	-.126	-.195	-.185	.043	-.224	.023	.166
Memories recall for positive words	.070	.174	.141	.187	.148	.159	.192	.111	-.069
Memories recall for negative words	-.072	.164	-.003	.124	.070	-.135	-.091	-.319*	-.213

	the RPA-ProMem					The PMQ			
	ST-PM	**LT-PM**	**EB-PM**	**TB-PM**	**Total-PM**	**LT Epi**	**ST Hab**	**Int cued**	**Aid PM**
Overall score	.103	.174	.111	.242	.181	-.028	.093	-.125	-.184
False Memory test									
Hits	.138	.068	.056	.139	.102	-.135	-.077	-.221	-.346*
False alarm	-.098	-.068	-.243	-.132	-.207	-.290*	-.173	-.275	-.274
False memory recall	-.051	.185	.249	-.025	.076	-.153	-.119	-.039	-.213
The WCST									
Correct	-.113	-.088	-.106	-.106	-.096	.004	-.014	.057	.315*
Errors	-.244	-.066	-.062	-.199	-.164	.193	.083	.199	.230
Perseverative errors	-.249	.031	-.055	-.095	-.087	.207	.104	.177	.197
Non perseverative errors	-.253	-.140	-.120	-.264	-.242	.105	.013	.147	.149
Categories completed	.053	.100	-.035	.127	.052	-.078	-.007	-.155	-.130
Total trials completed	-.231	-.081	-.061	-.214	-.169	.156	.051	.185	.258
Fail to maintain	-.048	-.257	-.061	-.261	-.167	.097	-.037	.027	.279
Source Memory test									
Present Hit	.365*	-.066	.018	.094	.115	.055	-.129	.052	.120
Present FA	-.365*	.066	-.018	-.094	-.115	-.055	.129	-.052	-.120
Total source Hit	.296*	-.003	.032	.169	.185	-.247	-.243	-.282	.013
Total source FA	-.296*	.003	-.032	-.169	-.185	.247	.243	.282	-.013
Stop-it Test									
P(respond|signal)	-.167	-.416**	-.203	-.434**	-.388**	.011	.111	.020	.142
Stop-signal delay	.048	.264	.001	.223	.156	.027	-.101	-.085	-.168
Stop-signal RT	.217	.038	-.158	.269	.136	-.300*	-.045	-.073	-.018
Signal-respond RT	.037	.042	-.240	.090	-.020	-.026	-.057	-.148	-.158
No-signal RT	.089	.228	-.093	.278	.174	-.097	-.113	-.181	-.174
No-signal HIT	.183	.126	.087	.247	.226	-.179	-.124	.074	.110
No-signal MISS	-.057	.003	-.084	-.040	-.071	-.017	-.019	-.222	-.147

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). LT Epi = Long-term episodic PM failures, ST Hab = Short-term habitual PM failures, Int cued = Internally cued PM failures, AidPM = use of memory aiding strategies. ST PM = short-term PM, LT PM = long-term PM, EB PM = event-based PM, TB PM = time-based PM

Appendix L: Interview questions

1. We are going to talk about your memory. There are different types of memory, for example, short-term memory which can be used to remember a phone number that has just been recited (read out).
   Can you give an example in as much detail as possible where you used your short-term memory to remember something?
2. How would you rate your short-term memory from 1 to 10, with 10 being excellent? Why do you think that?
3. Have you noticed any change in your short term memory after you started using drugs? If yes, can you describe a particular time when you noticed any changes and what those changes were?
4. Another type of memory is long-term memory, which can be used to remember what you had for breakfast or recollection of an important day, such as graduation, wedding, etc.
   Can you give an example in as much detail as possible where you used your long-term memory to remember something?
5. How would you rate your long-term memory from 1 to 10, with 10 being excellent? Why do you think that?
6. Have you noticed any change in your long term memory after you started using drugs? If yes, can you describe a particular time when you noticed any changes and what those changes were?
7. How good are you at paying attention to things? Can you give an example in which you had to pay attention to something while there was distraction present?
8. Have you noticed any change in your attention skills since you started using drugs? If yes, can you describe a particular time when you noticed any changes and what those changes were?
9. What disrupts your concentration the most while trying to focus on something, such as checking your phone or having different thought etc.?
10. How good are you at switching your focus from one thing to another? Can you give an example in which you had to switch your focus one thing to another?
11. Have you noticed any changes in your ability to switch your focus on things? If yes, can you describe a particular time when you noticed any changes and what those changes were?
12. Can you give me an example of a situation when you have to remember to do something in the next few hours or days after a particular event, such as buying bread when passing the store? In this example, the occurrence of an event (which is passing the store) may serve as a trigger to retrieve the memory to buy bread *(short-term event-based PM)*.
    a) Did you remember to do it?
    b) If yes, how did you manage to remember? Did you use a reminder or it just pops into your mind or someone reminds you?

c) If no, why? What did it make you forget to do it? What circumstances led you to forget?

13. Can you give me an example of a situation when you have to remember to do something in the next few hours or days at a particular time, such as switching on the TV at 6pm? *(short-term time-based PM)*
    d) Did you remember to do it?
    e) If yes, how did you manage to remember? Did you use a reminder or it just pops into your mind or someone reminds you?
    f) If no, why? What did it make you forget to do it? What circumstances led you to forget?
14. Can you give me an example of a situation when you have to remember to do something in the next week, next month or next year after a particular event, such as remembering to return an overdue book when driving past the local library? *(Long-term event-based PM)*
    a) Did you remember to do it?
    b) If yes, how did you manage to remember? Did you use a reminder or it just pops into your mind or someone reminds you?
    c) If no, why? What did it make you forget to do it? What circumstances led you to forget?
15. Can you give me an example of a situation when you have to remember to do something in the next week, next month or next year at a particular time, such as sending birthday wishes to a friend on his/her birthday? *(Long-term time-based PM)*
    d) Did you remember to do it?
    e) If yes, how did you manage to remember? Did you use a reminder or it just pops into your mind or someone reminds you?
    f) If no, why? What did it make you forget to do it? What circumstances led you to forget?

Appendix M: The results of RANCOVA tests in which associations between drug use and PM were examined while controlling for either retrospective memory or executive functions or both

	RANCOVA					
	Controlling for retrospective memory		**Controlling for executive functions**		**Controlling for both**	
	F	p	F	p	F	p
The RPA-ProMem						
Short-term PM	.89	.347	4.30	.041*	.56	.456
Long-term PM	7.24	.008**	18.23	<.001***	6.46	.013*
Event-based PM	3.16	.079	8.75	.004**	2.59	.111
Time-based PM	3.27	.074	12.41	.001**	2.66	.106
Total score	5.37	.023*	15.90	<.001***	4.45	.037*

*<.05,**<.01,***<.005

Appendix N: The crosstab for frequency of MDMA or ecstasy use and cannabis use

		MDMA or Ecstasy Use							
		Never	Ex-user	1 or 2 times a year	1 or 2 times every three months	1 or 2 times a month	1 or 2 times a week	3 or more times a week	Total
Cannabis Use	Never	48	1	2	1	0	0	0	52
	Ex-user	8	4	0	1	1	0	0	14
	1 or 2 times a year	4	0	5	6	1	0	0	16
	1 or 2 times every three months	3	0	3	3	1	0	0	10
	1 or 2 times a month	1	0	0	0	2	0	0	3
	1 or 2 times a week	0	0	1	0	1	0	0	2
	3 or more times a week	0	1	0	2	0	0	0	3
Total		64	6	11	13	6	0	0	100

Appendix O: The crosstab for frequency of cocaine use and cannabis use

		Cocaine Use							
		Never	Ex-user	1 or 2 times a year	1 or 2 times every three months	1 or 2 times a month	1 or 2 times a week	3 or more times a week	Total
Cannabis Use	Never	47	1	2	0	1	1	0	52
	Ex-user	9	2	1	1	0	0	1	14
	1 or 2 times a year	4	0	4	5	3	0	0	16
	1 or 2 times every three months	2	0	1	4	2	1	0	10
	1 or 2 times a month	1	0	0	0	2	0	0	3
	1 or 2 times a week	0	0	1	0	1	0	0	2
	3 or more times a week	0	1	0	1	1	0	0	3
	Total	63	4	9	11	10	2	1	100

Appendix P: The Subacute and Chronic Effects of illegal Recreational Drug Use on Executive Functions, Learning and Memory

Introduction

The psychoactive effects of recreational drugs are experienced immediately after taking, with peak levels of intoxication occurring after approximately 30 minutes and lasting several hours. During and after the intoxication, the way neurons send, receive, and process signals via neurotransmitters are interfered (Vik et al., 2004). For instance, cocaine inhibits the reuptake of dopamine by interacting with the dopamine transporter, resulting in increased levels of dopamine in the central nervous system (Kim & Park, 2019). Moreover, it has been thought that MDMA increases the activity of at least three neurotransmitters; dopamine, serotonin, and norepinephrine by enhancing their release and/or blocking their reuptake (Kalant, 2001).

The brain regions and neural processes that are affected by drug use overlap extensively with those that support cognitive functions, including learning, memory, and executive functions (Gould, 2010). Therefore, various cognitive impairments were observed in drug users (see Chapters 2, 3, 4, and 5). While the association between drug use and cognitive deficits is clear, determining causalities is difficult due to the complex interplay between these variables (Melugin et al., 2021). It has been suggested that people with cognitive deficits are more vulnerable to drug abuse than others (Flory et al., 2004; Lopez-Quintero et al., 2011); conversely, other proposals argue that drug abuse is the source of cognitive impairments (Bruijnen et al., 2019; Hadjiefthyvoulou et al., 2011b). The possible way to address this issue is to conduct a before-and-after study in which participants are tested before and after consuming drugs, so any change in cognition functions can be attributed to the drug use.

Several attempts have been made to investigate the possible changes in cognitive functions before and after consuming drugs. For instance, Freeman et al. (2012) used a mixed within- and between-subjects design to compare 20 mephedrone users, while intoxicated and drug-free; and 20 controls twice when drug-free. The results revealed that users displayed working memory impairments when intoxicated compared to non-intoxicated performance (Freeman et al., 2012). Furthermore, in another study, twenty-two healthy adults participated in experimental sessions in which THC (2.5 mg) was administered under double-blind, placebo-controlled conditions. In the 30 min following THC administration, there were marked deficits in executive functioning and working memory and a trend toward impaired episodic memory (Morrison et al., 2009).

Furthermore, the acute effects of drug use on cognitive functions have received a lot of attention in the literature, while the sub-acute effects of drug use on cognitive functions have received far less attention. For instance, Ramaekers et al. (2006) assessed the effects of high-potency marijuana (13% THC) on cognitive functions in 20 recreational users of marijuana. Participants were tested on motor control, executive function, motor impulsivity, and risk-taking at regular intervals between 15 min and 6 h post-smoking. THC significantly impaired performance on all the measures (additional in the motor control task and decreased the number of correct decisions in the Tower of London task. In addition, THC significantly increased stop reaction time and the proportions of commission and omission errors in the Stop signal task). Multiple experimental, placebo-controlled studies have repeatedly demonstrated that single doses of THC cause a dose-dependent reduction in the performance of neurocognitive tasks measuring memory, attention, impulse control and motor function (Crean et al., 2011; Gonzalez, 2007; Verheyden et al., 2003). Furthermore, a study examined the acute effects of MDMA and d-methamphetamine in comparison to placebo on cognitive measures assessing psychomotor function, attention, working memory, and perceptual speed

at peak concentration (3 hours after the administration) and 24 hours after the administration. The major findings concern poorer performance in the MDMA condition at peak concentration for the trail-making tests and an index of working memory (Stough et al., 2012). In another study, Mephedrone intoxication impaired short-term spatial memory (de Sousa Fernandes Perna et al., 2016).

Up to now, little attention has been paid to the sub-acute effects of drug use on cognitive functions. The subacute effects of drugs occur during a comedown period (usually last 3 to 7 days) in which the brain tries to return to its natural chemical balance that is impaired due to recent drug use. One approach to understanding drug-related impairments on cognitive processes and their underlying neurobiology is to study the sub-acute effects of drugs (Garavan et al., 2008). Huxster et al. (2006) recruited 38 volunteers who reported regular use of ecstasy to investigate the acute and sub-acute effects of recreational ecstasy use on sleep, mood (depression, irritability, rumination and anxiety), sexual desire and subjective cognition (memory and concentration) by administering a battery of psychological measures at an initial pre-drug baseline assessment on a Thursday and a daily basis for the next 8 days. The participants who opted to take ecstasy reported negative mood, disrupted sleep and cognitive impairment compared to the other group. While cognition and sleep returned to baseline within 48 h after use, negative mood tended to plateau before gradually returning to baseline 3–4 days after use. A similar study with 46 Mephedrone users who followed over a time period of 9 days was conducted by Homman et al. (2018). Twenty-one participants voluntarily opted to consume mephedrone 1–3 days after baseline and 25 opted to abstain. Those who consumed mephedrone reported negative mood, cognitive impairment, physical problems and fatigue, compared to those who did not. In another study, a semi-structured interview was conducted with 466 regular MDMA users to assess the perceived acute, sub-acute and long-term subjective effects of MDMA. Most participants reported experiencing

low mood (83%) and impaired concentration (80%) in terms of subacute effects (Verheyden et al., 2003). However, these results should be interpreted with care, as self-report measures were used to assess cognitive functions. As discussed in various chapters of this thesis, self-report information obtained from individuals with a history of illegal substance use may not be accurate as it relies on participants' abilities to recall their past memories correctly which might be impaired due to drug use (Cuttler et al., 2012; also see section 2.1.4). Furthermore, drug users appear to be impaired in metacognition (Balconi et al., 2014; Buckley et al., 2016; Goldstein, Craig, et al., 2009; Hester et al., 2007, 2009; Lysaker et al., 1998; Moeller et al., 2016, 2020; Verdejo-García & Pérez-García, 2008), therefore, they might not notice the possible negative effects of drug use on their cognitive functions.

The present study, therefore, investigated both sub-acute and chronic effects of recreational drug use on cognitive functions, using lab-based cognitive tests by recruiting drug naïve participants and recreational drug users which were then divided into two groups based on whether they voluntarily consumed drugs after baseline. Participants were assessed before (ideally on a Friday) and after a weekend (ideally on the following Monday or Tuesday) to investigate how drug users perform compared to non-users and whether those who did take drugs during the weekend differed from those who did not. Therefore, the performances of participants before and after the weekend were compared. It was hypothesised that drug users would perform worse than non-user controls in the first testing session. Furthermore, non-users and drug users who were not acutely intoxicated would perform better than drug users who were acutely intoxicated in the second testing session. It was also hypothesised that participants who used drugs at the weekend would perform poorly than their performance at baseline.

Methods

Participants

The study aimed to recruit 60 participants (20 non-users, 20 drug users acutely not intoxicated and 20 drug users acutely intoxicated). However, only 29 participants were recruited (19 non users and 5 drug users acutely not intoxicated and 5 drug users acutely intoxicated), due to the commencement of the COVID-19 pandemic at which point all face-to-face testing was halted. The impact of the successive lockdowns changed the drug taking behaviour of drug users and combined with additional restrictions on parties and crowds, this study could not be completed. The mean age was 37.8 (SD: 6.5). All participants were native English speakers or were fluent in English. They were requested to abstain from any recreational substance use for at least 7 days and to abstain from alcohol consumption for at least 24 hours before the first testing session.

Design and analysis

A mixed design methods was used in this study. The within-subject variable was the time point (before and after) and performance on the cognitive tests were dependent measures. The between-subject variable was group (polydrug drug users vs drug-naive controls as well as intoxicated polydrug users vs abstinent poly-drug users).

Procedure

Participants were recruited via advertisements, social media, leaflets, posters, Birkbeck Sona Experiment Management System and the snowball technique. The experiment consisted of three parts. In the first part, participants were asked to complete the self-report questionnaires via an online survey which takes around 15 minutes. In the second part, participants were asked to attend a meeting at Birkbeck University mostly on Fridays in which they completed various lab-based tests. For the second part of the study, participants were requested to abstain from any recreational substance use for at least 7 days and to

abstain from alcohol consumption for at least 24 hours prior to the test session. In the third part, participants were re-tested two or three days after the second part of the study with the different versions of the same tests, mostly on Mondays. Each meeting took 55 minutes with a 5-minute break. Participants were asked to provide a urine sample for drug assay on the day of the first (Friday) and second assessment (Monday). The tests were administered in the following order: Prospective Memory Task, Verbal Fluency, California Verbal Learning Test Part 1, Trail Making Test, California Verbal Learning Test Part 2 Short delay free recall, Tower of London, California Verbal Learning Test Part 2 Long delay free and cued recall, Autobiographical Memory Test, Stroop Task, Digit Span Test, Conceptual Span Memory Test. At the end of the third part of the study, each participant was given £25 Amazon voucher for compensation their time.

Materials:

The characteristics of sample population (ethnicity, gender, age, education level etc.) were investigated via background questionnaires. In relation to psychoactive drugs use, the Psychoactive Drug History Questionnaire was used to gather information on all psychoactive drugs used in the past 12 months, with more detailed information on drugs used over the past 90 days (Ventegodt, & Merrick, 2003). The RAPM, GHQ, and PSQI were used to assess IQ, general health and sleep respectively. The VFT, DS and AMT were also used (see section 5.3.3).

The Barratt Impulsiveness Scale (BIS; Patton et al., 1995) was used to measure the personality/behavioural construct of impulsiveness which has three sub-scales: Attentional, Motor and Non-planning impulsiveness. Participants were requested to answer 30 questions about their everyday behaviour, such as whether they buy things on impulse and whether they make comment without thinking by using a four-point scale (1=rarely/never, 2=occasionally, 3=often,4=almost always/always). The higher scores indicate greater impulsivity.

Paranoid Personality Disorder test was used to assess the symptoms of paranoid personality disorder based on upon Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013) by American Psychiatric Association criteria. There were 10 items, such as "Do you often suspect that people around you are planning to harm you?", "Are you sensitive to criticism?", Do you often suspect someone is plotting against you? etc. and each item was accompanied by five possible responses, "Never", "Rarely", "Sometimes", "Often" and "Very Often", scoring from 0 to 4, respectively. The total possible score ranges from 0 to 40. The higher scores indicate greater distrust and suspiciousness.

A short version of the RPA-ProMem (Radford, et. al., 2011) was used to assess PM in which two short-term tasks (event- and time-based) were administered. In the short-term time-based PM task, participants were asked to tell the researcher it's time for a coffee break in 15 minutes time. A digital watch was placed in the front of participants to enable them to monitor the time. In the short-term event-based PM task, participants were told to ask the researcher for an information sheet on note-taking strategies at the end of the testing session. The RPA-ProMem generated two scores for short-term event and time-based PM. Each category was scored out of 3 points, giving a maximum total score of 6. To achieve the maximum score for each item, participants needed to recall the task content correctly and either in response to the environmental cue or at the appropriate time. A low score indicates poor PM.

The brief form of the California Verbal Learning Tests (CVLT3) was used to assess participants' verbal learning and memory abilities. Participants were read a list of 9 target words by the experimenter at a rate of approximately one word per second. The words from the list were carefully selected for their frequency of use across multiple demographic variables and can be divided into three distinct semantic categories (e.g., fruits, clothing and tools), three words for each category (e.g., wrench, hammer and drill). The list was learned

across four trials, after which a 30-second distractor task (e.g., the Trail Making Test) was performed. After the distractor task, participants were asked to recall as many words as they could from the list (short delay free recall). Then, participants were engaged with a non-verbal test (e.g., the Tower of London test) for 10 minutes. After the delay period, free and cued recall of the list words was examined. After the delayed recall trials, yes/no recognition test, which consisted of all 9 target words and 9 distractors, was conducted. The CVLT III generates the same measures discussed in Chapter 5 (see section 5.3.3). Two different versions of the brief form were used. In the first phase of the study, the following categories were used: fruits, clothing and tools. In the second phase of the study, the fruits, clothing and insect categories were used with different words. Some of the words from the brief form of the CVL3 were changed in order to avoid learning effect as those words were used in the other tests. For example, the word "pliers" was swapped with "hammer". Raw scores were converted to scaled scores based on the participant's test age range. For all the scaled scores, higher scores indicate better performance.

The Trail Making Test (Rabin et al., 2005) was used to assess participants' visual attention and task-switching abilities. The test consists of two parts and each part contains 25 circles distributed over a sheet of paper. In the part A, participants were asked to draw lines to connect circled numbers in ascending order without lifting the pen from the paper. (e.g., 1-2-3, etc.) as rapidly as possible. In the part B, the circles include both numbers (1 – 13) and letters (A – L); participants were asked to draw lines to connect circled numbers and letters in an alternating numeric and alphabetic sequence (i.e., 1-A-2-B, etc.) as rapidly as possible. The Trail Making test can provide information about visual search speed, speed of processing, mental flexibility, scanning as well as executive functioning. Results for both part A and B were reported as the number of seconds required to complete the task; hence, higher scores indicate greater impairment.

The Tower of London Test (ToL; Shallice et al., 1982) was used to assess executive planning and problem-solving abilities. A computerised version of the ToL features three coloured balls (blue, red and yellow) and the three different height pegs that can hold one, two, or three balls, respectively. Participants were instructed to rearrange the balls from the starting positions which were presented in the lower half of the computer screen to match the goal positions which were presented in the upper field of the screen by using a computer mouse to move only one ball at a time. Participants were requested to solve the problem mentally first and execute the moves one by one on the screen subsequently. An adaptation of the standard problem set suggested by Kaller et al. (2011) was used in which there were 28 problems with three-, four-, five-, and six-moves (4, 8, 8, and 8 problems each respectively). For every move length, problems were balanced for the structural parameters goal hierarchy and search depth. It takes 10-15 minutes to complete the test. The following measures were recorded: number of correctly solved trials, movement time, weighted performance score (WPS), total number of moves and preplanning time. The number of problems solved in minimum number of moves was defined as the number of correctly solved trials. The summed number of moves for the correctly solved trials was defined as the WPS which reflects the quality of solution. The time between the appearance of each problem and the first touch of a ball was defined as the preplanning time while the time between the first touch of a ball and the final solution of the problem was defined as the movement time.

The Stroop test was used to assess the ability to inhibit cognitive interference, which occurs when responding to certain environmental stimuli while ignoring others (Stroop, 1935). Participants were presented with 100 trials in which colour names (green, red, yellow, blue) in different print colours appeared on the computer screen for 3 seconds one by one. They were instructed to press the key as quickly and as accurately as possible that corresponds to the colour of the ink that the word appears in on each trial, ignore the word

that is displayed (e.g., 1 for green, 2 for red, 3 for yellow and 4 for blue). It takes 4-5 minutes to complete.

The Conceptual Span Test (Haarmann et al., 2003) was used to measure individual differences in semantic short-term memory. Two versions of the task were administered for this study. In the cluster format, participants were presented lists of 12 words, with 4 consecutive words for each of 3 different semantic categories (e.g., parrot, owl, crow, pigeon, rugby, tennis, hockey, basketball, peso, quarter, nickel, million). In the Non-Clustered format, participants were presented lists of 9 randomly ordered words (e.g., cloud, kiwi, subway, snow, grape, taxi, drought, lemon, truck) that belonged to 3 different semantic categories (e.g.,fruit, transport, weather). In both, immediately after the list was presented, participants were asked to recall only the words from one cued category (e.g., fruit) in any order. Higher scores mean better performance.

Results

The demographic information of users and non-users together with alcohol/nicotine use, fluid intelligence, and health variables are presented in Table 1. T tests revealed that drug users did not differ from non-users on those background variables.

Table 1. Demographic information of users and non-users together with alcohol/nicotine use, fluid intelligence, and other background variables.

		Drug user	**Non-user**	**Total**
N		10	19	29
Gender (M/F)		7/3	10/9	17/12
Ethnicity[a]	White	9	9	18
	Asian	0	5	5
	Black	0	2	2
	Mixed	0	1	1
	Other	1	2	3
Education level	College	0	2	2
	Bachelor	6	7	13
	Masters	4	8	12
	Advanced/PhD	0	2	2
Alcohol use	Yes	9	6	15
	No	1	13	14
	Units M(SD)	105.44(53)	55.47(132)	

Nicotine use	Yes	4	4	8
	No	6	15	21
	Unit M(SD)	246.66(594)	72.84(225)	
Age	Mean (SD)	34.60(6.11)	39.50(6.32)	
RAPM	Mean(SD)	10.80(1.32)	10.32(1.73)	
GHQ	Mean(SD)	9.70(2.36)	8.95(3.08)	
PSQI	Mean (SD)	5.10(2.13)	4.58(2.52)	
PPDT	Mean (SD)	10.40(4.65)	9.95(6.12)	
BIS	Mean (SD)	35.10(8.12)	35.63(4.74)	

*Significant t test. [a] The following classification of ethnicity was used: Asian includes British-Asian, Black includes Black-British, African, and Caribbean. RAPM = Raven's Advanced Progressive Matrices, GHQ = General Health Questionnaire, PSQI = Pittsburgh Sleep Quality Index, PPDT=Paranoid Personality Disorder Test, BIS= Barratt Impulsiveness Scale. Alcohol use in unit for the last 90 days before the first testing session. Nicotine use in unit for the last 90 days before the first testing session.

As seen in Table 2, cannabis, cocaine and MDMA were the most used drugs in the current sample and most drug users were light users.

Table 2. Drug use frequency for the drug user group.

	1	**2**	**3**	**4**	**5**	**6**	**Total**
Cannabis	0	1	4	2	0	0	7
Cocaine	0	1	3	1	0	0	5
MDMA or Ecstasy	0	2	2	1	0	0	5
GHB	0	1	2	0	0	0	3
Hallucinogenic	1	1	0	0	0	0	2
Ketamine	0	1	1	0	0	0	2
Methamphetamine	0	0	1	0	0	0	1
Mephedrone	1	0	0	0	0	0	1

1 = Ex-users; 2 = Very Rarely: 1 or 2 times a year; 3 = Rarely: 1 or 2 times every three months; 4 = Occasionally: 1 or 2 times a month; 5 = Frequently: 1 or 2 times a week; 6 = Very Frequently: 3 or more times a week.

Table 3 shows the initial findings from the Part 1 and 2. The results for the Stroop test part 2 and the ToL part 1 and 2 were not included due to a technical problem in the investigator's laptop. T-tests were run to analyse the data for the part 1, however, due to a small number of participants in each group in the part 2, only descriptive statistics were

presented. The results showed that there were only significant group differences in the CVLT.

Table 3. Initial findings from the Part 1 and Part 2.

	Part 1		**Part 2**		
	Drug user N=10	**Non-users N=19**	**Drug users (intoxicated)N=5**	**Drug user (not intoxicated)N=5**	**Non-users N=19**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
The CVLT3					
Trials 1 to 4 recall	33.10(5.22)	38.32(7.82)	31.20(10.08)	37.20(6.94)	38.74(6.17)
Overall delay recall*	22.70(4.27)	31.74(7.38)	23.60(10.57)	35.20(20.58)	30.79(7.52)
Total recall*	55.80(7.33)	70.05(13.1)	54.80(20.50)	72.40(15.72)	69.53(12.17)
Total intrusions*	9.20(2.62)	11.00(1.53)	8.40(2.19)	9.00(2.83)	9.74(2.83)
Total repetitions	11.80(3.43)	11.26(2.60)	12.0(2.45)	10.8(3.03)	12.16(1.9)
Yes/no recognition hit	10.60(1.26)	10.26(1.79)	8.60(2.19)	9.40(2.19)	9.63(2.11)
Yes/no recognition FA	11.40(1.35)	11.79(.92)	9.80(4.92)	8.80(2.28)	10.21(2.90)
RPA-ProMem					
STEV	2.10(1.20)	2.37(1.26)	1.20(1.64)	2.40(1.34)	2.95(.23)
STTB	2.50(.97)	2.68(.75)	2.20(1.30)	2.20(1.30)	2.42(.84)
Total Score	4.60(1.90)	5.05(1.53)	3.40(2.30)	3.80(2.39)	5.37(1.09)
The VFT					
Semantic category	13.60(4.30)	15.21(4.49)	24.20(6.26)	23.80(6.76)	24.84(6.95)
Initial letter	17.70(4.85)	17.32(5.75)	19.40(3.51)	15.20(3.49)	18.74(4.16)
Total score	31.30(7.29)	33.00(8.97)	43.60(9.32)	36.80(8.61)	43.11(8.35)
The DS					
Forward	7.90(1.29)	8.32(1.67)	8.20(.84)	7.00(1.87)	7.63(1.92)
Backward	6.10(1.73)	7.21(1.84)	5.40(1.34)	6.00(2.74)	7.63(1.83)
Total score	14.00(1.83)	15.53(3.41)	13.60(.89)	13.00(4.18)	15.26(3.35)
The AMT					
Specific memories recall	6.20(1.69)	6.84(2.43)	6.40(1.52)	4.60(1.82)	7.47(1.68)
Non-specific memories recall	3.30(1.57)	2.42(2.48)	3.00(1.41)	3.80(2.17)	1.42(1.35)
Extended memories recall	1.90(1.10)	1.11(1.33)	1.40(1.34)	2.60(1.52)	.79(1.03)
Categorical memories recall	.80(1.03)	.68(1.11)	.60.(55)	.80(.84)	.47(.61)
Non-memories recall	.60(.52)	.63(.83)	1.00(.71)	.40(.55)	.16(.37)
Omission/no respond	.50(.53)	.74(1.28)	.60(.55)	1.60(.89)	1.11(1.66)
Overall score	32.00(3.68)	32.58(5.98)	32.0(4.42)	29.20(3.63)	33.32(6.30)
Trail Making Test					
Trail A	29.8(10.3)	29.21(6.86)	18.0(6.75)	25.20(8.17)	21.26(6.51)
Trail B	71.1 (32.3)	58.1(17.08)	42.20(7.12)	52.80(14.36)	47.42(16.26)
Total Score	100.9(40.1)	87.2 (22.2)	60.20(11.34)	78.00(22.07)	68.68(20.60)

	Part 1		Part 2		
	Drug user N=10	**Non-users N=19**	**Drug users (intoxicated)N=5**	**Drug user (not intoxicated)N=5**	**Non-users N=19**
Conceptual Span test					
Clustered	10.80(3.99)	13.05(3.03)	11.20(5.93)	15.00(3.00)	15.58(2.06)
Non-clustered	8.90(3.98)	9.05(1.93)	5.00(2.45)	7.40(3.65)	9.00(1.70)
Stroop test					
Congruent correct	.98(.04)	.96(.08)			
Incongruent correct	.98(.05)	.94(.07)			
Overall correct	.98(.04)	.95(.07)			
Congruent RT	841.6(165)	828.2(174)			
Incongruent RT	893.4(184)	902.9(209)			
Overall RT	881.2(177)	884.8(199)			

*Significant t test. CVLT: California Verbal Learning Tests, RPA-ProMem: Royal Prince Alfred Prospective Memory Test, STEV: Short-term event-based, STTB: Short-term time-based, RT: reaction time, AMT: Autobiographical Memory Test, DS: Digit Span.